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Deworming and adjuvant interventions for improving the developmental health and well-being of children in low- and middle-income countries: a systematic review and network meta-analysis

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Abstract

BACKGROUND

Soil-transmitted helminthiasis and schistosomiasis, considered among the neglected tropical diseases by the World Health Organization (WHO), affect more than a third of the world's population, with varying intensity of infection. There is debate about the effectiveness and cost-effectiveness of mass deworming of children as a strategy to improve child health in endemic areas.

OBJECTIVES

The objective of this review was to evaluate the effects of mass deworming for soil-transmitted helminths with or without deworming for schistosomiasis or co-interventions on growth, educational achievement, cognition, school attendance, quality of life and adverse effects in children in endemic helminth areas.

We also aimed to assess possible effect modifiers using pre-planned subgroup analysis of age, sex, prevalence of worms and baseline nutritional status.

SEARCH STRATEGY

Our librarian scientist designed a search strategy that was reviewed by the Campbell Collaboration librarian for the following 11 electronic databases: MEDLINE, CINAHL, LILACS, EMBASE, the Cochrane Library, Econlit, Internet Documents in Economics Access Service (IDEAS), Public Affairs Information Service (PAIS), Social Services Abstracts, Global Health CABI and CAB Abstracts, up to May 13, 2015. We also searched websites and clinical trial registers, other systematic reviews, and contacted authors and experts in the field.

STUDY SELECTION CRITERIA

We included studies if they included children aged six months to 16 years, carried out mass deworming for soil-transmitted helminths (alone or in combination with other

drugs or child health interventions), reported one of our primary outcomes of growth, school attendance, school performance, cognitive processing or development, well-being, or adverse events, and included a comparator to a control or active comparator. We included randomized trials, quasi-randomized trials, controlled before after studies, interrupted time series and quasi-experimental studies that used statistical methods of analysis to match participants with non-participants, or statistical methods to account for confounding and sample selection bias.

DATA COLLECTION AND ANALYSIS

We screened titles and abstracts in duplicate, as well as the full texts of those considered eligible at level 1. We used a pre-tested data extraction form to collect details on participants, interventions, outcomes, study methods and setting, and extracted data in duplicate.

We conducted random effects pairwise meta-analysis for all primary outcomes. If heterogeneity was acceptable (I^2 <75%), we conducted random effects, Bayesian network meta-analysis to compare different drugs and combinations of interventions, using WinBugs. We assessed risk of bias with the Cochrane risk of bias tool or the Campbell International Development review group tool, as appropriate. We assessed GRADE certainty of evidence for each outcome using the GRADE Working Group methods.

RESULTS

We analysed 65 studies with a duration from four months to five years (median 12 months) with 1,092,120 children and five long-term studies eight to 10 years after mass deworming programmes with >90,000 children. These studies were conducted in 23 low and middle income countries (L&MICs), in areas where prevalence of worms ranged from 0.5 per cent to 99 per cent infected. Most of the studies consisted of deworming twice per year or more frequently, with only two studies deworming once per year. Overall risk of bias was moderate.

Mass deworming for soil-transmitted helminths compared to controls probably has little to no improvement in weight (0.09 kg, 95%CI: -0·04 to 0·2; 35,430 participants, 11 trials), height (0.07 cm, 95% CI:-0.1 cm to 0.24 cm); 6,839 participants, nine trials) or attendance (1% higher, 95% CI: -1% to 3%; >30,000 participants, seven trials) (moderate certainty evidence). Mass deworming for soil transmitted helminths leads to little to no difference in proportion stunted (eight per 1000 fewer-from 48 fewer to 32 more; 4,286 participants, four trials), cognition measured by short-term attention (-0·23 points on 100 point scale, 95%CI -0·6, 0·14; 4,078 participants, three trials), or

mortality (1 per 1000 fewer, 95%CI: -3 to 1 per 1000 ; >1 million participants, six trials) (high certainty evidence). We found no data on short-term quality of life and little evidence of adverse effects. Mass deworming for schistosomiasis alone may slightly increase weight (0·4 kg, 95%CI: -0·2, 1·0) and has little to no effect on height (low certainty evidence) and cognition (moderate certainty evidence). Our analyses do not support indirect benefits for untreated children, from being exposed to treated children in the community (low certainty evidence). There may be increase in long-term economic productivity (1.58 hours more per week, 95%CI: -0.46 to 3.62) and school enrolment (0.29 years, 95%CI 0.01 to 0.58), little to no effect on height (-0.11 cm, 95%CI: -0.64 to 0.42) and self-reported health (0.04 units, 95%CI: 0.0 to 0.08) of mass deworming when combined with hygiene education, however, it is uncertain whether these effects are due to deworming alone or hygiene or the combination (very low certainty). We are uncertain about long-term effects on math or English at school and cognitive development due to very low certainty evidence.. Results were congruent across sensitivity and subgroup analyses by age, sex, worm prevalence, baseline nutritional status, impact on worms, infection intensity, types of worms (ascaris, hookworm or trichuris), risk of bias, cluster vs. individual trials, high compliance and low attrition bias. Deworming for children who screened positive for schistosomiasis or soil-transmitted helminths resulted in larger gains in weight and no difference in effect on height, cognition or school attendance.

IMPLICATIONS FOR POLICY AND PROGRAMMES

This independent analysis reinforces the case against mass deworming. These findings suggest that in addition to a reconsideration of mass deworming programmes in their current form, additional policy options need to be explored to improve child health and nutrition in worm-endemic areas. These include the needs for investing in interventions to address basic determinants of worm infestations such as poverty, living conditions, sanitation and inequities. Decisions on public health approaches in such settings need to be taken on the basis of human rights, ethics and evidence-based, sustainable cost-effective approaches. For schistosomiasis, the policy implication is that mass deworming may be effective at improving weight.

IMPLICATIONS FOR RESEARCH

Since all analyses of effect modification are limited by aggregate level data which may hide individual level differences, we propose that future research should assess which subset of children does benefit from mass deworming, if any, using individual patient data meta-analysis. This analysis and other work could focus on whether it is feasible to develop a case-finding tool with clinical data that could identify children and settings that would benefit from treatment.

Plain Language Summary

Mass deworming programmes have little or no effect on most welfare outcomes.

The Campbell review in brief

The effectiveness and cost-effectiveness of mass deworming of children to improve child health and other outcomes is debated. This independent analysis reinforces the case against mass deworming, finding little or no effect on most welfare outcomes.

What is this review about?

Soil-transmitted helminthiasis and schistosomiasis affect more than a third of the world's population. There is debate about the effectiveness and cost-effectiveness of mass deworming of children to improve child health and other outcomes in endemic areas.

This review evaluates the effects of mass deworming for soil-transmitted helminths on growth, educational achievement, cognition, school attendance, quality of life and adverse effects in children in endemic helminth areas.

What studies were included?

Included studies examine out mass deworming for soil-transmitted helminths (alone or in combination with other drugs or child health interventions) for children aged 6 months to 16 years, and report at least one of the following outcomes: growth, school attendance, school performance, cognitive processing or development, well-being, or adverse events. Included study designs are randomized trials, interrupted time series and non-experimental studies that used statistical methods of analysis to match participants with non-participants, or statistical methods to account for confounding and sample selection bias.

Sixty-five studies are analyzed in the review, with a treatment duration from 4 months to 5 years, covering 1,092,120 children, including five long-term studies 8-10 years after mass deworming programs with over 90,000 children. These studies were conducted in 23 low and middle income countries. Most programmes studied conduct deworming

twice per year or more frequently, with only two studies of programmes deworming just once per year.

Does deworming improve child health and other welfare outcomes?

Mass deworming for soil-transmitted helminths probably has little to no effect on weight, height, school attendance, cognition measured by short-term attention, or mortality. There are no data on short-term quality of life and little evidence of adverse effects.

Mass deworming for schistosomiasis alone may slightly increase weight but probably has little to no effect on height and cognition. The evidence does not support indirect benefits for untreated children from being exposed to treated children.

One moderate quality long term study showed an increase in economic productivity (hours worked) and increase in educational enrollment 10 years later of mass deworming and hygiene promotion. But, it is uncertain whether these effects are due to the deworming or the combined hygiene intervention.

Findings are consistent for various groups of the population by age, gender, worm prevalence, baseline nutritional status, compliance, impact on worms, infection intensity, types of worms, risk of bias, and study characteristics. Deworming for children who screened positive for schistosomiasis or soil-transmitted helminths results in larger gains in weight but no difference in effect on height, cognition or school attendance. Also, one low to moderate quality study showed long-term benefit on school enrolment of sanitation improvement combined with screening and treating people for hookworm infection.

What are the implications of this review for policy makers and decision makers?

This independent analysis reinforces the case against mass deworming. In addition to a reconsideration of mass deworming programs in their current form, additional policy options need to be explored to improve child health and nutrition in worm-endemic areas. For schistosomiasis, policy implications are that mass deworming may be effective at improving weight.

What are the research implications of this review?

Future research should assess which subset of children benefit from mass deworming using individual-level meta-analysis. This analysis could explore whether it is feasible to develop a case-finding tool to identify children and settings which will benefit from treatment.

Summary of findings tables

Mass deworming with albendazole 400 mg twice per year compared to control for children in STH endemic areas

Patient or population: children in STH endemic areas
Setting: L&MICs middle income countries
Intervention: mass deworming with albendazole 400 mg twice per year
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	What it means
	Risk with control	Risk with mass deworming with albendazole 400 mg twice per year				
Weight gain (kg)	The mean weight gain was **2.00** kg over one year	The mean weight gain in the intervention group was **0.09 kg higher** (0.04 lower to 0.2 higher)	-	35,430 (11 RCTs)	⊕⊕⊕◯ MODERATE[1] Due to in-consistency	There is probably little or no difference in weight gain in children who receive mass deworming compared to children who receive control
Height gain (cm)	The mean height gain was **3.7** cm over one year	The mean height gain in the intervention group was **0.07 cm higher** (from 0.1 cm lower to 0.24 cm higher)	-	6839 (9 RCTs)	⊕⊕⊕◯ MODERATE[2] Due to in-consistency	There is probably little or no difference in height gain in children who receive mass deworming compared to children who receive control
Cognitive processing: different scales	The mean at baseline was **78** points on 100 point scale (WISC IV memory index)	The mean cognitive development in the intervention group was **0.23 points** on 100 point scale (WISC IV memory index) lower (0.6 lower to 0.14 higher)	-	4,078 (3 RCTs)	⊕⊕⊕⊕ HIGH	There is little or no difference in cognitive processing in children who receive mass deworming compared to children who receive control
School attendance (%)	The mean school attendance at baseline was **80** %	The mean school attendance in the intervention group was one **% higher** (1 lower to 3 higher)	-	>30,000 (7 RCTs)	⊕⊕⊕◯ MODERATE[3]	There is little or no difference in attendance in children who receive mass deworming compared to children who receive control
Proportion stunted	400 per 1000	**392 per 1000** (352 to 432)	**RR 0.98** (0.88 to 1.08)	4,286 (4 RCTs)	⊕⊕⊕⊕ HIGH	There is little or no difference in proportion stunted in children who receive mass deworming compared to children who receive control
Mortality	25 per 1000[4]	**24 per 1000** (22 to 26)	**RR 0.95** (0.89 to 1.02)	over one million[5] (6 RCTs)	⊕⊕⊕⊕ HIGH	There is little or no difference in mortality in children who receive mass deworming compared to children who receive control
Long term hours worked per week	Mean number of hours worked/ week in control group (which received deworming an average of 2.41 years later)**: 18.4**	Mean number of hours worked was **1.58 hours more** (from 0.46 fewer to 3.62 hours more)	**-**	5,084 (1 RCT)	⊕◯◯◯ VERY LOW[6,7] Due to risk of	We are uncertain whether mass deworming improved hours worked after 10 years

Mass deworming with albendazole 400 mg twice per year compared to control for children in STH endemic areas

Patient or population: children in STH endemic areas
Setting: L&MICs middle income countries
Intervention: mass deworming with albendazole 400 mg twice per year
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	What it means
	Risk with control	**Risk with mass deworming with albendazole 400 mg twice per year**				
	hours/week				bias and indirectness	

*__The risk in the intervention group__ (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95 % CI). **CI:** Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Two studies were excluded due to baseline imbalance With these two studies included, the heterogeneity was very large (I^2 of 93%) and the pooled effect size was 0.25 SMD (standardized mean difference), equivalent to 0.35 kg
2. Heterogeneity was high (I^2 of 86%) with two studies that were excluded due to baseline imbalance. With these two studies included, the pooled effect size was SMD of 0.18 which is equivalent to 0.44 cm
3. School attendance rated down because of inconsistency: moderate heterogeneity was explained by a subgroup analysis of on-site vs. teacher records, but this difference could not be separated from differences in risk of bias across the same studies
4. Mortality estimate is driven by one large RCT (DEVTA 2013), which does not report the denominator for mortality, rather the mortality is reported as number of deaths per health worker for approximately one million children aged 1-6 years in the study at any one time
5. Control group rates for child mortality from Awasthi 2013 study.
6. Long term economic outcomes rated down by two levels for study limitations
7. Long term economic outcomes rated down for indirectness because of different cointervention in treatment arm but not control arms (hygiene promotion)

Mass deworming with albendazole 400 mg twice per year + Praziquantel 40 mg/kg once per year compared to control for children in STH and schistosomiasis endemic areas

Patient or population: children in STH and schistosomiasis endemic areas
Setting: L&MICs
Intervention: mass deworming with albendazole 400 mg twice per year + praziquantel 40 mg/kg once per year
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	What it means
	Risk with control	**Risk with mass deworming with albendazole 400 mg twice per year**				
Weight gain (kg)	The average weight gain over one year without deworming was **1.43** kg	The mean weight gain in the intervention group was **0.21 kg more** (from 0.14 lower to 0.56 higher)	-	438 (2 RCTs)	⊕⊕◯◯ LOW [1, 2] Due to risk of bias and imprecision	There may be little or no difference in weight gain in children who receive mass deworming compared to children who receive control
Height gain (cm)	The average height gain over one year without deworming was 2.4 cm	The mean height gain in the intervention group was **0.02 cm less** (from 0.5 lower to 0.4 higher)	-	438 (2 RCTs)	⊕⊕◯◯ LOW [1, 2] Due to risk of bias and imprecision	There may be little or no difference in height gain in children who receive mass deworming compared to children who receive control
Cognitive processing (short term attention)	The mean at baseline was **78** points on 100 point scale (WISC IV memory index)	The mean cognitive development in the intervention group was **0.23 points** on 100 point scale (WISC IV memory index) lower (0.6 lower to 0.14 higher)	-	4,078 (3 RCTs)	⊕⊕⊕⊕ HIGH	There is little or no difference in cognitive processing in children who receive mass deworming compared to children who receive control
School attendance (%)	The average school attendance at baseline was **80** %	The mean school attendance in the intervention group was **0 % higher** (17 % lower to 18 % higher)	-	4,718 (1 RCT)	⊕⊕◯◯ LOW[3, 4] Due to risk of bias and imprecision	There may be little or no difference in attendance in children who receive mass deworming compared to children who receive control
Proportion stunted	400 per 1000[6]	**368 per 1000** (176 to 764)	**RR 0.92** (0.44 to 1.91)	263 (1 RCT)	⊕⊕◯◯ LOW[5] Due to imprecision	There may be little or no difference in proportion stunted of children who receive mass deworming compared to children who receive control
Mortality	25 per 1000[8]	**24 per 1000** (22 to 26)	**RR 0.95** (0.89 to 1.02)	over one million (6 RCTs)	⊕⊕⊕◯ MODERATE[7] Due to indirectness	There is little or no difference in mortality in children who receive mass deworming compared to children who receive control
Economic productivity, as measured by long term hours worked	Mean hours worked in control group was: 18.4 hours	Mean hours worked was 1.58 hours more (from 0.46 lower to 3.62 hours higher)	-	5,084 (1 RCT)	⊕◯◯◯ VERY LOW[9, 10] Due to risk of bias and indirectness	We are uncertain whether deworming improved hours worked after 10 years

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Notes on data sources: We chose the direct comparison of albendazole+praziquantel vs. placebo for weight and height (2 studies), with the effect size from network meta-analysis converted to kg using typical standard deviation from included studies for weight and height. For cognition, we use our base case pooled estimate of short-term attention, since we found no difference in effect for one study of treating only children infected with schistosomiasis in our sensitivity analyses. For all other outcomes, we consider the results of primary analyses applicable to this comparison.

1. Rated down for possible reporting bias because for one study, we obtained the dataset for two out of the five sites of a larger study (Olds 1999).
2. Rated down for imprecision due to not meeting optimal information size
3. Rated down by one level for high risk of bias for allocation, concealment and blinding
4. Rated down by one level for imprecision
5. Rated down two levels for imprecision due to failure to meet optimal information size (263 children)
6. Control risk is average of all studies reporting stunting as an outcome.
7. Rated down for indirectness because no studies of albendazole + praziquantel assessed mortality.
8. Control group rates for child mortality from Awasthi 2013 study
9. Long term economic productivity rated down by two levels for study limitations
10. Long term economic productivity rated down for indirectness because of different cointervention in treatment arm but not control arms (hygiene promotion)

Mass deworming with praziquantel 40 mg/kg once per year compared to control for in children in schistosomiasis endemic areas

Patient or population: in children in schistosomiasis endemic areas
Settings: L&MICs
Intervention: mass deworming with praziquantel 40 mg/kg once per year
Comparison: control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **Praziquantel 40 mg/kg once per year**				
weight	The mean weight gain in the control groups was **1.66 kg**	The mean weight in the intervention groups was **0.32 kg higher** (from 0.15 to 0.8 higher)		182 (1 study)	⊕⊕⊖⊖ **low**[1]	There is probably little or no difference in weight gain in children who receive mass deworming compared to children who receive control
height	The mean height gain in the control groups was **2.8 cm**	The mean height in the intervention groups was **0.02 cm lower** (0.66 lower to 0.61 higher)		182 (1 study)	⊕⊕⊖⊖ **low**[1]	There is probably little or no difference in weight gain in children who receive mass deworming compared to children who receive control
Cognitive processing	See comment	See comment	Not estimable	-	See comment	not measured
School attendance	See comment	See comment	Not estimable	-	See comment	not measured
Proportion stunted - not measured	See comment	See comment	Not estimable	-	See comment	not measured
Mortality - not measured	See comment	See comment	Not estimable	-	See comment	not measured
Years of education 10 years follow-up	The average number of years in school at baseline was 8.13 years	The mean number of years in school in the intervention group was 0.6 years higher (0.17 lower to 1.11 higher)	Not estimable	> 80,000 (1 study)	⊕⊖⊖⊖ **very low**[2]	We are uncertain whether mass deworming improved the number of years of education after 10 years

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Rated down for imprecision and risk of bias
[2] Observational study rated down for study limitations, assessed as moderate risk of bias using IDCG tool

1 Background

1.1 THE PROBLEM

The burden of disease of soil-transmitted helminths and schistosomes was estimated at almost three million disability adjusted life years (DALYs) globally in 2004, according to the World Health Organization's (WHO) Global Burden of Disease (2004). The neglected tropical diseases of soil-transmitted helminthiasis and schistosomiasis affect more than a third of the world's population (http://www.who.int/neglected_diseases/diseases/en/). These infections rarely cause death, and therefore the burden is predominantly due to morbidity. Infections by worms affect the nutritional status of children through various mechanisms, such as feeding on host tissue and interfering with absorption of nutrients (Hall, Hewitt *et al.* 2008). These mechanisms lead to anaemia and related micronutrient deficiencies which may contribute to impaired growth, cause fatigue and hinder school attendance (Yip 2001; Jamison, Breman *et al.* 2006). Reduced school attendance at early ages has major implications throughout the life course and can impede upon labour market outcomes, maintaining cycles of poverty and worsening health equity gaps (Sianesi and Van Reenen 2003).

The four species of soil-transmitted worms most commonly associated with malnutrition and disease in children are: *Ascaris lumbricoides* (roundworm), *Trichuris trichura* (whipworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms). These worms cause infection through ingestion of eggs from contaminated soil, food (e.g. vegetables) or water or active penetration of the skin by larvae in soil. All four of these parasites are found in areas where there are poor sanitation practices and are often linked to areas of poverty. Factors associated with worm infections are poor hygiene practices, poor sanitation and lack of shoes (Bethony, Brooker *et al.* 2006).

Schistosomiasis (also known as Bilharzia) is a disease that affects over 200 million people, with over 95 per cent of infections in Africa (Schur, Hurlimann *et al.* 2011). Schistosomiasis is caused by trematodes (parasitic worms commonly called blood flukes). These worms cause infection when larvae, released by fresh water snails, penetrate the skin of the host during contact with infested water. Like soil-transmitted helminths, schistosomiasis is found in areas with poor sanitation and poor access to safe

drinking water. It is also prevalent in areas where there are bodies of fresh water, which is the habitat of the intermediate host, the snail. There are five species of schistosomiasis that infect humans: *Schistosoma mansoni, Schistosoma japonicum, Schistosoma mekongi, Schistosoma intercalatum* (which cause intestinal schistosomiasis) and *Schistosoma haematobium* (which causes urinary schistosomiasis). Schistosomiasis was previously thought to occur mainly in school-age children and above because younger children were less likely to be swimming in water bodies, but recent epidemiological monitoring data show that infants and preschool-aged children are also at risk of the disease (Stothard, Sousa-Figueiredo *et al.* 2011). Schistosome infection is hypothesized to cause iron deficiency anaemia, growth stunting and cognitive impairment, which lead to reduced school attendance, and this hypothesized effect may be mediated by the burden of infection as well as other factors (Engels and Savioli 2009).

1.2 PHARMACOLOGIC INTERVENTIONS

To combat the burden of helminths, the World Health Organization recommends concurrent deworming for soil-transmitted helminths and schistosomiasis in endemic areas, combined with improved sanitation and health education to sustain the effect of deworming and reduce reinfection rates (World Health Organization 2011). Pharmacologic therapy may be applied by: 1) mass drug administration to whole communities, 2) targeted pharmacologic treatment of high risk populations (e.g. schoolchildren), or 3) selective pharmacologic treatment of infected individuals (WHO 2011). Deworming of children has been described as the most cost-effective strategy for improving educational attendance in L&MICs (Evans and Ghosh 2008). In the last 10 years, the effects of deworming have been suggested to be improved by synergistic effects with other interventions such as hygiene promotion, iron or vitamin A supplementation and/or feeding programmes (Tanumihardjo, Permaesih *et al.* 2004; Gopaldas 2005; Nga, Winichagoon *et al.* 2009; Haque, Ahmed *et al.* 2010; Sufiyan, Sabitu *et al.* 2011).

The treatments for deworming are inexpensive, and because of the safety of the drugs, no medical staff are required for administration. Generic forms of albendazole and mebendazole, which are most commonly used to treat soil-transmitted helminths, and praziquantel, which is used to treat schistosomiasis, cost less than $0.02 USD per dose and have been donated to endemic regions since the 1980's from respective drug companies (IFPMA 2012). Either albendazole or mebendazole can be administered together with praziquantel. According to the WHO 2011 guidelines on deworming, chemopreventive therapy for soil-transmitted helminths with albendazole or mebendazole should be administered once a year where prevalence rates are ≥20%, and twice a year where prevalence rates are ≥50 per cent (World Health Organization 2011).

Schistosomiasis chemoprevention with praziquantel is dependent on the prevalence of infection in school-aged children, with treatment being yearly in high-risk communities (prevalence ≥ 50 %), once every two years in medium risk communities (prevalence ≥ 10 % but < 50%) and twice during primary schooling age in low risk communities (prevalence <10 %) (World Health 2006). This frequency of treatment is to prevent re-infection and maintain low worm burden in persons treated.

These drugs are effective in reducing worm loads in school-aged children over time periods of less than one month (Keiser 2008), but reinfection occurs in worm endemic settings. The anthelminthic action of praziquantel is not dependant on the location of the parasites within the body. The drug enhances Ca^{2+} permeability, which leads to an influx of Ca^{2+} and spastic paralysis in schistosomes. When damage is sufficient to the syncytial tegument, the resulting influx of Ca^{2+} will disrupt any processes using this ion, which results in parasite death (Harder, Andrews *et al.* 1987). Praziquantel is not effective against soil-transmitted helminths due to differences in morphology. Albendazole and mebendazole are effective in treating infections caused by soil-transmitted helminths. These drugs interrupt microtubule polymerisation, by binding to parasite's β-tubulin in the mitochondria of the worms, leading to the deaths of adult worms in the host (Lacey 1990). Serious adverse effects such as allergic reactions occur in less than one in 1000 treatments. Most adverse effects for anthelminthics against either STH or schistosomiasis are mild and short lived, and occur mainly in those infected, which implies that these symptoms are a result of the worms dying. The effects include abdominal pain, headache and nausea.

The issue of potential drug resistance to antihelminthic treatment has received greater attention in more recent years (Hotez, Molyneux *et al.* 2007), yet the evidence remains inconclusive, with few studies examining the effects among human populations (Vercruysse, Behnke *et al.* 2011). Drug resistance is defined by WHO (1996) when egg reduction rates are less than 70 per cent for ascaris and less than 50 per cent for trichuris post-albendazole treatment however this is often difficult to measure (Liabsuetrakul, Chaikongkeit *et al.* 2009). Given the current uncertainty around the longer-term implications of mass preventive chemotherapy, it is necessary to ensure ongoing surveillance of worm prevalence and reinfection rates alongside treatment programmes. Other authors suggest focusing on studies to assess availability of treatment (Harhay, Horton *et al.* 2010). Others urge that there is a need for interventions that target behavioural change and infrastructure such as hygiene, education and sanitation (Jia, Melville *et al.* 2012).

1.2.1 Concurrent interventions

In addition to deworming, the WHO and World Bank, as well as several other international organizations, such as the World Food Programme and Deworm the

World, propose providing feeding or micronutrients (such as vitamin A, iron or multiple micronutrient supplements) in conjunction with deworming (e.g. http://www.povertyactionlab.org/ scale-ups/ school-based-deworming). The World Bank recommends deworming as part of school health strategies.

Some international organizations that provide aid to developing countries such as UNICEF are increasingly taking an integrated approach to providing deworming in combination with other preventive strategies such as vitamin A, insecticide treated bednets and immunisation. These integrated approaches may produce economies of scale in providing multiple interventions together and increase attendance to the clinics or health days because parents value the number of interventions.

1.3 HOW THE INTERVENTION MIGHT WORK

Because this systematic review involved multi-component interventions, we developed a logic model to elucidate the causal chain from worm infection to nutritional status and educational effects, how deworming in combination with other strategies intervene in these causal pathways, and which factors are important in moderating these effects (Figure 2) (Anderson 2011). This logic model demonstrates generic relationships. However, different worms have specific effects that were investigated in the interpretation of results. For example, hookworm (*Necator americanus* and *Ancylostoma duodenale*) is the only worm expected to cause iron deficiency anaemia.

Deworming treatment, which involves chemopreventive therapy for soil-transmitted helminths or schistosomiasis, depending on endemicity, is administered directly to the child. Based on re-analysis of the Miguel 2004 study, there is debate about whether there are spill-over effects of decreased worm burden among untreated children and their household members who are exposed to treated children (Aiken 2015, Hicks 2015). If there are spillover effects, this may prompt governments to implement mass deworming of children as a public good since these spillover benefits may improve the health of other children and adults not reached by the programme (Ahuja 2015). One of the reasons that mass deworming of children is advocated is that screening for infection and treating infected children is prohibitively expensive, costing at least six times the cost of deworming itself, because it requires collection of stool samples, repeat visits and laboratory testing with the Kato-Katz method (Ahuja 2015). Cost-effectiveness analysis for mass deworming should also consider economies of scale (Turner *et al.* 2016).

Hygiene education and promotion and sanitation programmes are designed to reduce the likelihood of reinfection by reducing worm burden in water and surrounding soil, thus reducing the exposure of children to worms in both water and soil. Thus, hygiene

education and sanitation interventions are hypothesized to increase the duration of effect, and may also increase the effect size in the long term.

Micronutrient supplementation, including vitamin A, iron or multiple micronutrients (which may also include folic acid, iodine, vitamin B1, vitamin B2, vitamin B6,vitamin B12, vitamin C, copper, niacin, zinc and selenium) (Friis 2003) aim to reduce anaemia or improve nutrient absorption and therefore nutritional status. These nutritional co-interventions are hypothesized to have synergistic effects. For example, feeding programmes such as schoolfeeding or micronutrient supplementation may correct nutritional deficiencies hypothesized to be caused by worms.

Mediating factors affecting the causal pathway include poverty, under-nutrition, hygiene, sanitation, prevalence and intensity of infection and co-infections. With successful implementation and uptake of interventions and co-interventions, intended effects are expected in improved well-being, growth, cognitive development, and educational performance. Overall, deworming programming has the potential to improve health equity by benefiting the poorest individuals who are at greatest risk for exposure to worms (e.g. through poor sanitation) and most vulnerable to infection (e.g. due to poor nutritional status).

Many STH and schistosomiasis endemic areas now have deworming drugs available in health facilities and local shops, for treatment of children with symptoms. The availability of deworming drugs at local shops varied according to geographic setting and time. For example, Miguel 2007 reported that deworming drugs were not available over the counter for purchase in the study areas in Kenya in 1999 (i.e. none of 64 shops had alebdazole, praziquantel or mebendazole) and less than 5 per cent of children were dewormed prior to the programme. In contrast, Alderman 2006 reported that 30 per cent of control group children had been dewormed by their parents using locally available deworming drugs. The availability of deworming for the control group is a confounder that needs to be considered.

1.4 RATIONALE AND PREVIOUS SYSTEMATIC REVIEWS

A Cochrane Collaboration systematic review on deworming for soil-transmitted helminths which has been updated six times since its first publication in 2000, with the most recent update in 2015 (Taylor-Robinson 2015), found that regular treatment of children in endemic areas may have a small effect on weight gain, probably have no effect on height gain, cognition, school achievement, mortality and have uncertain effects on school attendance (Taylor-Robinson 2015). This Cochrane review has been criticized in the literature for four main reasons. Firstly, it did not address the possibility of treatment externalities or spill-over effects for individuals that do not receive treatment (both targeted individuals and household members) who may

experience a reduction in infection and reinfection rates because of their exposure to treated individuals in the same community or school (Bundy, Kremer *et al.* 2009). Secondly, the lack of effect on cognitive outcomes was not interpreted in the context of poverty, health status and the learning environment in these studies. Thirdly, effects on school attendance did not consider the validity of school attendance records (used in the studies included in the Taylor-Robinson review) compared to on-site checks (Bundy, Kremer *et al.* 2009). Fourthly, this Cochrane review excluded trials of soil-transmitted helminth treatment combined with other interventions unless these interventions were also given in the comparison group. Thus, it does not assess the effects of concurrent schistosomiasis deworming in endemic areas as recommended in the WHO guidelines, nor does it assess the effects of adjuvant interventions, such as nutritional, sanitation or hygiene interventions (Engels and Savioli 2009). The 2012 and 2015 updates of this Cochrane review were revised to consider some of these comments. For example, they obtained data from the study by Miguel and Kremer (Miguel 2004) that allowed the inclusion of this study despite the presence of praziquantel in some treatment schools where schistosomiasis was endemic. The updated review considers the evidence from the replication of the Miguel 2004 study by Aiken *et al.* (Aiken 2015) which re-assessed the evidence regarding the size of externalities (spillover effects). However, because of the focus on the single type of drug for soil-transmitted helminths, this review does not include treatment groups where cointervention with praziquantel for schistosomiasis or any other cointervention was included in only one of the treatment arms.

A second review (Hall, Hewitt et al. 2008) assessed the effects of soil-transmitted helminth treatment (albendazole, mebendazole, pyrantel or piperazone) alone on weight, height, mid-upper arm circumference, skinfold thickness and haemoglobin. Authors found statistically significant improvements in growth measurements but not in haemoglobin levels, when compared with control groups; no co-interventions were taken into consideration. A third review (Smith and Brooker 2010) found that concurrent treatment for both soil-transmitted helminths and schistosomiasis was more effective at reducing anaemia than albendazole alone, however this review did not assess the interventions' impact on growth or educational performance.

Thus, there is no systematic review which assesses the impact of the WHO guideline (WHO 2011) of deworming for both soil-transmitted helminths and schistosomiasis on school attendance, growth, well-being and adverse effects, nor the effects of combining with nutrition, hygiene or sanitation interventions.

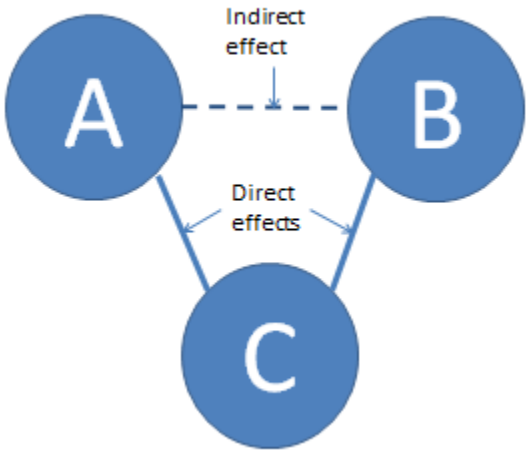
This systematic review was designed to build upon previous systematic reviews conducted on soil-transmitted helminth mass deworming interventions and address ten concerns raised about of the Cochrane review. Thus, this systematic review aimed to take into account: 1) reinfection; 2) the influence of poor learning environments on cognition; 3) combinations with co-interventions of hygiene, micronutrients and other

drugs; 4) long-term effects; 5) indirect (spillover) effects on untreated children across studies; 6) role of baseline nutritional status; 7) dilution of average effects because of uninfected children in studies; 8) possibility of different effects by worm type; 9) quality of school attendance measures; and 10) that only heavily infected children are affected by worms.

We assessed: 1) the effects of deworming children for soil-transmitted helminths, schistosomiasis or both, according to prevalence) as well as synergistic effects of co-interventions (such as micronutrients, feeding, and hygiene and/or sanitation interventions); 2) treatment externalities (spill-over effects) for untreated children living in endemic areas (see above); 3) the effects on school attendance and participation in light of validity of different measures of attendance, and 4) the effects on cognition, taking into account the learning environment, contextualized in areas of poverty and undernutrition. Long-term effects on weight, height, education and labour market outcomes will be taken into account by including non-randomised studies. We also assessed effects on HIV, tuberculosis and malaria as secondary outcomes since the WHO Partners for Parasite Control hypothesize that HIV, malaria and tuberculosis outcomes are influenced by deworming (WHO 2011). These latter outcomes were only included when studies reporting effects on nutrition or education reported them.

In order to assess the effects of multiple component, complex interventions, we conducted a systematic review and network meta-analysis. A network meta-analysis, also known as a mixed treatment comparison, is an extension of standard meta-analysis methods to synthesize two or more interventions (Wilson 2015 Campbell methods series; Salanti 2008). It allows the comparison of treatments that have not been compared directly in studies by using indirect comparisons. In the simplest setting, suppose we have three drugs (A , B and C), with drug A compared directly with drug C and drug B compared directly to drug C; we can then assess the indirect comparison of drug A to drug B, using drug C as a common comparator. Each drug is considered a "node" in the network. The solid lines between the drugs represent direct effects (assessed in a study) and dashed lines represent indirect effects (with no known study assessing the effect) as shown in Figure 1. A "closed loop" is a set of direct comparisons which joins more than 2 nodes, based on more than one trial. This provides for the assessment of the consistency of the direct and indirect evidence in the network. In the case of mass deworming, a number of studies have used different frequencies and types of deworming with or without other interventions such as iron, vitamin A or food or other drugs, thus creating closed loops. Thus, the evidence related to mass deworming was considered suitable for a network meta-analysis approach.

Figure 1: Simple network meta-analysis example



***Note**: "Closed loops are more than two arms joined by direct comparisons (e.g. A-B-C).

The credibility of the effect estimates of the network depends on two assumptions: 1) that effects are transitive, and 2) there is consistency. Transitivity is the assumption that if the effect of A vs. C is greater than the effect of B vs. C then A is greater than B. Transitivity requires a common anchor intervention (in most cases, placebo) and balance of the distribution of effect modifiers across the different treatment comparisons. Transitivity is difficult to test since effect modifiers may not all be known or reported. However, transitivity can be judged conceptually by assessing whether potential effect modifiers differ across comparisons, whether the anchor node is similar, and whether interventions are equally randomizable (implying people can be randomized to any of the interventions). Consistency means that there is agreement between direct effects (where two interventions have been compared directly in a trial) and indirect effects (where two interventions have not been compared in a trial). Consistency can be empirically checked using different model diagnostics, as well as comparing direct and indirect estimates, where both are available from closed loops (Jansen 2013; Campbell methods series; Salanti 2008). Presence of consistency is evidence of transitivity, and conversely, if there is a lack of consistency, transitivity cannot be assumed.

The advantage of the multiple treatment comparisons approach is that it allows: 1) the assessment of heterogeneity due to multiple components of a complex intervention

(Salanti, Higgins *et al.* 2008; Welton, Cooper *et al.* 2008) (i.e. hygiene education, sanitation, micronutrients, feeding programmes and type of deworming); 2) identification of areas in the network where evidence is limited (e.g. there are likely to be fewer studies of schistosomiasis control because schistosomiasis is endemic in fewer regions, mainly Africa and South-East Asia) and 3) meta-regression in a mixed treatment comparison systematic review allows more complete consideration of covariates (such as nutritional status and intensity of worm infection). By taking these factors into consideration, we assessed whether there are additive or synergistic effects of deworming and other programmes such as school feeding, micronutrient supplements and hygiene promotion, as well as assessing the effects on other outcomes such as HIV, tuberculosis and malaria burden (World Health 2005).

Studies including micronutrient co-interventions, such as iron, vitamin A, or multiple micronutrient supplementation or fortification, (including the aforementioned micronutrients plus folic acid, iodine, vitamin C, vitamin B1, vitamin B2, vitamin B6, vitamin B12, niacin, copper, zinc, and selenium) (Friis, Mwaniki *et al.* 2003; De-Regil, Suchdev *et al.* 2011) were grouped according to type of intervention and tested for heterogeneity due to differential effects on nutritional status as shown in Bandhu 2003 (Bandhu, Shankar *et al.* 2003), Donnen *et al.* 1998 (Donnen, Brasseur *et al.* 1998), and Hall 2005 (Hall 2007).

We consider the inclusion of schistosomiasis treatment to be a crucial component to this systematic review, since the previous Cochrane review of deworming excluded schistosomiasis treatment unless given to both groups. Schistosomes commonly cause anaemia affecting growth, development and functional disability (King, Dickman *et al.* 2005), and prevalence rates overlap with soil-transmitted helminth endemic areas (Utzinger and Keiser 2004). Treatment of children infected with schistosomiasis was associated with improved cognitive test scores for some domains in an observational study with no control group (Ezeamama, McGarvey *et al.* 2012). Thus, our review assesses the effects of the deworming strategy recommended by the WHO, which includes pharmacologic therapy with praziquantel for schistosomiasis where prevalence of schistosomiasis is greater than 10%.

Two other unique characteristics of this systematic review are: 1) the inclusion of quasi-experimental studies to capture long-term effects on growth and education as well as providing additional data on treatment externalities if treatment and control arms are conducted in different communities; and 2) the assessment of treatment externalities by comparing effects in cluster allocated studies (since cluster allocated studies should have less spill-over effects if the treated and control children are in different communities).

2 Objectives

The objective of this review was to evaluate the effects of mass deworming for soil-transmitted helminths, schistosomiasis or both (depending on endemicity) in conjunction with other co-interventions (such as hygiene promotion, school feeding and micronutrients) in children (six months to 16 years) in L&MICs on growth, educational status, cognition, well-being and adverse effects.

We assessed the evidence base for deworming as a complex intervention that takes into consideration context, synergistic effects, treatment externalities and the internal validity of educational status evaluations.

2.1.1 Research questions:

Definitive evidence on the effects of deworming in combination with other interventions such as feeding, nutritional supplements and hygiene promotion on educational and health outcomes is critical for those who make decisions about funding these programmes.

1. What is the effect of deworming for soil-transmitted helminths, schistosomiasis or both according to endemicity compared to placebo (or control) in children (six months to 16 years) in L&MICs on growth, educational status, cognition, well-being and adverse effects?

2. What is the effect of deworming for soil-transmitted helminths only or schistosomiasis only compared to the combination approach of deworming for both schistosomiasis and soil-transmitted helminths, in children (six months to 16 years) where both are endemic in L&MICs on growth, educational status, cognition, well-being and adverse effects?

3. What is the effect of deworming combined with hygiene education, sanitation, micronutrients or feeding programmes compared to placebo (or control) in children (six months to 16 years) in L&MICs, educational status, cognition, well-being and adverse effects?

4. What factors, either confounding (such as poverty) or effect modifiers (such as worm endemicity, infection intensity, baseline nutritional status, child age and sex, and spill-over effects) contribute to heterogeneity of effect?

3 Methods

This review is based on a published Campbell review protocol (Welch 2013).

3.1 CRITERIA FOR INCLUDING STUDIES IN THE REVIEW:

3.1.1 Types of studies

We included randomised controlled trials, quasi-randomized and controlled clinical trials, which could be randomised at the individual or cluster level.

We included quasi-experimental studies such as controlled before and after (CBA) studies and interrupted time series (with at least three time points before and after the intervention, with or without a control group), cohort, case-control and cross-sectional studies. Comparison groups for these study designs had to use statistical methods of analysis to match participants with non-participants, or statistical methods to account for confounding and sample selection bias. Methods of analysis to match participants and non-participants include regression discontinuity, propensity score matching (PSM) and covariate matching. Methods of analysis to control for confounding and selection bias include multivariate regression analysis using difference-in-differences (DID) estimation and instrumental variables (IV) estimation based on "natural experiments". Comparative studies with only post measurement were included, provided they used one or more of these techniques.

We decided to include quasi-experimental studies in addition to RCTs because these study designs are more likely to be able to assess long-term effects such as cognition, labour market outcomes and school attendance.

Studies were not excluded based on date, language or publication status. We did not exclude studies that used the above designs, based on risk of bias.

3.1.2 Types of participants

- Children from six months to 16 years of age in worm endemic areas in L&MICs (LMICs) as defined by the World Bank; at risk of infection from *Ascaris*

lumbricoides (roundworm), *Trichuris trichura* (whipworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms) or schistosomiasis.

3.1.3 Types of interventions:

- Mass drug administration or targeted chemoprevention which followed the WHO guidelines for treating soil-transmitted helminths and schistosomiasis according to prevalence (see Table 20).The programmes could have been administered in any location, such as schools, health facilities, community centres or through community outreach;

- Any of the following commonly used drugs for soil-transmitted helminths or schistosomiasis: albendazole, mebendazole, ivermectin, pyrantel and levamisole and praziquantel in the appropriate dose; or, for other pharmacologic treatments (such as metrifonate, thiabendazole), we included any licensed drugs, at the appropriate dose levels;

- May also include cointerventions of hygiene promotion and education, sanitation improvements (e.g. water treatment), micronutrients (e.g. vitamin A, iron or multiple micronutrients such as iron, folic acid, iodine, vitamin C, vitamin B1, B2, B6, B12, niacin, copper, zinc and selenium) or feeding programmes.

We included all studies with an arm of mass deworming according to WHO guidelines for soil-transmitted helminths with or without treatment for schistosomiasis (or both) and met other inclusion criteria. We assessed endemicity of schistosoma and soil-transmitted helminths as reported by the authors, or referred to a separate publication about prevalence of helminths in the region of the study. If endemicity was not reported, we contacted the authors. We also referred to maps of schistosomiasis and soil-transmitted helminthiasis prevalence (e.g. Global Atlas of Helminth Infections: http://www.thiswormyworld.org/). We classidfied the frequency of deworming according to the number of treatgments in a period of time for example studies with deworming twice a year included stujdies with one dose in 6 months as well as two doses in a year.

We conducted a sensitivity analysis to assess the effect of soil-transmitted helminth deworming in regions of low (less than 10 per cent), moderate (10-30 per cent) or high (greater than 30 per cent) schistosomiasis prevalence. Interventions of micronutrient supplementation, feeding, hygiene or sanitation compared to placebo will be excluded unless they are combined with or compared with deworming treatment which matches the WHO guidelines.

The helminth species targeted in this review are *Ascaris lumbricoides* (roundworm), *Trichuris trichura* (whipworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms) and schistosoma—those most commonly associated with malnutrition and greatest disease burden among children in worm endemic areas (Albonico, Allen *et al.* 2008). We excluded other soil-transmitted helminths (Strongyloides, lymphatic filariasis and onchocerciasis) because different treatment regimens are required or insufficient empirical evidence exists around prevalence, burden and accepted control strategies. The included worms are consistent with those addressed in the current WHO guidelines on helminth control in school-aged children (WHO 2011). Other helminth diseases, such as lymphatic filariasis and onchocerciasis were excluded; these use overlapping drug regimens but are covered in separate guidelines (http://www.who.int/lymphaticfilariasis/resources/en; http://www.who.int/apoc/publications/en/) due to non-school-based control approaches. Strongyloidiasis was excluded since it is less responsive to albendazole or mebendazole and lacks any formal public health strategy (http://www.who.int/neglected_diseass/diseases/strongyloidiasis/en/. Given the independent research efforts and protocols for the variety of worm types, we recognize the importance of ensuring that co-administration of helminth treatment is taken into consideration for analyzing the epidemiology of soil-transmitted helminthiasis and duplication of administrative efforts is minimised to improve effective resource usage.

This systematic review focuses on mass drug administration of children or targeted deworming in schools since the selective treatment of only infected individuals is not widely used due to the cost of screening tests. We excluded studies where children were screened for infection, and only infected children were treated. We investigated the influence of this decision in a sensitivity analysis of this eligibility criterion.

3.1.4 Comparisons:

We accepted studies that use one of the following three types of comparisons:

a) comparison that singles out the effect of the intervention of interest (i.e. all co-interventions are provided to both intervention and control group; and a control or placebo group is used as a comparison to the active intervention);

b) a placebo or "do nothing" control group; or

c) studies with a control group that receives an active intervention which is not given to the intervention group.

Comparison groups could be separate individuals, either using equivalent groups design (RCTs, RDDs) or non-equivalent groups using statistical methods to equalise groups.

For CBAs, a parallel control group was required. For interrupted time series, we required three time points before the intervention as a comparison group to three time points after.

For studies with a factorial design, we used all available data to populate the network meta-analysis.

3.1.5 Types of outcomes measures:

Primary outcomes:

- Anthropometry: weight, height, stunting, wasting, underweight, malnutrition, body mass index, mid-upper arm circumference, or skin fold thickness
- Educational status: school attendance, days absent, dropout rates, performance on test scores (e.g. math and reading)
- Cognition: memory, concentration, language development or concept formation (e.g. fluency, intelligence tests)
- Well-being: physical (energy, fatigue or fitness levels), emotional or social functioning; patient satisfaction; quality adjusted life years (QALYs) or disability adjusted life years (DALYs)
- Adverse events due to interventions: e.g. diarrhoea, vomiting or nausea

Secondary outcomes:

Intermediate outcomes

- Micronutrient status: i.e. vitamin A, iron, folic acid, vitamin B12
- Haematology: i.e. haemoglobin, plasma ferritin, transferrin, zinc, serum retinol
- Co-morbidities: malaria, HIV, tuberculosis, or number of recent infections.
- STH and schistosomal prevalence and intensities
- Helminth-related morbidities: anaemia, granuloma, intestinal bleeding, loss of appetite, diarrhoea/ dysentery, intestinal obstruction
- Other relevant intermediate outcomes relating to health or educational outcomes: e.g. sanitation, hygiene (e.g. measures of pathogen content in drinking water or on hands)

Other outcomes

- Costs and resource use
- Measures of health equity (e.g. concentration index)
- Labour market outcomes (e.g. participation rates, wages)

Studies had to assess at least one of the primary outcomes to be included for this review. Secondary outcomes were recorded only if at least one of the primary outcomes was also measured. Outcomes were recorded based on validated scales and calculated using standardized mean difference. We excluded studies which measured the outcomes of worm burden or worm prevalence alone since this is not demonstrated to be associated with health or educational outcomes. Minimum reporting time was four months since we felt based on clinical expertise that changes in the primary outcomes of growth, educational status and cognition require at least this amount of time to materialize.

All time points were recorded; however we used data reported closest to 12 months as the primary analysis, where possible, because this amount of time is deemed sufficient for growth, education and cognition changes. Also, the Cochrane review showed that study duration had no influence on weight gain, using meta-regression (Taylor-Robinson 2015). The time period for which the outcome was measured had to be the same in both groups given the effects of climate (e.g. rainy season).

3.2 SEARCH METHODS FOR IDENTIFYING STUDIES

3.2.1 Search strategy development

We developed a comprehensive search strategy with support from an information scientist (JM) for electronic databases and grey literature sources such as organizations active in deworming. The draft search strategy underwent review with PRESS (Peer Reviewed Electronic Search Strategies) (Sampson 2009) by John Eyers, information scientist of the Campbell International Development Group, and appropriate changes were made (Appendices A and B) to produce the finalised search strategy.

We identified relevant studies to inform the search strategy development: four randomised controlled trials and one cross-sectional study that used propensity score matching (Azomahou, Diallo *et al.* 2012) that compare deworming combined with other interventions such as hygiene education (Taylor, Jinabhai *et al.* 2001), feeding (Azomahou, Diallo *et al.* 2012) or micronutrient supplementation (Biovin and Giordani 1993; Jinabhai, Taylor *et al.* 2001; Friis, Mwaniki *et al.* 2003) to placebo or active comparison groups.

3.2.2 Electronic searches

The search included the following health and non-health electronic databases: MEDLINE, CINAHL, LILACS, EMBASE, the Cochrane Library, Econlit, Internet Documents in Economics Access Service (IDEAS), Public Affairs Information Service (PAIS), Social Services Abstracts, Global Health CABI and CAB Abstracts. Grey literature databases were also included (e.g. thesis dissertations, System for Information on Grey Literature in Europe (SIGLE)-ends in 2005).

We also searched websites of relevant organizations (UNICEF, Save the Children, Deworm the World, WHO, the World Bank, World Food Programme, International Food Policy Research Institute (IFPRI) and Red Cross, Helen Keller International, Micronutrient Initiative, Global Alliance for Improved Nutrition (GAIN), Schools & Health: Health Nutrition, HIV and AIDS).

Other sources of reports and non-published material were searched:

- AFROLIB Database (http://afrolib.afro.who.int/cgi-bin/wxis.exe/iah/?IsisScript=iah/iah.xic&lang=I&base=afrolib)
- 3ie Database of Impact Evaluations (http://www.3ieimpact.org/database_of_impact_evaluations.html)
- BLDS British Library for Development Studies (http://blds.ids.ac.uk/)
- ELDIS (http://www.eldis.org/)
- International Clinical Trials Registry Platform - Search Portal: http://www.who.int/trialsearch/
- East View Information Service Online Databases (httfp://online.eastview.com/index.jsp) – China, Russia and Soviet Union
- Index Medicus for the Western Pacific (WPRIM) (http://wprim.wpro.who.int/SearchBasic.php)
- South African Medical Database (SAMED) (http://www.mrc.ac.za/SamedSearch/

We screened the references of included studies and conducted a SCOPUS search to identify any studies which cited included studies, according to the Peer Review of Electronic Search Strategies' PRESS recommendations on developing search strategies (Sampson, McGowan *et al.* 2008).

3.2.3 Searching other resources

We used reference lists from previous systematic reviews, conducted within the last ten years, to identify potentially relevant, individual studies and assessed them based on the outlined eligibility criteria. We also screened the reference lists of included studies.

3.3 DATA COLLECTION AND ANALYSIS

3.3.1 Selection of studies

Two reviewers independently screened titles and abstracts based on the following questions: a) does the intervention include pharmacologic deworming treatment which is provided by mass or targeted administration to an identified high-risk group?; b) is at least one of growth, well-being, educational attendance, cognition or adverse events outcomes measured?; c) does the population include children between the ages of six months to sixteen years?; d) is the length of time from intervention to follow-up four months or longer?; and e) does the study design include an appropriate comparison group? (i.e. uses statistical methods to control for confounding such as propensity-score or covariate matching). We pre-tested the title and abstracts screening questions. If any one of these questions is answered as 'no', then the study was excluded from further consideration. If all questions were answered as 'yes', then the study was included for full-text screening. After each reviewer independently screened studies, any discrepancies around decisions for inclusion or exclusion were discussed and reconciled accordingly. The full text was retrieved for titles and abstracts accepted for inclusion after discussion by both reviewers.

The full text was screened by two reviewers for inclusion according to the pre-specified eligibility criteria. Any disagreements were settled by discussion with a third party who reviewed the full text and decide whether it meets the inclusion criteria. For judgments related to appropriate control for confounders, we consulted with a statistician (GAW).

3.3.2 Data extraction and management

Two reviewers conducted independent data extraction and risk of bias assessment of all included studies. The data extraction form was pre-tested. Information extracted included data on study design, statistical analysis, details about the participants (including the number in each group), setting (e.g. endemicity, sanitation), intervention (e.g. type of drugs, dose, frequency and process of implementation), comparison, cost-effectiveness, health and cognition outcomes (including whether outcomes were validated). We extracted process data on the implementation of the intervention such as method of delivering deworming (e.g. provision of deworming integrated with other programmes), amount of supervision and monitoring of attendance in school and attendance to the deworming sessions. Where possible, we extracted data about socio-demographic variables associated with disadvantage, across factors described by the acronym PROGRESS (Place of residence, Race/ ethnicity, Occupation, Gender/ sex, Religion, Education, Socioeconomic status and Social capital) (Tugwell, Petticrew *et al.* 2006). We extracted data on any effect modifier analyses (e.g. subgroup analyses and meta-regression) conducted in the primary studies. We compared the extraction by

both reviewers, and reached consensus by discussion and consultation with a third reviewer, if necessary.

We contacted authors for missing data such as missing standard deviations and means for each group (e.g. if results were reported as "not statistically significant" without providing group means).

3.3.3 Process of implementation

We extracted the following process elements, based on a process evaluation of schoolfeeding (Kristjansson, Petticrew *et al.* 2007):

- Multifaceted approaches (e.g. Were other supports or integrated provisions given, such as hygiene promotion, iron supplementation, bednets or vitamin A, in addition to providing deworming treatment?);
- Time of day interventions were given;
- Settings (where was the intervention administered? E.g. School, daycare, primary care clinics, immunisation days);
- Prior needs assessment to inform intervention design and delivery (to identify when, where and how to give interventions to maximise uptake efficacy);
- Who delivered the intervention (e.g. Supervised, and if so, by whom)?;
- Were interventions provided free of charge or for a reduced price according to income?
- Were prompts/ reminders provided (e.g. Was intake of food or medication monitored)?;
- Cost and time to run programme;
- Proportion of children in the community enrolled in school;
- Context in which the programme is given (e.g. Health systems context, community sanitation, availability of water to wash, infection intensity, poverty, whether the programme is delivered as a vertical programme);
- Reach of programme (e.g. What was the proportion of eligible children that are covered by the programme? For example school-based programmes will not reach children who are not enrolled in school and this could affect the reinfection rate in the community);

- Duration of the study (effects on cognition and education are expected only over longer time frames);
- Dose and type of drug given;
- Endemicity

For each of these process elements, we accepted the definitions provided by the studies. We considered the comparability of different methods of measuring these factors in grouping studies. For example, hygiene and sanitation were defined differently in different settings and studies.

3.3.4 Assessment of risk of bias in included studies

We used the Cochrane risk of bias tool to assess the risk of bias for randomised controlled trials, quasi-randomised trials and controlled before-after studies. We also assessed whether baseline characteristics were similar. For cluster randomised trials, we assessed recruitment bias, loss of clusters, incorrect analysis and comparability with individual RCTs, as recommended by the Cochrane Handbook.

For interrupted time series studies, we would have used the Cochrane Effective Practice and Organization of Care risk of bias checklist, but none were found.

For other quasi-experimental studies, we used the International Development Coordinating Group's risk of bias tool as it explicitly outlines assessment for study designs using propensity score and covariate matching (International Initiative for Impact Evaluation 2012).

The main categories of bias that were assessed were: selection bias, performance bias, detection bias, attrition bias and outcome reporting bias. Risk of bias was assessed for each outcome in each study. Since we were particularly interested in spill-over effects, we assessed this risk of spillover/ externalities under performance bias and made notes about the likelihood of spillover effects.

Any disagreements about the judgment relating to the risk of bias ratings was resolved by discussion with a third party.

3.3.5 Measures of treatment effect

Two levels of analysis were conducted: 1) meta-analyses for each outcome for each comparison of interest and comparisons which will be used to inform the network meta-analysis; 2) network meta-analysis for the main comparisons of interest. The main comparisons of interest were: a) combined deworming (STH and schistosomiasis) or single target deworming (STH or schistosomiasis) vs. placebo; b) combined deworming vs. single target deworming (STH and schistosomiasis vs. STH or schistosomiasis); c)

single target deworming vs. each other (STH vs. schistosomiasis); d) deworming vs. deworming and micronutrient(s); and e) deworming vs. deworming and feeding.

3.3.6 Step 1: Meta-analyses for each comparison

First, we conducted meta-analyses for each comparison of interest, where clinically sensible (e.g. for trials of clinically similar populations, interventions, comparisons and outcomes) using Review Manager 5.3 Software. We did not combine results from different study designs since these are of different risk of biases. For RCTs, we used unadjusted estimates. For quasi-experimental studies, we used adjusted estimates and generic variance methods.

RCTs, CBAs and quasi-experimental studies were analysed separately. Different interventions and comparisons were analysed separately. Studies with similar outcomes were grouped for analysis.

Calculating Effect Size

The effect size of weight and weight-for-age (WAZ) was analysed as standardised mean differences (SMD) of change from baseline, since this increased our sample of studies for exploring heterogeneity than if we had used weight (kg) alone or WAZ alone. We also did this for height (cm) and height for age (HAZ). This decision was based on discussion with the nutritionists and clinicians on the research team (ZB, SA, SK) and consultation with two external nutritionists. The SMD was back transformed to weight (kg) using the median standard deviation for studies which reported weight in kg, as described in the Cochrane Handbook in section 12.6.4.

Continuous outcomes of test scores and cognition tests were analysed as change scores using standardised mean differences as the scales used differed across studies. If studies reported baseline and end of study data, we calculated change scores and the standard deviation for change, using the formulae in the Cochrane Handbook. We used a correlation coefficient of 0.9 for weight, height and haemoglobin (based on before-after correlations used by Kristjanssson 2015 for school-feeding review), and 0.71 for cognition (based on correlation matrices in a study we included for sensitivity analyses (Sternberg 1997), and 0.71 was also used by Kristjansson 2015 for cognition). We consulted with a specialist in educational measures about whether to group similar tests together (EK). We decided to summarise three types of cognitive tests: 1) short-term attention tests (e.g. digit span, number recall), 2) general intelligence tests (e.g. Peabody Vocabulary Test and Raven's progressive matrices), and 3) development outcomes for young children (e.g. language and motor development). Where possible, we used unadjusted estimates. However, if these were not available, we used adjusted estimates.

Dichotomous outcomes were analysed as relative risks, using random effect methods. We used random effects models since we expected the underlying treatment effect would vary depending on the context, populations and setting.

We report analyses for each outcome separately, focusing on the time point closest to 12 months as the main analysis.

We did not conduct meta-analyses for the secondary outcomes.

Where the reported outcome data was not in the required format, (e.g. means, standard deviation and sample sizes), effect sizes were calculated using the appropriate formulae provided in the Cochrane Handbook (Higgins and Green 2011). If the data were adjusted, we used the adjustment included in the reported estimate. For regression studies, we planned to use the IDCG protocol and review guidelines, but we did not find any such studies.

Costs and resource use data were synthesized in tables, if provided. We did not conduct a cost-effectiveness analysis.

Unit of analysis issues

Where the unit of allocation was by groups (e.g. schools, communities, village, region), we used the standard deviation adjusted for clustering, if provided by the study. In the case of randomised studies, if the study had not adjusted for clustering, we adjusted the standard deviations using the variance inflation factor, as described in the Cochrane Handbook (Higgins and Green 2011). The variance inflation factor is calculated using the equation: (1 + (m-1) x ICC) where (m) is the cluster size and ICC is the intra cluster correlation. If cluster size is not reported, the number of participants in each analysis or total number of participants (where former is not available) was divided by the number of clusters to calculate cluster size. If ICC was not reported, we estimated ICC values for the corresponding outcome measure using published ICCs for similar outcome measures. The effect of ICC values was assessed using sensitivity analysis.

For quasi-randomised studies, where an adjusted estimate was determined but clustering was not taken into consideration, we would have derived procedures to accommodate for clustering in the modelling process, if possible, but no studies like this were found.

Effects of treatment externalities

Treatment externalities may occur if there are spillover effects to those individuals who live in the treatment locality but don't receive deworming (who in an individually

randomised study will be the control group). The effects of treatment externalities were assessed by two methods:

1) assessing the improvement in control groups for studies with cluster allocation versus those without cluster allocation (hypothesising that those without cluster assignment may have larger beneficial effect in the control group because geographical distance between control and intervention in cluster allocated studies may reduce the externalities to the control group); and

2) assessing whether individual studies assessed the extent to which control groups benefit.

Assessment of heterogeneity

Heterogeneity was assessed by visual inspection of forest plots, chi-squared test and I^2. I^2 was used to quantify heterogeneity across studies, as it describes the percentage of variability in effect estimates that is due to heterogeneity. We explored heterogeneity using subgroup and sensitivity analyses.

We explored heterogeneity using pre-planned subgroup and sensitivity analyses to assess the role of possible effect modifiers such as sanitation, poverty, under-nutrition, prevalence of different types of worms, intensity of infection, co-infection, concomitant interventions (e.g. micronutrients, hygiene) and risk of bias. We chose to assess the role of these factors based on prior theory or evidence, as shown in the logic model (Jamison, Breman *et al.* 2006; Bundy, Kremer *et al.* 2009; Kremer 2004). Subgroup analyses reported in the included studies were extracted and were compared to these subgroup and sensitivity analyses.

Subgroup Analyses

We assessed the following subgroup analyses for each pairwise comparison:

1) Age of children (<2 years, 2-5 years, >5 years)

2) Sex

3) Prevalence of worms (low, moderate, high)

4) Nutritional status (studies with >30 per cent underheight v.s. studies with <=30 per cent of children underheight, based on WHO standards, http://www.who.int/nutgrowthdb/about/introduction/en/index5.html

These subgroup analyses were conducted using Review Manager 5.3 using a test for interaction. To address possible concerns about not making use of all available data, we also conducted subgroup analyses for any mass deworming treatment vs. control. In

studies with more than two arms, we selected the intervention arm that was most similar to mass deworming twice per year and that had common cointerventions in both arms.

We also compared our subgroup analyses with subgroup analyses across the same factors reported within the primary studies.

Sensitivity analysis

Sensitivity analyses were planned to assess the impact of outlier individual studies (e.g. very large studies, very large effects, very precise confidence intervals) on the overall effect size, and studies that may not fully fit inclusion criteria.

We conducted sensitivity analyses to assess the influence of:

1) Including two studies that were removed due to baseline imbalance (Koroma 1996 and Stephenson 1989)

2) Choice of attendance effect size from Miguel 2004 (overall treatment effect considering externalities or ITT)

3) Cluster randomised studies alone

4) Impact on worms (as an indicator of first stage of causal pathway),

5) Low risk of bias- allocation concealment

6) Eligibility criteria: including studies which screened for infection

7) Intensity of infection (>30 per cent with heavy infection)

8) Using a lower ICC value to adjust unit of analysis errors of 0.01 instead of 0.17 for weight and 0.11 for height (reported in Awasthi 2008)

9) Using a higher ICC value for cognition of 0.15 instead of 0.07

10) Effect of unpublished studies

11) Prevalence of schistosomiasis (<10%, 10-30%, >30%)

Dealing with missing data

We contacted authors of the studies if information reported was insufficient to calculate effect size and standard deviation. When authors did not reply, we listed these studies and/or outcomes as pending. If other measures of variation were available, such as exact p-values or standard error of the difference between means, we used the formulae

in the Cochrane Handbook to calculate SD for each group. We did not impute missing values (e.g. missing variance or outcome data) for the primary studies, except for two studies where we received full datasets from the authors and we used information in those datasets to impute missing values (see below for details).

3.3.7 Assessment of publication bias

Publication bias is a risk for any systematic review. We attempted to minimise publication bias by conducting a comprehensive search strategy of published and grey literature, using trial registries and contacting experts in the field. We assessed the presence of publication bias using funnel plots, and interpreted these cautiously based on number of studies retrieved.

3.3.8 Step 2: Network Meta-analysis

At the next level, network meta-analyses (NMAs) were conducted. Network meta-analysis is increasingly being used in health research as it allows for simultaneous comparison of all available therapies and uses all available relevant data, and is thus extremely relevant to clinicians, researchers and decision makers. A two-phase approach was used, with the first phase using data from RCTs alone and the second phase using data from controlled before after studies separately. This method allows for estimation of the impact of the observational research on summary estimates.

Following careful assessment of heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols, NMAs were conducted for the pre-specified outcomes. We compared effect estimate according to outcomes of interest (growth, educational status, cognition, well-being, co-morbidities, costs and adverse effects, where available). There are four types of possible comparison including 1) isolation of deworming intervention compared to placebo or “do-nothing”, 2) deworming combined with active intervention(s) compared to control group and 3) deworming compared to deworming and other active interventions, and 4) Deworming compared to other active interventions was only assessed in situations where studies assessing one of the former three comparisons provide information that helps to close loops in the network meta-analyses. We assumed that placebo and “do nothing” control groups result in similar magnitude of effect in our network meta-analysis diagram. We tested this assumption in the assessment of heterogeneity, if possible.

We used a Bayesian approach to conduct random-effects models with selection based on the Deviance Information Criterion (DIC) and residual deviance. We used WinBUGS (MRC Biostatistics Unit, Cambridge, UK) for Bayesian network meta-analyses according to the routine that accommodates evidence structures, which may consist of multi-arm trials as developed at the Universities of Bristol and Leicester (www.bris.ac.uk/cobm/research/mpes/). Placebo or control was the reference group for

all Bayesian NMAs. Posterior densities for unknown parameters were estimated using Markov Chain Monte Carlo (MCMC) methods. Basic parameters were assigned non-informative or vague prior distributions. We constructed more informative priors for between study variance based on Turner 2012. Point estimates and 95 per cent credible intervals were used to summarize findings. Consistency between direct and indirect evidence was formally assessed using back-calculation and node splitting techniques (Dias, Welton *et al*. 2011). We used numerical summaries to present results from network meta-analysis (Dias, Welton *et al*.). We used model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic (Brooks 1998) to assess and ensure model convergence. Two chains were fit in WinBUGS for each analysis, each usually employing ≥30,000 iterations for burn-ins and ≥60,000 iterations for the full model.

We did not have sufficient data in the evidence network to conduct meta-regression (as planned in the protocol). We conducted pre-planned sensitivity analyses where there was sufficient data for model convergence to check the robustness of the network meta-aanlysis.

3.3.9 Summary of findings table

The magnitude of effect and quality of evidence is presented in a summary of findings table, with the seven most important patient outcomes (Higgins 2015). We define the patient important outcomes as anthropometry, educational participation and achievement, cognitive status, well-being, labour market outcomes and adverse effects. Quality was assessed using the GRADE criteria for this summary of findings table, as recommended by the Cochrane Handbook and the GRADE Handbook (http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html). We used the GRADE criteria for network meta-analysis as published by members of the GRADE Working Group (Puhan 2014).

3.3.10 Step 3: Weighted least squares regression and causal pathway analysis

We used weighted least squares regression outside of the NMA to assess the relationship between weight, height and attendance outcomes with causal pathway explanatory variables: prevalence of worms, impact on worms and weight gain. For this analysis, we chose from each study the comparison that was closest to deworming twice per year vs. placebo. We avoided using any multiple component interventions unless they were given in both arms (e.g. albendazole+vitamin A vs. vitamin A). The data for the outcome variables of weight, height and attendance were not normally distributed. Therefore, we used several transformations to make these distributions normal, but none of these improved the distribution.

3.3.11 Step 4: Power analysis

We assessed the power of our main analyses on weight and school attendance using a method developed for systematic reviews described by Hedges and Pigott (Hedges 2001). This method depends on the minimum important difference, the level of statistical significance, the sample size (both the number of studies and the within-study sample size) and the between-studies variance (for random effects models). We used the SAS procedure for this power analysis with inputs for the minimal important difference (based on published studies), the median sample size per intervention arm (from the meta-analysis), the number of studies, the heterogeneity ratio (I^2) and the random effects variance (Tau^2).

3.3.12 Step 5: Qualitative synthesis: Process evaluation

Data on process data was synthesized qualitatively. We used the process data to interpret results based on the assumptions about causal pathways shown in the logic model (Figure 2).

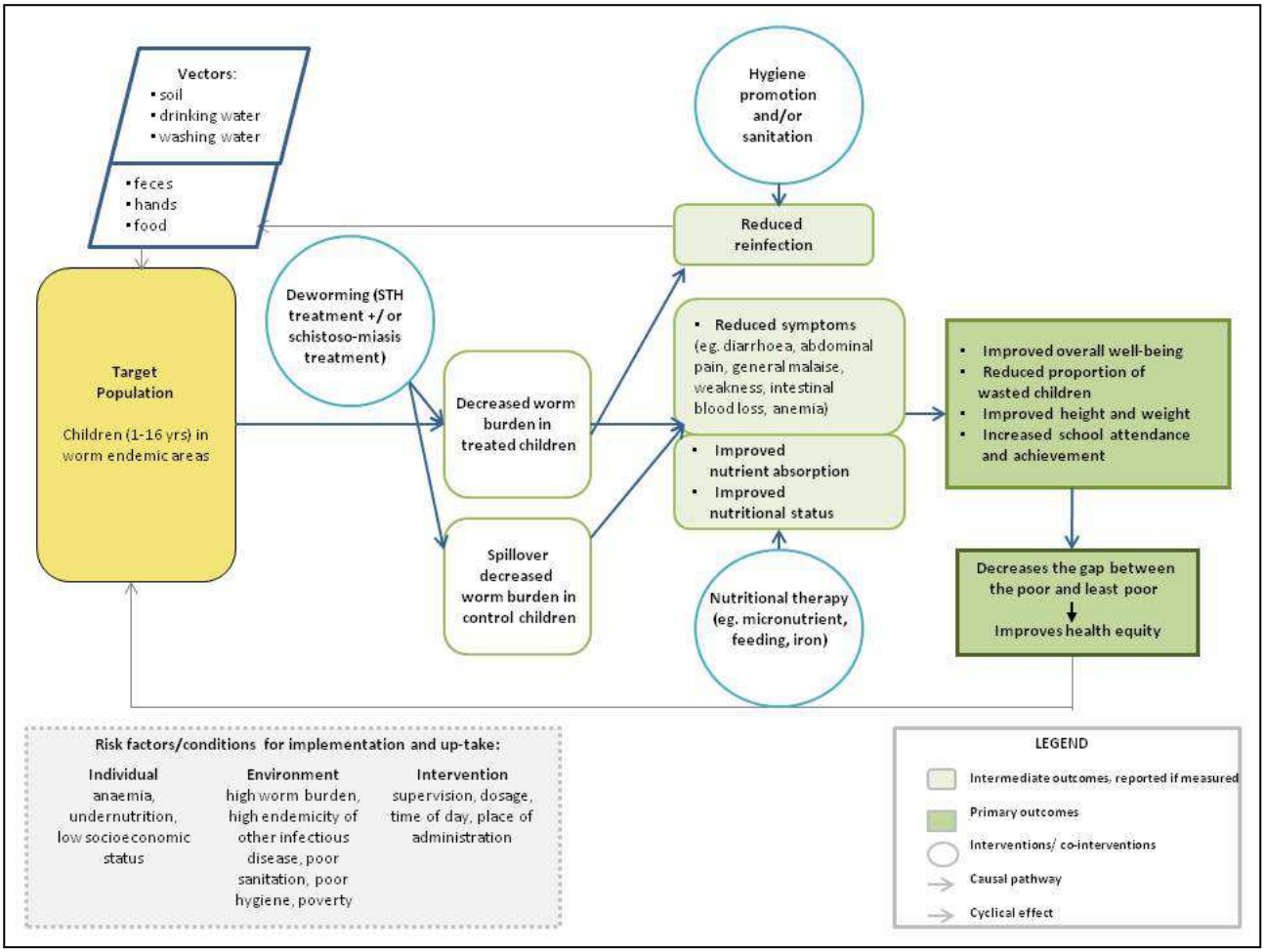


Figure 2: Logic model for deworming effects on child health

4 Results

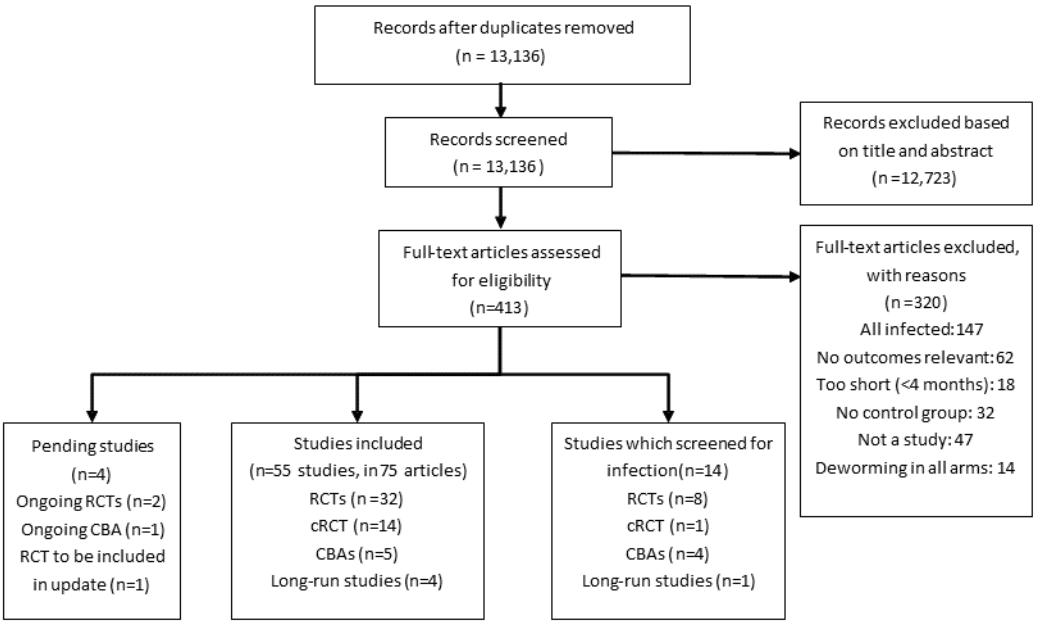
4.1 DESCRIPTION OF STUDIES

Included and excluded studies are described below.

4.1.1 Results of the search

We searched all databases and grey literature up to July 7, 2015, then updated this search to January 14, 2016. After duplicates were removed, we screened 13,136 records. After initial assessment of titles and abstracts, we retrieved 413 articles in full text (see PRISMA Flow chart in Figure 3). In total, we included data from 55 RCTs, 10 CBAs and five long-term studies (three of which were based on earlier RCTs). Details of excluded studies are listed in Additional Table 5.

Figure 3: PRISMA Deworming Flow Diagram



Notes: RCT: randomized controlled trial, cRCT: cluster randomized controlled trial, CBA: - controlled before after study

Based on our initial search to July 2015, we identified 46 RCTs and five controlled before-after studies that met inclusion criteria, and included 1,093,775children. These consisted of 14 cluster randomised trials, 32 individually randomised trials, five controlled before after studies, and one cluster-allocated controlled before-after study. We also identified three long-term studies which met inclusion criteria that followed children from two of the included RCTs 8-10 years later (Baird 2016, Croke 2014, Ozier 2016).

We considered Stephenson 1993B to be a subset of Stephenson 1993A because it reports that a subset of boys were chosen from the larger study. Thus, these two studies are considered as one study, and shown as a single study in the table of included studies.

In our update search, we identified one eligible RCT (Joseph 2015a, Joseph 2015b) and one eligible long-term study (Makamu 2016) (Additional Table 7 and Additional Table 8). As recommended by the Cochrane Handbook, we tested the impact of including the eligible RCT in the pairwise analyses. It's inclusion in the pairwise analyses of mebendazole twice per year vs. control did not materially alter the size of effect of the pairwise analyses for weight or height, although both were more precise with the addition of Joseph 2015. For weight, the effect for mebendazole twice per year vs. placebo was 0.23 kg, (95% CI 0.02, 0.44 kg) without Joseph 2015 (n=1 study, 2044 participants), and 0.11 kg (95%CI: -0.07, 0.29 kg) with Joseph 2015 (n=2 studies, 2924 participants, I^2 0%). For height, mebendazole twice per year vs. placebo was 0.02 cm (95%CI: -0.13, 0.17 cm) without Joseph 2015 (n=1 study, 2044 participants) and 0.03 cm (95%CI: -0.10, 0.16 cm) with Joseph 2015 (n=2 studies, 2924 participants, I^2=0%). For cognitive development, assessed with the Bayley III scale of cognitive development in 1760 children aged 12 months, there was little to no difference between mebendazole twice/ year and control for cognition (0.10, 95% CI: -0.08, 0.27), receptive language (-0.05, 95% CI -0.23, 0.12), expressive language (-0.06, 95% CI: -0.26, 0.15) and fine motor skills (-0.04, -0.29, 0.21). Since these results were congruent with the primary analyses reported below, we decided to include this RCT in the full set of analyses in the next update, and have not included Joseph 2015 in any of the analyses reported below. However, since Makamu 2016 was one of only five long-term studies, it is assessed in full detail and fully included.

We obtained reports of two unpublished studies from the authors (Hall 2006, Rozelle 2015).

As shown in Figure 2, we identified 15 studies which assessed the effects of deworming in populations who screened positive for infection, including nine RCTs, four controlled before-after studies and one long-term study (Additional Table 9).

Eight studies were not included in quantitative meta-analyses due to missing data (e.g. missing standard deviations, missing number of children) and partially reported data e.g. for infected children only rather than for the whole group as randomised) (Beach 1999, Reddy 1986, Kloetzel 1982, Michaelsen 1985, Lai 1995, Solon 2003, Gupta 1977). We describe the results of these studies narratively.

We identified three studies which have not been published yet: one conference abstract (Snider 2009) which included insufficient information to be included in the meta-analyses, one ongoing trial registered with the WHO trials register: isrctn83988447 (Stoltzfus 2007; Wright 2009), and one longitudinal stepped –wedge programmatic evaluation (Satoto 2003).

4.1.2 Included studies- randomized trials and CBAs

Studies include in our primary analysis are summarized in Additional Table 7 and Additional Table 8.

Study setting

Of the included 46 RCTs and five CBAs of mass deworming, 12 were conducted in India, five in Kenya, four in South Africa, three in Bangladesh, three in Tanzania, three in Vietnam, two in Haiti, two in Indonesia, two in Zaire, and one each in Benin, Botswana, Brazil, Cameroon, China, Guatemala, Malaysia, Papua New Guinea, Senegal, Sierra Leone, Sri Lanka, Uganda and one multi-country (China, Philippines, Kenya).

Of the 13 studies that described the socioeconomic or occupational characteristics of the households, eleven studies described all participants as belonging to low-income households. Forty-one studies did not provide detail on socioeconomic status.

Sanitation (e.g. water supply) and/or hygiene practices were described as poor, with high likelihood of reinfection in 17 studies. The setting of the studies was described as school for 22 studies, clinic for 13 studies, and 11 studies were described as home or community settings.

Participants

The median age was 6.5 years (range 0.8 to 12.9 years). Of 17 studies that reported the proportion underweight, the studies reported from 0.8 per cent to 73 per cent underweight, with a median of 42 per cent underweight. For studies which reported the sex distribution, the overall proportion was 51 per cent female.

Sick children were excluded from eight studies if they had severe anaemia or haemoglobin levels below cut-offs of 80 or 70 g/L (Beach 1999, Stoltzfus 1997, This Le Huong 2007, Nga 2009), infection (Kruger 1996, Monse 2013),or concurrent illness (Lai 1995, Monse 2013). Four studies (Garg 2002, Nga 2009, Olds 1999, Watkins 1996)

excluded children who had received deworming medicine in the last six months to one year.

Interventions

The most common intervention was albendazole 400 mg twice per year compared to placebo or untreated control (21 studies). Coadministration of praziquantel for schistosomiasis with deworming for soil transmitted helminths was conducted by four studies in locations where schistosomiasis was endemic (Jinabhai 2001A, Jinabhai 2001B, Olds 1999, Miguel 2004). One RCT assessed mass deworming of children for schistosomiais only (Olds 1999). One long term study evaluated the effects of a schistosomiasis control programme in Nigeria (Makamu 2016).

Co-interventions were provided in 21 studies, which included iron (Bhoite 2012, Bobonis 2006, Dossa 2001, Ebenezer 2013, Gopaldas 1983, Huong 2007, Kruger 1996, Rohner 2010, Taylor 2001), vitamin A (Awasthi 2001, Awasthi 2008, Awasthi 2013, Hall 2006, Reddy 1986), multiple micronutrient fortified biscuits or soup (Jinabhai 2001B, Nga 2009, Solon 2003), some type of unfortified food or drink (Huong 2007, Kruger 1996, Nga 2009, Pust 1985, Solon 2003), anti-giardial (Goto 2009, Gupta 1982), and intermittent presumptive treatment for malaria (Rohner 2010). Sixteen studies reported compliance with deworming medication, ranging from 65 per cent to 98 per cent. Deworming was administered by field workers (eight studies), school staff (e.g. teachers) in nine studies, study staff in 11 studies, health workers in seven studies and at home in one study. The method of administration was not reported in the other 29 studies (Additional Table 7).

Controls

The most common comparator was placebo, used in 33 studies. For the other RCTs and CBAs, the comparator group received “no treatment” (Alderman 2006, Awasthi 2013, Bhoite 2012, Donnen 1998, Linnemayr 2011, Miguel 2004, Monse 2013, Ostwald 1984, Rozelle 2015, Stoltzfus 1997) or an intervention given to both treatment and control arms which included vitamin A 100,000 or 200,000 iu (Awasthi 2001, Awasthi 2008, Bobonis 2006) or unfortified noodles (Huong 2007, Kruger 1996), biscuits without fortification (Jinabhai 2001B, Nga 2009), unfortified beverage (Solon 2003). Since all of these comparators were either equal in both groups or considered a “do nothing” control, we refer hereon to the comparators as “placebo”.

One RCT compared three different active deworming treatments, with no control group (Kaba 1978).

For the three long-term studies that followed participants of randomised trials, the control group was a group that received deworming at the end of the study period. For one study, which followed participants of the Kenya Primary School Deworming Project

(Miguel 2004), the control group received on average 2.41 years less deworming (Baird 2016). Ozier 2016 identified children who were not in school at the time of the Kenya PSDP study (children aged 8-14 years of age in 2009 and 2010; 11 and 12 years after the PSDP study), and compared children who were exposed to treated siblings before the age of one year to those exposed to treated siblings after one year of age (excluding children approximately age one). Ozier 2016 conducted two analyses: one for each of seven birth cohorts as randomized and one using age of exposure to a treated sibling to creat treatment groups. Croke 2014 identified children exposed to from 22 of 48 parishes in Alderman 2006, and compared children from 10 intervention parishes to children from 12 control parishes.

Worms: type and prevalence

Of the studies that reported STH worm prevalence, 36 were classified as high prevalence (>50 per cent worm prevalence), 7 were moderate prevalence (20-50 per cent), and six were low prevalence (<20 per cent).

Eight of the included studies reported schistosomiasis infection (ranging from 1 per cent to 80 per cent). Ascaris was reported in 47 studies, ranging from 0 per cent to 93 per cent, hookworm was reported in 38 studies, ranging from 0.3 per cent to 91 per cent, and trichuris trichuria was reported in 35 studies ranging from 1 per cent to 97 per cent (Table 14).

Outcomes

For all outcomes, data were sought for the full sample at the time-point of interest (12 months).

Weight or weight for age

Twenty-nine RCTs reported weight or weight for age that could be included in the network meta-analysis. One controlled before after study reported weight (Pust 1985). Also, weight was reported by 10 other studies but could not be included in meta-analyses due to missing data or data reported only for a sample of children allocated to treatment (e.g. for infected children only).

Body mass index, mid-upper arm circumference and skinfold

BMI was reported by five studies (Awasthi 2013, Bhoite 2012, Bobonis 2006, Monse 2013, Rozelle 2015). Mid-upper arm circumference (MUAC) was reported by 11 studies (Dossa 2001, Nga 2009, Rousham 1994, Stephenson 1989, Stephenson 1993A, Greenberg 1981, Hadju 1997, Kloetzel 1982, Donnen 1998, Pust 1985, Watkins 1996). Triceps skinfold was reported by seven studies (Dossa 2001, Stephenson 1989, Stephenson 1993A, Greenberg 1981, Kloetzel 1982, Pust 1985).

Height or height for age

Twenty-five RCTs reported height or height for age that could be included in meta-analyses (Rousham 1994B; Greenberg 1981; Awasthi 2000; Awasthi 2001; Awasthi 2008; Jinabhai 2001A; Ndibazza 2012; Watkins 1996; Garg 2002; Ostwald 1984; Hall 2006; Kruger 1996; Miguel 2004; Wiria 2013; Rozelle 2015; Goto 2009; Bhoite 2012; Donnen 1998; Stoltzfus 1997; Stephenson 1993A; Nga 2011; Dossa 2001; Gupta 1982; Olds 1999; Hadju 1997). Six other studies reported height outcomes that were missing data to be included in meta-analyses.

Haemoglobin

Seventeen RCTs reported average haemoglobin (Ebenezer 2013; Stoltzfus 2001; Ostwald 1984; Garg 2002; Kruger 1996; Awasthi 2000; Miguel 2004; Rozelle 2015; Goto 2009; Bhoite 2012; Stoltzfus 1997; Taylor 2001; Dossa 2001; Taylor 2001; le Huong 2007; Nga 2011; Olds 1999). Two studies reported haemoglobin but could not be used in meta-analysis (Bobonis 2006, Solon 2003).

Proportion stunted

Seven studies reported proportion of children stunted at the end of study (Bhoite 2012; Rozelle 2015; Awasthi 2000; Awasthi 2001; Stoltzfus 2001; Thi Le 2007; Jinabhai 2001A).

Cognition

Nine studies measured cognition or development. Of these, six studies assessed cognitive processing or development with the following tools: Coding test (Ebenezer 2013); Raven's coloured matrices (Nga 2009), language development in Kiswahili (Stoltzfus 2001), motor development (Stoltzfus 2001), Block test (Ndibazza 2012), Peabody vocabulary scale (Ndibazza 2012, Watkins 1996), and the WISC-IV processing speed index and working memory index score, each comprised of two sub-tests: Coding and Symbol Search for processing speed and Digit Span and Letter Number Sequencing (Rozelle 2015). Awasthi 2001 reported the Denver development questionnaire, and is reported separately. Two studies could not be meta-analysed because of missing standard deviations or data by group and are reported narratively (Solon 2003; Jinabhai 2001B). Ndibazza 2012 measured a battery of cognitive tasks including working memory, attention, fine motor function, as well as the Block test and Peabody Vocabulary scale.

School performance

Eight studies measured and reported outcomes on math or language tests (Jinabhai 2001 micronutrient; Solon 2003; Ebenezer 2013; Hall 2006; Miguel 2004; Rozelle 2015; Watkins 1996; Gateff 1972).

School attendance

Seven studies measured and reported attendance at school; four reported school records (Gateff 1972, Watkins 1996; Kruger 2006; Ebenezer 2013, Rozelle 2015), two recorded attendance in school or preschool on unannounced visits (Bobonis 2006, Miguel 2004).

For Miguel 2004, we selected the estimates for school attendance from their Table VIII for girls <13 years and all for the first year post-treatment (comparing group 1 treated schools with two groups of 50 untreated schools (group 2 and group 3), with small data corrections from Aiken 2015a. Since Dr. Joan Hamory Hicks kindly provided us with the statistical code and the schools which received praziquantel as well as albendazole, we conducted the analysis of 19 schools which received albendazole alone separately from the schools which received both albendazole and praziquantel in the first year. This estimate of the effect of deworming is the largest (0.093, standard error 0.031) of all of the estimates of the effect of deworming on school participation in any of the original analyses in Miguel 2004, the replication analyses (Aiken 2015a, Aiken 2015b) and the responses to the replication (Hicks 2015a and Hicks 2015b). Also, there was a change to consent procedure that resulted in less children receiving mass deworming in the second year, so we felt the first year of treatment was the better estimate for assessing the effects of mass deworming. We tested whether our meta-analysis was sensitive to choosing a different estimate of deworming effects in sensitivity analyses.

Mortality

Mortality was reported by six studies (Awasthi 2000; Awasthi 2001; Awasthi 2008; Awasthi 2013; Joseph 2015, Ndibazza 2012).

Adverse effects

Five studies reported adverse effects (Fox 2005, Sur 2005, Wiria 2013, Olds 1999, Gateff 1972).

Physical fitness

Three studies assessed physical fitness (Bhoite 2012; Stephenson 1993B; Solon 2003).

Comorbidities such as malaria

Only two studies reported malaria outcomes (Ndibazza 2012 and Wiria 2013).

4.1.3 Included long-term studies

Four studies reported long-term outcomes of mass deworming vs. control. One study reported long-term outcomes of screening for infection, treating infected individuals, and building latrines and raising awareness about sanitation and hygiene (Bleakley 2007).

Ozier 2016 reported eight-year follow-up outcomes of children up to the age of one during the Miguel 2004 study, who were exposed to treated siblings for the outcomes of cognitive outcomes (using Raven's matrices and the Peabody Vocabulary Test), height and proportion stunted. Two analyses were done:1) comparison based on age of exposure to a treated sibling, and 2) for each of 7 birth cohorts, as randomized.

Baird 2016 reported 10 year follow-up outcomes for children in the Miguel 2004 study for health (e.g. work days missed, self-reported health), education and economic participation (hours worked and economic sectors). The comparison in this study was created by comparing outcomes for children who received mass deworming an average of 2.41 years before the control group, since all of the control schools were treated by the end of three years.

Croke 2014 reported the eight year follow-up of children in the cluster RCT by Alderman 2006 for child health (height), math and English scores.

Makamu 2016 reported long-term effects of a mass deworming programme for schistosomiasis on education outcomes by comparing four states in Nigeria that had received mass deworming to 33 states which did not receive mass deworming, over a follow-up period of 10 years.

Study duration:

The median study duration for RCTs and CBAs was 12 months (range four to 60 months). Twenty-one studies had durations <12 months, 16 studies had a duration of 12 months, and 16 were longer than 12 months.

The long-term studies had a follow-up of 10 years (Baird 2016, Croke 2014), eight years (Ozier 2016) and 10 years (Makamu 2016).

Unit of analysis issues:

We included 16 cluster RCTs (Additional Table 11) and one cluster-allocated controlled before-after study (Pust 1985). We judged that 12 of these cluster RCTs had analysed data appropriately considering the cluster allocation, using methods described in Additional Table 11. We used the variance inflation factor method described in the

Cochrane Handbook to adjust growth and haemoglobin outcomes in three cluster RCTs (Hall 2006, Kruger 1996, Bhoite 2012) and one controlled before-after study (Pust 1985). For Hall 2006, we calculated the ICC for weight and height from their raw dataset, which was kindly provided to us by Dr. Don Bundy (ICC for weight= 0.021, ICC for height= 0.015). For Kruger 1996, Bhoite 2012, and Pust 1985, we used the more conservative ICC of 0.17 for weight and 0.11 for height as reported by Awasthi 2008, and tested the influence of a less conservative ICC of 0.01 in sensitivity analyses. Awasthi 2013 used an ICC of 0.25 for calculating sample size for effects of deworming on mortality.

We calculated ICC for school attendance from teacher records using the full dataset kindly provided for the Ebenezer 2013 study. The ICC was 0.42 for the treatment arm and 0.30 for the control arm (using last observation carried forward to account for children with missing data in one or more of the five month of data provided. The ICC was 0.44 and 0.28 for the dataset with missing data excluded.

For dichotomous outcomes (mortality, adverse effects, proportion stunted) reported as number of events in cluster trials, we adjusted for the unit of analysis by dividing both the numerator and denominator by the design effect, using an ICC of 0.02 for stunting (based on ICC for weight from Hall 2006) and 0.01 for mortality.

For one study of school attendance, we received the full dataset of monthly attendance for six months prior to the intervention, and analysed the average attendance during the study period (November 2009 to March 2010), with consideration for cluster allocation (Ebenezer 2013), using the formulae from Ukoumunne 2009.

Data received from authors:

We received data from 10 studies (Additional Table 4). We also received three replies that data had been archived or was not possible to find.

For Olds 1999, who kindly provided individual participant data for two sites of the five site study (371 children of 1,518 randomised in the original study), we imputed values for 76 children with missing data at the end of study for weight, height and haemoglobin using a single imputation technique, based on available information in the dataset on baseline characteristics of weight and height. We did a sensitivity analysis using the non-imputed values, and found no difference in the meta-analysis results (results not shown).

For Miguel 2004, we received from Dr. Joan Hamory Hicks the corrected dataset and analysis files from the replication study, led by Dr. Aiken. We first replicated the results tables using these files exactly. Then, using the identification numbers of schools which received albendazole and praziquantel combined (provided by Dr. Hicks), we ran the

analysis for tables II, V and VIII from the original Miguel 2004 study and the Aiken 2015 pure replication for the schools which received albendazole alone and also for the schools which received both albendazole and praziquantel. This allowed us to analyse this study as a four arm trial for weight and height (which were only collected for groups 1 and 2 in the first year of the study): of 1) albendazole twice per year + hygiene promotion (19 schools); 2) control receiving nothing in areas with low schistosomiasis prevalence (15 schools), 3) albendazole + praziquantel +hygiene promotion (6 schools), 4) control (10 schools), which received nothing in areas of 30 per cent schistosomiasis prevalence. For school participation, data was available on school participation for each of three groups of schools after one year of treatment, and after two years of treatment. We replicated the original author analyses with restriction to schools which received only albendazole and then for schools which received albendazole and praziquantel. For the control group, (group 3 which eventually went on to receive deworming treatment), we used the treatment assignment which they received in the third year (after the end of the Miguel 2004 study).

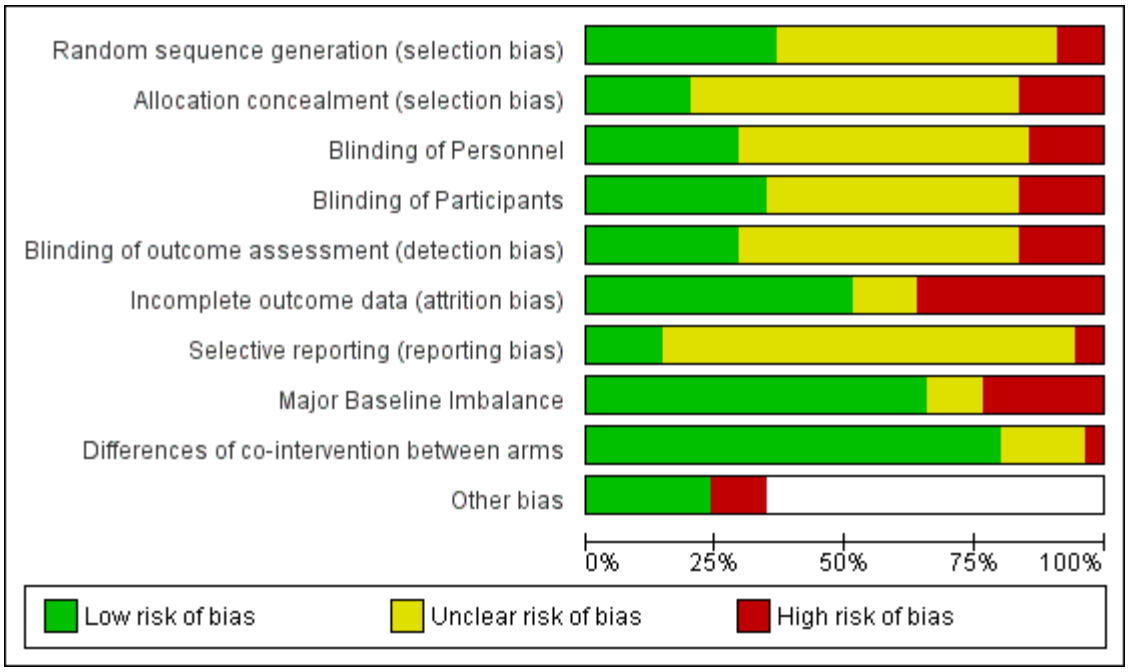
4.1.4 Excluded studies

We list 44 studies in our table of excluded studies (Additional Table 5). These studies were excluded because deworming was included in all arms of the study (three studies), study design issues such as lack of control (six studies), none of our primary outcomes (11 studies), or too short (<four months) (nine studies), adult population (one study), or intervention consisted of screening for infection (13 studies).

4.2 RISK OF BIAS IN INCLUDED STUDIES

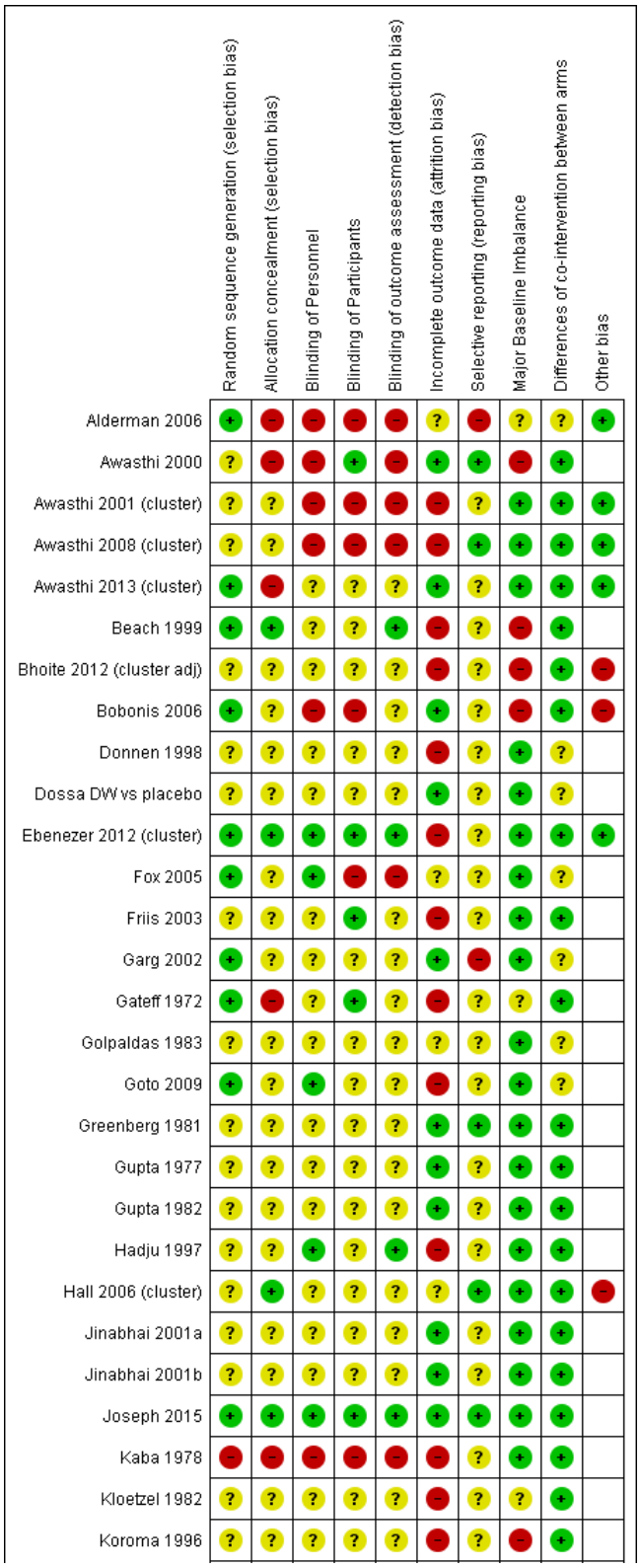
For the 46 RCTs and five CBAs, we summarize the judgments about the risk of bias using the Cochrane risk of bias tool in the risk of bias graph (Figure 4 and Figure 5). Detailed justification of these judgments for each study is available upon request. We provide a comparison of the risk of bias assessment for Miguel 2004 with the Cochrane review, with justifications (Additional Table 10). We differ for one domain: We judged a high risk of baseline imbalance because the children in the treatment schools were less clean (7 per cent difference, SE 3 per cent, as observed by field workers) and had more blood in the stool (7 per cent more, SE 3 per cent).

Figure 4: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



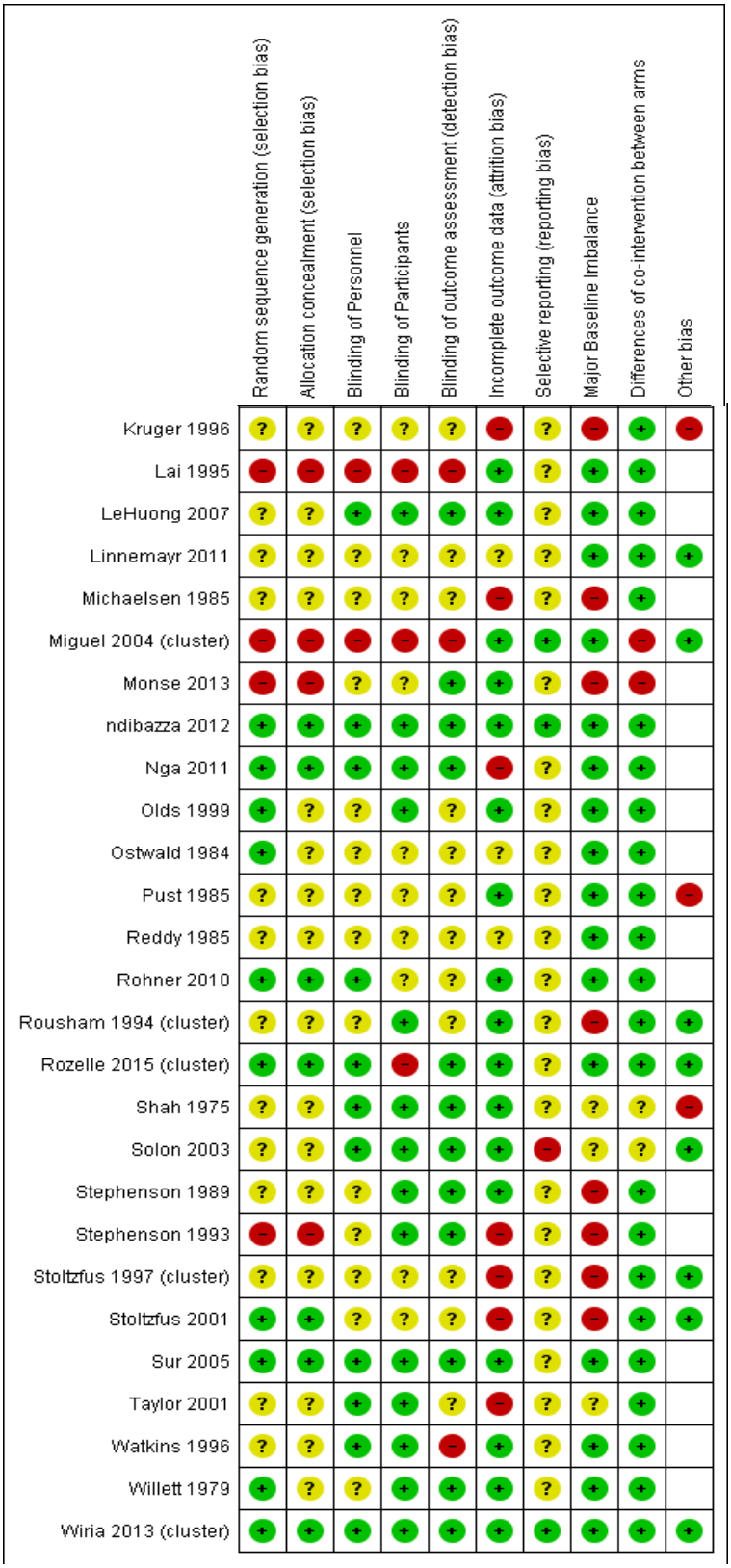
Note: "Other bias" *was only judged for cluster RCTs. Unit of analysis errors in cluster RCTs was judged high risk of bias*

Figure 5: Risk of bias for each study (Note: "other bias" was only judged for cluster RCTs regarding unit of analysis errors)



Other biases: were assessed only for cluster randomized trials to assess whether there were unit of analysis errors, loss of clusters

Continued: risk of bias



Other biases: were assessed only for cluster randomized trials to assess whether there were unit of analysis errors, loss of clusters

4.2.1 Allocation (selection bias)

We judged 18 studies (Alderman 2006; Awasthi 2013; Beach 1999; Bobonis 2006; Ebenezer 2013; Fox 2005; Garg 2002; Gateff 1972; Goto 2009; Ndibazza 2012; Nga 2009 and 2011; Olds 1999; Ostwald 1984; Rozelle 2015; Stoltzfus 2001; Sur 2005; Willett 1979; Wiria 2013) to have low risk of bias for random sequence generation; five (Kaba 1978; Lai 1995; Miguel 2004; Monse 2013; Stephenson 1993) at high risk and 28 (Awasthi 2000; Awasthi 2001; Awasthi 2008; Bhoite 2012; Donnen 1998; Dossa 2001; Greenberg 1981; Gupta 1977; Gupta 1982; Hadju 1997; Hall 2006; Jinabhai 2001 A; Jinabhai 2001 B; Kloetzel 1982; Koroma 1996; Kruger 1996; Le Huong (Thi) 2007; Linnemayr 2011; Michaelsen 1985; Pust 1985; Reddy 1985; Rousham 1994; Shah 1975; Solon 2003; Stephenson 1989; Stoltzfus 1997; Taylor 2001; Watkins 1996) at unclear risk of bias for random sequence generation.

For allocation concealment, we judged nine studies (Beach 1999; Ebenezer 2013; Hall 1996; Ndibazza 2012; Nga 2009 and 2011; Rozelle 2015; Stoltzfus 2001; Sur 2005; Wiria 2013) to have low risk of bias; nine studies (Alderman 2006; Awasthi 2000; Awasthi 2013; Gateff 1972; Kaba 1978; Lai 1995; Miguel 2004; Monse 2013; Stephenson 1993) to have high risk and the other 36 studies to have unclear risk of bias.

4.2.2 Blinding (performance bias and detection bias)

Personnel: We rated 14 studies as having low risk of bias for blinding of personnel (Ebenezer 2013; Fox 2005; Goto 2009; Hadju 1997; Le Huong (Thi) 2007; Ndibazza 2012; Nga 2009 and 2011; Rozelle 2015; Shah 1975; Solon 2003; Sur 2005; Taylor 2001; Watkins 1996 A &B; Wiria 2013); eight studies as having high risk for blinding of personnel (Alderman 2006; Awasthi 2000; Awasthi 2001; Awasthi 2008; Bobonis 2006; Kaba 1978; Lai 1995; Miguel 2004) and 29 studies as unclear risk of bias for blinding of personnel (Awasthi 2013; Beach 1999; Bhoite 2012 A & B; Donnen 1998; Dossa 2001; Garg 2002; Gateff 1972; Greenberg 1981; Gupta 1977; Gupta 1982; Hall 2006; Jinabhai 2001 A; Jinabhai 2001 B; Kloetzel 1982; Koroma 1996; Kruger 1996; Linnemayr 2011; Michaelsen 1985; Monse 2003; Olds 1999; Ostwald 1984; Pust 1985; Reddy 1985; Rousham 1994; Stephenson 1989; Stephenson 1993 A and B; Stoltzfus 1997; Stoltzfus 2001; Willett 1979).

Participants: We rated 17 studies (Awasthi 2000; Ebenezer 2013; Gateff 1972; Le Huong (Thi) 2007; Ndibazza 2012; Nga 2009 and 2011; Olds 1999; Rousham 1994; Shah 1975; Solon 2003; Stephenson 1989; Stephenson 1993 A and B; Sur 2005; Taylor 2001; Watkins 1996 A and B; Willett 1979; Wiria 2013) at low risk of bias for blinding of participants; 10 studies (Alderman 2006; Awasthi 2001; Awasthi 2008; Bell 1997; Bobonis 2006; Fox 2005; Kaba 1978; Lai 1995; Miguel 2004; Rozelle 2015) at high risk and 25 studies (Awasthi 2013; Beach 1999; Bhoite 2012 A and B; Donnen 1998; Dossa 2001; Garg 2002; Goto 2009; Greenberg 1981; Gupta 1977; Gupta 1982; Hadju 1997;

Hall 2006; Jinabhai 2001 A; Jinabhai 2001 B; Kloetzel 1982; Koroma 1996; Kruger 1996; Linnemayr 2011; Michaelsen 1985; Monse 2013; Ostwald 1984; Pust 1985; Reddy 1985; Stoltzfus 1997; Stoltzfus 2001) at unclear risk for blinding of participants.

Outcome assessors: We judged 14 studies (Beach 1999; Ebenezer 2013; Hadju 1997; Le Huong (Thi) 2007; Monse 2013; Ndibazza 2012; Nga 2009 and 2011; Rozelle 2015; Shah 2003; Solon 2003; Stephenson 1989; Sur 2005; Willett 1978; Wiria 2013) as having low risk of detection bias; nine studies (Alderman 2006; Awasthi 2000; Awasthi 2001; Awasthi 2008; Fox 2005; Kaba 1978; Lai 1995; Miguel 2004; Watkins 1996A&B) as high risk of detection bias and the other 31 studies as having unclear risk of detection bias.

4.2.3 Incomplete outcome data (attrition bias)

We rated 26 studies (Awasthi 2000; Awasthi 2013; Bobonis 2006; Dossa 2001; Garg 2002; Greenberg 1981; Gupta 1977; Gupta 1982; Jinabhai 2001 A; Jinabhai 2001 B; Lai 1995; Le Huong (Thi) 2007; Monse 2013; Ndibazza 2012; Olds 1999; Pust 1985; Reddy 1985; Rousham 1994; Rozelle 2015; Shah 1975; Solon 2003; Stephenson 1989; Sur 2005; Watkins 1996 A & B; Willett 1979; Wiria 2013) at low risk of attrition bias; 20 studies (Awasthi 2001; Awasthi 2008; Beach 1999; Bhoite 2012 A & B; Donnen 1998; Ebenezer 2013; Gateff 1972; Goto 2009; Hadju 1997; Kaba 1978; Kloetzel 1982; Koroma 1996; Kruger 1996; Michaelsen 1985; Miguel 2004; Nga 2009 and 2011; Stephenson 1993 A and B; Stoltzfus 1997; Stoltzfus 2001; Taylor 2001) at high risk of attrition bias and six studies (Alderman 2006; Fox 2005; Hall 2006; Linnemayr 2011; Ostwald 1984; Reddy 1985) at unclear risk.

4.2.4 Selective reporting (reporting bias)

We judged seven studies as having low risk of bias for selective reporting (Awasthi 2000; Awasthi 2008; Greenberg 1981; Hall 2006; Miguel 2004; Ndibazza 2012; Wiria 2013); three studies had high risk (Alderman 2006; Garg 2002; Solon 2003) and the other 45 had unclear risk of bias for selective reporting.

4.2.5 Other potential sources of bias

We judged 32 studies as having no major imbalance in baseline outcome measures or characteristics between groups (Awasthi 2001; Awasthi 2008; Awasthi 2013; Donnen 1998; Dossa 2001; Ebenezer 2013; Fox 2005; Garg 2002; Goto 2009; Greenberg 1981; Gupta 1977; Gupta 1982; Hadju 1997; Hall 2006; Jinabhai 2001 A; Jinabhai 2001 B; Kaba 1978; Lai 1995; Le Huong (Thi) 2007; Linnemayr 2011; Miguel 2004; Ndibazza 2012; Nga 2009 and 2011; Olds 1999; Ostwald 1984; Pust 1985; Reddy 1985; Rozelle 2015; Sur 2005; Watkins 1996 A & B; Willett 1979; Wiria 2013); 13 studies as having high risk of bias for major baseline imbalance (Awasthi 2000; Beach 1999; Bhoite 2012 A and B; Bobonis 2006; Koroma 1996; Kruger 1996; Michaelsen 1985; Monse 2013;

Rousham 1994; Stephenson 1989; Stephenson 1993 A and B; Stoltzfus 1997; Stoltzfus 2001); and six studies as having unclear risk of bias for baseline imbalance between groups (Alderman 2006; Gateff 1972; Kloetzel 1982; Shah 1975; Solon 2003; Taylor 2001).

There was no difference in the administration of co-interventions between groups (low risk of bias) in 45 studies. It was unclear if co-interventions were appropriately administered in six studies (Alderman 2006; Donnen 1998; Dossa 2001; Fox 2005; Garg 2002; Goto 2009).

Analysis at the level of the individual (rather than the cluster) was judged present in four cluster randomised controlled trials (Bhoite 2012 A and B; Ebenezer 2013; Hall 2006; Kruger 1996) and one cluster-allocated controlled before and after trial (Pust 1985).

There was high mobility of children within and between clusters with high risk of contamination in one study (Bobonis 2006).

4.2.6 Additional risk of bias domains assessed for CBAs

Baseline outcome measurement

This assesses whether the experimental and control groups were similar at baseline on the study outcomes. We judged all five CBAs (Gupta 1977; Kaba 1978; Michaelsen 1985; Monse 2013; Pust 1985) to have a low risk of bias as all outcome measures were similar at baseline in all the groups.

Baseline Characteristics

This assesses whether the characteristics of the intervention and control groups were similar at baseline. We assessed four CBAs (Gupta 1977; Kaba 1978; Michaelsen 1985; Pust 1985) as low risk of bias as all characteristics were similar at baseline in all the groups. One CBA (Monse 2013) had a high risk of bias for differences in prevalence of moderate/heavy infection of 17 per cent in the experimental vs. 31 per cent in the external concurrent control.

Protection against contamination

This assesses the extent to which controls had access to treatments. We rated all five CBAs (Gupta 1977; Kaba 1978; Michaelsen 1985; Monse 2013; Pust 1985) as unclear risk of bias since there was insufficient information to determine if controls had access to treatments.

4.3 RISK OF BIAS FOR LONG-TERM STUDIES

We rated the risk of bias for long-term studies using the Cochrane risk of bias tools for three studies which identified samples of children 8-10 years after they had participated (or been exposed to siblings) in randomized trials (Baird 2016, Croke 2014, Ozier 2016).

We used the Campbell International Development review group tool for observational designs (Hombrados 2012).

Table 1: Campbell IDCG Risk of bias for observational studies

Domain	Makamu 2016	Bleakley 2007
Selection bias and confounding	No	Unclear
Group equivalence	Unclear	Unclear
Hawthorne and John Henry effects: was the process of being observed causing motivation bias?	Yes	Yes
Spillovers	Unclear	Unclear
Outcome reporting	Yes	Yes
Analysis reporting	Yes	Yes
Other risks of bias	Unclear	Unclear
Confidence intervals	No	No
Overall risk of bias	Moderate	Moderate

Three long-term studies followed children as randomized (Baird 2016, Croke 2014, Ozier 2016).

Baird 2016 selected a random sample of 7,500 of the children who were in school during the Miguel 2004 study of 31,445 children, and were in grades 2-7 during the study period. Ten years later, they achieved an 82.7 per cent effective tracking rate, which is extremely high for a long-term study such as this, identifying 5,084 participants. They assessed balance on baseline characteristics between treatment and control across age, grade (1998), gender, school test scores, size of primary school and number of nearby primary school students.

Croke 2014 made use of a survey of 22 of 48 parishes from the Alderman 2006 trial, conducted by Uwezo. The sample included 710 individuals who were eligible to participate in the Alderman 2006 trial (which included 27,995 children) from 10 treatment parishes and 12 control parishes (out of 48 randomized).

Ozier 2016 surveyed 20,000 children aged 8-14 years in 2009 and ages 9-15 in 2010 in areas of the Miguel 2004 study. Enumerators did not know the original deworming program treatment assignments and were also blinded to the definition of treatment in this analysis, which involves the specific cohorts at specific schools. A computer-generated random sample (using Stata) of 2,474 respondents was chosen for cognitive tests. Ozier 2016 analyzes multiple comparisons of cognition outcomes (Raven's matrices); 21 within cohort, between arm comparisons were conducted of intervention schools (group 1 and group 2) compared to control schools (group 3 schools) for each of seven birth cohorts (from 1995 to 2001) to assess effect of age of exposure (Figure 1, Ozier 2016). Based on the number of children included, each birth year cohort contained approximately 353 children (2,474 divided by seven birth years). The main analysis of Ozier 2016 was based on the age of exposure to deworming of siblings of <1 year or >1 year of age (excluding those 1 year of age).

Table 2: Risk of bias for long-term followup of randomized trials

	Baird 2016	**Croke 2014**	**Ozier 2016**
Allocation Sequence	High	Low	High
Allocation Concealment	High	High	High
Blinding of Personnel	Unclear	High	Unclear
Blinding of Participants	Unclear	High	Low
Blinding of Outcome Assessors	Low	High	Low
Incomplete Outcome Data	Low	Low	Low
Selective Outcome Reporting	High	High	Unclear
Major Baseline Imbalance	Low	High	Unclear
Differences of co-interventions between arms	High	Unclear	High
Other biases relevant to cluster RCTs: Recruitment bias; loss of clusters, incorrect analysis; comparability with individual RCTs	Low	Low	Low
Other bias: Sampling bias	Low	High	Unclear

*Note: Baird 2016, Croke 2014 and Ozier 2016 were long-term follow-up of children from randomised trials. We assessed whether there was a risk of bias in the method of sampling children for follow-up. Baird 2016 selected a random sample of 7500 children and surveyed 82.7% of these. The attributes of those reached were compared on baseline characteristics to the full sample from 1998. Croke et al 2014 used data from another survey which sampled 22 of 48 parishes randomized in Alderman 2006. It is unclear why these 22 parishes were sampled or whether they were comparable to

unsampled parishes. Ozier 2016 identified 21,309 children who were born between 1995 and 2001 in the areas of the Kenya PDSP schools, then selected a sample using Stata random sampling of 2,584 non-migrants for cognitive testing. No data was provided on comparability of the sample (e.g. household characteristics) with the index study by Miguel 2004, and there were twice as many children sampled from intervention as control schools. Ozier and Baird were rated "high risk of bias" for cointerventions since the Miguel 2004 study included hygiene promotion in the form of regular public health lectures on handwashing, avoiding swimming, wearing shoes, wall charts and teacher training. Hygiene promotion has been shown by Cochrane systematic reviews to prevent 28% of diarrhea episodes (Ejemot-Nwadiaro 2015) and may improve growth (Dangour 2013). Miguel 2007 and Miguel 2004 showed that the hygiene promotion did not have an effect on three behaviours (being clean, wearing shoes and exposure to fresh water in the past week). These measures were not described as validated (e.g. cleanliness of face and hands was assessed by field workers on a 3 point scale of 1.clean, 2 a bit dirty, and 3. Very dirty, but there is no evidence provided that these rankings are validated as measuring hand-washing behaviour).

4.4 EFFECTS OF INTERVENTIONS

We decided to conduct our base case analysis on randomised trials because there were few CBAs and the randomised trials were considered at lower risk of bias. We assessed the effects of interventions in controlled before-after studies separately from the RCTs, and did not include CBAs in the network meta-analysis. We conducted a sensitivity analysis for weight gain to assess the influence of including CBAs in the network meta-analysis.

We constructed GRADE evidence profiles, using GRADE recommendations for network meta-analyses (Puhan 2014), for each of the main comparisons of interest with seven outcomes, as recommended by the Cochrane Handbook (Additional Table 17, Additional Table 18, Additional Table 19).

We used plain language to describe the results using plain language based on the effect size from meta-analysis and the rating of GRADE certainty, using Additional Table 1, developed by the Cochrane Effective Practice and Organization of Care review group (http://epoc.cochrane.org/epoc-specific-resources-review-authors). We judged the size of effect as important, small or little differences based on baseline values for outcomes, change in the control group in included studies over the duration of the study in these outcomes, and any available benchmarks for clinical importance of effects.

4.4.1 Causal pathway analysis

We report outcomes in order of our logic model to explore the causal pathway of deworming, as shown in Figure 2. Our causal pathway suggests that deworming first decreases worm burden (and reduces reinfection), then improves haemoglobin, then nutritional status, then cognitive and education outcomes, then school attendance, then long-term outcomes such as educational attainment and labour market outcomes.

STH prevalence

We assessed the impact of deworming interventions on worm burden at the end of each study. For the 23 studies that report impact on worms for mass deworming of children programmes, there is considerable variability in effectiveness at reducing worm prevalence at the end of study in these studies, ranging from a relative risk reduction of 9 per cent to 83 per cent (***Additional Figure 4***). Since some of the variation in relative risk reduction may have been due to differences in baseline prevalence, we also report the absolute risk reduction below, which ranged from 2 to 57 per cent (Table 1).

We explore the impact on worms and the worm prevalence as possible effect modifiers in subgroup, sensitivity and weighted least squares regression analyses, described below.

Table 3: Absolute risk reduction in Ascaris worm prevalence with deworming interventions

Deworming	Relative risk	Absolute risk difference
Albendazole 2/year vs. placebo	0.57 (0.53, 0.60)	-0.14 [-0.16, -0.13]
Albendazole 2/year + iron	0.62 [0.49, 0.79]	-0.26 [-0.38, -0.14]
Albendazole >2/year + iron	0.91 [0.73, 1.12]	-0.02 [-0.06, 0.02]
Albendazole >2/year	0.42 [0.35, 0.51]	-0.23 [-0.27, -0.18]
Albendazole 1/year	0.47 [0.27, 0.81]	-0.18 [-0.30, -0.06]
Mebendazole 2/year	0.69 [0.65, 0.73]	-0.26 [-0.30, -0.22]
Mebendazole 2/year+iron	0.58 [0.46, 0.74]	-0.10 [-0.15, -0.06]
Mebendazole >2/year	0.45 [0.42, 0.49]	-0.44 [-0.48, -0.41]
Piperazine >2/year	0.57 [0.36, 0.90]	-0.29 [-0.51, -0.08]
Pyrantel >2/year	0.33 [0.25, 0.44]	-0.57 [-0.66, -0.49]
Albendazole 1/year + PZQ	0.17 [0.08, 0.40]	-0.22 [-0.30, -0.14]
Levamisole >2/year	0.51 [0.26, 0.99]	-0.31 [-0.56, -0.05]

Haemoglobin

In summary, data from the included studies shows that mass deworming of children leads to little to no increase in haemoglobin, except for interventions where praziquantel was included in the mass deworming (moderate to high certainty evidence). These analyses do not represent the full spectrum of studies which have measured haemoglobin following mass deworming because we did not include studies if they did not report one of our primary outcomes.

Twenty-one studies reported haemoglobin in sufficient detail for meta-analysis. We did not meta-analyse haemoglobin since it was one of our secondary outcomes. Results are presented in ***Additional Figure 3***. For all comparisons of deworming vs. placebo, the range of effect sizes in individual studies is -0.61 to 0.30 g/dL.

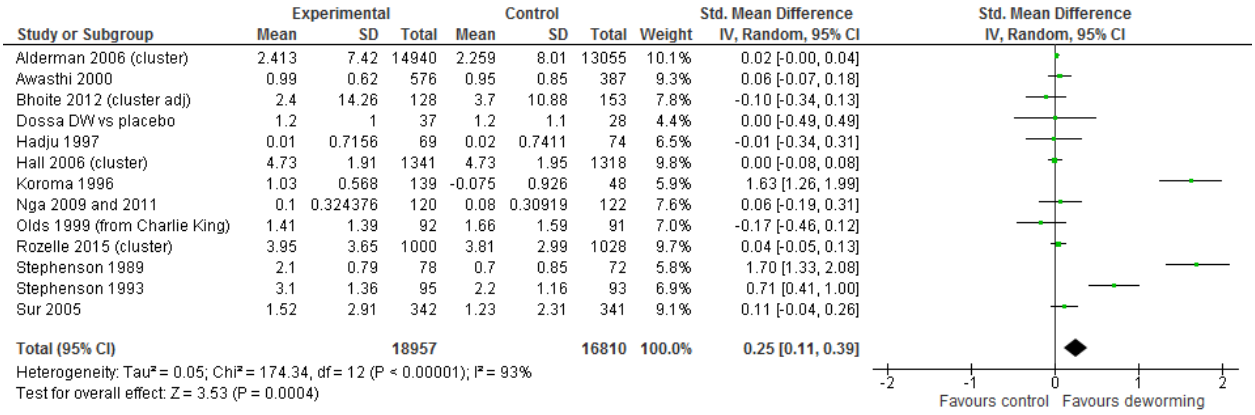
For six comparisons which included iron or praziquantel, statistically significant effect sizes of 0.27 to 0.93 g/dL were found in four studies (Olds 1999, Taylor 2001, Bhoite 2012, Nga 2009,). These four studies also measured anthropometric outcomes, and found no effect of deworming on anthropometric outcomes (Olds 1999, Taylor 2001, Bhoite 2012 and Nga 2009). Also, Nga 2009 assessed cognition using a general intelligence test, and found little to no effect of mass deworming on general intelligence (SMD 0.19, 95% CI: -0.07 to 0.44).

Weight or weight for age (WAZ) gain

In summary: based on our analyses, deworming probably leads to little or no difference in weight or weight gain compared to placebo (moderate certainty evidence). Based on our network meta-analysis, there is little to no difference between different types of deworming (or their frequency), their combinations with other deworming drugs or with micronutrients or food (moderate certainty evidence).

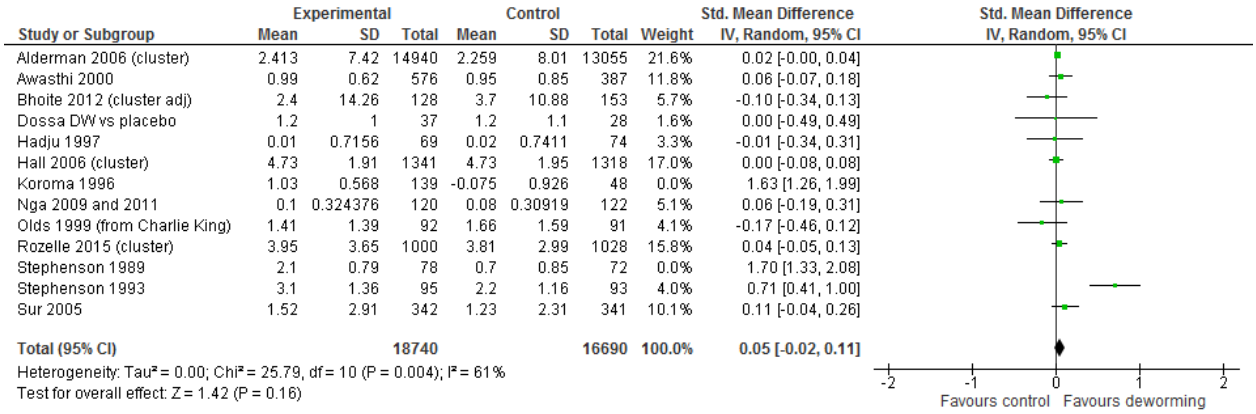
Pairwise meta-analysis: Thirty RCTs reported weight or weight of age with sufficient detail for meta-analysis. We conducted pairwise meta-analysis for each of the 26 nodes of our treatment network (Figure 8). All studies used standard doses of deworming drugs, with the exception of five studies which used Albendazole 600 mg instead of Albendazole 400 mg. Therefore, for our nodes, we combined all doses of each drug together. However, because frequency of treatment was considered a determinant of reinfection, we defined separate nodes for low frequency (1/year), standard frequency (twice per year) and high frequency (3-6 times per year). For albendazole 400 mg, twice per year, with 13 RCTs and 18, 957 participants, we found statistically significant heterogeneity with an I^2 of 93 per cent, which is considered very high. We considered it too high to allow pooling to estimate a single estimate of effect (Figure 6).

Figure 6: Albendazole twice per year versus control, standardized mean difference (SMD) of weight or weight gain, showing influence analysis with Koroma 1996 and Stephenson 1989



We conducted all of our pre-planned subgroup and sensitivity analyses for this comparison to assess whether any of them explained the high heterogeneity. None of these analyses explained this level of heterogeneity (results not shown). Therefore, we conducted influence analysis by removing single studies. The heterogeneity did not improve upon removal of any single study, with the exception of removing both Koroma 1996 and Stephenson 1989. Removal of each study yielded an I^2 of 89 per cent. Removal of both studies yielded an I^2 of 61 per cent.

Figure 7: Albendazole twice per year versus control, weight (SMD), influence analysis without Koroma 1996 and Stephenson 1989



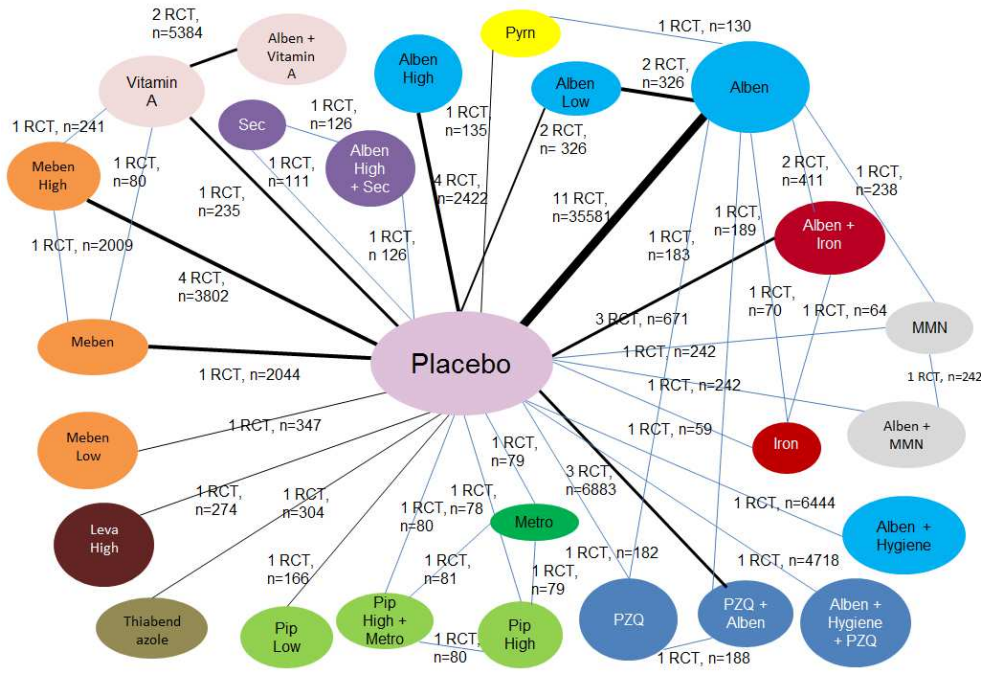
To explore reasons for these outlier studies, we assessed all studies for baseline imbalance, using standardized differences in baseline scores on prognostically important variables of worm prevalence, intensity, nutritional status (weight and height) and age (Austin 2009). The two outlier studies had baseline imbalance of ≥ 0.5

standardized difference on one or more of these variables and both were rated unclear for allocation concealment. Koroma 1996 had a clinically important baseline imbalance in weight for age of one standard deviation lower in the intervention group (e.g. -2.18 WAZ in the treatment group vs. -1.07 WAZ in the control group at baseline in the urban population). In Stephenson 1989, the albendazole group had higher initial prevalence of hookworm (95% vs. 79% for the control group) and higher intensity of hookworm infection (geometric mean egg counts of 1,183 vs. 384 epg for the control group). The pooled random effects effect size for albendazole 2/ year vs. control was 0.05 SMD (95%CI: -0.02, 0.11), I^2=61% without these two studies, compared to 0.25 SMD (95%Ci: 0.11 to 0.39), I^2=93% with these studies. If converting to kg using the median standard deviation for weight in kg from all included RCTs, this equates to a difference between 0.07 kg without these studies compared to 0.35 kg with these studies. We decided to run the pairwise and network meta-analyses without these two studies, and conducted sensitivity analyses to explore the impact of this decision on the results.

Network meta-analysis: The network meta-analysis of weight and weight for age included 29 trials with a total of 61,857 participants (Alderman 2006; Awasthi 2000; Awasthi 2001; Awasthi 2008; Bhoite 2012; Donnen 1998; Dossa 2001; Garg 2002; Gateff 1972; Goto 2009; Greenberg 1991; Gupta 1982; Hadju 1997;Hall 2006; Kruger 1996; Ndibazza 2012; Olds 1999; Ostwald 1984; Jinabhai 2001A; Miguel 2004; Nga 2008; Rousham 1994; Rozelle 2015; Stephenson 1993; Stoltzfus 1997; Sur 2005; Watkins 1996; Willett 1979; Wiria 2013). The study by Miguel 2004 was analysed as two separate studies because we obtained data from the authors on which schools received praziquantel due to >30 per cent schistosomiasis prevalence. Because we had data on intervention schools and control schools with >30 per cent schistosomiasis prevalence, we analysed this study as two separate comparisons with two separate control groups: 1) Albendazole vs. control for schools where no praziquantel was given, and 2) Albendazole+praziquantel vs. control for schools where praziquantel was given.

We assessed 26 interventions (defined by drug type, frequency of administration, and types of co-interventions) in 20 two-arm studies, five studies with three arms and five studies with four arms. The nodes with the most studies were placebo (28 studies), Albendazole two per year (11 studies), Mebendazole three-four per year (four studies) and Albendazole three to four per year (four studies) (see network geometry Figure 8). The network analysis was consistent, as assessed by the consistency plot, and model diagnostics (Additional Table 12), with a total residual deviance 55.67, DIC -31.69.

Figure 8: Evidence Network: Weight, n=29 randomised trials, 61,857 participants



Abbreviations:

Alb-std: albendazole 400 mg 2/year
Alb-LD: Albendazole 400 mg 1/year
Alb-HD: Albendazole 400 mg >2/year (3-6)
Sec: secnizadole (antigiardial)
Meb-high: mebendazole >2/year
MMN: multiple micronutrient fortified biscuit
PZQ: praziquantel once/year
Metro: metronizadole: antigiardial
Pip: piperazine twice/year
Leva-high: levamisole >2/year
Pyrn: pyrantel 2/year

Compared to placebo: For interventions compared to placebo, we found no statistically significant treatment effects in the pairwise analyses, with effect sizes ranging from -0.14 to 0.29 SMD, with three exceptions. The pairwise comparison of Albendazole twice per year+vitamin A vs. vitamin A was statistically significant with a random effects SMD of 0.06 (95%CI: 0.01 to 0.11) and mebendazole twice/ year vs. placebo was statistically significant with a random effects SMD of 0.10 (95%CI: 0.01, 0.18). These one-year effect sizes equate to 330 grams and 110 grams, respectively. Piperazine >2/ year + metronizadole (anti-giardial) vs. placebo was statistically significant in one four arm study with an SMD 0.46 (95% CI: 0.02, 0.91), equating to 0.35 kg (95% CI: 0.02 to 0.68 kg); this difference was not statistically significant in the

network analysis. The comparison of the network to pairwise results were consistent with each other, and found no statistically significant effects for any treatment or treatment combination on weight or weight for age (Table 2). The full comparison of all pairwise and network meta-analyses and interventions is in Appendix 2.

Table 4: Weight or weight for age, active interventions vs. placebo in pairwise and network meta-analysis

Comparison	Number studies with direct comparison and number participants	Pairwise SMD and 95% confidence interval	Network SMD and 95% confidence interval	GRADE Certainty
Albendazole, 400 mg twice/year	11 (18,740 treatment, 16,690 control)	0.05 (-0.02, 0.11)	0.05 (-0.05, 0.16)	Moderate[1]
Albendazole+ praziquantel, twice per year	2 (221 treatment, 217 control)	0.10 (-0.09, 0.29)	0.15 (-0.10, 0.40)	Low[2]
Albendazole, 400 mg (>2/year)	4 (1196 treatment and 1,226 placebo)	0.03 (-0.05, 0.11)	0.05 (-0.16, 0.18)	Moderate[1]
Praziquantel once/year	1 (91 treatment, 91 placebo)	0.13 (-0.16, 0.42)	0.23 (-0.11,0.57)	Low[2]
Albendazole 400 mg twice per year+vitamin A vs. vitamin A	2 (2,692 treatment, 2,692 placebo)	0.06 (0.01, 0.11)*	0.06 (-0.15,0.26)	High
Piperazine >2/year + metronizadole (antigiardial) vs. placebo	1 (41 treatment, 39 placebo)	0.46 (0.02, 0.91)*	0.46 (-0.07,0.98)	Low[3]

***GRADE Notes**: 1) Rated down for heterogeneity, 2) Rated down for optimal information size of SMD 0.2 is 400 and because of study limitations due to possible reporting bias since results include a study where we obtained data fromonly two sites of a five site study, and 3) Rated down two levels for imprecision because the sample size is 80, and optimal information size for a small effect of SMD 0.2 is 400*

Two studies reported only end of study difference between arms. Bobonis 2006 reported a non-statistically significant difference at end of study (without providing results for each arm of the study) between albendazole+iron+vitamin A vs. control in preschool children of 0.50 kg (95%CI: -0.09, 1.09). Linnemayr 2011 found a difference between a comprehensive nutrition package which included deworming, growth promotion, vitamin A, iron, bednets for a fee, cooking workshops and breast feeding

support vs. control of 0.26 kg (95% CI: 0.06, 0.46), which was robust to a number of sensitivity analyses (results not provided for each arm of the study).

Compared to active interventions, in the network analysis, we found no statistically significant or clinically important (using SMD of 0.3 to assess clinical importance) differences between any interventions. We report selected head to head treatments below (Table 3).

Table 5: Weight or weight for age; head to head comparisons, pairwise vs. network meta-analysis for selected comparisons

Treatment	Comparator	N RCTs (N participants)	Pairwise meta-analysis SMD and 95% CI	Network meta-analysis SMD and 95% CI	GRADE Certainty
Albendazole 400 mg twice/year	Albendazole 400 mg 2/year +Praziquantel	1 (189)	-0.36 (-0.79, 0.07)	-0.10 (-0.36, 0.16)	Moderate[1]
Albendazole 400 mg twice/year	Mebendazole twice/year	No direct studies		0.08 (-0.10, 0.30)	Low[1, 2]
Albendazole 400 mg twice/year	Albendazole >2/year	No direct studies		0.05 (-0.15, 0.24)	Moderate[2]
Albendazole 400 mg 2/year	Albendazole 2/year + hygiene promotion	No direct studies		0.01 (-0.28, 0.32)	Low[1, 2]
Albendazole 400 mg 2/year	Albendazole 2/year + iron	2 (411)	0.01 (-0.37, 0.40)	0.11 (-0.14, 0.36)	Moderate[3]

Notes*: 1) We downgraded for imprecision because optimal information size for a small effect of SMD 0.2 is 400; 2) Downgraded for intransitivity; 3) Downgraded for high risk of bias of Bhoite 2012*

Power analysis: We assessed the power to detect a difference of 0.2 kg (postulated by Croke et al 2016 to be clinically important if only a portion of the population benefits) for albendazole twice per year vs. placebo, using the methods described by Hedges and Pigott 2001. Using these methods, we had 99.98 per cent power to detect a difference of 200 grams in our analysis of albendazole twice per year vs. placebo, with an alpha of 0.05 (two tailed test).

Controlled before after studies: The results from the controlled before after study which reported weight (Pust 1987) agree with these, and the network meta-analysis including Pust 1987 converged, was consistent (as assessed with consistency plots, residual deviance and deviance information criteria) and agreed with these results (results not shown).

Publication bias: The funnel plot for albendazole twice per year vs. placebo for weight or weight for age does not suggest publication bias (Figure 35).

Studies not included in meta-analysis:

Five additional studies reported no statistically significant difference between deworming and control for weight or weight for age, without sufficient detail for meta-analysis (Kloetzel 1982, Taylor 2001, Beach 1999, Shah 1975, Solon 2003).

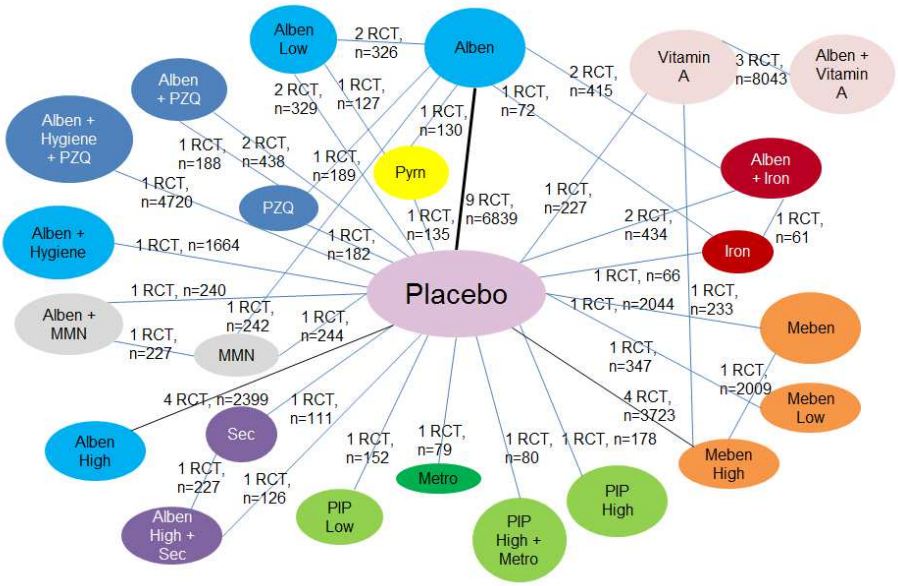
Height gain or Height for age (HAZ)

In summary: Deworming probably leads to little or no difference in height gain compared to placebo (moderate to high certainty evidence). There is probably little or no difference between different types of deworming, frequencies of deworming or combinations with other deworming drugs, micronutrients or food (moderate to high certainty evidence).

Meta-analysis: In pairwise analyses, we found high heterogeneity (I^2 of 86%) with two studies described above: Koroma 1996 and Stephenson 1989 because of baseline imbalance. For congruence with the weight analysis, we excluded these studies from the base case analysis, and conducted sensitivity analyses with and without them (Appendix 4 for forest plot). With these two studies, the pairwise results for albendazole vs. placebo had an SMD of 0.18 (95%Ci: 0.03, 0.33) vs. an SMD of 0.03 (95%CI: -0.02, 0.09) without these two studies (I^2 of 11%). Using a typical standard deviation for height in the included studies of 3.4 cm, SMD of 0.18 is equivalent to 0.44 cm and SMD of 0.03 is equivalent to 0.07 cm.

Network meta-analysis structure: The network meta-analysis for height or height gain had 25 studies (Awasthi 2000; Awasthi 2001; Awasthi 2008; Jinabhai 2001A; Ndibazza 2012; Watkins 1996; Garg 2002; Ostwald 1984; Hall 2006; Kruger 1996, Miguel 2004; Wiria 2013; Rozelle 2015; Goto 2009; Bhoite 2012; Donnen 1998; Stoltzfus 1997; Stephenson 1993; Nga 2011; Dossa 2001; Gupta 1982; Olds 1999; Hadju 1997) (Figure 9). As with weight, Miguel 2004 was entered as two separate studies because we received data from authors to identify which schools had prevalence of schistosomiasis >30 per cent and thus received praziquantel, thus it was entered as Albendazole twice per year vs. control and Albendazole+Praziquantel vs. control. There were 24 different treatment combinations, in 16 two arm studies, five three-arm studies and five four-arm studies. The network was consistent. Total residual deviance was 43.36 (sd 7.783) and the deviance information criterion was -39.794 (Additional Table 13).

Figure 9: Evidence Network: Height, n=25 randomised trials, 32,631 participants



Compared to placebo: For treatments compared to placebo (Table 4), there were no statistically significant differences in pairwise analyses or the network, with the exception of the pairwise analyses of height for age in the Miguel 2004 study, where there was a statistically significant difference in height for age between children who received one year of treatment of 0.13 Z-score (95% CI: 0.08, 0.18) with albendazole alone and hygiene promotion vs. children in control schools and of 0.12 Z score units (95% CI: 0.04 to 0.20) for albendazole+praziquantel and hygiene promotion vs. control, where praziquantel was given once per year only in regions with schistosomiasis >30 per cent [data provided by the authors]. These comparisons were not statistically significant in the network analysis with a 0.12 SMD (95%CI: -0.01, 0.25) and 0.11 SMD (95%CI: -0.03, 0.25), respectively. No effect sizes were greater than and SMD of 0.15, with the exception of combinations of deworming with anti-giardials, where the effect size was 0.2 SMD for deworming and secnizadole vs. placebo (Goto 2009) and 0.41 and 0.42 for piperazine and metronizadole and metronizadole alone vs. placebo, respectively (Gupta 1982). See Appendix 13.5 for comparison of all network and pairwise results.

One cluster RCT (Bobonis 2006) reported no difference in height gain for albendazole + iron + vitamin A in preschool vs. control -0.75 cm (95%CI: -2.40, 0.90 cm).

Table 6: Height and height for age (SMD): Comparison of pairwise and network meta-analysis for selected interventions vs. placebo

Intervention	Number RCTs Number participants	Pairwise SMD and 95% Confidence Interval	Network meta-analysis SMD and 95% CI	GRADE certainty
Albendazole 2/year	9 (6839 participants)	0.03 (-0.02, 0.09)	0.03 (-0.04,0.10)	Moderate[1]
Albendazole >2/year	4 (2399 participants)	0.08 (-0.01, 0.17)	0.08 (-0.01,0.20)	High
Albendazole 2/year + hygiene promotion	1 (6446 participants)	0.12 (0.07, 0.17)	0.12 (-0.01,0.25)	Moderate[2]
Albendazole 2/year + Praziquantel+ hygiene promotion	1 (4720 participants)	0.11 (0.04, 0.18)	0.11 (-0.03,0.25)	Moderate[2]
Praziquantel 1/year	1 (182 participants)	-0.11 (-0.40, 0.18)	-0.01 (-0.27,0.25)	Low[3]
Piperazine >2/year+metronizadole	1 (80 participants)	0.40 (-0.04, 0.85)	0.41 (-0.06,0.88)	Moderate[4]

***Notes**: 1) Rated down for inconsistency because two studies were excluded due to baseline imbalance (see p. 67). 2) Rated down for study limitation. 3) Downgraded for imprecision due to not meeting optimal information size of 400 participants for an SMD of 0.2 (small effect size), 4) rated down one level for imprecision due to not meeting optimal information size, and rated down one level for study limitations due to potential reporting bias since results are based on 2 sites of a 5 site trial (Olds 1999).*

Active comparators: For head to head comparisons of deworming compared to other active treatments, there were no statistically significant, nor clinically important differences in either the pairwise or network meta-analysis, with the exception of combinations with antigiardials (secnizadole or metronizadole), where there were effect sizes of 0.2 to 0.4 SMD, which was equivalent to a difference of 0.4 to 0.8 cm in the original studies (Table 5).

Table 7: Height or height for age; head to head comparisons, pairwise vs. network meta-analysis for selected comparisons

Treatment	Comparator	N RCTs (N participants)	Pairwise meta-analysis SMD and 95% CI	Network meta-analysis SMD and 95% CI	GRADE Certainty
Albendazole 400 mg twice/year	Albendazole 400 mg 2/year +Praziquantel	1 (189)	-0.17 (-0.59, 0.25)	-0.04 (-0.23,0.16)	Moderate[1]
Albendazole 400 mg twice/year	Mebendazole twice/year	No direct studies	-	-0.06 (-0.22,0.09)	Low[1, 2]
Albendazole 400 mg twice/year	Albendazole >2/year	No direct studies	-	0.05 (-0.06,0.19)	Moderate[2]
Albendazole 400 mg 2/year	Albendazole 2/year + hygiene promotion	No direct studies	-	0.09 (-0.06,0.24)	Low[1, 2]
Albendazole 400 mg 2/year	Albendazole 2/year + iron	2 (415	-0.13 (-0.33, 0.07)	-0.02 (-0.20,0.17)	Moderate[3]

***Notes**: 1) We downgraded for imprecision because optimal information size for a small effect of SMD 0.2 is 400; 2) Downgraded for intransitivity; 3) downgraded for high risk of bias of Bhoite 2012.*

Studies not included in meta-analysis: Three studies were not included in meta-analysis due to missing data. All of these studies reported no statistically significant effect of deworming vs. control on height (Taylor 2001, Beach 1999, Solon 2003).

Controlled before after studies: We did not find any controlled before after studies with data for height in a usable format.

Publication bias: A funnel plot of albendazole twice per year reporting height or height for age did not suggest publication bias (***Additional Figure 2***).

Subgroup and sensitivity analyses: As described below, these main effects on height were robust to four subgroup analyses and our pre-planned sensitivity analyses.

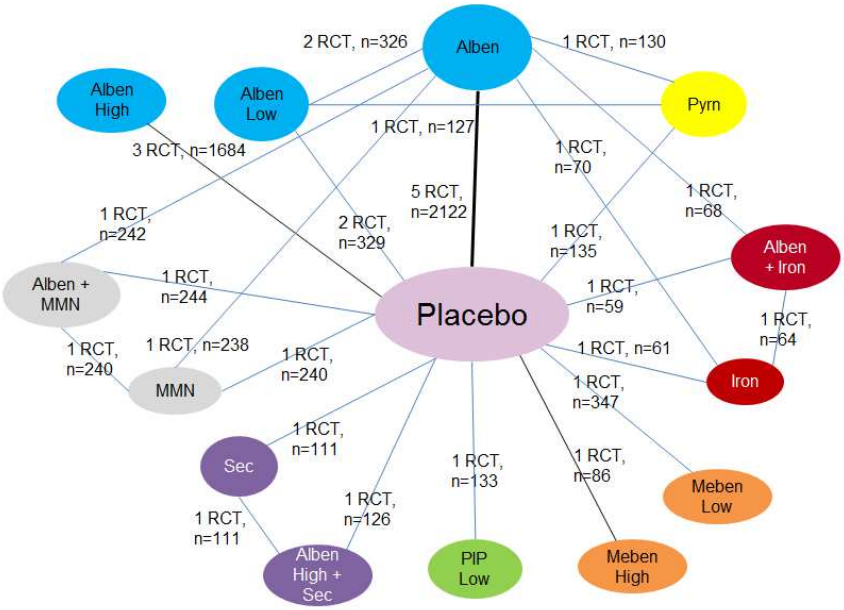
Weight for height (WHZ)

In summary: Mass deworming results in little to no difference in weight for height compared to placebo (high certainty evidence). There is probably little to no difference between different drug types, frequencies or combinations with food or micronutrients (moderate to high certainty evidence).

Pairwise meta-analysis: Twelve studies were included in pairwise analysis for weight for height (Awasthi 2001; Dossa 2001; Hadju 1997; Nga 2011; Stephenson 1993; Kruger 1996; Ndibazza 2012; Watkins 1996; Garg 2002; Ostwald 1984; Greenberg 1981; Goto 2009).

Network meta-analysis structure: The network meta-analysis comprised 15 different treatment comparisons, assessed in seven two-arm studies, two three-arm studies, and three four-arm studies (Figure 10). One study with five arms was coded as a four arm study for programming reasons (we dropped the arm with pyrantel once per year, considered not applicable to current deworming programmes) (Hadju 1997). The network was consistent; the total residual deviance was 33.54, DIC -7.733 (Additional Table 13).

Figure 10: Evidence network: Weight for height, n=12 randomised trials, 4687 participants



Compared to placebo: No comparisons of treatments vs. placebo were statistically significant in the pairwise or the network analysis for weight for height. The effect sizes in pairwise and network comparison vs. placebo were <0.2 SMD, with the exception of albendazole once/ year vs. placebo, which was based on two studies (Hadju 1997; Stephenson 1993) with an SMD of 0.44 (95% CI -0.58 to 1.46) and I^2 of 95% (low certainty evidence, downgraded for less than optimal information size) (Table 6). For full comparison of network to pairwise results, see Appendix 2.

Table 8: WHZ; comparison of pairwise to network meta-analysis: active interventions compared to placebo

Treatment	N trials (N children)	Pairwise SMD (95% CI)	NMA SMD (95% CrI)	GRADE certainty
Albendazole 2/year	5 (2311)	0.14 [-0.20, 0.49]	0.14 [-0.20, 0.47]	High
Alben >2/year	3 (1684)	-0.06 [-0.25, 0.13]	-0.08 (-0.67,0.51)	High
Alben 2/year + iron	1 (59)	-0.12 [-0.63, 0.39]	0.10 (-0.88,1.07)	Low[1]
Meben >2/year	1 (86)	0.25 [-0.18, 0.67]	0.25 (-0.82,1.33)	Low[1]

***Notes**: 1) Downgraded for imprecision due to not meeting optimal information size for small effect of 0.2 SMD for 400 participants*

Compared to active interventions: There were no statistically significant differences between any active comparators. All effect sizes were less than 0.4 SMD (Table 7) .

Table 9: Weight for height, head to head comparisons, pairwise vs. network meta-analysis

Treatment	Comparison	N trials (N children)	Pairwise SMD (95% CI)	NMA SMD (95% CrI)	GRADE certainty
Alben LD	Alben HD	5 (987)	-	0.37(-0.53,1.26)	Low[1,2]
Meben LD	Alben LD	3 (328)	-	-0.33 (-1.55, 0.90)	Low[1,2]
Meben LD	Meben HD	2 (204)	-	-0.28 (-1.76, 1.18)	Low[1,2]

***Notes**: 1) downgraded for intransitivity; 2) downgraded for less than optimal information size*

Controlled before-after studies: No controlled before after studies were found that reported WHZ.

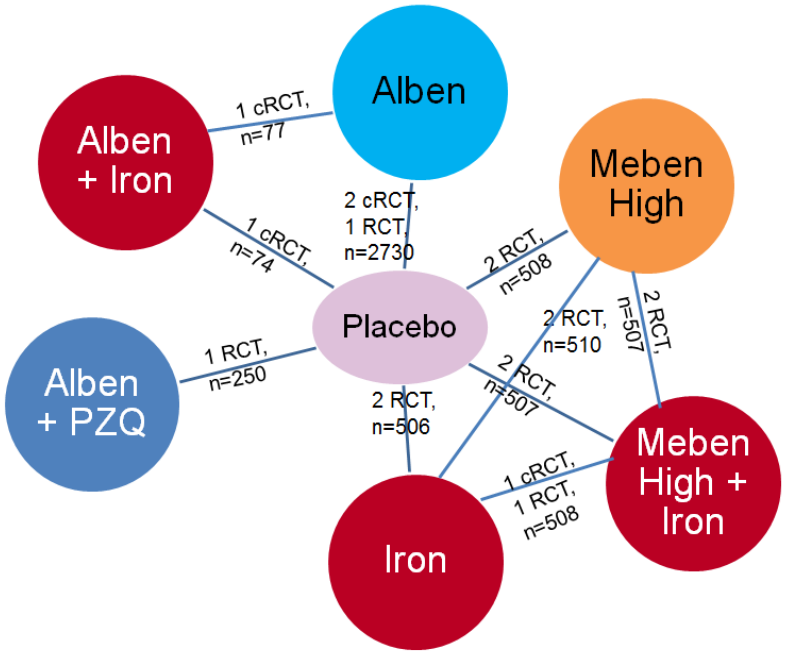
Proportion stunted

In summary: Mass deworming with albendazole twice per year leads to little to no difference in the proportion of stunted children compared to placebo (high certainty evidence). There was little to no difference between different drug types, combinations or frequency (low to moderate certainty evidence).

Pairwise meta-analyses: We included seven RCTs which reported proportion of children stunted at the end of study. The pairwise meta-analyses were not statistically significant and ranged from 0.63 to 0.98 relative risk (Appendix 6 for forest plots).

Network meta-analysis structure: Because there were three studies with multiple arms (Stoltzfus 2001, Bhoite 2012 and Thi Le Huong 2007), we judged that network meta-analysis was worthwhile. However, since there were no studies with vitamin A alone, the network failed to converge if we considered Awasthi 2001 as Albendazole twice per year+vitamin A vs. vitamin A. As we considered there to be a low risk of synergistic effects of vitamin A (and vitamin A was in both arms), we coded this study as Albendazole twice/ year vs. placebo (Figure 11). The network was consistent (residual deviance 18.58 vs. 19 data points, deviance information criteria 133.008).

Figure 11: Evidence network: proportion stunted, n=7 randomised trials, 5593 participants



Compared to placebo, mass deworming with albendazole twice per year leads to little to no effect on proportion of stunted children, with relative risk (RR) of 0.97 (95%CI: 0.78, 1.18) [high certainty evidence] (Table 10). Compared to placebo, deworming with mebendazole, albendazole+praziquantel, albendazole+iron, and mebendazole+iron probably leads to little to no effect on proportion of stunted children (low to moderate certainty evidence for mebendazole, albendazole combined with praziquantel, and mebendazole combined with iron).

For comparison of active treatments, there may be little to no difference in effect on proportion stunted between albendazole, albendazole +praziquantel, albendazole +iron and mebendazole (with or without iron) (relative risks range from 0.74 to 1.10) (low to moderate certainty evidence) (Table 8). Mebendazole + iron compared to iron alone may increase the proportion stunted with a RR of 1.49 (95%CI: 0.88 to 2.48) (low certainty evidence).

Table 10: Proportion stunted, as a relative risk (RR), Network Meta-analysis compared to pairwise meta-analysis active interventions compared to placebo

Treatment	Reference	N trials, N children	Pairwise meta-analysis, random effects (95% CI)	Network meta-analysis, relative risk (95% CrI)	GRADE certainty
Albendazole 2/year	Placebo	4 (4286)	0.98 (0.88, 1.08)	0.97(0.78,1.18)	High
Albendazole 2/year +iron		1 (74)	0.63 (0.16, 2.46)[1]	0.72(0.16,1.80)	Low[1]
Mebendazole > 2/year		2 (508)	0.79 (0.57, 1.10)	0.79(0.52,1.17)	High
Mebendazole >2/year +iron		2 (511)	1.08 (0.81, 1.44)	1.07(0.73,1.49)	High
Albendazole+PZQ		1 (263)	0.92 (0.44, 1.91)[2]	0.89(0.41,1.66)	Moderate[2]

***Notes**: 1) Downgraded for imprecision by two levels due to not meeting optimal information size; 2) Downgraded by one level for imprecision*

Table 11: Proportion stunted, relative risk (RR), mass deworming compared to active treatments, NMA vs. MA, random effects for selected comparisons

Treatment	Reference	N trials, N children	Pairwise meta-analysis, random effects (95% CI)	Network meta-analysis, relative risk (95% CrI)	GRADE certainty
Albendazole 2/year +iron	Albendazole 2/year	1 (74)	0.85 (0.20, 3.56)	0.74(0.17,1.87)	Low[1]
Mebendazole >2/year	Albendazole 2/year	-	-	0.81(0.51,1.27)	Low[2],[3]
Mebendazole >2/year +iron	Albendazole 2/year	-	-	1.10(0.72,1.63)	Low
Albendazole 2/year +PZQ	Albendazole 2/year	-	-	0.92(0.41,1.78)	Low
Mebendazole >2/year +iron	Mebendazole >2/year	2 (507)	1.30 (0.72, 2.36)	1.49(0.88,2.48)	Low[4]

***Abbreviations**: PZQ: praziquantel. **GRADE notes**: 1- downgraded for high risk of bias of Bhoite 2012, and imprecision due to not meeting optimal information size; 2- downgraded because of imprecision; 3-downgraded for transitivity; 4- downgraded for imprecision and risk of bias due to baseline imbalance in Stoltzfus 2004.*

Controlled before after studies: We did not find any CBAs that reported proportion of stunted children as an outcome.

Studies not included in meta-analysis: One study could not be included in the meta-analyses (Bobonis 2006) and reported no difference in height for age between albendazole+iron+vitamin A vs. control in preschool children five months after treatment.

Other measures of anthropometry: Body mass index, mid-upper arm circumference, skinfold, proportion wasted, proportion underweight

Because these outcomes were reported in a small number of studies (less than 10 studies, as described above), and all studies reporting these outcomes also reported either weight or height or both, we did not conduct analysis for these outcomes.

One CBA reported BMI but not weight or height (Monse 2013). It found little to no effect on BMI between a class treated with mass deworming and an external concurrent untreated control school, with an effect size of 0.02 BMI units (95% CI: -0.33 to 0.37) (very low certainty evidence).

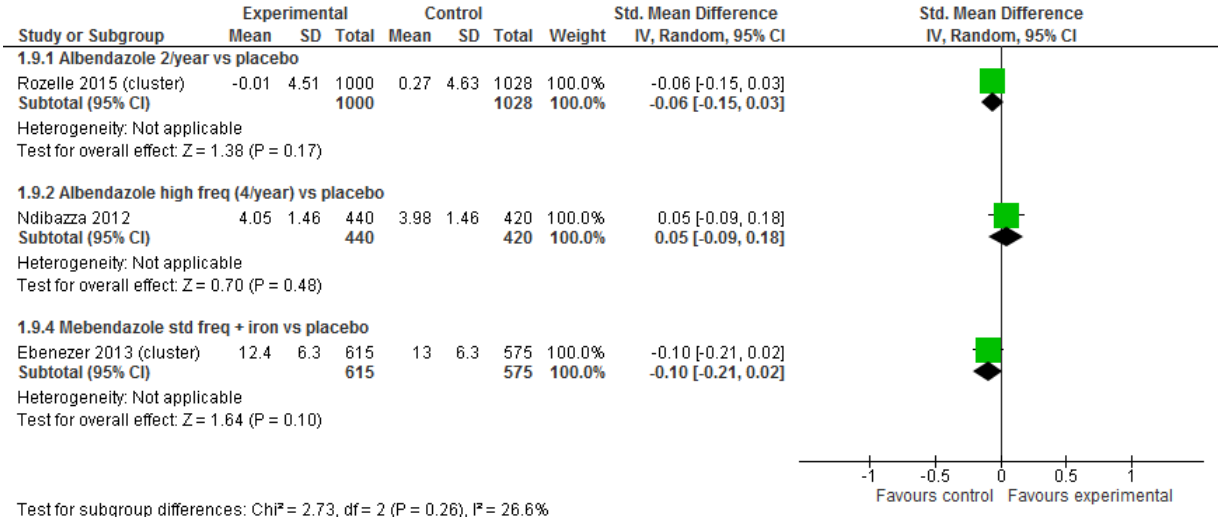
Cognitive processing and development

In summary: Based on our analyses, mass deworming results in little or no difference in short-term cognitive tasks (such as attention), little to no difference in general intelligence and little to no difference in childhood development compared to placebo (high certainty evidence).

Pairwise meta-analysis: We conducted three meta-analyses: 1) cognitive outcomes that are sensitive to attention and short-term memory (e.g. digit span, number recall); 2) general intelligence measures (e.g. Peabody Vocabulary scale and Raven's progressive matrices); and 3) childhood development measures (e.g. language development).

For short-term attention, three studies reported outcomes of tasks which measure short-term attention: 1) Ebenezer 2013 assessed a coding task; 2) Rozelle 2015 reported the WISC IV working memory index and processing speed index (in Chinese), and 3) Ndibazza 2012 measured an attention task. We used the WISC IV working memory index from Rozelle 2015, and tested whether choosing the Processing speed index would change results (it did not). These studies show little to no difference in short-term attention-focused tasks (high certainty evidence). Miguel also found no difference in short-term attention tasks (insufficient information for meta-analysis).

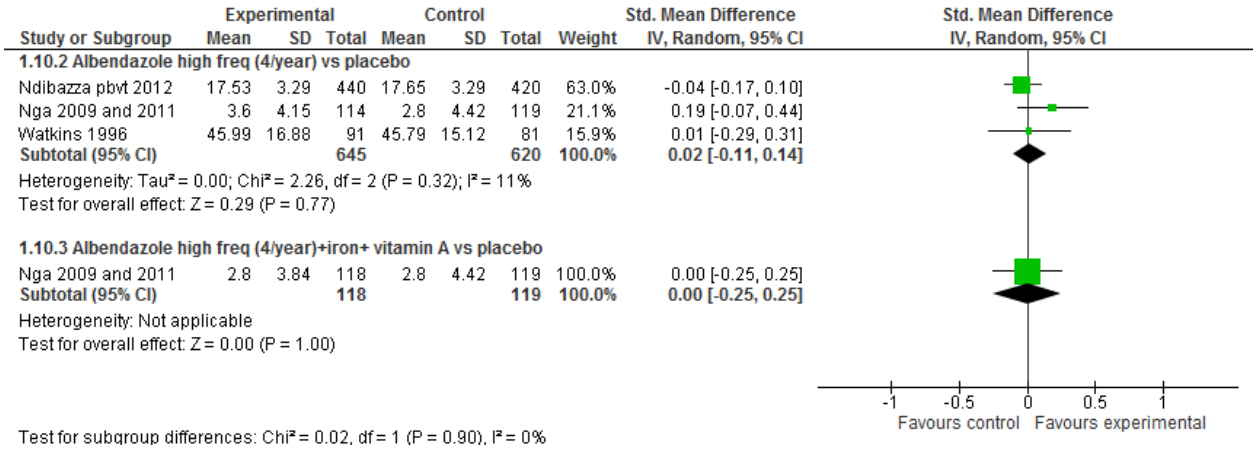
Figure 12: Short-term cognitive processing and attention, mass deworming vs. placebo



For general intelligence, we selected the outcomes common to more than one study (Peabody Vocabulary scale reported by Ndibazza 2012 and Watkins 1996). We also felt that Raven's progressive coloured matrices from Nga 2009 could be combined with this.

These results found little to no difference in general intelligence measures for mass deworming compared to control (Figure 13).

Figure 13: General intelligence, mass deworming vs. control



Ndibazza *et al.* 2012 also measured other cognition outcomes including working memory, cognitive flexibility, inhibition, planning, fine motor function, gross motor function, and reported no statistically significant differences for any of these outcomes in children at age five years who had been treated with albendazole 400 mg twice per year from 15 months of age.

For early childhood development, we decided to analyse language development reported in Stoltzfus 2001 separately from cognitive processing measures since the scale measured development in language over one year. This was done by assessing items such as “child can say three words” and “child uses the words I, me and you” and was considered to capture a different concept than the above cognitive processing outcomes. We also analysed the motor development scale separately (consisting of 20 items, Kohnbachs alpha=0.9492 (for children ages 12-36 months), with items such as “child can kick a ball forward, child can walk on tiptoe, child can stand for a moment on their own”). For language development, Stoltzfus 2001 used a scale of language development modified for use in Kiswahili (range 0-18). The main effect of mebendazole four times per year was not statistically significant (0.3 units out of 18 point scale (95%CI: -0.3 to 0.9) and the interaction term of mebendazole and iron was not statistically significant either. The main effect of iron vs. no iron was a statistically significant difference of 0.8 units on an 18 point scale (95% CI: 0.2 to 1.4). Stoltzfus 2001 also found no difference in motor development between mebendazole vs. no mebendazole, reported as a difference of 0.44 units on a 20 unit scale (95% CI: -0.22 to 1.10).

Awasthi 2000 assessed the revised pre-screening Denver questionnaire (also a measure of early child development), and found no difference in the outcome of questionable Denver questionnaire in children of 1.01 (95% CI: 0.82 to 1.23).

Network meta-analysis: We did not perform network meta-analysis due to the paucity of studies.

Studies not included in meta-analysis: Three studies had insufficient information for meta-analysis and reported no effect of deworming vs. control on cognitive processing. Miguel 2004 reported no statistically significant effects of deworming vs. control on a battery of cognitive tests given in 2000 (the third year of the study) to all groups, which included both attention/short-term memory tasks as well as general intelligence measures of "*picture search, Raven's matrix, verbal fluency, digit span …and a dynamic test using syllogisms*" (Miguel 2004). Solon 2003 reported no differences on a measure of general intelligence, the primary mental abilities test for Filipino children, which measures verbal and nonverbal quantitative abilities between children treated with albendazole twice per year or those receiving a placebo (Solon 2003). Jinabhai 2001B reported no differences in Raven's coloured progressive matrices, Rey Auditory Verbal Learning Test or Symbol Digit Modalities Test between children treated with albendazole and praziquantel compared to those with no deworming.

Controlled before after studies: We did not include any CBA with cognition outcomes.

Publication bias: There was an insufficient number of studies (<10) to rely on funnel plots.

School attendance or participation

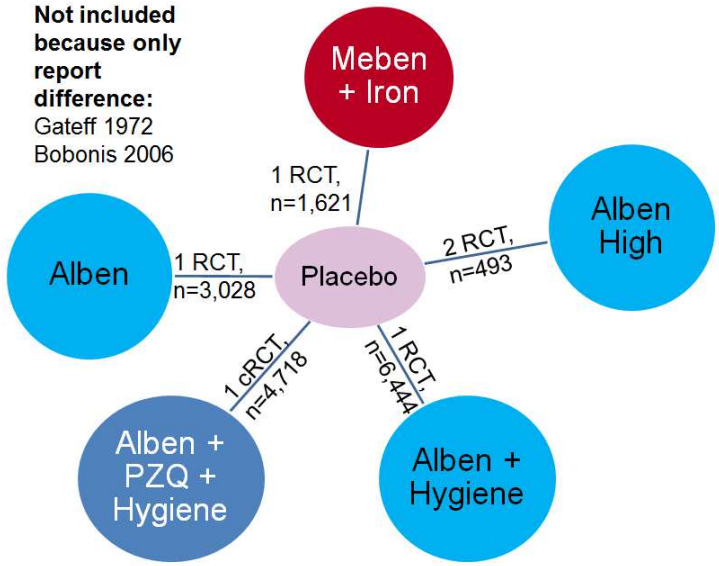
In summary: Based on our analyses, mass deworming results in little or no difference in school participation vs. placebo (moderate certainty evidence).

Pairwise meta-analysis: Seven studies reported school attendance, using either school records or unannounced site visits throughout the year. The interventions in the analysis included: Albendazole twice/year (Rozelle 2015), Albendazole four times per year (Watkins 1996), Albendazole twice/year +iron and vitamin A (Bobonis 2006), mebendazole+iron once in six month period (Ebenezer 2012), Albendazole 2/year +hygiene promotion with or without praziquantel once per year (Miguel 2004), Albendazole 4/year (Kruger 1996), and thiabendazole four times per year (Gateff 1972). We used generic inverse variance method because we only had difference scores for two studies (Gateff 1972 and Bobonis 2006). We converted all measures to percentage of

school attended over the duration of the study (e.g. by expressing days missed by the number of possible school days in the term).

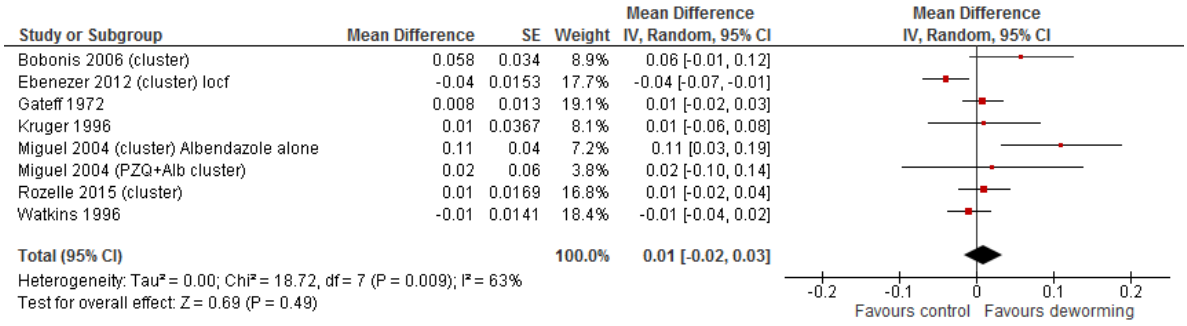
Network meta-analysis: We decided to attempt network analysis because we had ≥ five studies. However, two studies could not be included because they did not report attendance for each arm; they only reported the difference between groups (Gateff 1972, Bobonis 2006). The network contained five trials, with six nodes (Figure 14). The network converged, however, the credible intervals were wide (from -100 to +100 per cent attendance differences), and we could not assess the assumption of consistency because we had no closed loops (i.e. no studies with three or four arms). Therefore, we felt these results were not robust and do not report them here.

Figure 14: Evidence network: attendance, n=7 randomised trials, 16,304 participants



Compared to placebo, using pairwise analyses, the pooled result across all mass deworming interventions was a difference of 1 per cent attendance (95%CI: -1% to 3%), with moderate heterogeneity indicated by I^2 of 67 per cent and p=0.004 for the chi^2 of 21.05 with seven degrees of freedom (Figure 15). We rated down the certainty by one level (to moderate) because of heterogeneity (see below for sensitivity analyses).

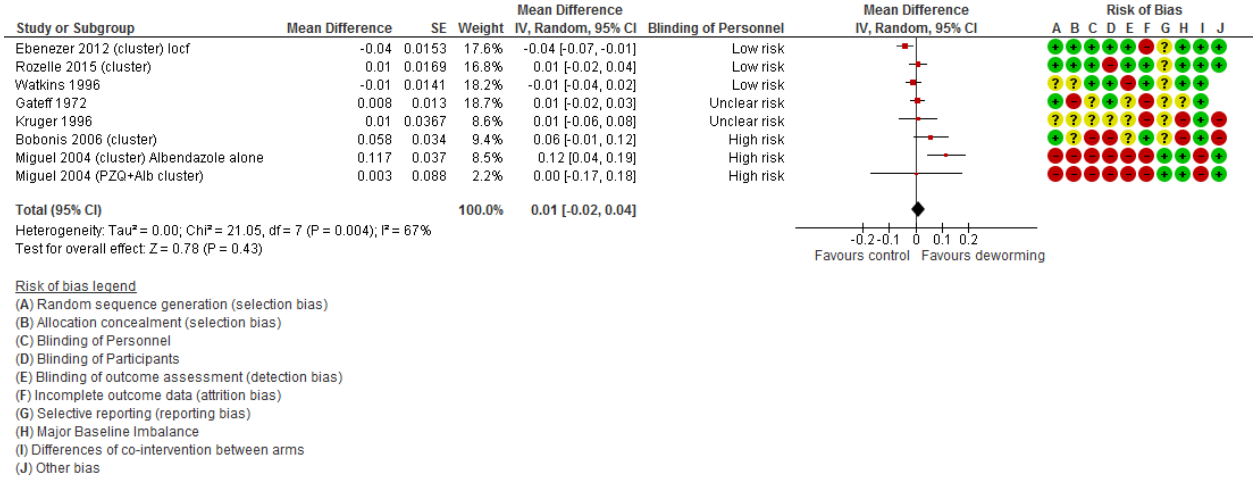
Figure 15: School attendance, pairwise results



We explored reasons for heterogeneity with pre-planned subgroup and sensitivity analyses (described in detail below). The pooled result was consistent for all sensitivity analyses and there were no subgroup differences, with one exception, described below.

The only subgroup or sensitivity analysis which explained heterogeneity was confounded by two factors: 1) risk of bias and 2) method of measuring school attendance (Figure 16). Two studies which measured school attendance with on-site visits also had high risk of bias for lack of blinding both personnel and participants (in contrast to the other studies which used school records to monitor attendance that had low or unclear risk of bias for blinding).

Figure 16: School attendance (difference in percentage of attendance), pairwise meta-analysis



Power analysis: These seven studies provided school attendance data on approximately 20,000 children (5,142 from six studies, and the remaining from the Miguel 2004 study). Using the Hedges and Pigott (2001) method, assuming 8 independent studies, we had 99.97 per cent power to detect a difference of 7.5 per cent

in school attendance with an alpha of 0.05 (two-tailed test). We used 7.5% as a minimum important difference since this was described as an important difference in Miguel and Kremer (2004).

Controlled before after studies: There were no CBAs with school attendance outcomes.

Studies not included in meta-analysis: Two long-term studies report attendance. These are discussed below in a section on long-term outcomes.

School performance (math and reading)

In summary: based on our analyses, mass deworming results in little or no difference in school performance in math or language compared to placebo (high certainty evidence).

We conducted separate analyses for math and language/ reading tests (e.g. English, Vietnamese, and French). We decided that network meta-analysis was not worthwhile since there were no closed loops, and five or fewer studies for each outcome.

Pairwise meta-analysis, math: For math, five studies could be combined using generic inverse variance. We used standardised mean differences in math scores at end of study since two studies reported math scores standardised to a mean of zero and a standard deviation of one (Miguel 2004 and Rozelle 2015), while the others reported the scores out of 100. There was no materially important difference between deworming and control, with a pooled difference of -0.03 SMD (95% CI: -0.07, 0.01) (Figure 17). This SMD difference is equivalent to 0.7 per cent when converted to percentage out of 100 scores.

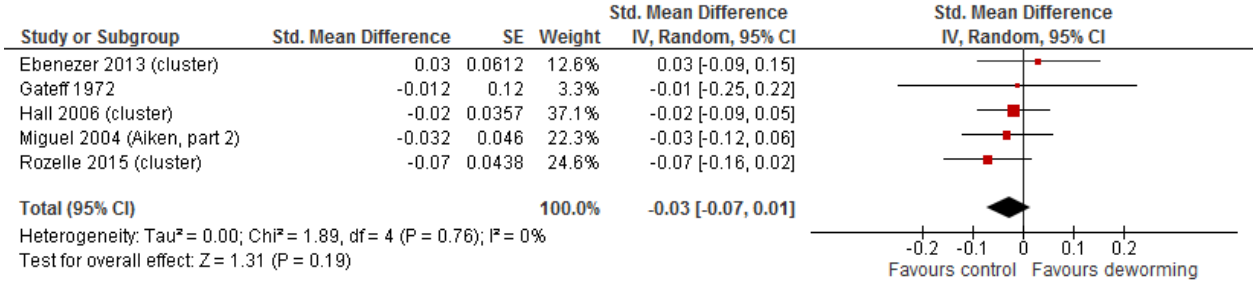


Figure 17: Math achievement tests

Pairwise meta-analysis, language: Tests of language or reading were reported in sufficient detail for meta-analysis by three studies (Ebenezer 2013, Hall 2006, Watkins 1996). We used standardised mean difference because two reported percentages and

one reported the mean on the Interamerican vocabulary test (Watkins 1996). The pooled effect of deworming vs. control showed no materially important effect with an SMD of -0.02 (95% CI -0.08, 0.04). This SMD difference is equivalent to 1.1 per cent when converted to a score out of 100 (Figure 18).

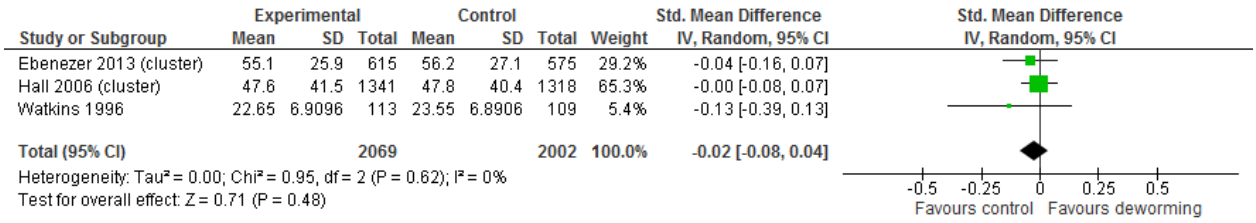


Figure 18: Language achievement tests

These results on school performance in language were robust to sensitivity analyses, as described below.

***Controlled before after studies*:** There were no CBAs with math or language outcomes.

Studies not included in meta-analysis: Two other studies reported no statistically significant difference between deworming and placebo for test scores. Nga 2011 reported no statistically significant differences between any groups (Albendazole, fortified biscuits, placebo or fortified biscuits+albendazole) for math or Vietnamese tests (size of effect not given). Jinabhai 2001B found no difference in math scores between deworming and control groups.

Mortality

In summary: based on our analyses, mass deworming results in little or no difference in mortality compared to placebo (high certainty evidence).

Pairwise meta-analysis: Six RCTs reported mortality. The DEVTA study (Awasthi 2013) was designed to assess the primary outcome of mortality. Deaths were also reported in five other studies. The pooled risk ratio showed no materially important effect of deworming vs. control with risk ratio of 0.95 (95% CI: 0.89 to 1.02), Heterogeneity I^2=0 per cent (Figure 19).

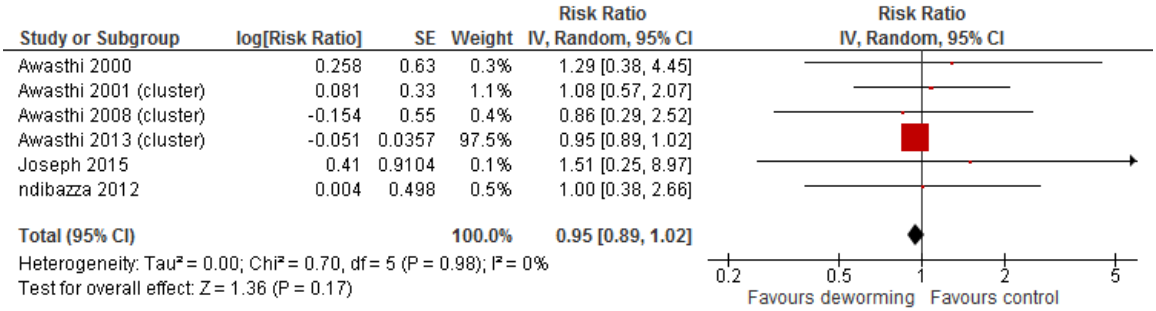


Figure 19: Mortality, deworming vs. control

Network meta-analysis: We did not perform network meta-analysis.

***Controlled* before after studies:** There were no CBAs with mortality as an outcome.

Adverse effects

In summary: Based on our analyses, deworming with albendazole results in little or no difference in adverse effects vs. placebo (moderate certainty evidence). Deworming with other drugs (thiabendazole, praziquantel, and tetrachloroethylene) may increase nausea, headache, vomiting and abdominal pain (low certainty evidence[1]).

Adverse effects were reported by Fox 2005, Gateff 1972, Michaelsen 1995, Olds 1999, Sur 2005 and Wiria 2013. Fox 2005 and Wiria 2013 both studied albendazole and reported no difference in fever, headache, myalgia or cough with albendazole vs. placebo (or for diethyl carbamazine in Fox 2005 vs. placebo or albendazole). Gateff 1972 reported statistically significant greater headache with thiabendazole 3/ year vs. placebo. Michaelsen 1995 reported nausea, drowsiness and sleepiness in 17 per cent of the children treated with tetrachloroethylene 0.1 ml/ kg vs. cough syrup (given as placebo). Olds 1999 studies albendazole alone, praziquantel alone and albendazole + praizquantel vs. placebo, and reported statistically significantly more nausea reporting an adjusted odds ratio of 2.11 (95% CI 1.49, 2.98) with praziquantel and praziquantel + albendazole vs. placebo or albendazole alone, as well as similar magnitude increase in vomiting, abdominal pain, headache, and diarrhea.

***Controlled* before after studies:** No CBAs reported adverse effects.

[1] We downgraded for two levels for imprecision due less than optimal information size (<300 events).

Long term outcomes

In summary: mass deworming for soil-transmitted helminths may slightly increase hours worked per week and school enrolment and have little to no effet on self-reported health and height (low certainty evidence) but it is uncertain if this is due to deworming alone or deworming and hygiene education. It is uncertain whether mass deworming leads to improved math achievement, language achievement or reduces work days missed due to sickness because the certainty of evidence is very low. It is uncertain whether early life (less than one year of age) exposure to dewormed siblings or communities leads to improved height, reduced stunting, or improved cognitive processing because the certainty of evidence is very low.

Details of long-term studies

Baird 2016 used the Kenya Life Panel Survey (2007-2009), which followed a sample of 7500 children in primary school in grades 2 to 7 at the time of the Kenya Primary School Deworming Project (PDSP) (Miguel 2004). The Kenya PDSP assigned 75 schools with 31,445 children to mass deworming using a stepped wedge design. Baird et al 2016 followed a representative sample of 7,500 children (randomly selected) from the Miguel 2004 study who were in grades 2 to 7 at the time of the PDSP study. Since all schools eventually received the mass deworming, the average difference in deworming between treatment and control children was 2.41 years in the 10 year follow-up study. The Kenya Life Panel Survey found 86.7 per cent of this pre-specified group of children(Baird 2016). The children were an average age of 11.9 years in 1998. The sample of found children included 5,569 respondents (3,686 treatment and 1,883 control), and there was no difference in the tracking rate across treatment or control children. Long-term outcomes were collected for 5,084 of these identified children (16 per cent of the children randomized to the original study). We rate the risk of bias for this follow-up study based on the original study and the follow-up study, as high risk of bias for allocation concealment, blinding and outcome reporting (Table 2). We downgrade the GRADE certainty by two levels for study limitations for all outcomes. While the original study did assess the potential for the control group to take up deworming on their own as very low since less than 5% of people were buying deworming medicines in a nearby area in Kenya, and the attitudes of parents to deworming were not positive. However, there is still the potential for the knowledge of the treatment schools to affect the participant behaviour. This study conducted a number of sensitivity analyses that increase the confidence in their findings and estimation strategy. Also, since the difference in time of treatment between the treatment and control arms was only 2.41 years, any differences observed are likely to be smaller than would be observed between a group which received no mass deworming at all. According to their results, mass deworming and hygiene education may improve hours worked per week and school enrolment, and may have little to no effect on height

and self-reported health. This study also reported differences in the size of effect for men compared to women for hours worked (3.49 hours for men, 95 per cent confidence interval: 0.71-6.27 and 0.32 hours for women (95%CI: -2.35 to 2.99), which was hypothesized to be related to differences in effects of educational investment for women and men in this setting. This was not reported as a pre-planned analysis, and when we conducted a test for interaction to assess subgroup differences, this subgroup difference was not statistically significant (results not shown), thus we assessed this subgroup analysis as very low certainty evidence.

Table 12: Long-term outcomes of mass deworming

Authors	Country	Length of followup (from exposure)	Main outcome	Treatment indicator and (95 per cent confidence interval)	Control group mean (sd)	Sample size	GRADE certainty[1]
Baird 2016	Kenya	10 years after exposure to deworming and hygiene promotion as part of school cRCT by Miguel *et al.* (2004)	Hours worked	1.58 hours [-0.46, 3.62]	18.4 (23.1)	5,084	Very low[2]
			School enrolment	0.29 years [0.01, 0.58]	6.69 (2.97)		Very low[2]
			Height (cm)	-0.11 cm [-0.64, 0.42]	167.3 cm (8.0)		Very low[2]
			Self-reported health "very good"	0.040 units [0.0,0.08]	0.673 (0.469)		Very low[2]
Croke 2014	Uganda	Followup 7-8 years after exposure to deworming as part of integrated management of child in Alderman 2006 study	Math	0.30 standard deviations [-0.00, 0.60]	NR	710	Very low[3]
			English	0.16 standard deviations [-0.17, 0.50]	NR		Very low[3]
Makamu 2016	Nigeria	Followup (1990-2013) of children who were part of the Schistosomiasis control programme (since 1999) in Nigeria	Years of education	0.642 years (0.17, 1.11)	8.13 years	>80,000	Very low[4]
Ozier 2016	Kenya	10 years after Miguel RCT Sampled children	Raven's Test scores	0.21 units [0.05, 0.37]	NR	2,423	Very low[5]

	who were not school age during the deworming programme (i.e. unexposed)	Height (cm)	0.21 cm [-0.38, 0.80]

1. *GRADE certainty was rated for the question of mass deworming compared to control*

2. *Baird 2016 was rated down for indirectness due to co-intervention of hygiene promotion, study limitations*

3. *Croke 2014 was rated down two levels for risk of bias because of high risk of bias in selecting a sample to follow-up from only 22 of 48 parishes that were originally randomized and rated down for imprecision (optimal information size) for both height and cognitive outcomes*

4. *Makamu 2016 started at "low" certainty because of observational design, and was rated down for risk of bias (moderate risk of bias using IDCG tool).*

5. *Ozier 2016 started at "low" because the main analysis created a "treated" group from children exposed <1 year of age from treatment groups and control groups from the original randomized trial and a "control" group from children exposed to dewormed siblings at age >1 year, and was rated down for indirectness due to the cointervention of hygiene.*

Ozier 2016 collected data on 21,309 children in Kenya from the areas of the Primary School Deworming Project cluster randomized trial conducted in Kenya in 1998 (Miguel 2004). Children were sampled if they were aged 8-14 years in 2009 and 9-15 years in 2010, according to self-reported age by the children (who often could only report age to the nearest year). A random sample of eligible non-migrants were selected for cognitive testing, using a Stata random number generator, which resulted in a sample of 923 from group 1 schools, 934 from group 2 schools and 514 from group 3 schools (control). It is unclear why the sampling strategy selected almost twice as many children from intervention schools as from control schools; this was described as an error in the Stata code (Ozier 2011). This study was rated at unclear risk of bias due to sampling strategy. As described above, Ozier 2016 conducted two analyses: 1) comparing 21 within birth cohort two-arm tests to contrast intervention and control schools for cognition measured with Raven's matrices; and 2) to compare each of the primary outcomes for children exposed to a treated sibling before age 1 to children exposed toa treated sibling after age 1. Tests of falsification and robustness were conducted to support the hypothesis of the article. However, the tests as randomized were described as "*low power*", and consisted of about 353 children per comparison. Exposure to mass deworming and hygiene promotion of school-age children in the community before age one year may lead to long-term improvements in Raven's test

scores but not height or height for age, but it is uncertain whether this effect is due to mass deworming or to hygiene promotion (Table 12) [very low certainty evidence].

Croke 2014 followed the sample from the Alderman 2006 RCT conducted in church parishes in Uganda, where there was a baseline prevalence of 60 per cent of STH (mostly hookworm). Children in intervention groups were offered albendazole 400 mg at the health clinic days. The authors estimated that 34 per cent of the control children had accessed deworming medicine through an external source in the original RCT by the end of the three year study. Croke 2014 used data collected by Uwezo in 2010, which surveyed 22 out of the 48 parishes in the deworming study (10 treatment and 12 control), and identified 763 children who were aged 1-7 years in the study period of 2000-2003 and were eligible for the Alderman 2006 study (2.7 per cent of the original sample of 27,995 children). This follow-up study was rated at high risk of sampling bias, since it is unknown why the 22 parishes were sampled and whether they were a representative sample of the original 48 parishes randomized. Data on math and English scores were available for 710 children, standardised to a mean of zero and a standard deviation of 1. The unadjusted effect of deworming was 0.30 standard deviations [95% CI: -0.00, 0.60] for math and 0.16 standard deviations [95% CI -0.17, 0.50] for English. When adjusted for age, gender, survey year and interactions of these variables, the effect for math was 0.36 standard deviations (95% CI: 0.11, 0.62) and for English was 0.25 standard deviations (95% CI: -0.01, 0.50). Croke 2014 found these results were robust to a range of sensitivity analyses, and the effect was larger in poorest income quintiles and girls. Using the correlations from Ozier 2016, these effect sizes equate to 0.5 to 0.8 years of education. Despite the importance of this magnitude of effect, it is uncertain whether mass deworming leads to long-term improvements in English or math scores because of very low certainty evidence[2].

Makamu 2016 compared four states in Nigeria which received mass deworming with praziquantel for schistosomiasis control to 33 states in Nigeria which did not, and assessed education outcomes. The findings of 0.642 more years of education (7.9 per cent more than the average years of education of 8.13 years in control states) are

[2] Since Croke 2014 is a follow-up of an RCT, GRADE quality starts at high. We downgraded by two levels for risk of bias because of risk of sampling bias.We downgraded for imprecision for math because the optimal information size was estimated at 864 for an effect of 0.3, with standard deviation of 2.24. We also downgraded for imprecision for English because the optimal information size was calculated at 905 for the effect size and standard deviation found.

considered very low certainty evidence because of the observational design and the moderate risk of bias. The study conducted two analyses: a difference in differences analysis with 1990 as the pre-intervention year and 2008 and 2013 as post-intervention, and a cohort study. Baseline characteristics and comparability across groups in 1990 were not shown (Table 12).

4.4.2 Secondary outcomes

Costs or resource use

Five studies reported the cost per single dose of deworming or the cost per year for deworming (Alderman 2006, Awasthi 2000, Garg 2002, Gateff 1972, Nga 2011). These estimates ranged from less than $0.05 per dose of albendazole (Nga 2009) to $0.40/dose of albendazole (Alderman 2006). These do not consider delivery or implementation costs.

Eight studies conducted some type of economic evaluation within their studies or using study data. We did not appraise the quality of these economic evaluations. Three studies reported the cost to deliver deworming drugs (considering the administration and services required when incorporated into health or school systems). Alderman 2006 estimated $US 1-1.33 per child to deliver deworming once to twice a year when incorporated into child health days in Uganda; Awasthi 2013 estimated $USD 0.10/child incorporated into child health management by Anganwadi workers in India; Bobonis 2006 estimated $1.70 per child per year for preschool delivery in India. Two studies compared costs of deworming to cost of providing school meals. Gupta 1977 estimated deworming drugs for one year cost less than 4 per cent of a year's ration of food for a child. Gateff 1972 calculated that deworming cost seven to 18 times less than food programmes. Four studies calculated the incremental cost-effectiveness ratio per unit of outcome. Alderman 2006 reported $0.42 per 10 per cent increase in weight, Awasthi 2000 reported 543 Indian rupees per case of stunting, Miguel 2004 reported $USD 3.5 per additional year of school participation, and Stoltzfus 1997 reported $USD 3.57 per case of moderate to severe anaemia prevented.

Miguel 2007 found that a cost-recovery programme reduced the take-up of deworming medicine by 80 per cent.

Physical fitness

In summary: It is uncertain whether mass deworming leads to differences in physical fitness (very low certainty evidence[3]).

Three studies reported physical fitness; two reported no effect of deworming vs. control (Solon 2003, Bhoite 2012). We decided not to statistically pool the two studies with sufficient data for meta-analysis (Bhoite 2012 and Stephenson 1993) due to high heterogeneity (I^2 of 93%), with results going in opposite directions.

In one cluster randomised trial (Bhoite 2012) of three schools, which we adjusted for unit of analysis errors, there was a small difference of 3.40 steps on the Harvard Step Test [0.05, 6.75] (very low certainty evidence).

In the other study of 53 boys (Stephenson 1993), there was an increase in the Harvard step test score of five units with single dose of deworming vs. 0 units in the placebo group (95% CI: 3.34 to 6.66), when assessed four months after deworming (very low certainty evidence). The Harvard step test score is calculated as 300*100 divided by sum of heart rates per minutes at one, two and three minutes after test completion. Scores of <55 are considered poor fitness, and scores >90 are considered excellent. The difference of five units between intervention and control is thus approximately equivalent to 5 per cent of the whole scale.

Malaria, HIV, tuberculosis outcomes

These outcomes may be subject to selective reporting since 48 studies were at unclear or high risk of bias for selective reporting. HIV and TB outcomes were not reported by any of the included studies.

Malaria incidence was reported by three studies. Ndibazza found reduced malaria incidence in children who received albendazole from age six months to five years compared to placebo (hazard ratio 0.85, 95% CI 0.73, 0.98). Wiria 2013 found a significant increase in malaria parasitemia (P=0.0064) in children treated with

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[3] Certainty for evidence on physical fitness starts at high because it is based on three RCTs. We downgraded by one level for inconsistency, and we downgraded by one level for risk of bias because all studies had high risk of bias on at least one domain of the Cochrane risk of bias tool. We also downgraded for optimal information size because there were fewer than 400 children in the comparisons (required size to detect a small difference of SMD 0.2).

albendazole every three months for 21 months, which the authors attribute to the transient increase in malarial parasitemia observed at six months post treatment (odds ratio 4.16 (95% CI: 1.35, 12.80) in children treated with albendazole. In Stoltzfus 2004, malaria outcomes were similar across four groups of mebendazole, mebendazole+iron, iron alone and placebo (results not shown).

4.4.3 Follow-up beyond period of deworming

In summary: Mass deworming of children may lead to little to no difference in weight, height, haemoglobin and worm prevalence six months after the mass deworming (low certainty evidence).

Kruger 1996 and Bhoite 2012 measured outcomes beyond the end of deworming.

Kruger 1996, found little to no difference in weight at 5 months after a period six months of deworming: 0.07 kg [95% CI: -0.23, 0.37] (moderate certainty evidence). Similarly, there was probably little to no difference in height gain for deworming vs. control 5 months beyond the deworming period: 0.15 cm [95%CI: -0.15, 0.45] (moderate certainty evidence).

Bhoite 2012 assessed growth and hemoglobin six months after a 30 month period of deworming. They reported no sustainable effect of deworming with Albendazole 2/year on growth (underweight, stunting, thinness) and hemoglobin (very low certainty evidence).

Within the deworming period, Watkins 1996 reported that 50 per cent of children who were dewormed were reinfected within 12 weeks of the mass deworming.

4.4.4 Externalities and spillovers analyses

In summary: It is uncertain whether mass deworming leads to spillover benefits for untreated children living in proximity to treated children. Only two studies have assessed this within study and found conflicting results.

If there are spillover benefits to untreated children living in proximity to treated children, one would expect children in individually randomized trials to experience greater benefits because they are in the same classroom as treated children in comparison to control group children in geographically separated cluster trials. Our analyses do not support this hypothesis: i.e. children in control groups of individually randomised trials experience similar growth, less gain in haemoglobin and less decrease in worm burden. However, this analysis should be interpreted with caution due to differences in the populations of these studies.

Within studies: Two studies assessed whether control children received spillover benefits of being exposed to treated children (Miguel 2004, Bobonis 2006). One found a difference and the other did not. In the Miguel 2004 study, with corrections to formulae and data from a replication by Aiken 2015, the within-school benefits of deworming on school attendance was 6.2 per cent and for worm infection, 18 per cent (Updated Table VII of Aiken 2015). Between schools, for distance of 0-6 km, the effect on attendance was -1.7 per cent and the effect on any worm infection was 15 per cent (SE 1.4). Controversially, Aiken combined these to estimate an overall treatment effect of mass deworming on attendance of 3.9 per cent (SE 3.2), which was not statistically significant. Hicks 2015 used the corrected data and analyses from Aiken 2015, and demonstrated that the between school externalities for both worm infections and school participation were observed up to 4 km. For distances up to 4 km, the between school effect on school attendance was 2.7 per cent (SE 1.3) and for worm infections, the between school effect was 10.2 per cent (SE 4.3)[4]. Bobonis 2006 reported that cross-school treatment externalities for nutritional status (weight) and school attendance were small and not statistically insignificant (regressions were not shown). Bobonis 2006 commented that the lack of externalities may have been due to low prevalence and intensity of infection in their population. Overall, we rate the certainty of between and within school externalities as very low since these two studies found different results.

Between study assessment of indirect effects (spillovers): We assessed the control group gain in weight, height, haemoglobin and worm prevalence for cluster randomized trials compared to individually randomized trials to explore the hypothesis that untreated children in individually randomized trials receive a greater benefit from exposure to treated children in the same school or class than control group children in cluster randomized trials, where the distance between treated and untreated children is larger. This analysis is restricted to studies which provided sufficient data to calculate the change from baseline for each outcome for the control group children in natural units (kg, cm or g/dL for weight, height and haemoglobin, respectively).

[4] Based on these analyses, Hicks 2015 calculates the overall treatment effect of 8.5 per cent (SE 1.7%) for school participation, and argued that the estimate of 3.9 per cent treatment effect calculated by Aiken 2015 was erroneous because it included a term for externalities at 3-6 km which had too much noise to be reasonably included in the estimate.

Table 13: Difference in change from baseline for children in the control groups

Outcome	Cluster trials (n=10) (95% CI)	Individual trials (n=14) (95% CI)	p-value for test for interaction for subgroup differences
Weight	Median Baseline: 25.3kg Pooled change from baseline: 2.63 kg (1.75, 3.51) (n=10) per cent change relative to baseline: 10 per cent (7-14%)	Median Baseline: 12.7 kg Pooled change from baseline: 1.64 kg (1.37, 1.91) (n=14) %change relative to baseline: 13 per cent (11-15%)	P=0.04
Height	Pooled change from baseline: 7.02 cm (95%CI: 4.59, 9.45)	Pooled change from baseline: 4.67 cm (95%CI: 3.51, 5.83)	P=0.09
Hemoglobin	Pooled change from baseline: 2.67 g/dL (95%CI: -3.15, 8.49)	Pooled change from baseline: 0.41 g/dL (95%CI: -0.10, 0.92)	P=0.45
Reduction in ascaris prevalence (from baseline)	RR: 0.82 (95%CI: 0.70, 0.96)	RR: 1.26 (95%CI: 1.03, 1.53)	P=0.0009

Notes: RR: relative risk, CI: confidence interval. Test for interaction for subgroup differences conducted in Review Manager 5.3.

For weight: The test for interaction for subgroup differences was statistically significant (P < 0.04), with a larger weight gain for children in the control group of cluster randomised trials of 2.63 kg (95% CI: 1.75, 3.51) than in individually randomised trials of 1.64 kg (95% CI: 1.37, 1.91). This finding suggests there was no spillover benefit to control children in individually randomised trials from being exposed to their classmates who are dewormed (***Additional Figure 5***). When considering differences in baseline weight of the children in different studies, the percentage change in weight is similar between cluster and individually randomized trials for control groups (Table 11). Similar weight gain in control children in cluster and individually randomized trials does not suggest that children in individually randomized trials are receiving a spillover benefit of exposure to their treated classmates.

For height gain: We find the same direction of effects, with a larger height gain in the control group children of cluster RCTs of 7.02 cm (95% CI: 4.59 to 9.45 cm) than children in control groups of individual RCTs of 4.67 cm (95% CI: 3.51 to 5.83 cm). The test for interaction for subgroup differences was not statistically significant (P=0.09) (***Additional Figure 6***).

For haemoglobin: We found the same direction of results: greater gain in haemoglobin in the control group of cluster RCTs compared to individual RCTs with deworming (cluster RCTs: 2.67 g/dL (95% CI: -3.15 to 8.49) vs. individual RCTs: 0.41 g/DL (95% CI: -0.10 to 0.92). The test for interaction for subgroup differences was not statistically significant (p=0.45).

For worm prevalence: We found the same direction of results; worm prevalence increased over time in individually randomized trials from baseline to endline (RR 1.26, 95% CI: 1.03, 1.53) vs. cluster trials where the worm burden decreased over time in the control groups (RR: 0.82, 95% CI: 0.70 to 0.96). The test for interaction for subgroup differences was statistically significant (p=0.0009, I^2 90.9%).

4.4.5 Subgroup analyses

In summary: The effects of mass deworming vs. control for weight, height and school attendance probably do not differ across four pre-planned subgroup analyses of age, nutritional status, sex and deworming prevalence (moderate certainty evidence).

Age

In summary: For age, we found no subgroup differences across three categories of age (<2 years, 2-5 years or >5 years) for weight, height or school attendance. These agreed with within study analyses for weight and height. However, for school attendance, two studies showed that children aged 4-7 years had greater benefits than younger children or older children for attendance.

Pairwise meta-analysis, for weight and height: In the pairwise analysis, there was no statistically significant difference in effect across three age groups for albendazole 400 mg twice per year vs. control and albendazole >2/year vs. control (**Error! Reference source not found.** and **Additional Table 21**).

Pairwise meta-analysis for school attendance: The test for interaction for subgroup effects across age was not statistically significant for any deworming vs. control for school attendance (**Additional Table 21**).

Overall pairwise meta-analysis for weight and height: When we conducted subgroup analysis for any deworming vs. control, the test for interaction for subgroup effects was not statistically significant across age for weight gain (p=0.59) or height gain (p=0.93) (Additional Table 23).

For height and weight within studies: Three studies found no differences across age: Awasthi 2008 found no differences in weight or height amongst one year age groups from 1-5 years of age), Awasthi 2013 (no difference between 1-3 and 3-6 years in weight, height and haemoglobin), Bobonis 2006 (no difference between 2-3 year olds

and 4-6 year olds for weight). Stoltzfus 1997 found a statistically significant interaction between age and treatment, with larger weight and height gains for children younger than 10 years vs. those older than 10 years.

For wasting, stunting and anaemia within studies: Stoltzfus 2004 conducted a *post-hoc* analysis for children < 30 months vs. children greater than 30 months because they found age differences in effect of deworming on wasting, and chose the cut-off of 30 months because it differentiated the pre-intervention relationship between parasitic infection and iron status. Their analyses showed a statistically significant difference in effect of deworming on wasting malnutrition for children <30 months (relative risk 0.30 [0.11, 0.79]) vs. children >30 months (relative risk 1.18 (0.73 to 1.90). The effect of deworming on stunting was not statistically different between <30 months vs. >30 months, and there was no effect on anaemia in either age group.

For haemoglobin, within studies: Olds 1999 found no difference in effect on haemoglobin across age. Thi Le Huong 2007 found younger children had greater increase in haemoglobin than older children.

For attendance within studies: Bobonis 2006 found effect on school participation was larger for 4-6 year olds than 2-3 year olds and Miguel 2004 found the effect on school participation of albendazole vs. control was larger for preschool to grade 2 [10 per cent] than grade 3-5 [7 per cent], and grade 6-8 [5.9 per cent]) .

Nutritional status (<30 per cent stunted or =>30 per cent of population stunted)

In summary: For baseline nutritional status, we found no differences in height, weight or school attendance effects for populations more stunted at baseline than less stunted.

Pairwise meta-analysis for weight and height: We found little to no difference across baseline nutritional status in effect on weight gain in the pairwise meta-analysis for albendazole twice per year vs. placebo, with effect of 0.02 SMD (95%CI: -0.05 to 0.09) for populations with <30 per cent stunted vs. 0.05 SMD (95% CI: -0.62 to 0.72) for populations with >30 per cent of children stunted at baseline, test for interaction for subgroup effects not statistically significant (p=0.61) (**Error! Reference source not found.**).

Overall pairwise meta-analysis for weight and height: There was also little to no difference in the effect on weight gain or height gain when all studies of deworming were pooled together, test for interaction for subgroup differences was p=0.92 for weight and p=0.80 for height (Additional Table 23). These results were robust to using

a different cut-off of population proportion stunted (varying the cut-off from 20 per cent to 60 per cent) (Appendix 13.8)

Pairwise meta-analysis for attendance: We did not have sufficient information to conduct a subgroup analysis because we could not ascertain the proportion stunted in three studies (Ebenezer 2013, Kruger 1996, Watkins 1996). The other studies all had less than 30 per cent of the population stunted at baseline, and the result was similar to the overall effect for school attendance with a difference of 5 per cent [95% CI: -1% to 11%]).

Within studies, weight: Four out of five primary studies that assessed whether effects of deworming were different for stunted children found no difference in effects on weight. Awasthi 2008 and Dossa 2001 found no difference in effect on weight for children <-2 HAZ vs. children greater than -2 HAZ. Ebenezer 2013 reported no interaction between baseline stunting and treatment effect on haemoglobin and attendance outcomes. Stoltzfus 1997 found a statistically significant interaction between HAZ and programme group for both weight gain (p<0.047) and height gain (p=0.008) for children <10 years of age, with greater weight and height gain in the children <10 years who were not stunted. The weight gain compared to control was 0.24 kg for normal HAZ vs. 0.20 kg for stunted children for mebendazole twice yearly, and 0.36 kg for normal HAZ vs. 0.1 kg for stunted children for mebendazole 3/ year). Height gain compared to control for the twice-yearly mebendazole was 0.36 cm (0.38 cm for HAZ=0 vs. 0.02cm for HAZ=-2). A similar interaction was found in the older age group. The cut-off of age 10 years was a *post-hoc* decision.

Worm prevalence

In summary: There was no difference in effect of mass deworming on weight, height or school attendance depending on baseline prevalence of worms.

Pairwise meta-analysis for weight and height: The test for interaction for subgroup effects was not statistically significant for effects on weight or height for albendazole twice per year vs. placebo or for albendazole >2/ year vs. placebo between categories of prevalence of <20 per cent , 20-50 per cent or >50 per cent (using WHO cut-offs for low, moderate and high prevalence) (**Additional Table 21**).

Overall pairwise any deworming vs. control, weight and height: There was no difference in the effect for weight or height gain between these three prevalence categories for any deworming vs. control (p=0.12 for weight, p=0.69 for height) (Additional Table 23). We also assessed the influence of the prevalence cut-offs by assessing the effect on weight gain for studies above the threshold from 10 per cent prevalence to 90 per cent prevalence, and there was no difference in effect of deworming at any of these cut-offs (Appendix 13.8).

Pairwise school attendance: The test for subgroup differences for studies <50 per cent prevalence or >=50 per cent prevalence was not statistically significant (p=0.21) (Additional Table 22). We also assessed the influence of prevalence cut-off by assessing the effect on attendance for studies above the threshold from 10 per cent prevalence to 90 per cent prevalence, and there was no difference in effect of deworming at any of these cut-offs (Appendix 13.8).

Sex

In summary: There is probably no difference in effect of deworming between boys and girls for weight or height gain. For school attendance, two studies at high risk of bias found greater effects on attendance for girls than boys.

Meta-analysis: We did not have sufficient data to conduct subgroup analyses across sex in meta-analysis for any outcome.

Within study, weight and height: Eleven studies assessed whether the treatment effect for weight or height was different for boys compared with girls. Seven found no difference in effects of deworming across sex. Of the other four studies, two found a larger treatment effect for girls (Donnen 1998 for weight gain of 1.9 vs. 1.6 kg, respectively and Bobonis 2006 for WHZ), and two found a larger treatment effect for boys (Stoltzfus 1997 for height, Awasthi 2001 for weight gain). Awasthi 2001 reported greater weight gain with albendazole+ vitamin A vs. vitamin A alone for males compared to females (3.31 kg in males vs. 3.11 kg in females).

***Within study, attendance*:** Miguel 2004 and Bobonis 2006 found larger effect of deworming vs. control for girls than boys (in Miguel 2004, (0.067 difference for girls vs. 0.043 for boys in the second year; and 0.098 for girls vs. 0.041 for boys in first year of treatment). Gateff 1972 reported no significant difference between sexes for attendance.

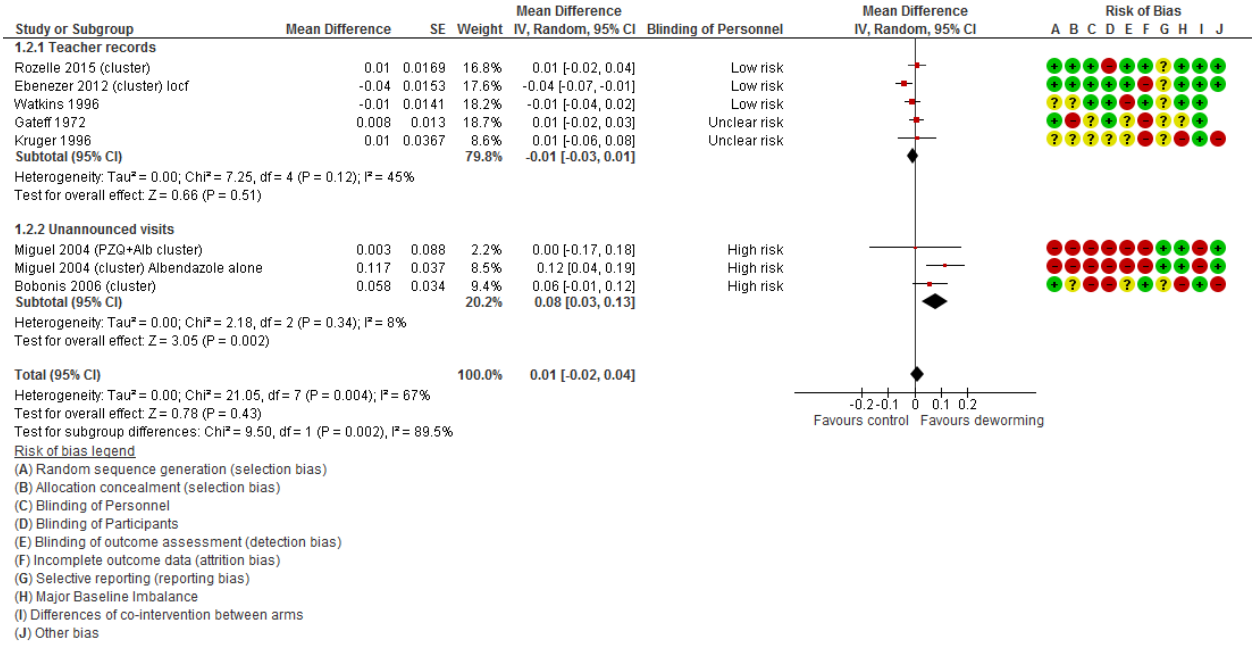
Subgroup analysis for method of measuring school attendance: unannounced visits or school records

In summary: This analysis was confounded because the two studies which measured attendance with on-site visits were also at high risk of bias for lack of blinding personnel and participants (Bobonis 2006 and Miguel 2004). On-site enumerators were likely aware of the treatment status of the schools which may have affected their behaviour. However, the on-site visits were not announced thus decreasing the chance that students or teachers would influence the school attendance data collected.

There was a larger effect of deworming vs. control on school attendance in two cluster randomised trials which measured school attendance using unannounced site visits, with a pooled effect of 8 per cent (95%CI: 3 to 13%), low certainty evidence (Bobonis 2006, Miguel 2004) compared to an effect of deworming in five studies that used school

records to measure attendance of -1%, 95%CI: -3 per cent to 1 per cent , high certainty evidence. As indicated in Figure 24, the studies with unannounced visits were at high risk of bias for blinding of personnel and participants.

Figure 20: Subgroup: school attendance according to method of measurement: unannounced visits vs. school records



4.4.6 Step 4: Weight: Interrogating causal pathway

We assessed the relationship of the effect of deworming on weight across the baseline prevalence of worms, using weighted least squares regression. We found no statistically significant relationship between effect size for weight gain (SMD) and prevalence of worms at baseline (when using highest prevalence of any worm for each study). We also found no statistically significant relationship between effect size for weight gain (SMD) and prevalence of each of the different types of soil transmitted helminths; ascaris, hookworm and trichuris (Figure 21).

We chose comparisons from each include study that were most similar to deworming twice per year vs. placebo. We avoided including co-interventions unless they were given to both groups. For weight, this resulted in 16 studies of deworming twice per year vs. placebo/ control; 10 studies of deworming >twice per year vs. placebo/ control, and two studies of deworming once per year vs. placebo/ control. Only two of these studies had a co-intervention that was not provided in the other group in the deworming arm (Miguel 2004 and Jinabhai 2001 both had praziquantel in the treatment arms).

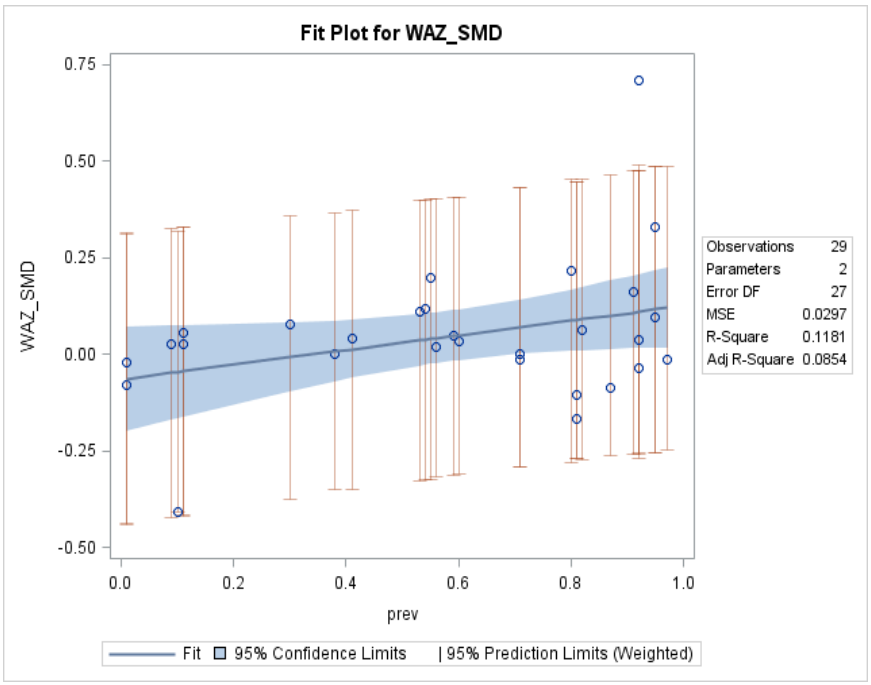
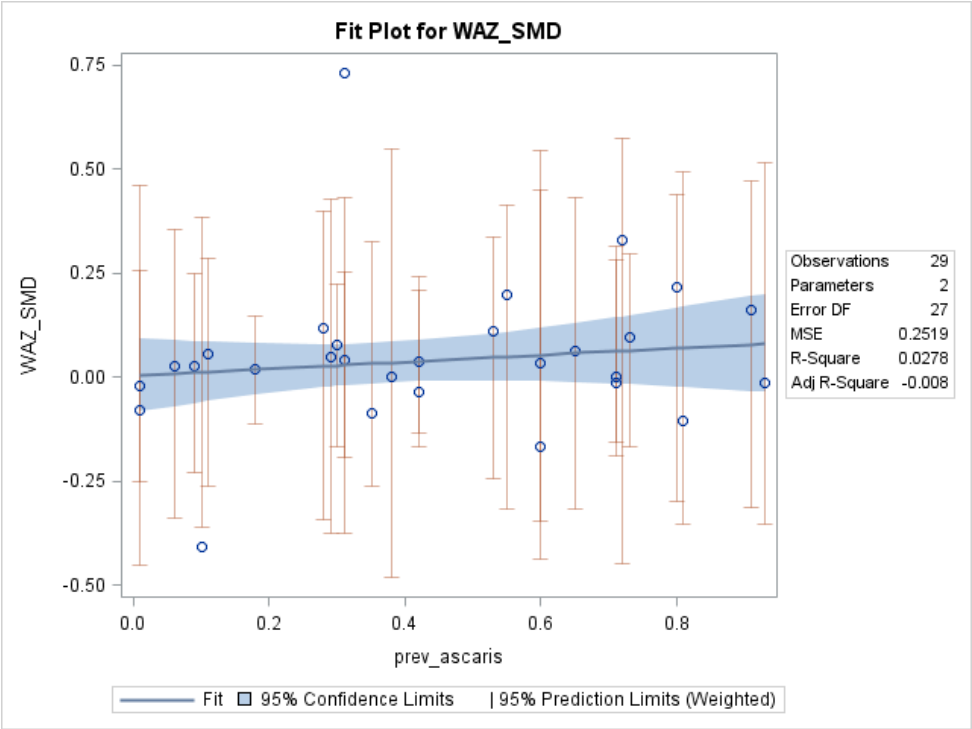


Figure 21: Weighted least squares regression of relationship between effect size on weight gain (SMD) and worm prevalence (using highest prevalence of any worm as the study prevalence)

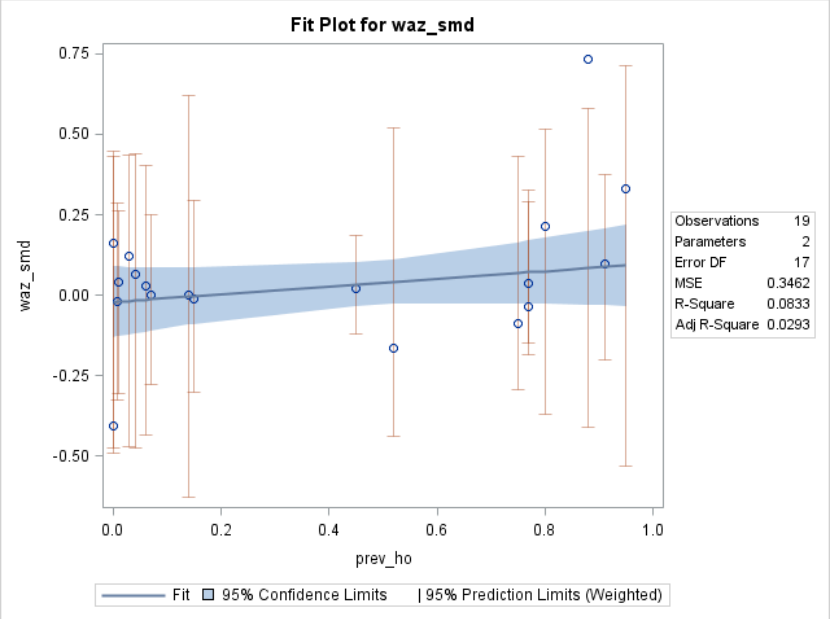
***Note**: WAZ_SMD: Weight or weight for age standardized mean difference: prevalence of worms. Intercept of -0.06536, standard error 0.06673 (p=0.3361), and slope of 0.1911 SMD, standard error 0.10053 (p=0.0680).*

Figure 22: Weighted least squares regression of relationship between weight (SMD) and prevalence of ascaris



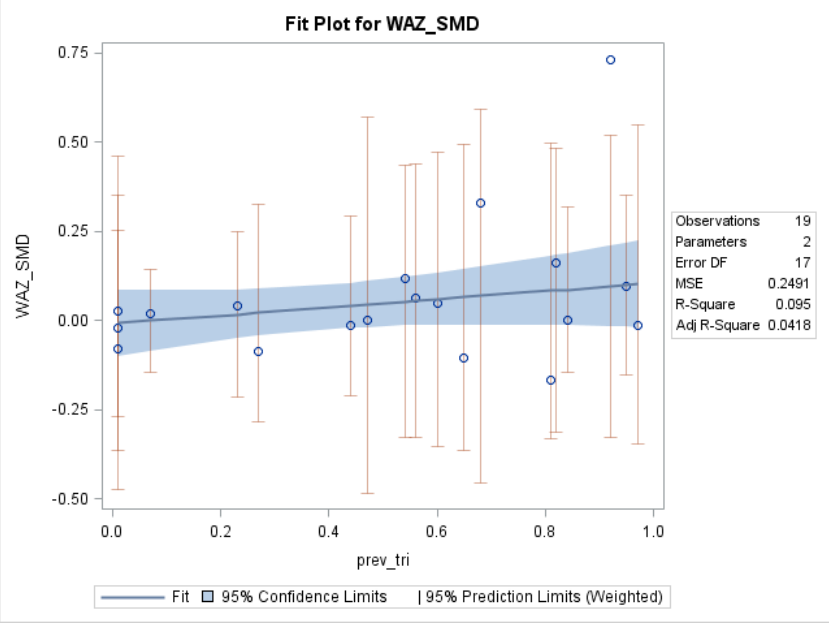
***Note**: WAZ_SMD: Weight or weight for age standardized mean difference; prev_ascaris: prevalence of ascaris. Slope: 0.08358, standard error 0.09508 (p=0.3871); intercept: 0.00333, standard error 0.04326 (p=0.9392)*

Figure 23: Weighted least squares regression of relationship between weight (SMD) and prevalence of hookworm



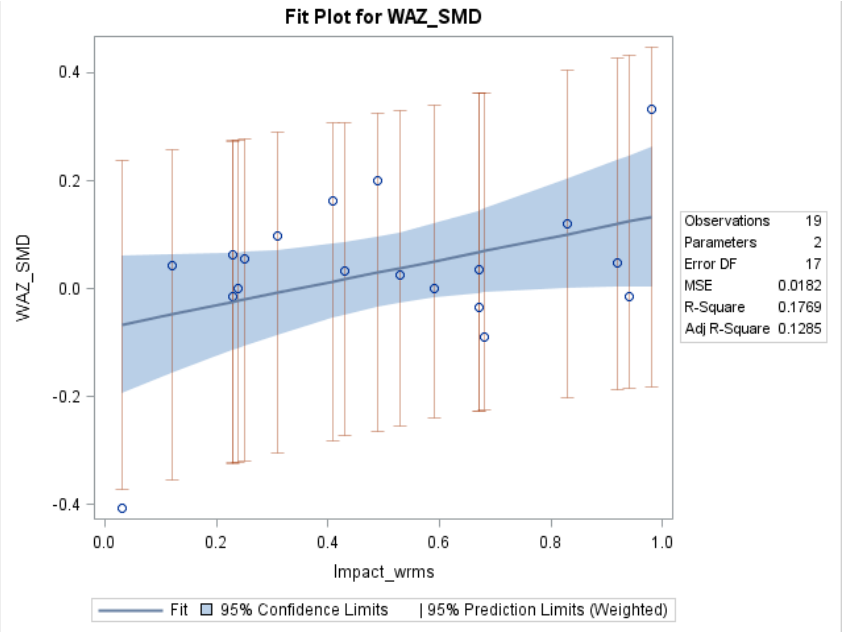
Note: AZ_SMD: Weight or weight for age standardized mean difference; prev_ho: prevalence of hookworm. Slope: 0.12047, standard error 0.09696 (p=0.2309); intercept: -0.02188, standard error 0.05214 (p=0.6800)

Figure 25: Weighted least squares regression of relationship between weight (SMD) and prevalence of trichuris



Note: *WAZ_SMD: Weight or weight for age standardized mean difference; prev_tri: prevalence of trichuris. Slope: 0.11373, standard error 0.08512 (p=0.1991); intercept-0.00869, standard error 0.04473 (p=0.8482)*

Figure 24: Weighted least squares regression of weight gain against impact on worms



Note*: WAZ_SMD: Weight or weight for age standardized mean difference: impact of worms. Intercept of -0.07279, standard error 0.06308 (p=0.06028), and slope of 0.20981, standard error 0.10977 (p=0.44141).*

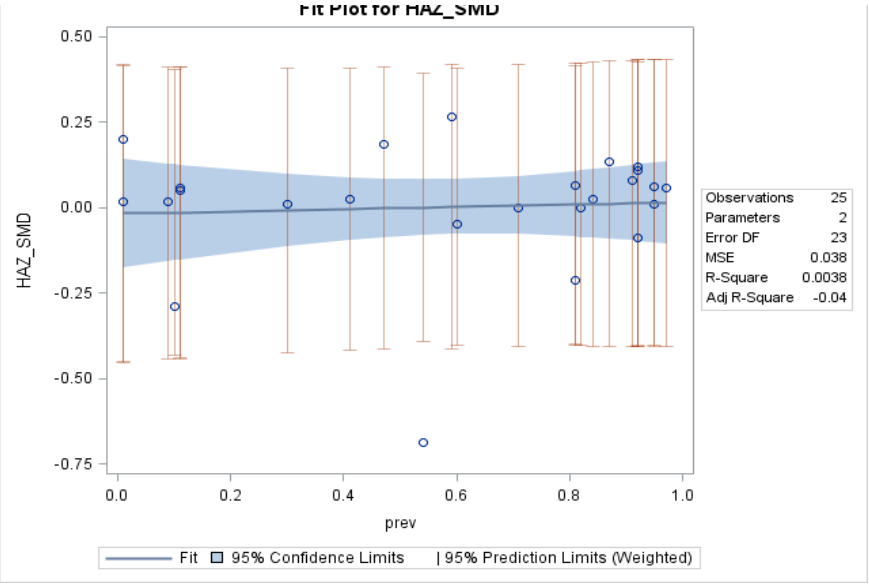
The relationship of weight gain with impact on worms (as an indicator of first stage of causal pathway success) showed a very poor fit with an R-Square of 0.2271. However, the slope was statistically significant with greater weight gain in studies with a greater impact on worm prevalence (slope 0.32951, SE 0.14326, p=0.0336, intercept -0.10708, SE 0.084575, p=0.2225) (Figure 25).

We also assessed whether effect on weight was greater for studies which were more effective at reducing worm burden by conducting a sensitivity analysis where we conducted a meta-analysis for all studies above each of 10 10 thresholds of effectiveness against worms (from 10 per cent relative risk reduction to 90 per cent relative risk reduction of worm burden). There was no difference in effect of deworming at any of these cut-offs (Appendix 13.8).

4.4.7 Height: interrogating causal pathway variables

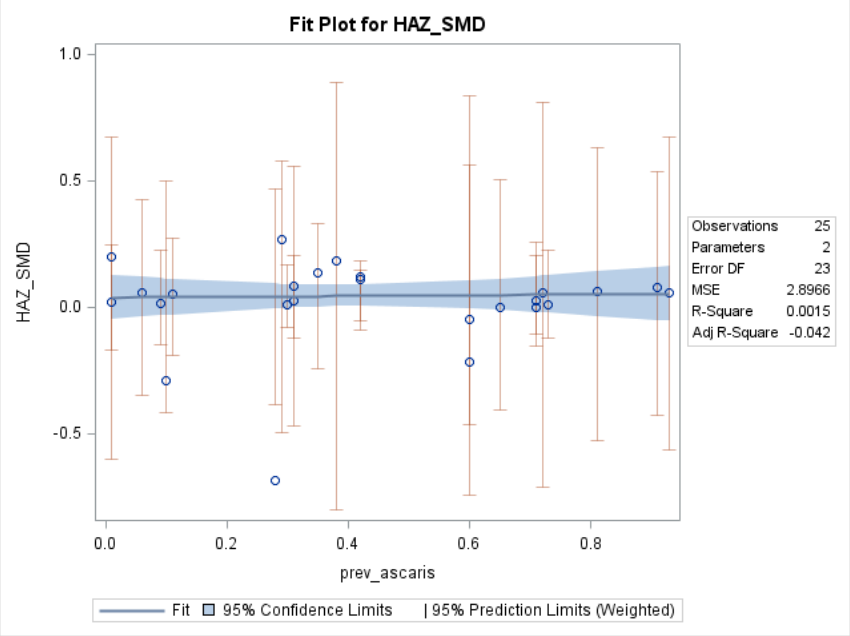
We assessed the relationship of effect size on height (SMD) and baseline worm prevalence (taking highest prevalence of any worm as the prevalence for this study), prevalence of ascaris, hookworm and trichuris using weighted least squares regression. We found no relationship, (Figure 26).

Figure 26: Weighted least squares regression of height effect size (SMD) vs. baseline worm prevalence



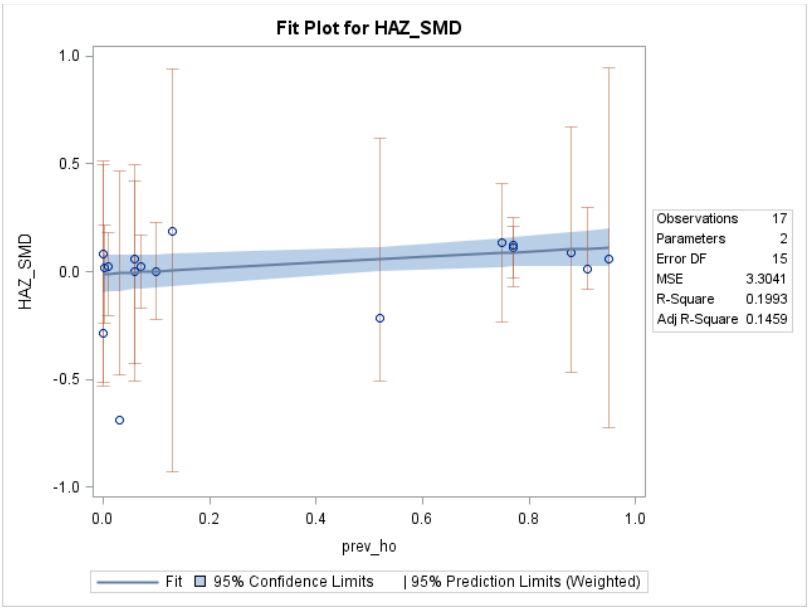
Note: HAZ_SMD: Height or height for age standardized mean difference: prevalence of worms. Intercept of -0.01736 (standard error 0.07781, p=0.8255), and slope of 0.03376 (standard error 0.11439, p=0.7706)

Figure 27: Weighted least squares regression of relationship between height (SMD) and prevalence of ascaris



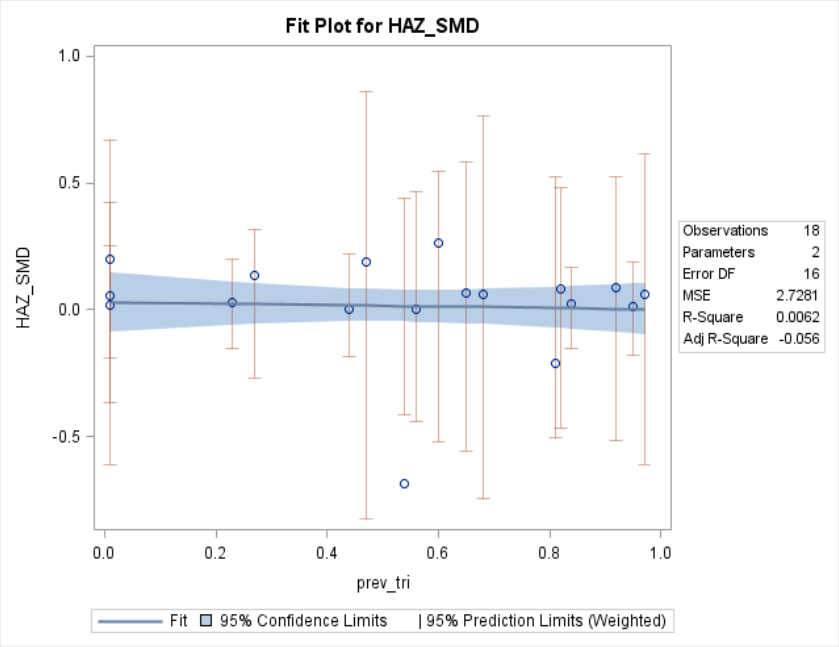
***Note**: HAZ_SMD: Height or height for age standardized mean difference; prev_ascaris: prevalence of ascaris. Slope: 0.01737, standard error 0.09227 (p=0.8524); intercept: 0.03834, standard error 0.04284 (p=0.3801)*

Figure 28: Weighted least squares regression of relationship between height (SMD) and prevalence of hookworm



***Note**: HAZ_SMD: Height or height for age standardized mean difference; prev_ho: prevalence of hookworm. Slope: 0.13048, standard error 0.06753 (p=0.0724); intercept: -0.01094, standard error 0.04092 (p=0.7928)*

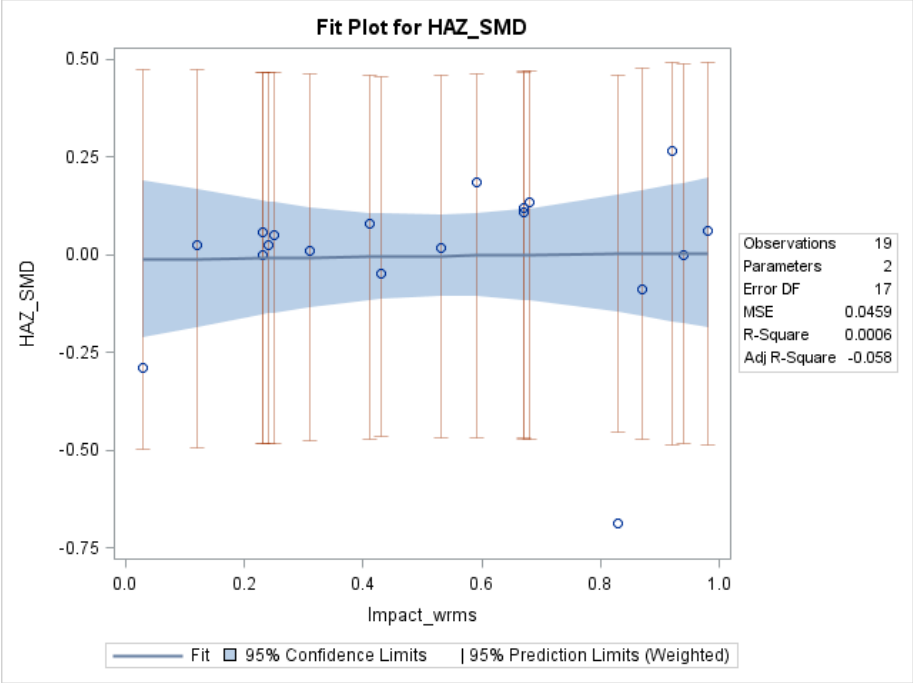
Figure 29: Weighted least squares regression of relationship between height (SMD) and prevalence of trichuris



***Note**: HAZ_SMD: Height or height for age standardized mean difference; prev_tri: prevalence of trichuris. Slope: -0.02740, standard error 0.08707 (p=0.7571); intercept: 0.02983, standard error 0.05579 (p=0.6002)*

For impact on worms, there was also no relationship with height gain, with a slope of 0.01639, SE 0.1674, p=0.9230 and intercept of -0.01180, SE 0.10014, p=0.9076).

Figure 30: Weighted least squares impact on worms vs. height gain (SMD)



We also assessed the influence of impact on worms cut-off by assessing the effect on height gain for studies above the threshold from 10 per cent impact on worms to 90 per cent impact on worms, and there was no difference in effect of deworming at any of these cut-offs (Appendix 13.8).

4.4.8 School attendance: Interrogating causal pathway

We assessed the relationship of school attendance to prevalence of worms, impact on worms and weight gain to explore assumptions about the causal pathway. These analyses must be interpreted with caution since there are very few data points for a regression analysis (only eight data points). Taken together, they do not show greater effects on attendance in areas with higher worm prevalence, in studies with greater impact on worms or studies with greatest impact on weight gain (as an intermediate child health outcome).

Weighted linear regressions (weighted by the inverse of the variance) found no relationship between prevalence of any worm and school attendance, with an intercept of 0.00550 (SE 0.02218, p=0.8125) and slope of -0.00758 (SE 0.028, p=0.7957). (***Additional Figure 8*** for graph of relationship with prevalence of worms). We also assessed the influence of prevalence cut-off by assessing the effect on attendance for studies above the threshold from 10 per cent prevalence to 90 per cent prevalence, and there was no difference in effect of deworming at any of these cut-offs (Appendix 13.8).

For attendance vs. weight gain (as an intermediate causal pathway variable), the weighted least squares regression also showed no relationship (***Additional Figure 7***). The intercept was 0.00310 (SE 0.01872, p=0.8749), slope of -0.0154 (SE 0.1044, p=0.9236).

The weighted least squares regression for impact on worms (relative risk reduction) and effect of deworming on school attendance was not statistically significant with intercept of -0.00687, standard error 0.01757, p=0.7118 and slope of 0.00265, SE 0.03417, p=0.9413 (***Additional Figure 9***).

We also assessed the influence of impact on worms cut-off by assessing the effect on attendance for studies above the threshold from 10 per cent impact of worms to 90 per cent impact of worms, and there was no difference in effect of deworming at any of these cut-offs (Appendix 13.8).

4.4.9 Health equity considerations

In summary: There is little evidence to suggest that deworming is pro-poor since the effects on weight, height and attendance remain small when restricted to very poor settings. Only two studies reported conducting within-study analyses and were rated as very low certainty evidence that mass deworming may be more effective for poorer populations or those with parents with lower education (very low certainty evidence).

Within study analysis of health equity: Bobonis 2006 reported statistically significant greater effect on both weight for height and preschool attendance for mothers with less education (<3 years) (for mothers with <3 years education, deworming resulted in increase of attendance of 9.6 per cent (se 4.7%) compared to increase in attendance of 0.6 per cent (se 4.8%) for mothers with ≥ three years education). Croke 2014 explored interactions of long-term outcomes with poverty and gender. These analyses suggested greater benefit for mass deworming on math and English scores for girls than boys, and for those living in poverty compared to less poor children (very low certainty evidence).

Studies conducted in low income settings: Thirteen studies were conducted in very low income settings such as urban slums (Awasthi 2000, Awasthi 2001, Awasthi 2008, Hadju 1997), people with low income (Goto 2009, Jinabhai 2001a, Kloetzel 1982, Reddy 1986) or in populations with other markers of low SES such as low education level (Bobonis 2006, Rozelle 2015), very poor sanitation (Gateff 1972), rural settings (Ndibazza 2012) or poor food security (Donnen 1998). When the pairwise analyses were restricted to these studies which were described as low-income, the results for weight, height and school attendance were congruent with the overall analyses, showing little to no effect of mass deworming (results not shown). This suggests that even in very poor populations and settings, mass deworming is not effective on average.

However, this analysis is limited since socioeconomic status indicators were only reported by one third of the included studies.

4.4.10 Other subgroup or correlation analyses reported by primary studies

In summary: Based on subgroup analyses within studies across other possible explanatory factors, we conclude there is low certainty evidence to support subgroup effects across any of these factors (including intensity of infection), because of differences in direction of effects both between and within studies and post-hoc observational analyses.

Infection status: Six studies reported effects for egg-positive children compared to egg-negative (uninfected children). Three of these studies reported statistically significant improvements in growth for egg-positive children compared to egg-negative children or overall results (Beach 1999, Gupta 1977, Willett 1979), and three studies did not find differences (Olds 1999, Shah 1975, Bell 1973). Beach 1999 found increased weight gain of 0.56 kg (but not height) for hookworm-infected children, height gain of 0.62 cm (but not weight) for trichuris infected children but not ascaris-infected children. Gupta 1977 found the effect of mass deworming compared to control on number of children with improved nutritional status was greater for infected children than uninfected children. Willett 1979 reported greater weight gain with levamisole vs. placebo for ascaris positive children of 0.39 kg/ year compared to only 0.16 kg in overall sample. Olds 1999 found that improvement in haemoglobin was similar for both infected and uninfected children receiving albendazole and praziquantel. Shah 1975 found no difference in effect on weight across infected or uninfected children. Uninfected children had higher Raven's test scores at baseline than infected children, but there was no difference in improvement in Raven's test scores (Bell 1973).

Intensity of infection: Six studies assessed the treatment effectiveness of mass deworming vs. control according to infection intensity. Four found no differences in effects of deworming vs. control across different levels of infection intensity (Watkins 1996 for attendance, Greenberg 1981 for anthropometry, Shah 1975 for weight gain, Ebenezer 2013 for attendance, educational tests or cognitive processing). Two reported greater weight gain and height gain for those with greater reduction in intensity of worm infection (Stephenson 1989, Stephenson 1993).

At baseline, higher infection intensity was associated with worse baseline cognitive test scores but not school attendance in Watkins 1996. Regardless of treatment arm, Rozelle 2015 found statistically significant correlation between baseline egg count and outcomes of cognitive processing, proportion stunted, proportion underweight, attendance and math scores. Similarly, Hadju 1997 found a correlation in reduction in ascaris egg count with height gain, but not with HAZ or WAZ. Kloetzel 1982 found no

statistically significant correlation between changes in nutritional status and changes in egg counts.

Duration between treatments: Alderman 2006 offered albendazole at child health days, and found the more frequent the deworming (i.e. less than 7.5 months apart), the larger the effect on weight gain.

Proportion underweight: Awasthi 2008 found no difference in deworming vs. control across baseline underweight status. Awasthi 2001 and Shah 1975 found larger effect of mass deworming vs. control on weight for children who were underweight at baseline.

Wasted: Awasthi 2008 reported no difference in effect of deworming vs. control between those who were wasted (-2 WHZ) at baseline vs. those who were not wasted.

Vitamin A deficiency: Donnen 1998 reported greater weight gain with mebendazole for children who were not vitamin A deficient.

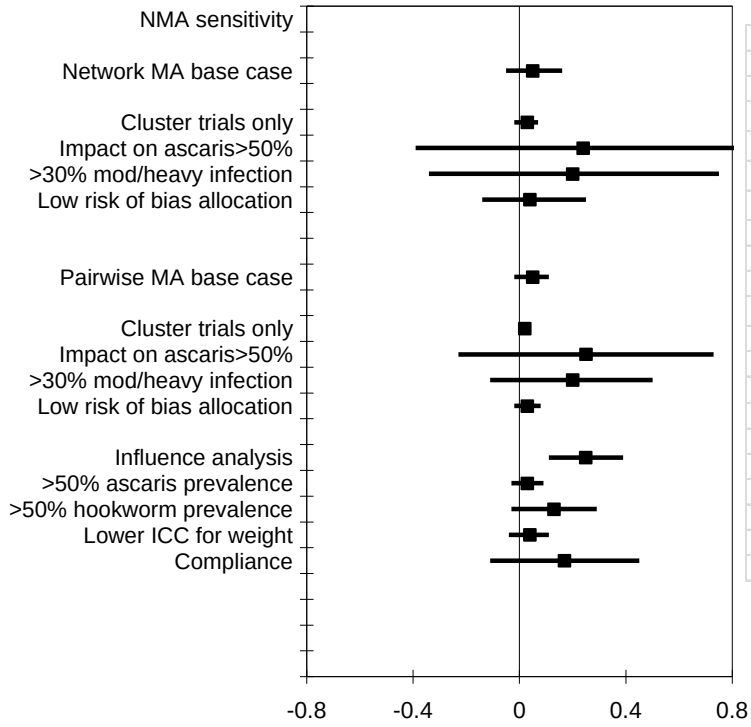
Anaemia at baseline: Four studies reported no difference in deworming effect according to baseline anaemia: Dossa 2001, Ebenezer 2013, Kruger 1996, Stoltzfus 2001. Three studies reported differences in effects of deworming according to baseline anaemia. Bobonis 2006 reported greater effect on attendance and WHZ for children with higher probability of severe anaemia (0.114 vs. -0.011 for attendance, and 0.62 vs. 0.32 for WHZ). Solon 2003 reported that more severely anaemic children improved on haemoglobin more with deworming vs. control than children who were less anaemic at baseline (no data provided). In a post-hoc analysis, Kruger 1996 found that children with low iron at baseline gained 0.4 kg more weight (95%CI: 0.03 to 0.79) than placebo with deworming vs. placebo (with or without iron fortified soup). In children with adequate iron, weight gain was 0.17 kg less in the group of children who received deworming vs. control (95%CI: -0.59 to 0.25), and this subgroup effect was statistically significant (p=0.05).

Proportion stunted: Ebenezer 2013 found no interaction between baseline height for age and outcomes of attendance, cognitive processing or educational tests.

4.4.11 Sensitivity Analyses

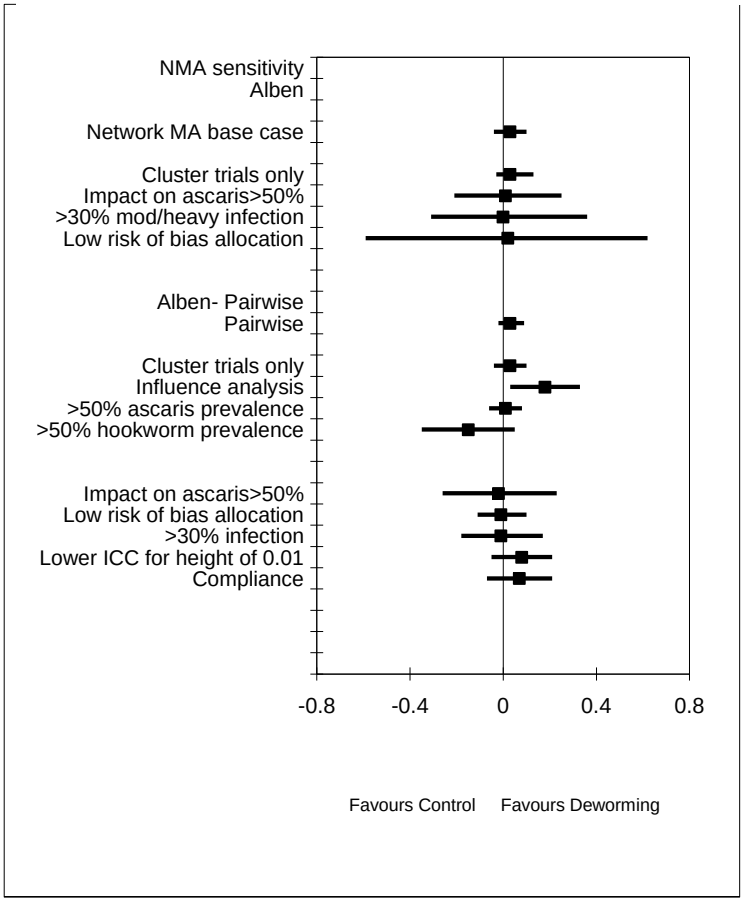
We summarize the results of sensitivity analyses in three figures for weight (Figure 31), height (Figure 32) and attendance (Figure 33) and describe results below.

Figure 31: Sensitivity analyses for weight gain



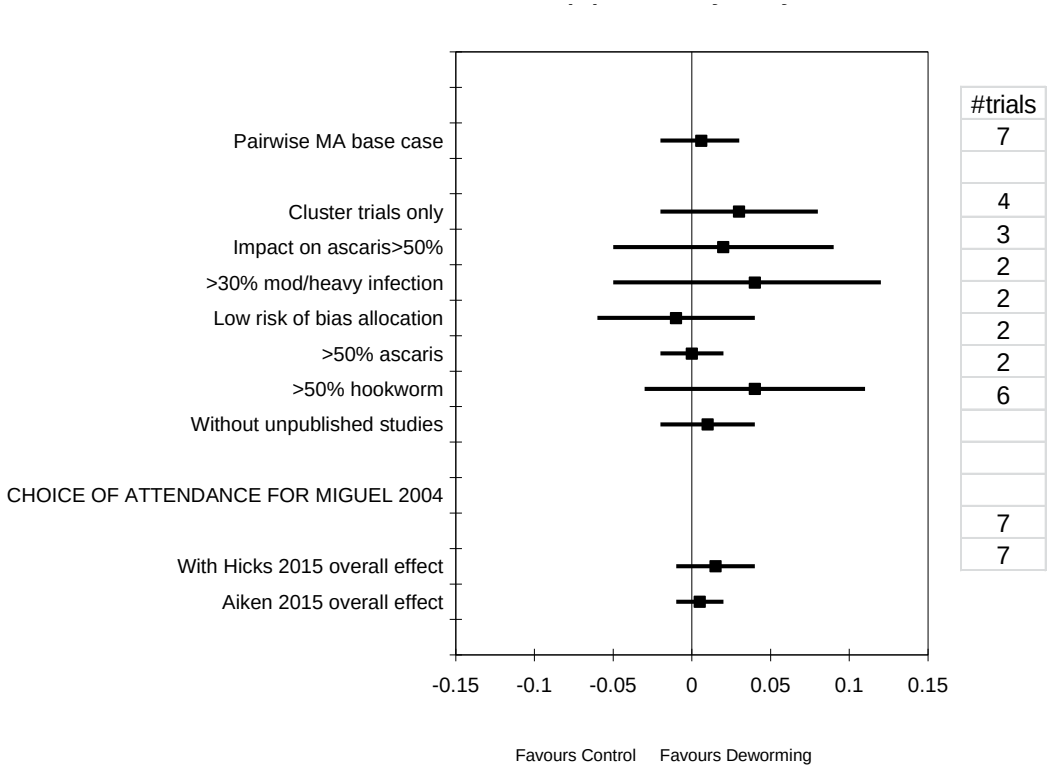
#trials	participants (treatment/control)
6	18254/20093
3	964/961
4	15097/13298
3	1803/1781
11	18,740/16,690
6	20,101/18,246
3	964/961
4	15,192/13,298
4	2,803/2,809
13	18,957/16,810
4	2,379/2,168
3	16,376/14,466
11	18,740/16,690
4	919/755

Figure 32: Sensitivity analyses for height



#trials	participants (treatment/ control)
5	5153/5199
3	965/965
3	253/247
2	1461/1440
9	3484/3355
5	4245/4262
11	3701/3475
4	1622/1605
2	187/184
2	133/125
3	1553/1531
3	253/247
9	3484/3355
4	944/812

Figure 33: Sensitivity for attendance



Sensitivity including Koroma 1996 and Stephenson 1989

As described above, we excluded two studies from our base case network meta-analysis because they contributed significantly to the heterogeneity for the most common intervention of albendazole twice per year vs. control (Koroma 1996, Stephenson 1989). The pooled random effects effect size for weight for albendazole twice per year vs. control was 0.05 SMD (95 % CI: -0.02, 0.11), I^2=61 per cent without these two studies, compared to 0.25 SMD (95 % CI: 0.11 to 0.39), I^2=93 per cent with these studies. Using the median standard deviation of all studies which measured weight in kg, this equates to a difference of 0.4 kg with the two studies or 0.08 kg without them.

For height, with these two studies, the pairwise effect size for albendazole twice per year vs. placebo was an SMD of 0.18 [95% CI: 0.03, 0.33] vs. an SMD of 0.03 [95% CI: -0.02, 0.09] without these two studies (I^2 of 11%). This equates to a difference of 0.43 cm with the two studies vs. 0.07 cm without.

Choice of attendance effect size from Kenya PSDP (Miguel 2004)

Our analysis was robust to which measure of attendance from the Miguel 2004 study. As described above, for Miguel 2004, we chose to use the measure of deworming effect on school participation for intended recipients (girls <13 years and all boys) in the first year of treatment which was 0.093 (SE 0.031) for the whole study (in both Miguel 2004 and the pure replication Aiken 2015a). We chose this estimate because it was also used in the Cochrane review on deworming (Taylor-Robinson 2015), and also it is one of the largest estimates of the direct effect on treated children. The analysis of Miguel 2004 and Aiken 2015 that combined the first year of treatment for group 1 schools and first year of treatment of group 2 schools, yielded a more precise estimate of 0.062 (SE 0.015) [or 0.60, se 0.015 in Aiken 2015a) for school participation. We tested the pooled effect on school participation with this estimate, as well as with the overall treatment effect of 0.039 (SE 0.031) from Aiken 2015a and the overall treatment effect estimated by Hicks 2015a in response to Aiken 2015a of 0.085 (SE 0.017). Our meta-analysis results remained non-statistically significant with less than 2 per cent difference in attendance between deworming and control for all of these analyses.

For Ebenezer 2013, there was no difference in the results for attendance if we used the dataset with missing children or the dataset where we imputed missing values using last observation carried forward.

Cluster randomised trials

In summary: Our analyses for weight, height and school attendance were robust to restricting to cluster randomised controlled trials.

Network meta-analysis: When the network meta-analysis for weight gain was restricted to cluster-randomised trials, the network was consistent (total residual deviance 11.72, deviance information criteria -36.6). Deworming compared to placebo in cluster randomised trials probably leads to little to no difference in weight gain, with effect sizes of between -0.12 to 0.17 (moderate certainty evidence) (Additional Table 24).

In the pairwise analysis for weight: The pairwise meta-analysis restricted to cluster trials only confirms the base case analysis of little to no effect of deworming on weight, with no statistically significant effects, and no effect size greater than SMD of 0.22 (equivalent to 300 grams).

In the pairwise analysis, for height in cluster randomised trials, deworming probably has little to no effect on height gain compared to placebo (moderate certainty evidence).

In pairwise meta-analysis, for school attendance: When restricted to cluster randomised trials, results were robust, and there was little to no effect on attendance 1 per cent (95% CI: -1% to 3%).

In pairwise meta-analysis, for worm prevalence: When restricted to cluster randomised trials, there is an important reduction in worm burden in the mass deworming compared to control at end of study (results not shown).

Studies with >50 per cent reduction in ascaris

In summary: Our results for weight, height and attendance are robust to restricting to studies with >50 per cent relative reduction in ascaris prevalence.

Network and pairwise meta-analysis, weight: We restricted the network meta-analysis for weight gain to studies with greater than 50 per cent relative risk reduction in burden of worms, when compared to the control group. The network was consistent, total residual deviance 12.43, DIC -10.625. The results are consistent with the base case analysis, with no statistically significant or clinically important (all less than 0.15 standard deviations) effects of deworming vs. placebo or any head-to-head comparisons, with two exceptions. The effect of albendazole twice per year (0.70 SMD (95% CI: 0.02, 1.41)] and albendazole once per year (0.73 (95% CI: 0.03, 1.43)) were statistically significant, with a clinically important effect size. This is driven by a network with a small number of studies, and only one trial of Albendazole of these doses had >50 per cent impact on worms: Stephenson 1993 (Additional Table 25).

Weight, sensitivity for threshold impact on worms: We tested the threshold for impact on worms by comparing deworming vs. placebo for threshold cutoffs of high impact on worm burden from 10-90 per cent in 10 per cent increments, and found that

the effect on weight with deworming vs. control was not statistically significant or clinically important at any threshold for impact on worms.

Network and pairwise meta-analysis for height: The network meta-analysis was consistent. There were no clinically or statistically significant differences in height for studies with >50 per cent impact on worm prevalence. As above, we tested the threshold for the cutoff from 10 to 90 per cent , and found no statistically or clinically important differences at any threshold for impact on worms.

Pairwise meta-analysis, attendance: Results for school attendance were robust to restricting to studies with >50 per cent impact on ascaris, with effect on attendance for deworming vs. control of 3 per cent (95% CI: -4% to 10%).

Studies with >50 per cent hookworm infection

In summary: Results for weight, height and attendance are robust to restricting to studies with >50 per cent hookworm infection.

Pairwise meta-analyses for weight: When restricted to studies with >50 per cent hookworm at baseline, effect on weight was less than 0.21 SMD for all comparisons, with none statistically important, with the exception of albendazole once per year (Stephenson 1993). This study found an effect of 0.73 SMD [95% CI: 0.44, 1.03] on weight for deworming vs. control (low certainty evidence)[5].

Pairwise meta-analyses for height: The effects on height gain were robust to restricting to studies with >50 per cent hookworm infection, with no effect size greater than SMD 0.15 (equivalent to 0.36 cm). One exception is that the Miguel 2004 study found a small difference in height for age at the end of one year of treatment that was statistically significant (0.11 SMD [95% CI: 0.04, 0.18]).

Pairwise meta-analysis for attendance: Pairwise meta-analysis for attendance was robust to restricting to studies with >50 per cent hookworm (Gateff 1972, Miguel 2004), with mean difference in attendance of 5 per cent (95% CI: -4% to 13%, I^2=74%).

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[5] GRADE certainty starts at high for an RCT. We downgraded for risk of bias due to lack of blinding and imprecision since it does not have optimal information size (<400 participants), resulting in low certainty.

Low risk of bias for allocation concealment

In summary: results of little to no effect on weight, height and attendance were robust to restricting to studies at low risk of bias.

Weight, network and pairwise meta-analyses: The network meta-analysis of studies at low risk of bias for allocation concealment was consistent, residual deviance 6.125, DIC -10.952. The results are congruent with the base case analysis, showing no statistical or clinically important differences between deworming and placebo or any head to head comparisons (effect sizes were between -0.09 and 0.13 SMD, equating to -125 grams to 181 grams). Pairwise results were in alignment with these results.

Height, network and pairwise meta-analyses: The network meta-analysis was consistent, residual deviance 5.552, DIC -9.401. Results were congruent with the main analyses, showing little to no effect on height.

Pairwise meta-analyses, school attendance: When restricted to studies at low risk of bias for allocation concealment (Rozelle 2015, Ebenezer 2013), the effect on school attendance was small and not statistically significant:-2% (95% CI: -6% to 3%).

Sensitivity for eligibility criteria: including studies which screened for infection and treated infected children

We conducted a sensitivity analysis to assess the effect of including studies where children were screened for infection, and infected children were randomised to deworming or control.

Weight:

In summary: Effects on weight were congruent when we included studies that screened for STH infection and treated for STH infection. In contrast, studies that screened for schistosomiasis infection and treated children with infection had larger effects on weight (of 1.1 kg vs. 0.13 kg).

We included three studies which screened for STH infection (Yap 2013, Sarkar 2002, Bell 1973), treated infected children for STH with or without treatment for schistosomiasis and reported weight or weight for age as an outcome.

We conducted a test for interaction to assess subgroup effects, and if these were not statistically significant, we combined mass deworming and screen and treat studies.

For albendazole twice per year vs. placebo in infected children, we included one study of triple dose albendazole twice per year vs. placebo (Yap 2014). When compared with 11 other studies of mass deworming with albendazole twice per year vs. placebo, the test for subgroup differences was not statistically significant (p=0.09). The effect of

deworming vs. control was small and not statistically significant (SMD 0.06 [95%CI: -0.01, 0.12], results not shown). This SMD equates to 80 grams.

Table 14: Mass deworming with albendazole vs. screen and treat for weight gain

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)
Mass deworming albendazole	0.05 (-0.02, 0.11)	11	18,740/16,690
Screen and treat albendazole	0.24 (-0.04, 0.52)	1	99/95
Test for subgroup differences, p= 0.09			
Pooled	0.06 (-0.01, 0.12)	12	18,839/16,785

For pyrantel twice per year, we included one study of screen and treat with pyrantel twice/ year (Sarkar 2002). When combined with the only mass deworming study with this treatment (Hadju 1997), the test for subgroup differences was not statistically significant. The pooled effect of deworming vs. placebo showed little to no effect on weight (SMD 0.30, 95% CI: -0.17, 0.76) (Table 13). This SMD equates to 361 grams. We consider the evidence very low certainty because any subgroup analysis in a systematic review is observational in nature, and also this comparison failed to meet the optimal information size (<300 participants in the two studies).

Table 15: Mass deworming vs. screen and treat for pyrantel for weight

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)
Mass deworming	0.08 (-0.26, 0.42)	1	61/74
Screen and treat	0.56 (0.12, 1.01)	1	40/41
Test for subgroup differences, p= 0.09			
Pooled	0.30 (-0.17, 0.76)	2	101/115

Considering the sparse evidence from screen and treat studies, we also conducted an overall analysis of all screen and treat STH studies compared to all mass deworming for STH studies.

Table 16: Mass deworming vs. screen and treat for all types of STH for weight

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)	I2
Mass deworming	0.03 (0.00, 0.06)	30	28,710/30,981	46 %
Screen and treat	0.35 (0.05, 0.65)	2	139/136	30 %
Test for subgroup differences, p= 0.04				
Pooled	Not appropriate to pool	32	28,849/31,117	

STH: soil transmitted helminths

For schistosomiasis infection, screening and treating children with praziquantel or metrifonate increased weight gain by 1.1 kg (95%CI: 0.6 to 1.52) compared to mass deworming effect of 0.13 kg (95% CI: -0.16 to 0.42) (test for subgroup differences: p=0.0009) (Table 15).

Table 17: Mass deworming vs. screen and treat for praziquantel or metrifonate vs. placebo for weight

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)
Mass deworming with PZQ	0.13 (-0.16, 0.42)	1	91/91
Screen and treat with PZQ or metrifonate	1.06 (0.59, 1.52	2	409/302
Test for subgroup differences, p= 0.0009			
Pooled	Not appropriate to pool		

One screen and treat study for schistosomiasis could not be included in meta-analysis. Bell 1973 screened all children in two schools. Fifty-six children were randomly selected to receive hycanthone for shistosomiasis, regardless of infection status. Children with any other parasite (including 5 per cent of children with hookworm) were treated immediately with appropriate drug (drugs not named). This study reported no statistically significant effect on weight (no data provided).

Height:

We identified four RCTs which screened for STH infection and treated only infected children with albendazole twice per year (Simeon 1995, Yap 2014), albendazole once per

year (Tee 2013), and pyrantel twice per year (Sarkar 2002). For albendazole, the effect on height remained small 0.04 SMD [-0.01, 0.09].

Table 18: Mass deworming with albendazole vs. screen and treat for height

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)
Mass deworming	0.03 [-0.02, 0.08]	9	3484/3355
Screen and treat	0.18 [-0.08, 0.44]	2	114/113
Test for subgroup differences, p= 0.18			
Pooled	0.04 [-0.01, 0.08]	11	3598/3468

For pyrantel twice per year, the effect on height remained small at 0.07 SMD [-0.20, 0.34].

Table 19: Mass deworming vs. screen and treat for pyrantel 2/year for height

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)
Mass deworming	0.06 [-0.28, 0.40]	1	61/74
Screen and treat	0.08 [-0.35, 0.52]	1	40/41
Test for subgroup differences, p= 0.93			
Pooled	0.07 [-0.20, 0.34]	2	101/115

When combining across all types of deworming for STH, the effect on height for all types of STH was also small at 0.10 SMD [-0.00, 0.21].

Table 20: Mass deworming vs. screen and treat for all types of STH for height

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)
Mass deworming	0.03 [-0.01, 0.08]	26	13,066/17,398
Screen and treat	0.10 [-0.00, 0.21]	6	769/657
Test for subgroup differences, p= 0.22			
Pooled	0.10 [-0.00, 0.21]	32	13,835/18,055

For schistosomiasis infection, there was little to no effect on height when comparing mass deworming to screening and treating children with praziquantel (-0.05 SMD; 95%CI: -0.36, 0.26) (test of subgroup differences p=0.05).

Table 21: Mass deworming vs. screen and treat for praziquantel or metrifonate vs. placebo for height

Cutoff	SMD (95%CI)	Number studies	Participants (Tx/control)
Mass deworming with PZQ	-0.21 [-0.50, 0.08]	1	91/91
Screen and treat with PZQ	0.10 [-0.17, 0.37]	1	105/102
Test for subgroup differences, p= 0.05			
Pooled	-0.05 [-0.36, 0.26]	2	197/193

One study of screening and treating for schistosomiasis infection could not be included in meta-analysis. Bell 1973, which screened and treated for STH infection as well as providing mass deworming with hycanthone regardless of infection, reported no statistically significant difference in height (data not provided).

Cognition- short term attention tasks:

In summary: Results on short-term attention tasks were robust to including studies which screened for infection and treated infected children. We identified six RCTs (Boivin 1993, Hadidjaja 1998, Nokes 1999, Nokes 1992, Simeon 1995, Sternberg 1997) which screened for infection and treated only infected children. We selected the short-term attention cognition outcome common to all studies: digit span or number recall. Hadidjaja 1998 was a cluster RCT which we adjusted for unit of analysis errors using an ICC of 0.07 for cognition, as described in the methods). We did not include Boivin 1993 in our base case because it was designed as a four-arm trial, but three arms were

combined together for analysis due to power issues. Pooling all studies, there was little to no effect of deworming compared to placebo on short term cognitive processing outcomes (SMD 0.03 [95% CI: -0.08, 0.14]) (moderate certainty evidence)[6]. This result was robust to choosing different short-term cognitive outcomes (since these studies measured a battery of cognitive outcomes) or if we included Boivin 1993.

Cognition- general intelligence measures

In summary: The result on general intelligence was robust to including studies that screened and treated for STH infection.

We identified three RCTs which screened and treated for STH infection and measured a general intelligence outcome (Sternberg 1997, Hadidjaja 1998, Bell 1973).

Boivin 1993 measured the Kaufman Assessment Battery for Children (K-ABC) which includes measures of attention such as number recall as well as an overall mental processing composite score, which is a measure of general intelligence that correlates well with the WISC-IV and Raven's progressive coloured matrices. Hadidjaja 1998 randomised four schools to mebendazole, health education, mebendazole and health education or placebo, and assessed the Raven's progressive coloured matrices as a measure of general intelligence. We used the exact p-values reported in Hadidjaja 1998 to calculate standard deviation, then corrected these for unit of analysis error using an ICC of 0.071, as described in the methods. When these two studies were combined with the other studies which assessed general intelligence (Ndibazza 2012, Nga 2011, Watkins 1996), deworming had little to no effect on general intelligence with SMD 0.06 [95% CI: -0.06, 0.18].

Bell 1973 (screen and treat for STH, mass deworming for schistosomiasis) reported an important improvement in Raven's score with treatment with hycanthone compared with untreated children. The prevalence of schistosomiasis in the treated school was 68 per cent, which is much higher than most of the included studies.

School attendance:

We identified one study that screened for infection and treated only infected children (Simeon 1995). Adding this study to our meta-analysis did not affect the results. There

[6] Since all of the studies were RCTs with no serious concerns about risk of bias, we rated the evidence high certainty of evidence.

was still little to no effect of deworming on attendance vs. placebo (1% difference, 95% CI: -0.01 to 0.03) (moderate certainty evidence) (***Additional Figure 10***).

Long-term outcomes:

In summary: When we consider one other long-term study of the effects of deworming that met our study design eligibility criteria, we are still very uncertain about long-term effects of mass deworming.

We identified one long-term study of the effects of screening for infection and treating infected children (Bleakley 2007). This study compared areas with higher hookworm prevalence (>40 per cent) to areas with less than 40 per cent prevalence, before and after a 10 year eradication campaign (from 1910-1920) which comprised intensive awareness campaigns about the symptoms of hookworm, to encourage parents, teachers and adults to seek treatment for those infected with hookworm. We rated this study as moderate risk of bias using the IDCG tool.

Based on this study, we are very uncertain about whether mass deworming improves school enrollment (9%, 95% CI: 4 to 13%) and full time school attendance (by 16%, 95%CI: 11 to 21%) (very low certainty evidence). We downgraded our certainty in the results because the intervention was a complex programme of raising awareness about symptoms, building latrines (where needed), and education in communities about how to prevent infection and reinfection, which is more extensive than the question of mass deworming vs. control assessed by our primary analysis.

Intensity of infection, >30 per cent with heavy infection

In summary: Results of little to no effect of mass deworming vs. control were robust to restricting to studies with >30 per cent heavy infection.

Network and pairwise meta-analysis, weight: For weight, network meta-analysis of 11 studies (8 two-arm, one 3-arm, and two 4-arm studies) converged and was consistent (total residence deviance 16.22, DIC -12.714). Compared to placebo, deworming had little to no effect for all comparisons (less than SMD 0.20), with one exception. Albendazole once per year vs. placebo may increase weight gain compared to placebo (SMD 0.48, 95% CI: -0.51 to 1.48). This was a weight gain of 1.1 kg in one year in Stephenson 1993. Pairwise meta-analyses agreed with these results (results not shown).

Network and pairwise meta-analysis, height: For height, network meta-analysis of 10 studies (7 two-arm, one 3-arm, two 4-arm studies) converged and was consistent (total residence deviance 13.75, DIC -24.283). Compared to placebo, deworming had little to no effect for all comparisons (less than SMD 0.13). There was agreement with pairwise meta-analyses (results not shown).

Pairwise meta-analysis for attendance: For attendance, pairwise analyses of studies where >30 per cent of infected children had moderate to heavy infections (Miguel 2004, Watkins 1996) showed no effect on attendance (-1%, 95% CI: -4 to 2%).

Lower ICC for weight and height (0.01 instead of 0.17 and 0.11)

Using a lower ICC had no effect on the pooled estimates for weight and height for any deworming treatment.

Higher ICC value for cognition of 0.15 instead of 0.07

We did not need to adjust for clustering in our base case analysis. In the sensitivity analysis for eligibility criteria, we adjusted Hadidjaja 1998. Using a higher ICC of 0.15 (as used by Kristjansson 2015 for cognition outcomes of schoolfeeding) does not change the results.

Effect of unpublished studies

We included two unpublished studies (Hall 2006, Rozelle 2015). The effects for weight, height, cognition and attendance were not changed when these studies were removed (results not shown).

4.5 PROCESS EVALUATION

As described above, we assessed the process of implementation in each study, and also assessed reasons proposed by authors for failure or success of deworming on the primary outcomes.

We group these barriers and facilitators according to whether we were able to assess these factors in our analyses.

4.5.1 Facilitators not supported by our analyses

High prevalence and intensity of worms, and infection with trichuris and hookworm were hypothesized by authors as associated with greater impact on weight gain and hemoglobin (Alderman 2006, Beach 1999, Fox 2005, Kruger 1996). Similarly, greater infection intensity was expected to be associated with greater effect on cognition and growth (Koroma 1996). Our analyses did not support this hypothesis since we found no relationship between prevalence of worms or impact on worms and the effect on weight gain, height gain or attendance. We also found little to no effect on weight or height when restricted to studies with high intensity of infection.

Children who were younger, more iron/iodine deficient, with higher prior malnourishment may be more able to grow faster with deworming (Garg 2002, Gupta 1977, Solon 2003). Our analyses did not support this hypothesis because we found no

difference between populations that were more underweight vs. less underweight (at any cutoff of population underweight from 20-60 per cent below -2 WAZ), and we also found no relationship between age of children and treatment effect. Subgroup analyses within studies on age and underweight were conflicting.

Combination treatments with deworming and praziquantel or iron, food or micronutrients were described by some studies as improving the effects on growth and haemoglobin (Donnen 1998; Kruger 1996; Taylor 2001). We found no greater effect on any outcome with combined treatment for STH and praziquantel, iron, food or micronutrients than STH deworming alone.

Untreated children in comparison schools were found to benefit from children in treatment schools that were close to the comparison schools, and this could dilute the overall treatment effect (Miguel 2004; Baird 2011). We found larger weight gain for children in the control group of cluster randomised trials (who would presumably experience less spillover due to geographic separation of the clusters by village, church parish or health worker areas) than in individually randomised trials (where treated and untreated children are in the same classroom) which does not support the hypothesis of spillover effects.

4.5.2 Facilitators for achieving impact on child outcomes described by study authors, which we did not test in our analyses

Political support, supportive delivery systems (e.g. school or health care workers), adequate drug supply were described as important facilitators in some studies (Awasthi 2013, Jinabhai 2001A). Similarly, training of health workers was described as important (Sur 2005).

Education of parents and children was described as important to decrease the rate of reinfection (Sufiyan 2011).

Deworming may lead to an improved immune system which may increase resistance to reinfection (Nga 2009).

4.5.3 Barriers not confirmed in our analyses

Control groups may have sought deworming (up to 30 per cent in Alderman 2006) and this may have been facilitated by project workers who were unblinded also changing the assigned therapy (Awasthi 2000), and/or by parents who witnessed roundworms passing shortly after deworming was given (Awasthi 2000, 2001). We did not find any difference in treatment effect between studies with greater impact on worm burden in the treatment group (i.e. where there was less contamination by the control group seeking deworming elsewhere).

Control groups may have received a benefit of deworming if exposed to treated children thus diluting the treatment effect (Miguel 2004). Our analyses did not support this hypothesis since the lack of effect on weight, height and attendance was confirmed when restricted to cluster trials only, and growth in control groups exposed to treated children in the same class or school was less than in cluster trials.

Lower parasite levels could dilute deworming effect (Beach 1999, Jinabhai 2001A, Jinabhai 2001B). Our analyses did not support this hypothesis since there was no relationship between baseline worm prevalence (ascaris or hookworm) or impact on worms and weight or attendance outcomes.

Reinfection was described as occurring shortly after deworming and a reason for failure to find effects (Donnen 1998, Goto 2009, Greenberg 1981, Gupta 1977, Kaba 1978, Kloetzel 1982, Kruger 1996, Michaelsen 1985, Stoltzfus 2001, Sufiyan 2011, Thein Hlang 1991, Watkins 1996, Willett 1979). Our analyses did not support this hypothesis since we found no relationship between the impact on worms (as an indication of reinfection) and effects of deworming vs. control on weight, height or attendance.

4.5.4 Barriers to impacts on child outcomes, which we did not test in our analyses

Control groups may have been differentially provided other interventions such as measles immunisation by unblinded health workers (Awasthi 2000).

Poor implementation may have affected results (e.g. mixing up of placebo and micronutrient powders in Friis 2003), equipment failure (or changes to equipment during the study affecting baseline and endline measures, Ebenezer 2013), and poor compliance and absenteeism (Hadju 1997, Solon 2003, Stoltzfus 2001).

Other factors may be needed to observe changes from deworming such as environmental factors of improved learning stimuli to influence cognitive processing, prevention of giardial infections (Rousham 1994), sanitation and hygiene practices (Stephenson 1993, Sufiyan 2011), social factors (Watkins 1996) and chronic infections (Thi Le Huong 2007).

Very disadvantaged children may have had a reduction in food intake during the study period which could contribute to lack of effects (Kloetzel 1982). Association between helminth infection and poverty may confound results.

Growth limiting nutritional deficiencies may have reduced ability of children to benefit from deworming (e.g. low iron in adolescent girls at menarche, lack of zinc or iron for normal growth) (Kruger 1996, Gopaldas 1983, Dossa 2001, Stoltzfus 2001).

5 Implications

5.1 SUMMARY OF MAIN RESULTS

After screening over 10,000 articles, we included 55 studies from 23 countries in our primary analysis. We used a logic model to interrogate the presumed causal chain from mass deworming to improvements in child health outcomes. Our review provides novel insight into mass deworming by addressing the criticisms of previous reviews, by taking into account: 1) reinfection; 2) the influence of poor learning environments on cognition; 3) combinations with co-interventions of hygiene, micronutrients and other drugs; 4) long-term studies; 5) indirect effects on untreated children across studies; 6) role of baseline nutritional status; 7) uninfected children in studies may dilute the effects; 8) possibility of different effects by worm type; 9) quality of school attendance measures; and 10) that only heavily infected children are affected by worms. With consideration of the above ten criticisms, we find that there is little to no effect of mass deworming for soil transmitted helminths with or without deworming for schistosomiasis on growth, short-term attention, cognitive development, attendance, school achievement and mortality. Overall, our analyses do not support causal pathway assumptions about influence of mass deworming on child health and school performance.

Summary of findings for mass deworming with albendazole vs. control:

***Hemoglobin*:** For haemoglobin, we found small effects of less than 0.30 g/dL unless mass deworming was combined with iron or praziquantel.

Worm burden: For worm burden, we found absolute effects on reducing worm prevalence ranged from two to 57 per cent, suggesting reinfection occurred since these drugs are known to be over 95 per cent effective at curing worm infections in the short-term (Taylor-Robinson 2015).

Weight: Mass deworming for children had little to no effect on gain in weight and weight for age. Meta-analyses of 11 RCTs of albendazole twice per year for weight, with 35,430 children, showed a mean increase in weight of 0.09 kg (from 0.04 lower to 0.2 higher) (moderate certainty evidence). Weight gain needs to be considered in

perspective of age and sex. The median age of children in our review was seven years. According to the WHO growth standards, weight gain for children aged seven years who are below one standard deviation for weight (-1 WAZ) in one year is 1.9 kg for boys and 2 kg for girls (from seven year old normal weight of 20.2 kg for boys and 19.4 kg for girls). This is congruent with the median weight gain observed in our trial populations of 2.0 kg. For children who are severely under-weight (-3 WAZ), the yearly weight gain for seven year olds, according to the WHO growth charts, is 1.3 kg for girls (from 14.9 kg) and 1.5 for boys (from 15.8 kg). So, for severely underweight children, this average weight gain represents a 7 per cent increase over the average weight gain in one year, based on WHO updated growth charts. We did not find any relationship between effect on weight and any child characteristics (age, sex, baseline nutritional status), setting characteristics (prevalence, intensity of infection), intermediate effects on any type of worm burden (as an indicator of successful implementation and reduction of worm burden), or design (cluster vs. individual studies). We are moderately confident in this estimate. Uncertainty arises from large heterogeneity due to very different effects in two studies with baseline imbalance that were excluded from this analysis.

Height: Mass deworming for children had little to no effect on gain in height or height for age (HAZ). Meta-analysis of nine RCTs, with 6,839 children, showed a mean increase of 0.04 cm (from 0.3 lower to 0.41 higher). Placing this in the context of typical height gain in our study population of 3.7 cm over one year, or of the WHO growth standards for seven year old children of 5 cm per year for girls with -1 SD HAZ or 5.2 cm for boys; this is equivalent to 1 per cent or less of typical growth for this age group. We found no relationship between this effect on height and age, sex, baseline nutritional status, prevalence, intensity or effect on worms (as an indicator of implementation success). We are moderately confident in this estimate for the same reasons as above (heterogeneity arising from two studies with baseline imbalance).

Proportion stunted: There was little to no effect on the proportion of children stunted (defined as -2 HAZ), with an effect of eight fewer children stunted per 1000, if the baseline risk of stunting is 40 per cent (taken from the control group prevalence of stunting in the four trials with 4,286 children which reported this outcome). However, these findings need to be considered with caution since children over the age of three who are stunted may not be able to catch up growth.

Cognition: We found little to no effect on short-term attention tasks based on three RCTs with 4,078 children, equivalent to 0.23 points on the 100 point scale for working memory in the WISC IV. The average baseline score on this index was 78 points.

School attendance: We found little to no effect on school attendance of 1 per cent (from 1 % less to 3 % more), relative to a baseline average attendance of 80 per cent in seven RCTs, with >30,000 children randomized. We are moderately confident that the

true effect is close to the estimate of effect. We rated down our certainty due to a moderate heterogeneity (I^2 of 67%) that was explained by a subgroup analysis of onsite visits vs. teacher records, which was confounded by higher risk of bias due to lack of blinding.

Mortality: There was little to no effect on mortality (assessed in six RCTs, with over one million children randomized) equating to a reduction of one death per 1000 in a population with baseline child mortality of 25 per 1000 observed in the DEVTA trial of over one million children in India.

Long-term economic productivity: We are very uncertain in long-term effects on economic productivity as measured by hours worked in the past week due to risk of bias (due to lack of blinding of both participants and field workers) and indirectness (due to a hygiene co-intervention which was not provided in the control group). Subgroup analyses of these data (e.g. across gender, type of employment and sector) were considered as very low certainty of evidence also.

Summary of findings: Albendazole and praziquantel vs. control in areas with endemicity of both STH and schistosomiasis

We found little to no effects on weight (0.16 kg more, from 0.15 lower to 0.47 kg higher) or height (low certainty evidence), little to no effect on diverse cognitive tests including short-term attention tasks (low certainty evidence), little to no effect on school attendance (0 % higher, from 17 % lower to 18 % higher, low certainty evidence) after one year. In longer term studies, we are uncertain in long-term effects on economic productivity due to low certainty evidence.

Summary of findings: Praziquantel vs. control for schistosomiasis endemic regions

Mass deworming with praziquantel may improve weight gain slightly (by 0.13 kg, from 0.16 lower to 0.42 kg higher), has little to no effect on height (0.11 cm lower). We are uncertain in effects on school attendance, cognition, stunting, mortality due to lack of evidence. We are uncertain in effects on long-term educational enrolment due to very low certainty evidence.

Addressing concerns about the Cochrane review

The Cochrane review is a high quality systematic review (Taylor-Robinson 2015) which addressed a focused question about mass deworming for soil-transmitted helminths for children, and assesses the certainty of evidence for each outcome. The Cochrane review found that regular treatment of children in endemic areas may have a small effect on weight gain, probably have no effect on height gain, cognition, school achievement, mortality and have uncertain effects on school attendance. We designed our review to

address concerns raised about whether the conclusions of the Cochrane review would be influenced if additional factors were considered in the interpretation and analysis of results. In summary, we reached similar conclusions to those of the Cochrane review, after conducting extensive analysis of effect modification and considering these factors. Our review provides additional evidence regarding co-administration with treatment for schistosomiasis, and additional evidence on school attendance.

1. Reinfection

We considered reinfection in different ways. Using subgroup analysis, we found no difference in effects on weight, height or attendance between low (<30%), moderate (30-50%), or high prevalence (>50%) of ascaris, where reinfection is expected to be higher in higher prevalence areas. We also found no relationship between effect on weight, height or attendance and baseline prevalence of worms, using weighted least squares regression. Similarly, we found no effect of mass deworming on weight, height or attendance at any cut-off for high prevalence from 10 per cent to 90 per cent of ascaris, even with eight studies with 7,022 participants with >70 per cent ascaris. We also calculated the impact on worm burden as a relative risk reduction, and found no relationship between the impact on ascaris prevalence as an indicator of the first step of the causal pathway and effect size for height, weight or attendance. At the higher threshold of >90 per cent relative risk reduction of ascaris prevalence, there were fewer studies, with only three studies (1,500 participants) for weight and height, and only one study for school attendance. We compared different frequencies of deworming separately in our network meta-analysis to assess whether more frequent deworming, hypothesized to reduce reinfection, had larger effects. We found no difference in effects for less or more frequent deworming for weight or height. We also assessed studies with follow-up beyond the period of deworming treatment, which demonstrated no benefits on worm prevalence or child health outcomes beyond the period of deworming.

2. Poor learning environments affect cognition and school performance

We did not find any information describing the school environment of these studies. However, for short-term attention, unlikely to be affected by the learning environment, we found little to no effect in four studies of mass deworming SMD -0.05 [95% CI: -0.12, 0.03], conducted in >4400 children in a range of geographic settings, worm burden, and child age (high certainty evidence). We also found no effect on general intelligence measures with SMD of 0.02 [95% CI: -0.11, 0.14]. This is equivalent to a difference of 0.2 units on the Peabody Vocabulary Scale, a test of verbal intelligence with a scale from 0-100. Three out of four studies that could not be pooled because of insufficient data also reported no effect of deworming on cognitive tests (Miguel 2004 which used both static and dynamic tests of cognition), Solon 2003 and Jinabhai 2001B). These results were robust to including studies which screened for infection and

treated only infected children. Academic performance may be affected by the learning environment, and some of the learning environments were poor. For example the average scores on the math tests in Ebenezer 2013 was 36.7 per cent and for Tamil education test was 44.7 per cent. The combined effect of five studies, conducted from 1972 to 2015 in Vietnam, Cameroon, Sri Lanka, China and Kenya, showed little to no difference in math achievement tests between deworming and control, equivalent to less than 1 per cent difference in scores out of 100, and three other studies with insufficient detail to be pooled also reported no difference in math achievement (Nga 2011, Bell 1973, Jinabhai 2001B). While we agree with Miguel 2004 that the poor learning environment of many of these schools may have affected the ability for improved attention to improve academic performance, we have found high certainty evidence of little to no effect of deworming on short-term cognitive memory and attention, general intelligence or school performance.

3. Combination of mass deworming with food, micronutrients or other worm control programmes

We used network meta-analysis to be able to compare different combinations of drugs, food and micronutrients with each other, using both direct and indirect estimates. This provides more robust estimates of effect by taking advantage of direct comparisons in trials (e.g. in factorial trials which compared combinations directly) as well as indirect comparisons because of comparison to a common comparator. The results of the network meta-analysis find little to no effect of any deworming combination vs. placebo. This includes comparisons of treating for both STH and schistosomiasis with treating for STH alone, schistosomiasis alone or placebo. We also found little to no difference in effects when deworming was combined with food or micronutrients. We assessed the consistency of these network meta-analyses and also compared all comparisons (both to placebo and for head to head comparisons of different types of deworming) to pairwise analyses of direct estimates only. These analyses increase our confidence in the robustness of these results.

4. Long-term outcomes

We include four long-term studies in our primary analysis. However, due to risk of bias, indirectness and imprecision, we are very uncertain about the effects of long-term deworming on labour market outcomes, long-term school enrolment and child health. We searched for additional randomised or quasi-experimental studies assessing the long-term effects of deworming, and did not find any that matched our eligibility criteria. The long-term study by Bleakley 2007 *et al.* was rated down for indirectness since it involved case finding and screening to treat infected individuals and also included latrine-building and improve sanitation, thus we are uncertain whether the effects are due to targeted deworming, sanitation or synergistic effects of both.

5. Indirect effects (spillover or externalities)

Regarding treatment spillovers to untreated control group children that could dilute the observed treatment effect in individually randomized trials (Bundy 2009), we found our results of little to no effect on weight, height and school attendance were congruent even when restricted to cluster studies, which are expected to be less susceptible to dilution because of indirect effects. We also found no evidence of spillover benefits to control children when we compared control children growth and worm burden in individually randomised trials to control children in cluster trials. In fact, we found the opposite; with less effect on worm burden in individually randomized trials than cluster trials. This could be due to the pragmatic nature of cluster trials, where parents of control children may be more likely to seek deworming medicine elsewhere (since they may know their children are not receiving it in the trial). For the two studies which directly assessed the presence of spillovers, the results were conflicting. Miguel 2004 estimatesd a spillover benefit for both worm prevalence and school participation, but Bobonis 2006 reports small and statistically insignificant externalities on child weight and school attendance. Overall, we conclude there is evidence that spillover benefits are unlikely. In the Miguel 2004 PDSP study, as suggested by Aiken 2015a, the spillover benefit may be due to concurrent hygiene promotion and education in this trial since the indirect (spillover) benefit on attendance to untreated children in the same school was almost as large as the effect on the treated children.

6. Baseline nutritional status

Regarding considering underlying host and environmental factors that could influence the effectiveness of deworming, such as nutritional status (Bundy 2009), we conducted a subgroup analysis across baseline nutritional status for studies where >30 per cent of children were stunted at baseline. This analysis found no difference in effect across baseline nutritional status and was robust to varying the threshold. In terms of environmental factors, we found no relationship between the effect size on weight, height and school attendance in relation to prevalence of worms or impact on worms (as a measure of first stage of causal pathway). We also assessed the relationship between the effect on weight (as an intermediate measure of treatment impact) and the effect on school attendance, and found no relationship. These analyses suggest that variations in deworming effects are not explained by baseline nutritional status, baseline worm prevalence or treatment success on reducing worm burden. We were not able to explore the relationship of hygiene or sanitation conditions on deworming effects because these were reported by only 16 of our included studies, and all of these reported poor sanitation and hygiene and high risk for infection.

7. Dilution of effect due to uninfected children

We assessed whether including studies which screened for STH infection and treated for STH affected our results. Including these studies had no effect on our estimates for weight, height, short-term cognition, general intelligence or school attendance for soil-transmitted helminths. In contrast, screening and treating children infected with schistosomiasis improved weight (by 1.1 kg).

8. Different worms need to be considered separately

Regarding appropriateness of combining different pharmacologic interventions and different worms (Hotez 2.0), we conducted network meta-analyses which assessed different pharmacologic interventions and co-interventions separately, taking advantage of the common comparator of placebo. These analyses found no differences in effects for any deworming drugs or their combinations for weight, height or proportion stunted. Furthermore, these analyses were robust to sensitivity analyses according to prevalence of worms (using cut-off thresholds from 10 to 90 per cent, low risk of bias for allocation concealment, studies with greater than 30 per cent of children with moderate to heavy infections, and type of worm (restricting to studies with >50 per cent ascaris, trichuris or hookworm).

9. Quality of school attendance measures

We found a larger effect on school attendance in two cluster randomised trials which measured school attendance using unannounced site visits, with a pooled effect of 8 per cent (95% CI: 3 to 13%), low certainty evidence (Bobonis 2006, Miguel 2004) compared to an effect of deworming in five studies that used school records of -1%, 95%CI: -3 per cent to 1 per cent , high certainty evidence. As indicated in Figure 20, the studies with unannounced visits were also at high risk of bias for blinding of personnel and participants. Intervention schools could be identified by both participants and field workers because wall charts about hygiene promotion were placed in the schools for Miguel 2004, and in the preschool study by Bobonis, there was no mention of blinding the albendazole from the teachers or school personnel providing it. Teacher and school records are considered unreliable by some in these settings because they may be influenced by other factors such as incentives for high school enrolment (Miguel 2004). One recent trial found that school records were comparable to pupil self-report for student absences (Banerjee, https://www.econ.iastate.edu/sites/default/files/publications/papers/p12167-2010-12-07.pdf), but another recent study found that directly observed attendance did not correspond with roll call data (Clasen 2014). We rated the effect of school attendance measured by on-site visits in the studies as uncertain because of lack of blinding the assessors in schools where the intervention status was known.

10. Only heavily infected children are affected by worms

We found no difference in effects on weight, height or attendance in sensitivity analysis of studies with >30 per cent of children with moderate to heavy infection.

Other criticisms and issues:

Regarding analyzing data by different years and by different comparisons, thus reducing the precision of estimates (Duflo: http://www.poverty-action.org/blog/cochrane%25E2%2580%2599s-incomplete-and-misleading-summary-evidence-deworming), we chose to analyse all studies at a common time point, closest to one year. Taylor-Robinson 2015 demonstrated there was no difference in effectiveness of deworming on child health outcomes when assessed at different time points. Also, by using network meta-analysis, we draw on the information from other studies using a common comparator (in most cases, placebo), to increase our power to detect differences. These demonstrated little to no effect on weight, height or proportion stunted.

Our main analyses were congruent for studies with high compliance (>75 per cent), low attrition (<2 per cent) and low risk of bias for allocation concealment.

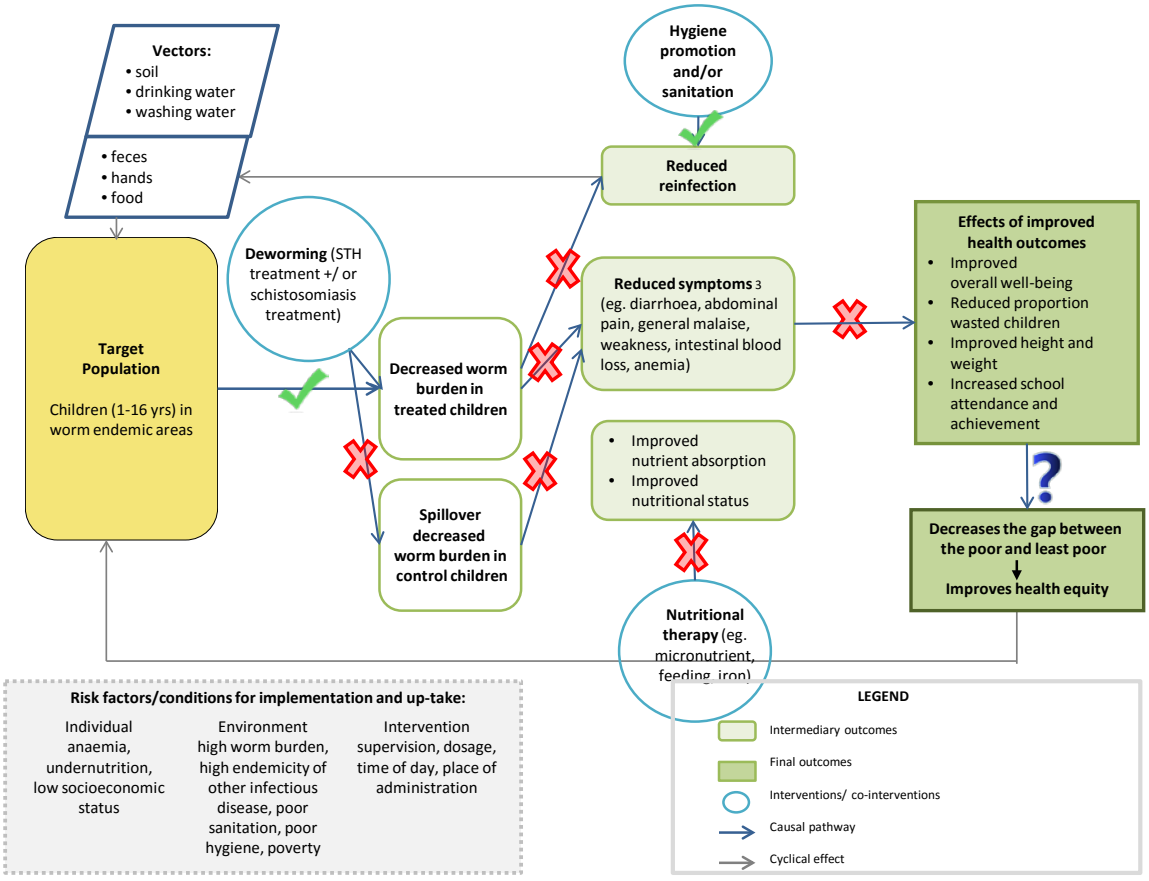
Causal pathway analysis

We explored the causal pathway by which mass deworming is hypothesised to improve child health. Even in studies with a large impact on reducing worm infection, we find little to no improvement in weight, height, cognition, or school attendance. We also found no relationship between proximal outcomes in the causal pathway (relative risk reduction of worm prevalence, effect on weight or height) and the more distal outcomes of school attendance. This was assessed in three ways: 1) weighted least squares regression, 2) cumulative meta-analysis and 3) sensitivity analyses exploring cut-off thresholds..

Subgroup analyses across expected effect modifiers of age, baseline nutritional status, prevalence of worms and sex did not support differences in effects across any of these factors.

In our logic model, we hypothesized that the effect of mass deworming might be pro-poor because poorer populations might be exposed to poorer sanitation environments and at a higher risk for reinfection. Results of our main analyses were congruent when restricted to studies described as very low income settings or populations. Two studies assessed differences in effects across income or education level that provide very low certainty evidence of greater effects in poorer or less educated populations. Based on these results, we are uncertain whether deworming leads to improvement in health equity.

Figure 34: Revised logic model, with evidence along causal pathways



5.2 OVERALL COMPLETENESS AND APPLICABILITY OF EVIDENCE

We conducted a comprehensive search of electronic databases (updated in May 2015), including clinical trial registers and websites of relevant organizations. We also searched the references of included studies. We contacted authors for missing data or clarification, and obtained data from nine out of 19 authors. We identified two additional RCTs (Gateff 1972, Sternberg 1997) and one unpublished study (Rozelle 2015) that met the eligibility criteria of the Cochrane review on this topic (Taylor-Robinson 2015). We included a range of study designs to extend beyond randomised trials and compared results across study designs.

We used network meta-analysis to take advantage of the whole evidence base from studies with multiple comparisons (e.g. for weight gain, 13 studies compared more than

two interventions). We evaluated the transitivity assumption to be reasonable based on our clinical knowledge of the interventions being jointly randomizable as well as empirical examples of trials which had randomized different frequencies and combinations of treatments. Studies differed across potential effect modifiers of baseline age, prevalence and nutritional status. However, subgroup and sensitivity analyses did not show differences in effects across any of these factors. Thus, we judged the transitivity assumption was reasonable. Consistency was empirically tested for each network meta-analysis using consistency plots and model diagnostics, and this was facilitated by a number of closed loops for each network. We also provide tables showing the direct and indirect estimates where both were available for all comparisons in the appendices. In most cases, our indirect estimates were in agreement with direct estimates, and our sensitivity analyses increased confidence in robustness of the network. Convergence of all NMAs and the consistency of the models and estimates provide evidence to suggest the transitivity assumption is plausible. Although network meta-analysis is subject to a number of assumptions, these assumptions were empirically tested, as much as possible.

We found that the effect estimates had greater imprecision based on the network meta-analysis. This can happen with a sparse network, such as ours. We considered collapsing the network by combining some nodes, however, our research team felt that combining different drugs or frequencies was not justified clinically. The network meta-analysis provided added information by allowing direct and indirect estimates of comparisons of different frequencies of deworming, different drug combinations and combinations of deworming with iron, vitamin A, multiple micronutrients and food. These comparisons suggest that combinations of different drugs, nutritional interventions, and different frequencies were no more effective than deworming twice per year compared to placebo. These findings are supported by comparison with direct estimates from factorial trials comparing these different interventions and the consistency and convergence of the models. These conclusions are subject to uncertainty due to the sparsenesss of the network, however, their plausibility is increased by the evaluation of the underlying assumptions of network meta-analysis.

Power analysis for weight and school attendance show that we had greater than 95 per cent power to detect differences in weight of 200 grams, and 7.5 per cent difference in school attendance. Thus, it is unlikely that we falsely failed to find statistically significant effects because of insufficient power. In order to consider aggregation of all possible mass deworming studies, we conducted an analysis of any mass deworming treatment (any drug, any frequency) compared to placebo, and found an effect size of 0.03 SMD for weight (95%CI: 0.00 to 0.07, 30 trials, I2=46%) with a total of 59, 691 participants. This corresponds to a difference of 0.05 kg. Conducting this same analysis restricted to higher prevalence areas found no relationship between prevalence of ascaris and effect size (for studies which reported prevalence), from a cutoff of 10 per

cent up to 90 per cent. For example, for studies in areas with >50 per cent prevalence of ascaris, the effect size for weight was 0.07 kg (95%CI: -0.00, 0.16 kg), with 11 studies, 8,299 participants, I^2=2%).

The studies are heterogeneous across population (e.g. age, nutritional status), geographic location, type of worm present and interventions (e.g. whether cointerventions of hygiene, food and micronutrients are provided). Despite this, most of our analyses had acceptable between study heterogeneity, with the exception of weight and height outcomes, for which two studies found large effects of deworming compared to control. We identified baseline imbalance in both of these studies (Koroma 1996, Stephenson 1989). We appraised all other studies carefully and did not find any other study with the same degree of baseline imbalance. We also did not find any subgroup analyses that were statistically significant or clinically important across age, sex, prevalence or nutritional status at baseline. All of our sensitivity analyses were congruent with our main analyses, albeit with wider 95 per cent confidence intervals due to fewer studies, with the exception of including the two studies with baseline imbalance. These analyses increase our certainty in the findings.

There were only seven studies of school attendance, and this limited our ability to assess the role of potential explanatory variables. Adverse effects were rarely reported. There was very little data available from these studies on whether mass deworming has any effect on other comorbidities such as malaria or HIV.

Our subgroup analyses and least squares regression analyses exploring relationships between explanatory variables was limited by incomplete reporting of some variables in the primary studies. For example, of 28 studies contributing data for meta-analysis for weight, only six studies reported the baseline prevalence of schistosomiasis. For impact on worms (as an indication of the first stage of the causal pathway and lack of contamination of the control group), 12 out of 28 studies did not report the effectiveness of the deworming on reducing worm prevalence. For baseline nutritional status (proportion stunted), only seven out of twelve studies of albendazole twice per year vs. control reported the proportion of children stunted at baseline. When considering health equity, only two studies used subgroup analysis to compare effects in poorer and least poor children, despite 13 studies reporting collection of detailed information about socioeconomic status. This incompleteness of data on causal pathway variables is a limitation for some of our analyses.

5.3 QUALITY OF THE EVIDENCE

Overall, the included studies had unclear risk of bias, with only 10 per cent being rated at high risk of bias for any single domain. Although, only 20 per cent of studies were low risk of bias for allocation concealment, we rated baseline imbalance as low risk for most

of the studies (75 per cent). Blinding of outcome assessment was unclear or high risk for most studies (about 70 per cent). All but four of the cluster studies used appropriate methods to consider unit of analysis issues. The risk of bias domain that was rated most frequently as high risk of bias (40 per cent of studies) was incomplete outcome reporting.

It must be recognized that blinding of participants may not be possible for some development interventions for ethical reasons (White 2011). This lack of blinding may lead to changes in behaviour of the treatment group or the control group because of their knowledge about their treatment arm (Smith and Morrow 2015). Only three studies in our sample reported assessing behaviours related to deworming in the study sample (Alderman 2006; Awasthi 2001, Miguel 2004). One of these found that up to 30 per cent of control group children were dewormed by parents privately (Alderman 2006), one found less than 5 per cent of children sought deworming outside the trial (Awasthi 2001) and Miguel 2004 found no difference in cleanliness, contact with fresh water or shoe-wearing behaviours between intervention and control schools. Blinding of assessors or enumerators is often possible, and serves to minimize the risk of detection bias (White 2011; Smith and Morrow 2015).

We used GRADE for network meta-analysis (Puhan 2014) to rate the certainty of evidence for each outcome. For our main analysis, all outcomes were rated as moderate to high certainty, with the exception of the long-term outcomes, which were downgraded because of risk of bias, loss to follow-up and indirectness of the intervention (which included hygiene promotion for two of these long-term studies). For mass deworming for schistosomiasis, there was very little evidence available and it was rated low certainty due to concerns about imprecision and risk of bias.

5.4 POTENTIAL BIASES IN THE REVIEW PROCESS

We reduced bias in our review process by using transparent methods, an *a priori* protocol with few deviations from protocol (that are documented), duplicate study selection, extraction and data entry and crosschecking of data and results.

Publication bias is possible, particularly if the direction of results leads to differential publication. We provide funnel plots for weight and height, which do not suggest publication bias. We identified two abstracts (Snider 2009, Pollitt 1991) published in conference proceedings and one programmatic stepped wedge evaluation (Satoto 2011) in a WHO report, and there may be more trials published in conference proceedings or reports that we have not found. The direction of bias if we missed other unpublished studies is likely to lead to even smaller estimates of deworming effects since it is more likely that studies with negative results or null results are not published. We searched the reference lists of included studies, systematic reviews, websites of relevant

organizations and contacted experts to increase the comprehensiveness of our search. Thus, we feel we have a comprehensive coverage of eligible studies.

Another potential bias in our review process is our assessment of risk of bias. We used tools appropriate to the study design, and these tools were pre-specified in our study protocol. However, these tools assess risk of bias, which does not mean that bias has been demonstrated. If these studies were rated at lower risk of bias then our conclusions for the long-term studies of mass deworming for albendazole twice per year vs. control would change to state that small effects were found for school enrolment of 0.3 years relative to a baseline of 6.69 years (95%CI: 0.01 to 0.58 years), self-reported health of 0.04 units on a four point scale (95%CI: 0 to 0.08), economic productivity (as assessed by hours worked) of 1.58 hours on a baseline of 18.4 hours (95%CI: -0.46 to 3.62), and little to no effect on height (-0.11 cm, 95%CI: -0.64, 0.42 cm) (low certainty evidence).

We made several methodological decisions, which could influence our conclusions. We tested the influence of each of these decisions using sensitivity analyses. The most notable is the decision about which measure of attendance to choose from the Miguel 2004 study and its replications. We chose the treatment effect in the first year on the treated children (all boys and girls <13 years), partly for comparability with Taylor-Robinson 2015, but also because it was the largest estimate of effect. We conducted sensitivity analyses which showed our results did not change if we used the more precise (but smaller) overall treatment effect calculated by Hicks *et al.* 2015, using data and analyses corrected following replication analyses (considering the clustered nature of the multiple years of this stepped wedge study design). Other methodological decisions and methods were also tested such as adjustments for unit of analysis errors with less conservative ICC.

The weighted least squares regression analyses were based on non-normal data that we were unable to correct for using different transformations, and few data points. However, these analyses were supported by sensitivity analyses exploring the importance of cutoff thresholds for impact on worms and prevalence for the same outcomes (height, weight and attendance). As above, these analyses are limited by incomplete reporting of causal pathway variables in the primary studies.

5.5 AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES OR REVIEWS

Our results are in alignment with the Cochrane review by Taylor-Robinson 2015, finding little to no effect on important outcomes of growth, cognition, attendance, mortality and stunting. We provide new evidence not assessed in the Cochrane review by comparing different STH drugs, combinations of STH and schistosomiasis

anthelminthics or combinations with micronutrients, nutrition or hygiene promotion. We also tested whether there was evidence of externalities in individual randomised trials that could dilute the effect size in individual RCTs, and found no evidence for this. We found there was little to no evidence of differences in effects across age, baseline nutritional status, sex or worm prevalence. By using weighted least squares regression, we found no relationship between causal pathway variables of worm prevalence, impact on worms with outcomes of weight, height and attendance. In addition, we found no association between improvement in weight gain (as an intermediate outcome) and attendance. We identified one additional trial of cognition (Sternberg 1997) and two of school attendance (Gateff 1972, Rozelle 2015), each showing little to no effect of deworming on cognition or attendance. We included 21 other studies that were not included in the Cochrane review with combined treatments for STH and other infections such as schistosomiasis (e.g. albendazole and praziquantel/ metrifonate), giardiasis (e.g. albendazole and secnidazole/ metronidazole) or non-RCTs. All of these analyses support the conclusions of the Cochrane review that mass deworming has little to no effect on child health and educational outcomes.

Three older reviews (Hall 2008, Albonico 2008, deSilva 2003) found significant effects of mass deworming on weight, height or cognition. Our findings of little to no effect on growth are partly due to the publication of an additional eight trials since 2008 review, all reporting no difference in weight and height between deworming and placebo.

An evaluation of the Primary School Deworming Project (PSDP) that was run in Kenya, by Jameel 2012 included four studies using data collected during the study or in follow-up surveys of a sample of the included children (Miguel 2004; Miguel 2007; Baird 2011 and Ozier 2016) found that deworming children had a positive effect on school attendance and health (anaemia, self-reported illness) with a spillover effect on untreated children in comparison schools that were close to the treatment schools. Cognitive outcomes also improved in untreated infants 10 years later. Treated children ate more meals, worked more hours and earned higher wages 10 years later. Our results differ from these conclusions because we included an additional six studies which measured school attendance, and also because we rate the certainty of evidence as very low because of concerns about indirectness (due to the presence of hygiene promotion in treatment schools) and risk of bias due to lack of blinding of participants, teachers and field workers collecting data.

Our results are congruent with McEwan 2015 of studies to improve learning in primary schools that concluded school based de-worming medications had no effect on learning impact (language or reading, mathematics, or a composite), based on five studies of deworming

A recent review (Croke 2016) found a statistically significant effect of 0.134 kg (95%CI: 0.031, 0.236) in their full sample of 22 studies. Heterogeneity was high (I^2 of 85%, evaluated by our group with their data). They found larger effects in higher prevalence areas of 0.148 kg (95%CI: 0.039, 0.258) in areas with >20 per cent prevalence (16 studies) and 0.182 kg (95 per cent CI: 0.070, 0.293) in areas with greater than 50 per cent prevalence (14 studies). The reason for them finding a relationship with prevalence whereas we did not may be because their full sample does not include 10 studies which we included in our meta-analyses (Bhoite 2012, Garg 2002, Goto 2009, Green berg 1981, Hadju 1997, Jinabhai 2001, Nga 2009, Olds 1999, Stoltzfus 1997, and Rousham 1994). Our analysis that most closely matches this analysis is the Appendix 13.8, which assesses sensitivity to prevalence cut-offs. At greater than 50 per cent prevalence of ascaris, we found a pooled effect size of 0.04 SMD (95%CI: 0.00, 0.09) using random effects, with total of 12 studies, and 8.299 participants). This SMD corresponds to an effect of 0.09 kg (95%CI: 0.0, 0.16 kg), with p=0.07, and low heterogeneity (I^2= 2%). When using our full sample, we did not find a relationship between effect size for weight and prevalence of any type of worm in weighted least squares regression. We also found that our pooled effect size was not sensitive to restricting the studies in higher prevalence areas, from greater than 10 per cent up to 90 per cent. Our analysis of the relationship of prevalence to weight gain, height gain and attendance using the slope of least squares regression as well as sensitivity analysis for different cutoff thresholds of high prevalence increase confidence in our findings.

Our results are in agreement with Smith 2010 and Gulani 2007 which found marginal improvement in haemoglobin concentration after mass deworming, especially the combination of STH treatment and praziquantel.

6 Author's conclusions

6.1 IMPLICATIONS FOR POLICY

The implication for policy is that mass deworming is probably not effective on average at improving weight, height, cognition, school attendance or mortality at a population level, even in areas with very high intensity and prevalence of infection or when combined with food or micronutrients. Given our analyses across socioeconomic status, baseline nutritional status, gender and age were limited by data availability; there still remains the possibility of effects in subpopulations. Interaction between factors may also be hidden because our analyses were done on aggregate level data.

Mass deworming alone is insufficient to improve growth, cognition, school performance or school attendance for children living in endemic areas. These findings suggest that in addition to a reconsideration of mass deworming programmes in their current form, additional policy options need to be explored to improve child health and nutrition in worm-endemic areas. These include the needs for investing in interventions to address basic determinants of worm infestations such as poverty, living conditions, sanitation and inequities. Decisions on public health approaches in such settings need to be taken on the basis of human rights, ethics and evidence-based, sustainable cost-effective approaches. For schistosomiasis, policy implications are that mass deworming may be effective at improving weight.

6.2 IMPLICATIONS FOR RESEARCH

Since all analyses of effect modification are limited by aggregate level data which may hide individual level differences, we propose that future research should assess which subset of children do benefit from mass deworming, if any, using individual patient data meta-analysis. Explanatory variables identified in this review include infection status, infection intensity, age, sex, socioeconomic status and baseline nutritional status at the individual level and study-level factors such as environment or sanitation facilities. This analysis should assess the feasibility of developing a case-finding tool on the basis of clinical data that could allow targeting of deworming to the most vulnerable children.

There was a relative paucity of evidence about effects of deworming on school attendance (seven studies). If future studies of mass deworming are conducted measuring school attendance, we propose including a comparison of different methods of measuring school attendance (i.e. school visits and teacher records).

We found incomplete reporting of explanatory variables such as impact on worm burden and nutritional status at baseline. We recommend that any future studies should assess and report worm burden, intensity by each worm type at baseline and end of study as well as baseline and endline nutritional status.

Five long-term evaluations of deworming were assessed in our review, and rated very low certainty of evidence due to judgements about risk of bias, not meeting optimal information size and indirectness (due to including co-interventions of hygiene promotion or sanitation). Future long-term studies, whether randomized or non-randomized, need to minimize threats to internal and external validity as well as consider optimal information size to detect meaningful differences.

6.3 DEVIATIONS FROM PROTOCOL

Risk of bias

In the protocol, we proposed using the SIGN-50 quality assessment tools because they had tools for both RCTs and cohort studies, but given the recent development by the Cochrane Collaboration of ROBINS (Risk Of Bias for Intervention studies), we decided to use the Cochrane risk of bias tool for RCTs, quasi-RCTs and CBAs. If future non-randomized studies can be included in this review, this will allow comparability with the ROBINS tool, which assesses the same domains.

Meta-regression

In assessment of heterogeneity, we proposed using meta-regression to assess the influence of different study characteristics on the effects. However, we could not do this due to small number of studies in the network.

Sensitivity analysis

In the protocol, we described that: "*Sensitivity analyses will be conducted to assess the impact of outlier individual studies (e.g. very large studies, very large effects, very precise confidence intervals) on the overall effect size. Meta-analysis will be conducted with and without studies that may not fully fit inclusion criteria. We will also assess effects of risk of bias, missing data, treatment compliance, imputed variance inflation factor and the effect of unpublished studies using sensitivity analysis.*"

We changed this to a list format and added additional analyses of:

-choice of attendance measure from Miguel 2004 and its replications

-cluster trials vs. individual trials was performed as a sensitivity analysis rather than subgroup analysis
-high prevalence of hookworm (>50 per cent)
-intensity of infection (>30 per cent of children with moderate/ heavy infection)
-impact on worms >50 per cent relative risk reduction (as a measure of the first stage of the causal pathway)

Network meta-analysis ranking of treatments

In the protocol, we planned to rank the probability of each deworming treatment being optimal. We did not do these analyses, since there are doubts about the reliability of these analyses.

Power analysis

In response to peer review comments, we did power analyses for weight and school attendance for albendazole twice per year vs. placebo, using the methods described by Hedges and Pigott 2001.

7 Support and authorship

7.1 ACKNOWLEDGEMENTS

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7.2 CONTRIBUTION OF AUTHORS

Author	Contribution
Vivian Welch	Question formulation, framework design, methodology, analysis, and knowledge translation
Alomgir Hossain	Statistical analysis of data received from authors, adjusting for clustering, network meta-analysis
Elizabeth	Data analysis, presentation and organization

Ghogomu	Nutritionist content expertise
Zulfi Bhutta	
Shally Awasthi	Question formulation and technical advice
Chisa Cumberbatch	Logic model generation
Katelyn Merritt	Logic model generation and protocol development
Robert Fletcher	Question formulation and technical advice
Shari Krishnaratne	Question formulation and technical advice
Jessie McGowan	Search strategy and peer review editorial process
Salim Sohani	Question formulation and knowledge translation
Shalini Suresh	Developed analyses of relationship between worm burden and outcomes
Peter Tugwell	Question formulation, framework design, and knowledge translation

George Wells	Network meta-analysis design, risk of bias assessment, and statistical analysis
Howard White	Policy implications and plain language summary

Advisory Committee

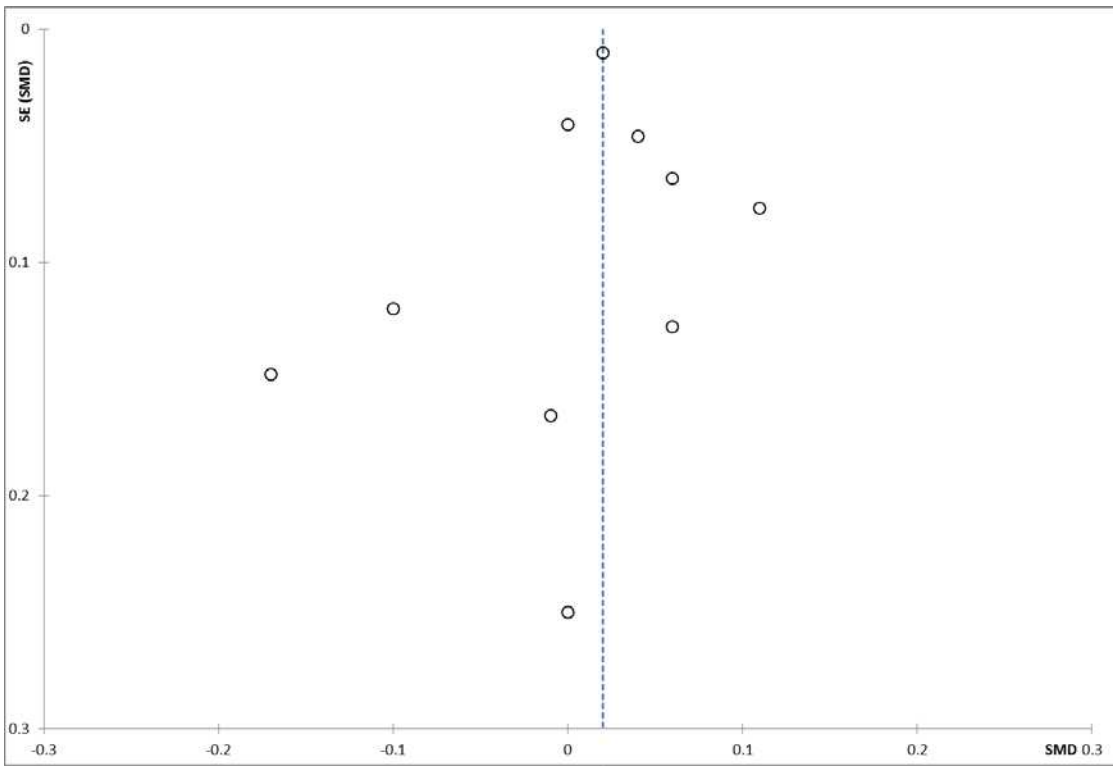
We assembled an advisory committee who informed the development of the research questions and protocol and were asked about possible sources for studies, consisting of Dr. Antonio Montresor, WHO Neglected Tropical Diseases; Dr. Anthony Danso-Appiah, Liverpool School of Tropical Medicine; and Dr. Richa Pandey, UNICEF.

7.3 DECLARATIONS OF INTEREST

The authors are not aware of any conflict of interest, financial or otherwise, that may influence the objectivity of the review.

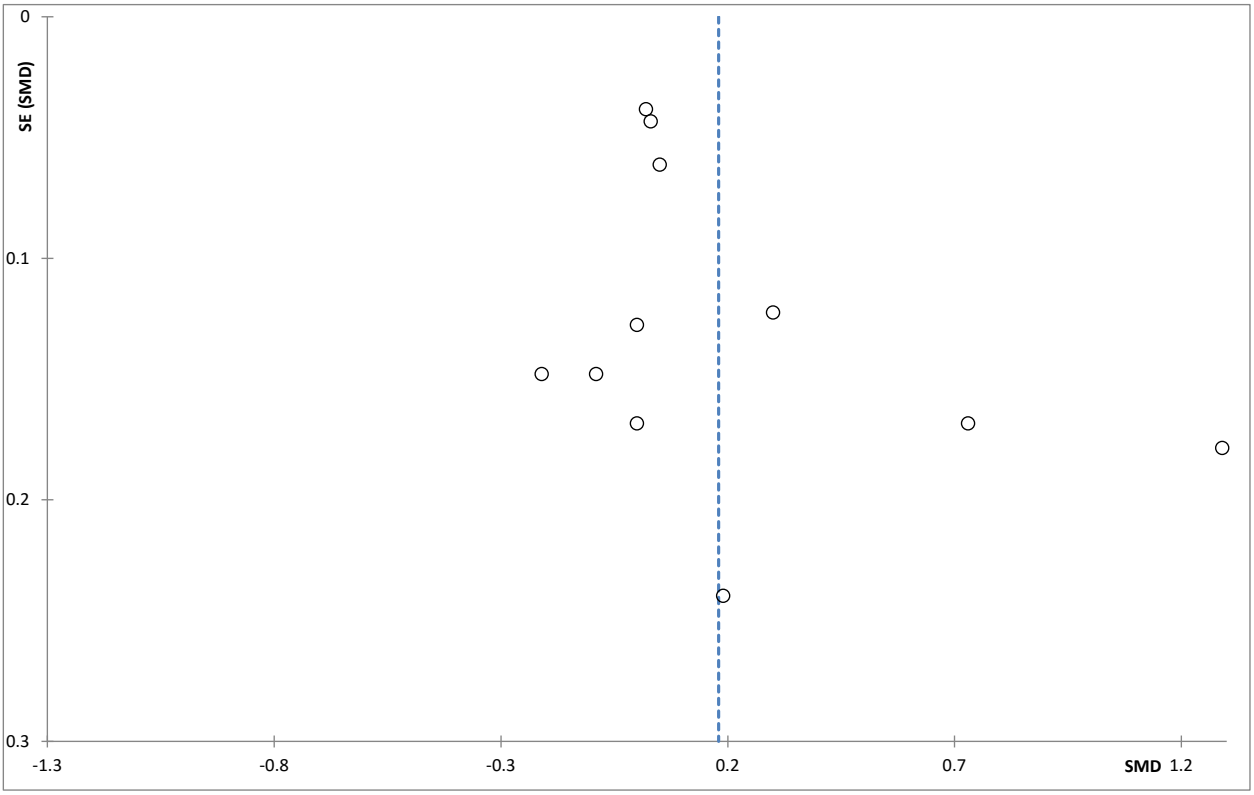
8 Additional Figures

Additional Figure 1: Weight or weight for age: funnel plot for albendazole twice per year vs.

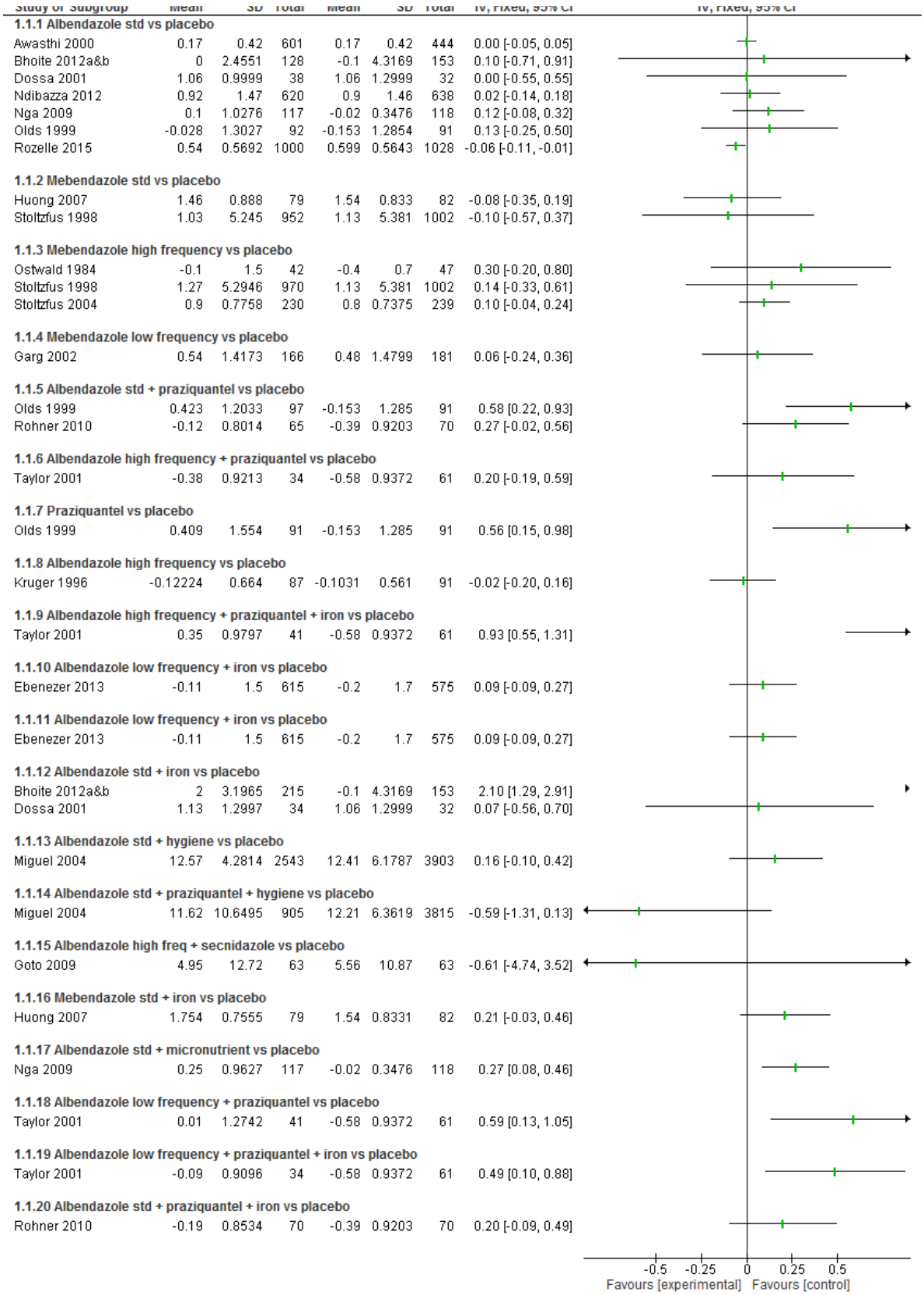


placebo

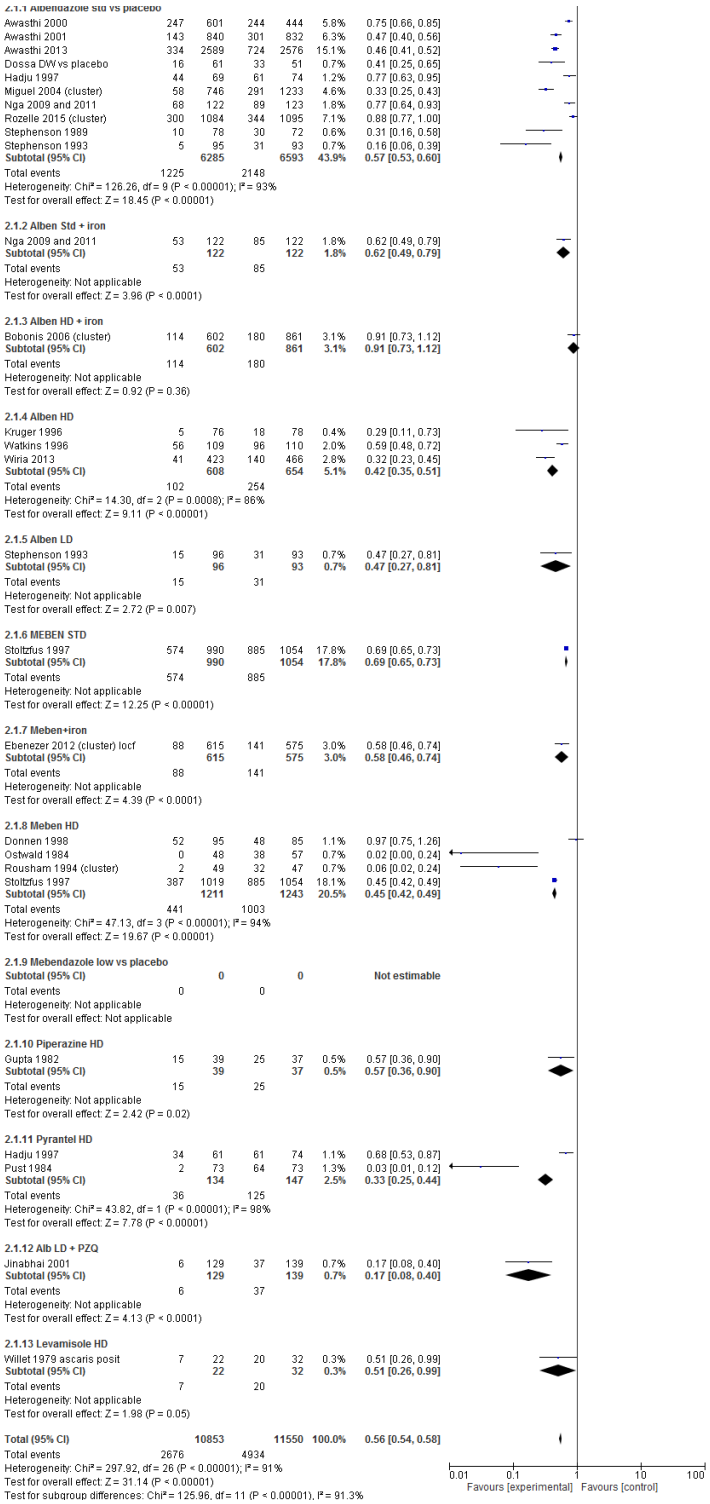
Additional Figure 2: Height or height for age, funnel plot for albendazole twice per year vs. placebo



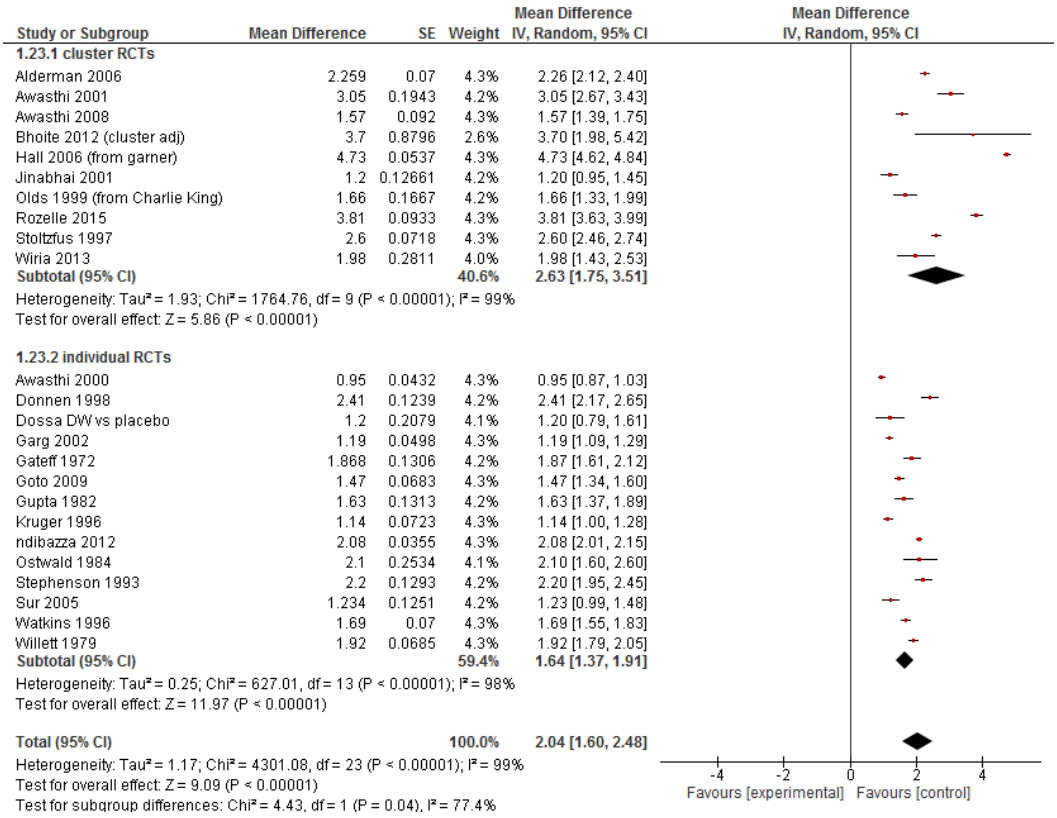
Additional Figure 3: Hemoglobin, g/dL for mass deworming vs. placebo



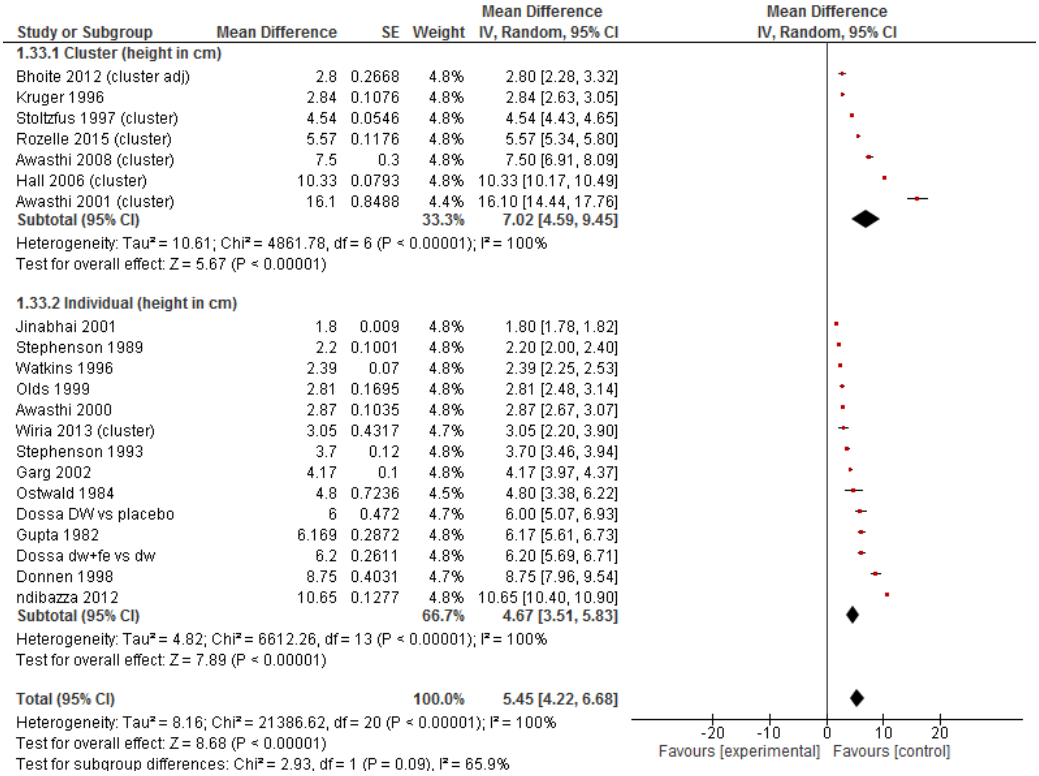
Additional Figure 4: Impact of deworming interventions on worm prevalence (ascaris)



Additional Figure 5: Externalities assessed within study (for studies where control group weight gain in kg could be calculated or was provided)

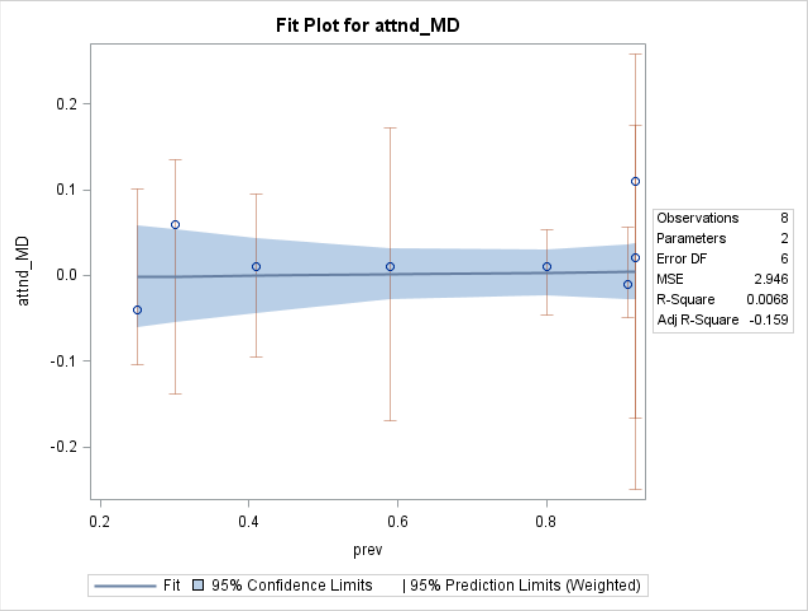


Additional Figure 6: Externalities to control group children, between studies for height gain in cm (for studies which reported height gain or height gain could be calculated)



Additional Figure 8: Weight least squares regression of attendance vs. prevalence of worms

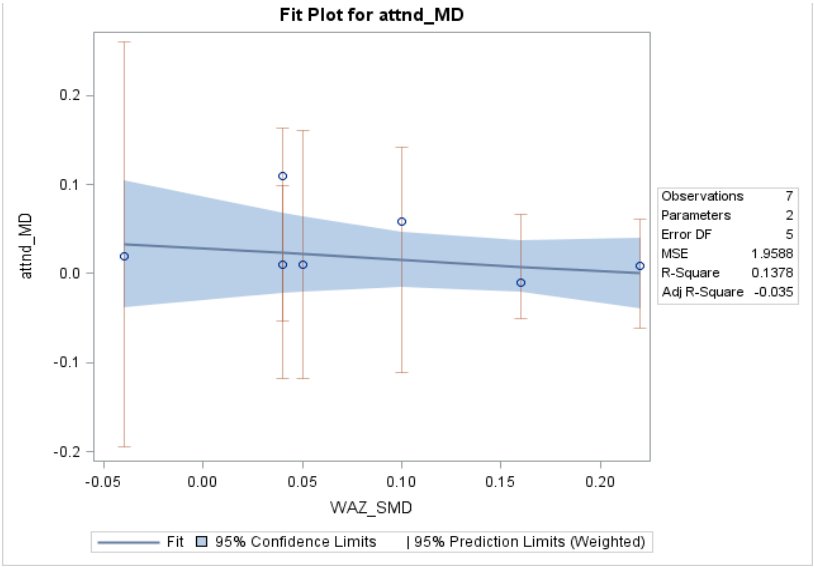
Note: *attnd_MD: attendance mean difference, prev: prevalence of ascaris. Slope: 0.00914, SE*



0.04500 (p=0.8457); intercept: -0.00409, SE 0.03460 (p=0.9096)

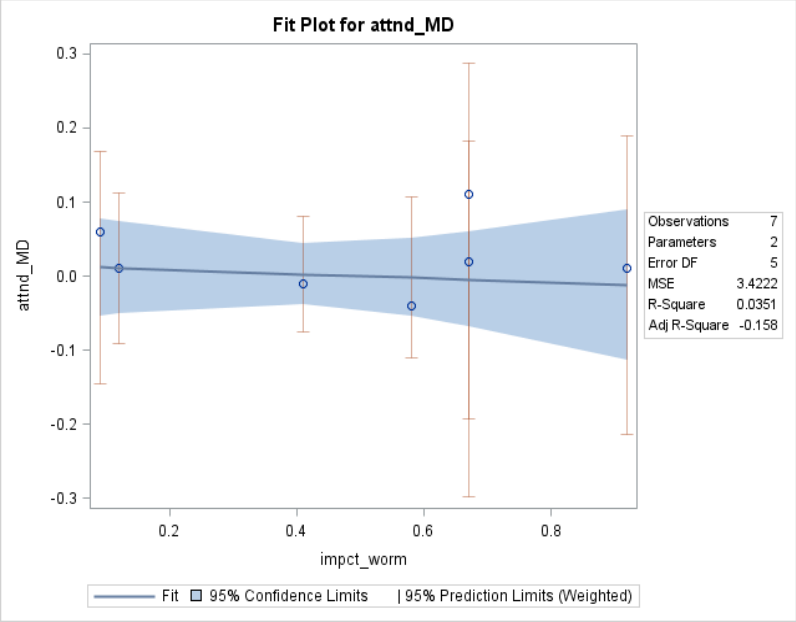
Note: *attnd_MD: attendance mean difference, WAZ_SMD: weight or weight for age*

Additional Figure 7: Weighted least squares regression of attendance vs. weight gain (as SMD)



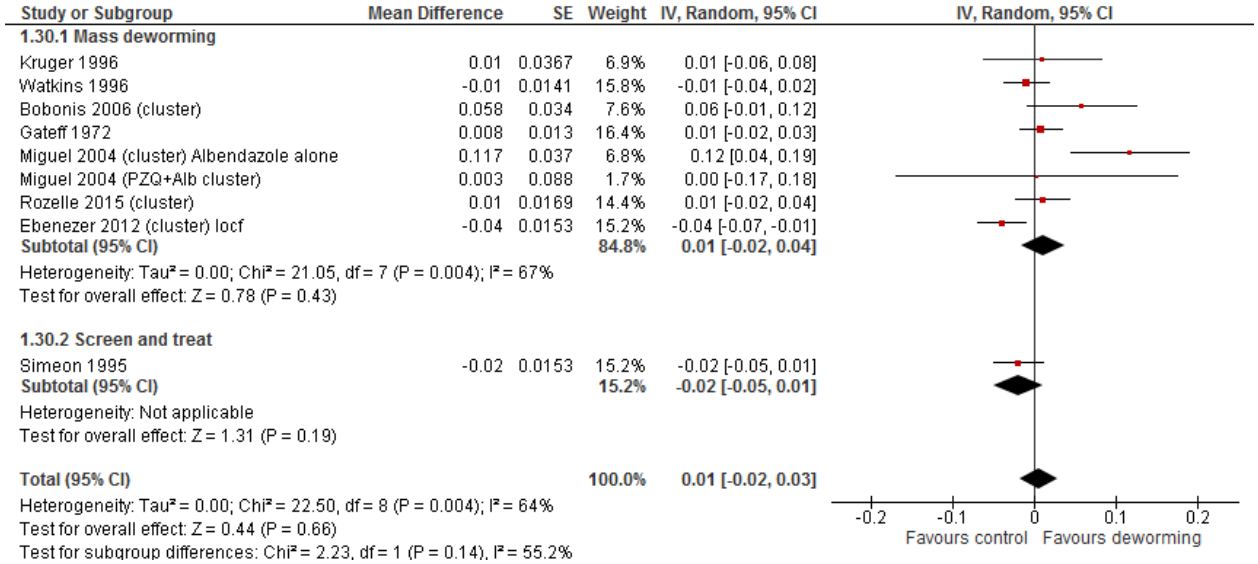
standardized mean difference. Slope: -0.12601, SE 0.14095 (p=0.4123); intercept: 0.02792, SE 0.02245 (p=0.2687)

Additional Figure 9: Weighted least squares of impact on worms and attendance



Note: *attnd_MD: attendance mean difference, impct_worm: relative risk reduction of ascaris. Slope: -0.02909, SE 0.06823 (p=0.6876); intercept: 0.01451, SE 0.03078 (p=0.6573)*

Additional Figure 10: Sensitivity on eligibility criteria: including screen and treat studies for attendance



9 Additional Tables

Additional Table 1: Recommended mass and/or targeted control strategies for soil-transmitted helminths and schistosomiasis in school-age children *Modified from 2011 WHO Guidelines Table 2.2 and 2.3

Soil-transmitted helminths		
Category	Prevalence of schistosomiasis among school-age children at baseline	Preventive chemotherapy
Schools in high-risk areas	≥50 %	Treat all school-age children (enrolled and non-enrolled) twice a year)
Schools in low-risk areas	≥20 % and ≤50 %	Treat all school-age children (enrolled and non-enrolled) once a year)
Schistosomiasis		
Schools in high-risk areas	≥50 % if based on parasitological methods or ≥30 % if based on questionnaires for visible haematuria	Treat all school-age children (enrolled and non-enrolled) once a year)
Schools in moderate-risk areas	≥10 % and <50 % if based on parasitological methods or >1 % and < 30 % if based on questionnaires for visible haematuria	Treat all school-age children (enrolled and non-enrolled) once every two years)
Schools in low-risk areas	≥1 % and <10 % if based on parasitological methods	Treat all school-age children (enrolled and non-enrolled) twice during primary – school years (e.g. once on entry and once on exit)

Additional Table 2: Final search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Helminths/ (46381)

2 (deworm* or de-worm* or whipworm* or whip worm* or hookworm* or hook worm* or roundworm* or round worm* or pinworm* or pin worm* or flukes).tw. (3116)

3 (helmint* or geohelminth* or ancylostoma or Necator* or Ascaris or Ascaridida or Ancylostoma or Necator americanus or Enterobius or Oxyuroidea or Oxyurida or Trichuris or Trichuroidea or Capillaria or Trichinella or Strongyloid* or Oesophagostomum or Oesophagostomiasis or Strongylus or Acanthocephala or Moniliformis or Adenophorea or Enoplida or Secernentea or Ascaridida or Rhabditida or Nematoda or Cestoda or Trematod* or Turbellaria or Platyhelminth* or Rotifera or trichuriasis or ascariasis or trichinellosis or or Trichostrongyloidiasis or ancylostomiasis or enterobiasis or nematode* or cestode* or trematode* or ascarid* or Toxocara* or toxocariasis or schistosomiasis or Schistosoma*).tw. (34746)

4 exp Helminthiasis/ (35533)

5 or/1-4 (65257)

6 Albendazole/ (2219)

7 Mebendazole/ (543)

8 exp Piperazines/ (32356)

9 Levamisole/ (786)

10 exp Pyrantel/ (173)

11 Ivermectin/ (2831)

12 exp Anthelmintics/ (19113)

13 (Ivermectin or Albendazole or Mebendazole or Piperazine* or Levamisole or pyrantel or tiabendazole or anthelmint*).tw. (9572)

14 exp Antiplatyhelmintic Agents/ (4233)

15 (Anticestodal or Antiplatyhelmintic or Anti-platyhelmintic or Albendazole or Dichlorophen or Niclosamide or Quinacrine or Bithionol or Diamfenetide or Nitroxinil or Oxyclozanide or Rafoxanide or Schistosomicide* or Antimony Potassium Tartrate or Antimony Sodium Gluconate or Hycanthone or Lucanthone or Niridazole or Oxamniquine).tw. (3152)

16 or/6-15 (55365)

17 5 and 16 (9423)

18 limit 17 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)") (2028)

19 adolescent/ or exp child/ or exp infant/ (1200007)

20 (child* or paediatric* or pediatric* or youth or infant* or adolescen* or school age* or preschool or pre-school or teen* or schoolchild*).tw. (637932)

21 17 and (19 or 20) (2137)

22 18 or 21 (2137)

23 randomised controlled trial.pt. (226901)

24 random*.ti,ab. (420355)

25 control*.ti,ab. (1394574)

26 intervention*.ti,ab. (338937)

27 evaluat*.ti,ab. (1231245)

28 or/23-27 (2726220)

29 animals/ (2349358)

30 human/ (6490993)

31 29 not (29 and 30) (1537702)

Additional Table 3: Plain language to describe size of effect and GRADE certainty of evidence

	Important difference	Small difference (May not be important)	Little or no difference
High certainty evidence	Improves/ decreases/ prevents/ leads to [outcome]	Improves slightly/ decreases slightly/ leads to slightly fewer (more) [outcome]	Results in little or no difference in [outcome]
Moderate certainty evidence	Probably improves/ decreases/ prevents/ leads to [outcome]	Probably improves slightly/ decreases slightly/ leads to slightly fewer (more) [outcome]	Probably leads to little or no difference in [outcome]
Low certainty evidence	May improve/ decrease/ prevent/ lead to [outcome]	May slightly improve/ slightly decrease/ lead to slightly fewer (more) [outcome]	May lead to little or no difference in [outcome]
Very low certainty evidence	It is uncertain whether [intervention] improves, decreases, prevents, leads to [outcome] because the certainty of the evidence is very low		
No data or no studies	[Outcome] was not measured or not reported, or no studies were found that evaluated the impact of [intervention] on [outcome]		

Additional Table 4: Data received from authors

Author and year	Reason to contact author	Response
Awasthi 2001	-Asked about discrepancy between abstract and tables in manuscript -Asked if data by year used in Cochrane review could be provided to us	Clarification received
Awasthi 2013	Asked authors to provide data for four groups from factorial design: 1) Albendazole; 2) Alb+vitamin A; 3) Vitamin A only; 4) neither vitamin A nor albendazole	Additional analyses provided
Ebenezer 2013	Requested dataset for attendance because we wanted to calculate average attendance as a percentage (rather than number of "good" attenders, as reported in the article)	Full dataset for attendance provided
Goto 2009	Data for ages six months to <16 years	Additional analyses provided
Hall 2006	Requested full report	Full dataset provided
Liu 2015 (Scott Rozelle)	Requested full report	Unpublished report provided

Miguel 2004	Requested data separated for sites that received albendazole only and Albendazole+PZQ	Full dataset provided, with data on which schools received albendazole alone and those that received albendazole+praziquantel in each year of the study
Ndibazza 2012	Requested data for weight and height	Additional analyses provided
Olds, 1999	Full results for hemoglobin and anthropometric measurements were not reported in the paper publication.	Full data set for two out of four sites. Since randomization was within sites, we used this data
Wiria 2013	Requested details on mean for weight and height	Additional analyses provided

Data pending from authors

Author and year	Reason for contacting authors
Beach 1999	We asked for variance for overall sample for weight, height, WAZ, HAZ and WHZ. Data on children egg positive for specific worms reported in subgroup analysis
Fox 2005	We asked for the anthropometric measurements for all children since study reports outcomes for those infected with Trichuris. We asked for the SD or SE with the means for anthropometric data.
Greenberg, 1981	We asked for numerical values for WHZ, WAZ and HAZ (was reported but in graphical representation) and for values for weight, height, triceps skinfold, mid-arm circumference

Author and year	Reason for contacting authors
Gupta, 1977	We asked for weight, height, WAZ (WAZ is used as measurement for nutritional status but only shows change as in whether there was improvement or not)
Hadju, 1997	We asked for end of study weight and height, and for WHZ, HAZ, WAZ, MAC, we asked for mean or SD. We asked for skinfold measurements (taken but not reported)
Jinabhai, 2001(A)	We asked for mean, weight and height, mean SD. For WAZ, HAZ , the article reports proportion improved but not mean and SD
Jinabhai, 2001(B)	Data was reported across intervention arms. We asked for data for each intervention group
Kloetzel 1982	Data on variance was not available
Satoto 2003	Pending. Stepped wedge programmatic evaluation of 55,000 children, with and without mass deworming, reported in a report but no outcome data were provided in the report
Snider 2009	Pending: This is a conference abstract. We wrote to ask if the full report was available
Stoltzfus 1997	Requested data for all age groups combined (because data was reported split across two age groups which were not defined a priori). We also asked for data without adjusting for baseline covariates
Stoltzfus 2007	Pending: One paper has been published in PloSNTD (Wright 2009), but the results for weight for height and anemia (described in the trial registration at ISRCTN83988447) have not been published to our knowledge

Additional Table 5: Excluded Studies

Author year	Reason for exclusion
1. Anto 2011	Too short, three months
2. Araujo 1987	Before-after study, with no control
3. Azomahou 2012	Propensity score matching. Groups were formed from the baseline assessment for an RCT of schoolfeeding. Excluded because there was no data on endemicity or prevalence of worm infection of children, such that groups could have been unbalanced across prevalence of worms
4. Beasley 1999	Screen and treat only children infected with s haematobium and at least one species of geohelminth.
5. Belkind-Valdovinos 2003	Screen and treat only infected children (15%) of population. Excluded since it is not mass treatment
6. Bhargava 2003	Screen and treat only infected children. Treatment group consisted of children with no infection (not treated) and children with heavy infection (who were treated) compared to unscreened group.
7. Bhutta 2009	Exclude since <4 months, duration three months
8. Biggelar 2004	No outcomes of interest. RCT of albendazole+praziquantel vs. control to assess effects on skin sensitivity.
9. Bradfield 1968	Too short- 10 weeks
10. Cooper 2006	No outcome of interest. Cluster RCT of albendazole vs. control to assess effect on atopy and allergy outcomes.
11. Cowden 2000	Review of previous trials, Not a randomised controlled trial.

Author year	Reason for exclusion
12. Diouf 2002	Too short (60 days): Mebendazole, vitamin A, iron and metronizadole for children aged 6-36 months.
13. Evans 1986	Treatments randomised, but some placebo groups accessed treatment. Analysis was by the treatment received, and randomization was ignored. (Included in the Dickson 2000a Cochrane Review).
14. Fernando 1983	Cluster RCT of children aged 0-10 in two villages. Excluded because the results are not reported for the entire randomised population (only reported for children aged 4-5 years)
15. Forrester 1998	Screen and treat, RCT of infected children only
16. Friis 2003	RCT, no primary outcomes (measured hemoglobin)
17. Gilgen 2001	Population included adults.
18. Gopaldas 1983	RCT, no primary outcomes (measured hemoglobin)
19. Hadju 1996	RCT of pyrantel. All children were infected Trichuris trichiura (100%). Prevalence of Ascaris lumbricoides (86%).Not mass treatment.
20. Hathirat 1992	All children received albendazole. Children were randomised to iron or a placebo (iron) Companion paper assessed cognition- all children received deworming (Pollitt 1989)
21. Jalal 1998	Screen and treat, all children were infected
22.Kamble 2011	All adolescent girls received mebendazole, and were randomly allocated to iron.
23.Karyadi 1996	Too short, 10 days

Author year	Reason for exclusion
24.Kirwan 2010	RCT, did not measure one of primary outcomes, plasmodium infection was primary outcome, haemoglobin was also reported
25.Krubwa 1974	Screen and treat, all children were infected, not an RCT
26.Kvalsvig 1991b	Screen and treat infected children
27.Latham 1990	Screen and treat, all infected with schistosomiasis
28.Lynch 1993	No outcomes of interest- allergic reactivity only
29.Marinho 1991	No primary outcomes of interest (blood vitamin A levels)
30. Mwaniki 2002	Screen and treat, all children infected
31. Palupi 1997	Too short- nine weeks. RCT of albendazole+iron vs. iron alone for effects on hemoglobin.
32.Pollitt 1991	Screen and treat infected children, CBA
33.Rohner 2010	RCT, no primary outcomes of interest (hemoglobin measured)
34.Steinmann 2008	Excluded since it measures cure rate only, no growth or cognition
35.Stephenson 1980	No untreated controls, compared to levamisole
36.Sufiyan 2011	Too short (3 months)
37. Tanumihardjo 1996	Screen and treat, children infected with Ascaris, retinol outcome only
38.Tanumihardjo 2004	Screen and treat. All children were infected with Ascaris or Trichuris. Timing of deworming was randomised
39.Thein-Hlaing	Excluded because they selected a sample of children for analysis, and the methods for selecting the sample was not

Author year	Reason for exclusion
1991	provided
40. Tripathi 2004	Too short- three months. Study of albendazole single dose combined with iron vs. iron alone.
41. Uscátegui 2009	Too short: only 30 days
42. Wright 2009	No relevant outcomes. Measured only immune responses. Wrote to ask whether WHZ and anemia were reported elsewhere
43. Yang 2003	Did not consider nutritional or cognitive outcome measures.

Additional Table 6: Ongoing studies

Reference	Study design	Status	Contact with authors
Satoto 2003	Stepped wedge programmatic evaluation	No publication found, report of the design in a book chapter	Wrote to members of the original team but have not been successful in finding a report of this study
Snider 2009	Completed RCT of albendazole 2/year vs. Albendazole 4/year, children aged 2-5 year,	Weight for age, haemoglobin, worm prevalence and intensity of infection at 12 months	Published in conference proceedings only, www.astmh.org, abstract #315, page #90, 2009
Stoltzfus 2007	RCT of Mebendazole vs. placebo in children six to 36 months of age http://www.isrctn.com/ISRCTN83988447	Haemoglobin, MUAC, anorexia, WHZ, HAZ, inflammation	

Additional Table 7: Table of included studies, participants and setting

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Alderman 2006	cRCT intervention: 25 parishes control: 25 parishe	Uganda	Proportion female: 50% SES:	Baseline weight: NR Mean WAZ (control group): -1.17 (SD 1.45) Proportion underweight: 26%	NR	Proportion anemic: nr; Hemoglobin: nr vitamin A/retinol: nr	Weight gain (Alderman) Long-term math, English, height (Croke 2014)	Overall: 55.9% Ascaris: 17.5% Hookworm: 44.5% Trichuris: 7.3%	Not reported	"Controlled for using multivariate regression models"

Authors	Study designs	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Awasthi 2000	RCT	India	Proportion Female: 48%; Place of origin: Education: illiterate mother: 80.3% Religion: 67 % Hindus; 33	Baseline weight: 10.2 (SD 2.1); WAZ: NR Proportion underweight: 66.3%	Baseline height: 81.7 (SD 8.7); HAZ: NR Proportion stunted: 54.77%	Proportion Anemic: 91.1 % (less than 11g/dl); Hemoglobin baseline: 9.5 (SD 0.9) Vitamin A: NR	Number underweight, number stunted, weight (kg), height (cm), hemoglobin (g/dl), development (R-PDQ-Denver Questionnaire), cost per child prevented from becoming underweight. Not used: illness episodes	Ascaris: 11-13%	Not reported	Field defecation: 52.5%

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			Percentage Muslims SES < 1000 rupees/month: 94.4%							
Awasthi 2001	cRCT	India	Proportion female: 49% SES: Family income below poverty line, Setting: suboptimal living	Baseline weight: 7.03 (0.15); WAZ: -1.99 (SE 0.13), Proportion underweight: 47.1%	Baseline height: 64.9 (SE 3.25) HAZ: -2.44 (SE 0.2) Proportion stunted:	NR	Weight, height, WAZ, HAZ, WHZ, number underweight, number stunted, number wasted	Ascaris: 9%	NR	Suboptimal living conditions

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			conditions		59.7%					
Awasthi 2008	cRCT	India	Proportion female: 51%, Place of origin: Lived in slums	Baseline weight: 11.6	Baseline height: 85.2	NR	Height and weight gain	NR	NR	Government defined slum areas
Awasthi 2013 (DEVTA	cRCT	India	Proportion female: 50%	Baseline weight: 11.05 Proportion underweight:	Baseline height: 81.6	Hemoglobin level: 99.4	Helminth egg count, weight gain, deaths, height gain, BMI, hemoglobin, illness in past four weeks	Ascaris midstudy: 27%; Hookworm:	Ascaris 96 epg Hookworm 83 epg	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
articles)				NR				midstudy:8.0%;		
Beach 1999	RCT	Haiti	Proportion female: 47.7% no others reported	Baseline weight: 20.8 WAZ: -0.859 Proportion underweight: nr	Baseline height: 117.6 HAZ: -0.770 Proportion stunted: nr	Baseline anemia: mild = 5%; moderate = 0.3%, severe = 0%	Nutritional benefits, prevalence and intensity of intestinal helminth infection post treatment, anthropometric measurements (height, weight, HAZ, WAZ, WHZ), reinfection	Ascaris: 29.2 % Hookworm: 6.9% Trichuris: 42.2%	5 % of infections heavy	NR
Bhoite 2012	cRCT	India	NR	Weight (kg): 23.7 (4.8)	Baseline height: 131.4 cm	Proportion anemic:	Weight, height, weight for age, height for age, BMI,	NR	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
a& B				Proportion underweight: 50.9 %	(SD 9.1) Proportion stunted: 26.7%	90.6 Hemoglobin:10.5 +/- 1.4 g/dL	hemoglobin levels and physical work capacity (number of steps)			
Bobonis 2006	cRCT Intervention: 59 clusters Control	India	Proportion female: 55 % Occupation: Mother Housework: 78%. Father Labourer: 35 % Religion:	WAZ: -1.02 Proportion underweight. 30 %	HAZ: -0.45 Proportion stunted: 24 %	Proportion anemic: 7 % (severely) and 41 % (moderately) 69 % of children in group 1 had	WHZ, WAZ, HAZ, weight, height, BMI, hemoglobin, school participation	Overall: 30% Ascaris: 21 %	NR	Reinfection deemed likely

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
	: 96 clusters		Hindu: 75%, Muslim 25% Education: Mother: education level (years): 3.3; father 5.8;			anemia. Mean hemoglobin: 9.95g/dL in group 1				
Donnen 1998	RCT	Zaire	Proportion female: 0.436	Weight: NR WAZ: NR Proportion underweight: 50.4 %	HAZ: NR Proportion stunted: 65%	Proportion anemic: NR Hemoglobin: NR	Weight gain, height gain, WAZ, HAZ, WHZ, mid-upper-arm-circumference, fecal egg counts (prevalence and intensity); hematology: levels	Ascaris: 10.5 %	NR	Food supply is constantly poor in energy and periodically poor

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
						Retinol deficient: 19.2 to 25.6%	of retinol, albumin, retinol binding protein (RBP), c-reactive protein (CRP)			in protein, depending on the season. Diet very poor in lipids.
Dossa 2001	RCT	Benin	NR	Weight (kg) 12.7 (1.5) (Arm 1-control)	HAZ -2.48 +/- 0.88 (control). proportion stunted: 0.66 (control)	Proportion anemic: 78 % Hemoglobin: 10.2+/- 0.9(control)	Change in weight, height, MUAC, triceps skinfold thickness; hemoglobin level and eggs per gram of feces	Ascaris: 38% Hookworm: 13% Trichuris: 47%	Ascaris: 19,874 epg Hookworm 781 epg Trichuris	Results suggest that reinfection was a continual process as sanitatio

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
									1918 epg	n and hygiene conditions did not improve throughout study
Ebenezer 2013	cRCT Intervention: 49 schools	Sri Lanka	Proportion females: 0.468	WAZ: not reported. proportion with low BMI : 0.438 (control)	HAZ: not reported. proportion stunted: 0.294 (control)	Proportion anemic: 16.5 % (control) mean hemoglobin levels (sd): 12.4(1.3)	Code transmission test to measure children's attention, hemoglobin levels were estimated, egg count using the modified kato-katz techinque	Any helminth infection: 25.2% Hookworm : 5% Roundworm: 21.2 %	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
	Control: 49 schools					(control)		Whipworm: 4.7 %		
Fox 2005	RCT	Haiti	Proportion female: 54.3%	NR	NR	NR	Weight, height, WAZ, HAZ, adverse effects (eg headache, fever, stomach pain, etc), egg count in the feces sample, and nutritional benefits if any.	Ascaris: 31.7 % Hookworm: 10.1% Trichuris: 51.0%	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Garg 2002	RCT	Kenya	Proportion female: 44 % Education: 90-93 % of parents had at least primary education, SES (reported similar socio-economic status, but no data	Weight: 12.92+/-0.19 WAZ: -1.24 (0.08) Proportion underweight: 28%	HAZ: -1.48 (0.08)	Proportion anemic: 61% hemoglobin:11.24 +/- 0.11; Hb concentration <11 g/dL	Mean differences for weight, height, weight for age, height for age and weight for height in SD units; change in hemoglobin concentration; egg counts (intensity).	Ascaris: six % Hookworm: six % Trichuris:1 %	Moderate to heavy infection: 1.6%	Low: most/all of the children had access to a pit latrine (not associated with helminth infections)

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			shown),							
Gateff 1972	RCT	Cameroon	212 female, 180 male -very poor hygiene, poor sanitation (open excretion), shoes rare, poor	Not reported	NR	NR	Weight (difference), School notes (difference), attendance (difference)	Any parasite: 80% (mostly ascaris, ankylostoma duodenale (hookworm), or	NR, hyperendemic area	High: almost no access to toilets, poor hygiene, poor sanitation (open excretion

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			hygiene					strongyloides)		)
Goto 2009	RCT	Bangladesh	Proportion female: 20 % (FSA) Occupation-FSA grp: (fathers) None or daily income: 15 % (mother) household: 32 % Education-FSA grp:	WAZ: -1.95 Proportion underweight: 48 % of infants	HAZ: -1.22 Proportion stunted: 23 % of infants	Proportion anemic: 96 % at baseline, 82 % at end of study Hemoglobin: 91.9+/-12.2	Hemoglobin, HAZ, WAZ, WHZ, plasma albumin, IgG, Alpha-1-acid glycoprotein, Giardia-specific IgM titre, lactulose/mannitol ratio, prevalence of Giardia-specific IgM titre, prevalence of Giardia cysts, prevalence of Ascaris/Trichuris, prevalence of	Ascaris: 1% Trichuris: 1%	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			(father's) None: 17%; (mother's) None: 14%; SES: Housing condition: Poor= 5 %				Intestinal mucosal damage, prevalence of Anaemia			
Greenberg 1981	RCT	Bangladesh	Proportion female: nr Gender/sex: comparable Religion: comparable	Weight/WAZ: measured but not reported proportion underweight: 71.4 % (<-2)	baseline stunted: 88.9 % (Arm 1)	NR	Weight, height, weight-for-age, height-for-age, weight-for-height, triceps skinfold, midarm circumference, triceps-skinfold-for-	Ascaris: 81% Hookworm: 5% Trichuris: 65 %	Moderate to high: 36%	Inadequate sanitation

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			Education: comparable SES: comparable				age, pot belly, abdominal girth to chest circumference ratio, cure rates, reinfection rates, severity of infection			
Gupta 1977	CBA	India	Proportion female: NR; SES: comparable	baseline weight (% WAZ): 71.15, (group 1)	baseline height (% HAZ): 85.36 (group 1)	Hemoglobin: NR Nutritional status improved: 0.372 (16//43) (placebo)	Weight, change in nutritional status, presence of ascaris in stools	Ascaris: 60%	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Gupta 1982	RCT	Guatemala	Proportion female: nr Place of origin: Santa Maria Cauque village in Guatemala SES: comparable	Baseline weight (%WAZ): 71.15+/-7.57 (group 1) Proportion underweight: NR	Baseline height (%HAZ): 85.36 (group 1) Proportion stunted: NR	NR	Height, weight, %height for age, % weight for age, % weight for height, slope of height on age, slope of weight on age, ascariasis prevalence, giardiasis prevalence	Ascaris: 60%	NR	NR
Hadju 1997	RCT	Indonesia	Proportion female: 1.05, Place of origin:	Weight: 18.9 (2.9) kg (Arm 1)	HAZ: -2.08 (0.8) (Arm 1)	NR	Prevalence and intensity of infection, anthropometric measurements	Ascaris: 93 % Trichuris: 97%	Ascaris: 4,518 epg Trichuris 2,427 epg	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			urban slums; SES: socioeconomic data was not collected				(weight, height, mid arm circumference, WAZ, HAZ, midarm circumference Z score).			
Hall 2006	cRCT	Vietnam	Proportion female: NR Place of origin: Dong Thap province, Vietnam;	Baseline weight: 17.8 kg +/- 2.54 (comparison group) WAZ: -1.541 +/- 0.907 (comparison	Height (cm): 121.0 (4.81) HAZ: NR Proportion stunted:	NR	Weight, height, height for age, weight for age, weight for height, body mass index, appetite	Ascaris: 70.7% Hookworm: 7.2% Trichuris: 83.6%	Ascaris: 7533 epg Hookworm: 7 epg Trichuris: 518 epg	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			SES: nr	group) Proportion underweight: NR	29%					
Huong 2007	RCT	North Vietnam	Proportion female: 51.2 % (Arm 1)	WAZ: -1.9(0.6) (placebo) proportion underweight (baseline) : 45.1 % (Arm 1); [defined as z-scores <-2 SD (WHO, 1995)]	HAZ: -1.7 (0.8) (placebo) proportion underweight: 31.7 % (Arm 1) [defined as z-scores <-2	Proportion anemic: 91.5 % (Arm 1) [defined as: Hb concentration of <115 g/l]; Hemoglobin: 107.8 (6.2) (Arm	Hemoglobin, prevalence of underweight, stunting and wasting, prevalence of anemia, body iron (serum ferritin, TfR, CRP, haemoglobinopathies), parasite infection status, inflammations, and	Ascaris: 69.5 % Hookworm: 11 % Trichuris: 73.2%	Data on intensity not reported in paper, however, "most infections were 'light' or 'average' and only	Lack of adequate sanitation and safe water supplies, poor sanitation facilities.

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
					SD (WHO, 1995)]	1) [Mean Hb in g/l - (SD)]	IgE		27 % and 2 % among infected children showed severe infection with Ascaris or Trichuris ".	
Jinabhai 2001	RCT	South Africa	Place of origin: rural;	Weight: Arm 1 = 26.8kg (SD 3.5) WAZ: 0.7 % or one child	HAZ: 9.5 % or 13 children (<-2 SD);	vitamin A deficiency found in 34.7 % of	Weight, height, % stunted, % underweight, worm burden, prevalence	Ascaris:28.8% Hookworm	Mod to heavy infection:	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
A			SES: low SES;	(<-2 SD); virtually none underweight (7%)	stunted: 6.8%	the children (retinol <0.70)	and intensity of helminth infection	: 3.1% Trichuris: 53.7% Schistosomias: 24.5%	40.3%	
Jinabhai 2001 B	RCT	South Africa	NR	Mean Weight (kg): 26.89 +/- 3.75; underweight: 0.8 %	Height (cm): 127.73 +/- 5.87; stunted: 7.3%	Proportion anemic: 15.5 % (Hb<120g/L); Hemoglobin: 128.09+/1.10 (control)	Serum albumin, serum retinol, haemoglobin, haematocrit, serum ferritin,serum iron and percentage transferrin saturation). Helminthic infections	Ascaris: 28.8 % Hookworm: 3.1 % Trichuris: 53.7 % Schistosomiasis:	Mod to heavy infection: 40.3 %	Only 50 % of children had access to portable water at home

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
						vitamin A deficiency : 34.7 % of the children (retinol <0.70);	(prevalence and intensity). Nutritional status. Weight, height and knee–heel length. Scholastic and cognitive tests.	24.5%		
Joseph 2015	RCT (to be added in next update)	Peru	Proportion female:45.5 % Maternal secondary education:	Weight: 8.7 kg (0.9)	Height: 72.2 cm (2.5)	NR	Weight, height, WAZ, HAZ, adverse events, mortality, Bayley Scales of Infant and Toddler Development, Third Edition	Ascaris: 20.2% Hookworm : 1.5% Trichuris: 10.8%	No heavy infections	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			32% Employment outside the home: 8% Peri-urban or rural residence: 91% Earth or wood house: 76%				(Bayley-III)	Schistosomiasis: NR		
Kaba 1978	CBA	Zaire	Proportion female: 61.7 %	Baseline weight: 20.01 kg (range 10-	not done	Proportion anemic: 63 % (defined	Weight, hemoglobin, parasite load	Any infection: 85 %	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			PROGRESS+: NR	30) Weight: 20 kg, sd 5 kg		as <12 g percent hemoglobin) Baseline Hemoglobin: 11.73g p.cent		Ascaris: 40%; Hookworm: 43% Trichuris: 68% Schistosomiasis: 1.1%		
Kloetzel 1982	RCT	Brazil	Proportion female: nr Place of origin: rural	NR	NR	after 10 months of treatment nutritional status	Weight (for undernourishment-number improved/ deteriorated), length, head, chest	Ascaris: 53% Trichuris: 20%	Mod to heavy infection: 18%	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			communities SES: children were from poor socioeconomic			improved more than it deteriorated for both the experimental and control groups	and mid-arm circumference, and triceps skin fold.	Hookworm: 8%		
Koroma 1996	RCT	Sierra Leone	NR	proportion underweight: rural: -1.17+/-0.21 urban: -1.07+/-0.77	mean stunted: rural: -1.68+/-0.30 urban:	NR	WAZ, HAZ, WHZ, egg counts (prevalence and intensity)	Ascaris urban: 32%; Rural: 46% Hookworm: urban:	Ascaris: 2278epg Hookworm: 588 epg Trichuris	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
					-1.14+/-0.09			10%; Rural: 25% Trichuris: urban: 65%; Rural: 1% Schistosomias: urban: 6%; rurual: 14%	: 262epg	
Kruger 1996	RCT for deworming vs. placebo	South Africa	Proportion female: nr; Ethnicity: mixed ethnic	Weight: 19.1 (2.6) (low Iron) 19.6 (2.3) (adequate iron) p=	Height 113.8 (5.2) (low Iron) 115.5 (4.6) (adequate iron) p=	Proportion anemic: 0.235 or 0.425 according	Weight, height, WAZ, HAZ, WHZ, hemoglobin, iron status (MCV, serum ferritin, MCH, TIBC, TS, WCC),	Overall: 58.7% Ascaris: 20.0 %	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
	cRCT for iron vs. no iron, with and without deworming		origin (European, African, Malay);	.2264	0.432	to WHO Hemoglobin: Mean SD p (g/dl) 11.7g/dl (0.9)-Arm 1	attendance (school records), egg counts	Trichuris: 38.1% Any STH infection: 58.7%		

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Lai 1995	RCT	Malaysia	Proportion female: 60.5%; Place of origin: urban/periurban, Ethnicity: same ethnic groups (eating similar food), Education: similar mother's	Weight: 19.12kg (Arm 1) WAZ-underweight: 29.35	HAZ: 15.6 % (male and female both) Stunted: 14.35 (Arm 1)	NR	Weight and height (weight for age, height for age, weight for height), worm prevalence, eggs/g feces	Ascaris: 66 % Hookworm: 5 % Trichuris: 69%	Mod to heavy Ascaris: 26% Mod to heavy trichuris: 34 %	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			education, SES: similar SES							
Linnemayr 2011	cRCT	Senegal	Gender, parent's occupation and level of education are presented as regression coefficients and not	WAZ: -1.317 (1.417) proportion underweight not reported	HAZ and proportion stunted not reported	NR	Weight for age Z scores	NR	NR	Poor sanitation with limited piped water/latrines

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			proportions.							
Makamu 2016	observational	Nigeria	Baseline not reported	Weight not measured	Height not measured	Not measured	School enrolment, years of education completed	NR	NR	Poor hygiene practices, less likely to use latrines, educated on the importance of hand washing, wearing shoes,

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
										and not swimming in infected fresh water.
Michaelsen 1985	CBA	Botswana	NR	Not mentioned	NR	anaemia: the lowest value: 9.6 g/100 ml, hemoglobin baseline: 12.91 g/ml (control)	Hemoglobin, weight, height, weight-for-height, egg counts.	Hookworm: 86%	Mod to heavy infections: 1%	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Miguel 2004	cRCT	Kenya	Proportion female: 47%; Place of origin: farming region, SES: similar socioeconomic characteristics;	WAZ: -1.44	HAZ: -1.44 +/- 0.86; Proportion stunted : 25.5 %	Proportion anemic: 4%, hemoglobin: 12.4g/dL	WAZ, HAZ, hemoglobin, malaria, exam score performance, cognitive tests, school participation, worm prevalence and intensity, self-reported sickness, worm prevention behaviours: proportion “clean” as per health worker observation, proportion	Overall: 92% Ascaris: 42% Hookworm: 77% Trichuris: 55% Schistosomiasis in schools <5 km from Lake Victoria:	Any worm mod to heavy:37 % Ascaris: 16% Hookworm mod-heavy:15 % Trichuris mod to heavy:10 %, Schistoso	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
							wearing shoes as per health worker observation, self-reported contact with fresh-water in past week, access to home latrine, malaria/ fever	80% Any STH: 92%	miasis mod to heavy:39 %	
Monse 2013	CBA	Philippines	Proportion female: 49.4%; SES: low-middle income	NA	NR	NR	Prevalence of STH infections, dental caries, BMI	NR	Mod to heavy infection: 32%	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Ndibazza 2012	RCT	Uganda	Proportion female: 5 % Place of origin: rural settings, education of mothers: none or primary: 54%	2 yrs: WAZ: 20.57 (1.07) (placebo) proportion underweight: not reported.	2 yrs: placebo=20.98 (1.37) proportion stunted: not reported	hemoglobin levels: 2yrs placebo=11.06 (1.27)	WAZ, HAZ, WHZ, Hemoglobin, cognitive tests, adverse events, death, prevalence of helminth infection, post immunisation recall responses to BCG and tetanus antigens, incidence of malaria, diarrhoea, pneumonia, and eczema, fine motor function and gross motor function	Trichuris: 2.3%, 4.4%, 5.2 % and 5.3 % in 2, 3, 4 and 5 yr olds Ascaris: 1%, 0.9%, 0.9 % and 0.5 % in 2, 3, 4, 5 yr olds. Hookworm: 0.3%, 0.1%, 0.7 %	Intensity of helminth infection was generally low	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
								and 0.5 % in 2, 3, 4, and 5 yr olds		
Nga 2009	RCT	Vietnam	Proportion female: 0.508	WAZ: -1.56 (0.69) , proportion of underweight: 0.285	HAZ: -1.41 +/- 0.87. proportion of stunting: 0.251	Proportion anemic: 23.7 % (placebo) hemoglobin concentration levels: 12.03(0.7) Vitamin A deficiency : 11.2 % of	WAZ, HAZ, WHZ, mean MUAC, cognitive function, hemoglobin, worm prevalence, changes in zinc, iodine and ferritin concentrations	Overall helminth prevalence: 92 % Ascaris: 66.7 % Trichuris: 56.1 % Hookworm	Ascaris mod-heavy: 4.1% Hookworm mod-heavy: 12% Trichuris mod-heavy:	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
						the sample		: 4.1%	8%	
Olds 1999	RCT	China, Philippines and Kenya	proportion female: 0.525 PROGRESS+: NR	29.6 kg (10.7)	33.54 cm (20.1)	Initial hemoglobin level: 11.8 (1.8) (placebo) (all values are in g/dL).	Hemoglobin levels, egg counts, anthropometric measurements, side effects	Ascaris: 60.2 % Hookworm: 52.1% Trichuris: 81% Schistosomiasis Japonicum (46%),	Study conducted in an area with generally light infections	There was increase in infestation among the control group due to environmental

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
								Mansoni (79%), Haematobium (87%)		exposures of the toddlers
Ostwald 1984	RCT	Papua New Guinea	Proportion female: NR Place of origin: central highlands of Papua New Guinea SES: NR	Baseline weight: 27.8 kg (control) WAZ and proportion underweight: NR	Baseline height: 126.6 cm (control) HAZ and proportion stunted: NR	Proportion anemic: NR Hemoglobin baseline: 14.2 g/dl	Weight, height, weight for height, hemoglobin, ferritin, transferrin, serum folate, serum ascorbate, parasite prevalence.	Ascaris 67 % Hookworm 92 % Trichuris 64%	Majority light infections	Few public taps served as water supply, non-hygienic as there were few public toilets hence

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
										defecation on the streets.
Pust 1985	Cluster CBA	Papua New Guinea	NR	NR	NR	Proportion anemic: 5 %	Anthropometry (weight, mid-upper arm circumference, triceps skin fold and length), haematocrit, vitamin A and serum albumin analysis, morbidity and mortality	Ascaris: 63 % Hookworm: 60 % Trichuris 37%	Heavy infections: 30%	There was no apparent difference between villages in terms of environmental factors or housing which

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
										might have led to an increased prevalence of trichuris in the mebendazole group
Reddy 1986	RCT	India	Place of origin: rural residence, Ethnicity: majority	NR	NR	Vitamin A Deficiency: 13 % and 45 % had low levels of vitamin	Height and weight, serum vitamin A, ascaris prevalence	Ascaris: 35%	NR	High, 5 % drink boiled water only, 65 % use

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			muslims, Occupation: dependent on rickshaw pulling or casual labor, some have clerical jobs SES: low socio-economic strata.			A				feces as fertilizer, 84 % washes hands before eating, 87 % washes hands after toilet,

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Roushan 1994 B	RCT	Bangladesh	NR Occupation: diverse: farmers, business men and professionally employed.	Children of Farmers: - 2.61, Children of Business Men: - 2.48, Children of other Professionals: - 2.18; underweight: 73%	Male: -2.76 Female: -2.99 Children of Farmers: -2.98, Children of business men: -2.74, children of other professionals: -2.31	NR	Height weight, HAZ, WAZ, WHZ, MUAC, worm prevalence and intensity (egg counts)	Ascaris: 71% Hookworm: 10% Trichuria: 44%	Mean intensity was low. No mod-heavy infections.	Dependent on shallow wells for water supply, adult habit of indiscriminately defecating in the field and children on the streets.

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Rozelle 2015	cRCT Intervention: 56 townships Control: 56 townships	China	43 % female (control group) Migrant workers: 31% Mother attended secondary school: 7%	Weight: 28.63 kg WAZ: nr Underweight: 24%	Height: 132.95 cm HAZ: nr Proportion stunted: 23.48%	Proportion anemic: 16.62% Hemoglobin: 125.17 g/dL Vitamin A deficient	STH infection prevalence, stunting and underweight prevalence, working memory index, processing speed index, school attendance, mathematics test scores, infection intensity (fecal egg counts), anemia prevalence (Hb levels), height, weight, HAZ, WAZ, BMI,	Ascaris: 30.5% Trichuris: 23.3% Hookworm: 1.0% Any STH: 41.1%	Ascaris: 728.3 epg Trichuris: 55.9 epg Hookworm: 17.3 epg	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Shah 1975	cRCT Intervention: 2 villages Control: three villages	India	NR	NR	NR	NR	Severity of ascarial infection, weight gain and helminth count	Ascaris 33.5% Hookworm 6% Trichuris 7 %	Majority of the infections are of a mild intensity.	NR
Solon 2003	RCT	Philippines	Proportion female: 0.481	WAZ: -1.70 (0.71)	HAZ: -1.83 (0.88)	Proportion anemic: 0.52 hemoglobi	Weight, height, hemoglobin, UIE, stool egg count, physical fitness, heart rate, cognitive	Overall: 54 % Ascaris: 43 %	Most of the infections were of light	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
						n concentration 11.92(1.23)	ability	Hookworm: 11% Trichuris: 22 %	intensity.	
Stephenson 1989	RCT	Kenya	Proportion female: 50-51% per group Place of origin: Kwale district, Coast Province,	Baseline weight (kg): 21.8+/-0.50 (placebo) %WAZ: 74.2+/- 1.19 (placebo) Proportion underweight:	Baseline height (cm): 122.3+/-0.95 (placebo) %HAZ: 91.5 +/-0.54	NR	Weight, % weight for age, height, % height for age, % weight for height, MUAC, %MUAC for age, triceps skinfold thickness, % triceps for age, subscapular skinfold thickness, % subscap for age, Harvard step test,	Ascaris: 49% Hookworm: 87% Trichuris: 97 %	Ascaris: 32044epg Hookworm: 2795epg Trichuris: 10234epg	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
			Kenya	NR	(placebo) Proportion stunted: nr		prevalence and mean egg counts			
Stephenson 1993A and B (Note: Stephenson 1993B considered to	cRCT intervention 1: four schools intervention 2:	Kenya	Proportion female; 50-51%	weight=29.1kg, once per yr (placebo)	HAZ: 72.1 +/- 1.30	NR	Weight, % weight for age, height, % height for age, % weight for height, MUAC, %MUAC for age, triceps skinfold thickness, % triceps for age, subscapular skinfold thickness, % subscap for age, hemoglobin, Harvard step test,	Ascaris: 49 % Hookworm: 87 % Trichuris: 97%	Hookworm: Average of 2600 epg Trichuris: average 4330 epg Ascaris: 8470 epg	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
be sample of children from Stephenson 1993A)	4 schools control: four schools						work prevalence, appetite.			
Stoltzfus 1997	RCT	Zanzibar, Tanzania	Proportion female: 0.512	NR	< 10yrs HAZ: 1.44 (1.30) (control) ≥10 HAZ : 2.33 (1.25) (control)	Proportion anemic: 0.623, 22 % <5 % BMI for <10 years, 48 % <5 % percentile	Weight, Height, prevalence and intensity of helminth infections, hemoglobin, serum ferritin, anemia, severe anemia	Ascaris: 73% Hookworm : 91.2 % Trichuris: 94.7%	Ascaris: 239 epg Hookworm: 332 epg Trichuris	62 % and 52 % had access to safe water supply in the treatmen

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
					<10yrs, proportion stunted: 0.307 (control) ≥10 proportion stunted was 0.640 (control)	for >10 years Hemoglobin: 68g/l			: 531epg	t and control groups respectively. 82 % and 76 % indiscriminately disposed of their children feces in the treatment and control groups respectiv

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
										ely. Low percentages hand washed with soap before food, and other activities
Stoltzfus 2001	RCT	Zanzibar	Proportion female: 0.465	Proportion underweight: 0.345	Proportion stunted: 0.385	Proportion anemic: 0.96 Hemoglobin: 86+/-15 gl/L	Anemia , hemoglobin, erythrocyte protoporphyrin, serum ferritin, prevalence of helminth infection, motor and language	Ascaris: 42 % Hookworm: 46 % Trichuris: 68%	Ascaris: 26 epg Whipworm: 57 epg Hookworm:14 epg	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
							development			
Sur 2005	RCT	India	NR	Baseline weight ~11 kg (only graphically presented)	NR	NR	Weight gain, Ascaris prevalence, diarrhoeal episodes	Ascaris: 51.8%	NR	NR
Taylor 2001	RCT	South Africa	NR	WAZ: -0.62 (0.86) proportion underweight was not recorded	HAZ: -0.60 (1.16). Proportion stunted was not recorded	Hemoglobin: 12.53g/dL, (group 1)	Height, weight, blood count, anemia (haemoglobin concentration), urine analysis, helminth infection prevalence	Ascaris: 55.9% Hookworm: 59.4 % Trichuris: 83.6%	Most pupils had light infections.	Second half of study carried out during rainy season

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
								Schistosomiasis: 44 % with blood in the urine		when people collect rain from roofs; and water taps were not working during study

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
Watkins 1996A&B	RCT	Guatemala	Proportion female: not reported Education: parental education: 0.42 (se 0.03)- scale not given	Weight: 23.37 (0.36 se); WAZ: -1.66 (0.06 se); Proportion underweight: not reported	Height: 119.58 (se 0.72); HAZ: -2.71 (se 0.09); Proportion stunted: NR	NR	Worm burden, weight, height, WAZ, HAZ, WHZ, mid-upper arm circumference, cognitive tests (vocabulary (InterAmerican vocabulary test), reading (InterAmerican reading test), Peabody picture vocabulary test), Attendance by teacher's attendance books, information processing (different	Ascaris: 91 % Trichuris: 82 % Hookworm: 0%	Ascaris heavy: 45%. Trichuris heavy: 36 %	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
							paper)			
Willett 1979	RCT	Tanzania	NR	Baseline weight: 11.45 (SD 0.25)	Baseline height: 87.56 (SD 0.99)	Nutritional status, expressed as the ratio of observed over expected weight for age, baseline mean =	weight, length, ascaris prevalence	Ascaris: 53% Hookworm: 10.9%	NR	NR

Authors	Study design	Country	Proportion female; Socioeconomic status	Baseline weight (kg); weight-for-age (WAZ); proportion underweight	Baseline height (cm); height-for-age (HAZ); proportion stunted	Nutritional status	Outcomes measured	Worm prevalence	Worm intensity	Environmental risk for worm infection
						0.79				
Wiria 2013	cRCT, households	Indonesia	Proportion female: 53.9 % (placebo). SES: most in the middle percentile;	NR	NR	NR	Weight, height (provided by author), adverse effects, allergen response (skin prick test, IgE to aeroallergens), malarial parasitemia	Overall 87.2% Ascaris: 34.9% Hookworm: 74.5%	Ascaris: 23 % high or moderate Hookworm: 67 % high or moderate Trichuris: NR	

Additional Table 8: Included Studies: interventions, duration and age of participants

Author	Year	Interventions	Sample Size (by intervention)	Duration (months)		Mean age (years)
				Treatment	Follow-up	
Albendazole standard (2/year)						
Alderman	2006	ALB vs. CL	27,995 (14940/13055)	36	N/A	3·7
Awasthi	2000	ALB vs. PL	1061 (451/610)	24	N/A	2·7
Bhoite	2012	ALB vs. ALB+FE vs. CL	496 (128/215/153)	8	6	Range: 8-12
Dossa	2001	ALB vs. ALB+FE vs. FE vs. PL	140 (38/34/36/32)	13	N/A	Range: 3-5
Fox	2005	ALB vs. ALB+DEC vs. DEC vs. PL	1292 (328/324/322/318)	6	N/A	7·7
Hadju	1997	ALB vs. PYR vs. ALBlf vs. PYRlf vs. PL	505 (69/61/66/60/74)	12	N/A	8·3
Kruger	1996	ALB+NS vs. ALB+IRS vs. IRS+PL vs. NS+PL	178 (37/50/54/37)	6	5	Range: 6-8
Monse	2013	ALB vs. HE	412 (200/212)	48	N/A	7·5
Olds	1999	ALB vs. PZQ vs. ALB+PZQ vs. PL	>1500 (NR)	12	N/A	10·5

Rozelle	2015	ALB+HE vs. CL	2179 (1084/1095)	12	N/A	10·6
Stephenson	1993 A&B	ALB vs. ALBlf vs. PL	284 (95/96/93)	8.2	N/A	NR
Sur	2005	ALB vs. PL	702 (351/351)	12	N/A	Range: 2-5
Miguel	2004	ALB vs. ALB+PZQ vs. CL	>30,000 (NR)	3	N/A	Range: 6-18
Watkins	1996 A&B	ALB vs. PL	227 (116/111)	6	N/A	Range: 7-12
Albendazole high (>2/year)						
Ndibazza	2012	ALBhf vs. PL	2016 (1010/1006)	45	N/A	Range: 1·25-5
Wiria	2013	ALBhf vs. PL	4004 (2022/1982)	21	N/A	Range: 5-15
Albendazole low (<2/year)						
Beach	1999	ALBlf vs. IVE vs. ALBlf+IVE vs. PL	958 (244/240/245/229)	4	N/A	7·4
Stephenson	1989	ALBlf vs. PL	150 (78/72)	6	N/A	Range: 6-16
Koroma	1996	ALBlf vs. PL	297 (197/100)	6	N/A	Range: 6-10
Albendazole standard (2/year) + PZQ standard (2/year)						
Taylor	2001	ALB+PZQ vs. ALB+PZQ+FE vs. ALBhf +PZQ+FE vs.	428 (60/56/63/57/101/91)	12	N/A	11·2

		ALBhf+PZQ vs. FE vs. PL				
Albendazole standard (2/ year) + PZQ low (1/ year)						
Jinabhai	2001 A	ALB+PZQlf vs. PL	268 (129/ 139)	4	N/ A	Range: 8-9
Albendazole low (1/ year) + PZQ low (1/ year) + biscuits with vitamin A+iron+nutrients						
Jinabhai	2001 B	ALBlf+PZQlf+FBS vs. FBS vs. ALBlf+PZQlf+FBN vs. FBA vs. FBN	579 (NR)	4	N/ A	9·1
Albendazole standard (2/ year) + fortified beverage						
Solon	2003	ALB+FBV vs. FBV vs. ALB+FVN vs. FVN+PL	831 (203/ 209/ 213/ 206)	4	N/ A	9·9
Albendazole high (>2/ year) + iron						
Bobonis	2006	ALBhf + FE vs. CL	2392 (930/ 1462)	11	N/ A	3·65
Nga	2009	ALBhf+FBS vs. ALBfh+FBN vs. FBS vs. FBN+PL	510 (127/ 127/ 128/ 128)	4	N/ A	Range: 6-8
Albendazole standard (2/ year) + Vitamin A						
Awasthi	2001	ALB+VA vs. VA	2020 (988/ 1022)	18	N/ A	9·6
Awasthi	2008	ALB+VA vs. VA	3935 (1968/ 1967)	24	N/ A	Range: 1-5
Awasthi	2013	ALB+VA vs. VA	1000000 (NR)	60	N/ A	Range: 0·5-6

Hall	2006	ALB+VA vs. PL+VA	2659 (1341/1318)	24	N/A	6·8
Levamisole high (>2/year)						
Willett	1979	LEV vs. PL	341 (166/175)	12	N/A	3·2
Mebendazole standard (2/year)						
Kloetzel	1982	MEB vs. PL	337 (165/172)	10	N/A	Range:1-8
Garg	2002	MEB vs. MEB+AM+FE vs. PL	574 (177/191/193)	6.5	N/A	Range: 2-4
Joseph	2015	MEB vs. MEBlf+PL vs. PL+MEBlf vs. PL	1760 (440/440/440/440)	12	N/A	1
Stoltzfus	1997	MEB vs. MEBhf vs. CL	3605 (1170/1175/1260)	12	N/A	10
Mebendazole standard (2/year) + iron						
Ebenezer	2013	MEB+FE vs. PL	1621 (813/808)	6	6	9·5
Huong	2007	MEB+NFN vs. MEB+IFN vs. MEB+FE vs. IFN+PL vs. NFN+PL	425 (85/85/84/88/84)	6	N/A	7·2
Mebendazole high (>2/year)						
Donnen	1998	MEBhf vs. VA vs. CL	358 (123/118/117)	18	N/A	1·9
Kaba	1978	MEBhf vs. LEVhf vs. MEBhf+LEVhf	176 (44/45/87)	15	N/A	Range: 6-11
Ostwald	1984	MEBhf vs. CL	87 (42/45)	5	N/A	Range: 7-10

Rousham	1994 B	MEBhf vs. PL	1402 (688/714)	12	N/A	3·9
Stoltzfus	2001	MEBhf vs. MEBhf+Fe vs. Fe vs. PL	614	12	N/A	2·4
Mebendazole high + Pyrantel high (>2/year)						
Lai	1995	MEBhf+PYRhf vs. PL	353 (186/167)	24	N/A	7·5
Nutrition Enhancement Programme (1/year)						
Linnemayr	2011	DW+VA+FE+GP+BN+CW	4296 (2321/1975)	32.4	N/A	Range: 0-3
Piperazine standard (2/year)						
Greenberg	1981	PIP vs. PL	185 (92/93)	11	N/A	Range: 1·5-8
Piperazine high (>2/year)						
Gupta	1982	PIPhf vs. MET cs PIPhf+MET vs. PL	159 (39/40/41/39)	12	N/A	Range: 2-5·1
Praziquantel 1/year						
Makamu	2016	PZQ vs. CL	37,385	120	n/a	7-14
Pyrantel high (>2/year)						
Pust	1985	PYRhf vs. PO vs. PYRhf+PO vs. PL	789 (80/317/92/300)	12	N/A	Range: 1-4·5
Secnidazole (>2/year)						
Goto	2009	SEC vs. ALB+SEC vs. PL	410 (141/142/127)	9	N/A	Range: 0·25-1·25

Tetrachloroethylene (1/year)						
Michaelsen	1985	TCE vs. PL	228 (114/114)	5	N/A	Range:5-7
Tetramisole standard (2/year)						
Reddy	1986	TET vs. TET+VA vs. VA vs. PL	487 (66/110/98/53)	12	N/A	Range: 1-5
Tetramisole low (<2/year)						
Shah	1975	TETlf vs. IFA	325 (165/160)	12	N/A	Range: 1-5
Tetramisole high (>2/year)						
Gupta	1977	TEThf vs. PL	154 (74/80)	12	N/A	Range: 0·5-2
Thiabendazole high (>2/year)						
Gateff	1972	THIhf vs. PL	392 (196/196)	8	N/A	Range: 6-15

ALB=albendazole. BN=bed nets. CL=control. PL=placebo. IR=iron. DEC=diethylcarbamazine. PYR=pyrantel. PYRlf=pyrantel low frequency. NS=non-fortified soup. IRS=iron-fortified soup. HE=health education. PZQ=praziquantel. ALBlf=albendazole low frequency. MN=micronutrients. ALBhf=albendazole high frequency. IVE=ivermectin. IPT=intermittent preventive treatment of malaria. PZQlf=praziquantel low frequency. FBS=multi-micronutrient fortified biscuits. FBN=non-fortified biscuits. FBA=vitamin-A fortified biscuits. FBV=micronutrient-fortified beverage. FVN=non-fortified beverage. VA=vitamin A. LEV=levamisole. MEB=mebendazole. AM=antimalarial. MEBlf=mebendazole low frequency. MEBhf=mebendazole high frequency. APR=antiprotozoal. IFA=iron-folic acid. NFN=non-fortified noodles. IFN=iron-fortified noodles. LEVhf=levamisole high frequency. LEVlf=levamisole low frequency. PYRhf=pyrantel high frequency. DW=unspecified deworming. GP=growth promotion. CW=cooking workshops.PIP=piperazine. PIPhf=piperazine high frequency. MET=metronidazole. PO=palm oil. SEC=secnidazole. TCE=tetrachloroethylene. TET=tetramisole. TETlf=tetramisole low frequency. TEThf=tetramisole high frequency. THIhf=thiabendazole high frequency.

***Note:** Miguel 2004 has two long-term follow-up studies (Ozier 2016 and Baird 2016), and Alderman 2006 has one long-term follow-up study (Croke 2014)

Additional Table 9: Studies which screened for infection, included in sensitivity analyses

Study	Design	Number allocated	Duration	Screened for which worm	Country	Mean Age (years)	Intervention	Outcomes analysed
Bell 1973	CBA	58/58	12 months	STH	Zimbabwe	8-12 years	Hycanthone mesylate	Weight, height, Cocgnition (Raven's), math, English
Bleakley 2007	Quasi-experimental	NR	5 years	Hookworm	Southern United States	NR	Thymol	School enrolment and attendance, literacy
Boivin 1993	CBA (not analysed according to randomization)	50 allocated to four groups	one month	Ascaris and hookworm	Zaire	Boys=7.7Girls=8.0	Decaris+iron vs. decaris alone, control or iron alone	K-ABC evaluations of cognitive performance

Study	Design	Number allocated	Duration	Screened for which worm	Country	Mean Age (years)	Intervention	Outcomes analysed
Grigorenko 2006	CBA	160	19 months	S. haematobium and hookworm	Tanzania	11-13	Praziquantel, albendazole or control	Dynamic tests, static tests, test of academic achievement, nutritional status.
Hadijaja 1998	cRCT	696 children initially. 5 schools allocated each to a different treatment	3 months	Ascaris Excluded >500 epg of trichiura infection	Indonesia	6-8	Mebendazole, health education, mebendazole + health education, placebo, or control for egg-negative schools.	Raven's test, tests of arithmetic, coding, digit span forward and backward, and oddity learning.

Study	Design	Number allocated	Duration	Screened for which worm	Country	Mean Age (years)	Intervention	Outcomes analysed
Nokes 1992	CBA	103	9 weeks	T. trichiura (> 1900 eggs/gram (epg) of faeces)	Jamaica	10.4	Albendazole or placebo	Digit span forwards/backwards, Arithmetic and Coding test from Wechsler Intelligence Scale for Children, Matching familiar figures test, listening comprehension test, Fluency

Study	Design	Number allocated	Duration	Screened for which worm	Country	Mean Age (years)	Intervention	Outcomes analysed
Nokes 1999	RCT	181	three months	Schistosoma japonicum	China	10.1	Praziquantel and albendazole, praziquantel alone, albendazole alone or placebo	Cognitive function tests: fluency, digit-span forwards, corsi block, picture search and free recall
Sarkar 2002	RCT	85	4 months	Ascaris	Bangladesh	7	Pyrantel pamoate syrup or placebo syrup	Weight, height, WAZ, WHZ, HAZ
Simeon 1995	RCT	407	6 months	Trichuris, >1200 eggs/gram	Jamaica	9.2	800 mg Albendazole, every three months or placebo	School attendance, school achievement, height, weight

Study	Design	Number allocated	Duration	Screened for which worm	Country	Mean Age (years)	Intervention	Outcomes analysed
Stephenson 1985	RCT	399 with light-moderate infections to treatment or placebo. Additional 19 heavily infected to treatment.	six months	Schistosomiasis	Kenya	10.7	Metrifonate or placebo	Weight, height
Stephenson 1989b	RCT	312	8 months	Schistosomiasis	Kenya	NR (primary school)	Metrifonate, praziquantel or placebo	Weight, height
Sternberg 1997	RCT	133 randomised; outcomes also measured in 63 uninfected controls	10 weeks	Trichuris	Jamaica	10.3	Albendazole or identical placebo	Cognitive function tests, height, weight

Study	Design	Number allocated	Duration	Screened for which worm	Country	Mean Age (years)	Intervention	Outcomes analysed
Tee 2013	RCT	37	12 months	Trichuris	Malaysia	6.6-8.5	Albendazole or placebo	Height, weight, WAZ, HAZ, WHZ, worm loads
Yap 2014	RCT	211	six months	Any STH	China	Male=10.4 Female=10.2	Triple-dose albendazole or placebo	Height, weight

Additional Table 10 : Risk of bias assessment for Miguel 2004

ROB domain	Cochrane review		Campbell review	
	Judgement	Support	Judgement	Support
Random sequence generation (selection bias)	High risk	Schools in a deworming project were stratified by zone, their involvement with other NGO programmes, and then listed alphabetically and every third school assigned to start the programme in 1998, to start it in 1999, or to be a control	High risk	Schools in a deworming project were division name, zone name, and school enrollment every third school assigned to start the programme in 1998, to start it in 1999, or to be a control Three schools originally excluded (2 due to remote location and 1 because it was a high quality school) were added to boost sample size, arranged alphabetically (Baird 2016)
Allocation concealment (selection bias)	High risk	Not concealed (see above).	High risk	Schools were listed alphabetically and every third school was assigned to a given project group. High probability of investigators foreseeing assignments and thus introduce selection bias.
Blinding (performance bias and	High risk	Pragmatic cluster implementation trial with no blinding.	High risk	Not mentioned (for blinding of participants, personnel and outcome assessors)

detection bias) All outcomes				
Incomplete outcome data (attrition bias) All outcomes	Low risk	For haemoglobin, weight and height the outcomes have been measured on a random sub-sample of the quasi-randomized population	Low risk	Some attrition was described, but it was less than 20 % difference. p. 171, Miguel 2004 describe a discrepancy in overall treatment rate of 72 % vs. 57 % because of dropouts in Group 2 schools (who could not be matched in the data cross years, despite the efforts of the NGO field staff) between years one and 2 of the project.
Selective reporting (reporting bias)	Low risk	Outcome data not reported for cognitive tests, though authors state: Deworming treatment effects are not significantly different than zero for any component of the cognitive exam (results available on request)	Low risk	insufficient information to permit judgement because no protocol was available.

Other bias	High risk	Baseline imbalance: low **Recruitment bias: low** (no asymmetric migration between schools) **Loss of clusters:** low (none reported) **Incorrect analysis: low** (correctly adjusted for clustering). Comparability with RCTs randomizing individuals: low **Other sources of bias: high for confounding due to a co-intervention.** The drug intervention is accompanied by intensive health promotion that could account for some of the effects with key outcomes such as school attendance	High risk	**Baseline imbalance: high risk** (there were statistically significant differences between groups for some variables with treatment groups worse off - blood in stool (self-report), age, sick often (self-report), fewer were "clean" as observed by field workers. Table 1) Incorrect analysis: low **Differences of co-intervention between arms: high risk** : the intervention schools also received hygiene promotion including wall charts and teacher education

Additional Table 11: Cluster randomized studies, with notes on adjustments for unit of analysis issues if done

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
Alderman 2006	church parish, 25 parishes to each group; total n with 2 or more weight measures was: treatment: 14,940; control group: 13,055	weight	two types of results presented; table 2 gives overall weight for all children with at least 2 measurements and is not adjusted for clustering; Table 3 provides multivariate regression adjusted for clustering, which separates those who received albendazole <7 months apart, <13 months and > 13 months	We used confidence interval reported in letter to BMJ	multivariate regression adjusts for clustering, but separates out different frequency of treatment. In letter to BMJ editor, Alderman writes: .., once the design effect is taken into consideration the confidence intervals should, in fact, be [CI=2295 - 2533] and [CI=2121 - 2396].	0.01 (based on letter to BMJ)	We divided the confidence interval in BMJ letter [tx: CI=2295 - 2533] and control: [CI=2121 - 2396] by 3.92 to get standard error
Awasthi 2001	urban slum are with anwangadi health worker	weight, height	Cluster randomization was done to have about 60 slums, with about 15 children, aged 0.5-1year, within	no	analyzed at cluster level.	no	not done because they analyzed at the cluster

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
			each cluster, in each arm. There were 63 slums with 988 children in the albendazole plus vitamin A group and 61 slums with 1022 children in the vitamin A group				level
Awasthi 2008	urban slum area with anganwadi worker	weight, height	From 200 slums with a functional AWC in urban Lucknow, 124 were randomized to receive either vitamin A (100,000 units) alone or albendazole (400 mg)	no	analyzed at cluster level. Based only on the 50 area-specific mean gains.	weight: 0.17; height 0.11	not done because they analyzed appropriately at cluster level
Awasthi 2013 (DEVTA	rural administrative blocks, with	weight, height, hemoglobin,	Neighbouring blocks (clusters), in groups of four (where possible	no	analyzed at cluster level. Sensitivity analyses showed the main	no ICC for weight and height.	not done because they analyzed

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
articles)	anganwadi worker	mortality	in the same district), were randomly allocated in Oxford, UK, using a factorial design, to: (1) usual care; (2) 6-monthly vitamin A; (3) 6-monthly albendazole; or (4) both.		findings were unchanged when adjusted for district.	For mortality: The inter-block correlation between numbers of infant and child deaths per AWC was 68·7% ignoring trial treatment allocation	appropriately at cluster level
Bhoite 2012 a&B	3 schools allocated "at random" to three treatments: albendazole+iron, albendazole or	weight, height, hemoglobin	control school, n=153; iron+albendazole: 215; albendazole: 128	yes	not accounted for	no icc reported	adjust using ICC of 0.17 for weight and 0.11 for height from Awasthi

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
	placebo						2008. Since only three schools were assigned to groups (1 to each group), we adjusted with a cluster size the size of the school.
Bobonis 2006	preschools (268 preschools were assigned to 189 different "clusters" at the start of the study, where each cluster contained one to three preschools, usually all located on the same city	attendance (observation spot checks), weight for age		no	regression equations, OLS	no icc reported	not done- they used adjusted analyses

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
	block.)						
Ebenezer 2013	cluster consisted of one grade 4 class in a school, 100 schools were chosen	cognition, hemoglobin	As it was assumed that there was a degree of correlation between the subjects at school level, they used a mixed effects regression model , including the school and classroom as well as various background: child's age, sex and baseline nutritional status; as well as individual socio-economic indicators	no	included in the calculation of effect a variable: uj = The classroom-level residual shared by all students in school j.	no icc reported	used values reported in the article because analysis accounts for clustering Authors provided attendance data which was analyzed to account for

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
			such as parental education; and school-level indicators, (i.e. whether midday meal programme was present)				clustering
Hall 2006	schools	weight, height, cognition	80 schools, 2659 children. We asked Dr. Hall and Don Bundy for data. They refused saying that they are adjusting for clustering themselves, and that the control group was contaminated	yes	Study did not adjust for clustering- although the report mentions entering school as a random effect in the model, the tables with outcome data do not report that they are adjusted, thus to be conservative, we adjusted	no icc reported, we calculated ICC from the data provided to us as: Weight gain: 0.021 Height gain:0.015	obtained data tables from authors, and adjusted with ICC calculated using their data

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
Kruger 1996	schools for iron fortification; individual children for deworming	weight, height, attendance	5 school randomly selected; three were assigned to iron fortified soup; 2 were assigned to unfortified soup; within each school, 65 students randomly assigned to deworming or placebo	yes	combine children with adequate and inadequate iron stores since this was not stratification variable or pre-planned analysis Tables 2 and 3). For fortified arms, three clusters contributed data; for unfortified arms, 2 clusters contributed data	no icc reported	adjust using ICC of 0.17 for weight and 0.11 for height from Awasthi 2008. for Because three schools assigned to fortified soup, and 2 schools assigned to unfortified soup; we calculated the cluster size by dividing the number of children by the number of clusters that

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
							contributed.
Linnemayr 2012	village	weight for age	cluster RCT- village as unit of randomization	no	regression equations accounted for clustering of standard errors at the village level	no	we did not adjust because their analysis accounted for clustering
Miguel 2004	schools	weight for age, height for age, attendance	75 schools were assigned to three groups using quasi-randomization. They were ordered alphabetically, then assigned to groups 1,2, and 3	no	adjust for clustering in their regression estimates, and present robust standard errors.	no icc reported	not done, their regression estimates account for clustering
Pust 1985	health clinics	weight,	7 health clinics allocated to control, one to palm	yes	not done	no	adjust using ICC of 0.17 for weight

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
			oil+deworming, one to deworming and eight clinics to palm oil				and 0.11 for height from Awasthi 2008. calculated cluster size by dividing number of children by number of clinics
Rousham 1994	village	weight, height	Treatment was randomized by village for ethical and logistic reasons. Six villages were allocated to the mebendazole group and seven to the placebo group. Sixteen local Bangladeshi field	no	Since the allocation of mebendazole or placebo tablets was randomized by village rather than individual, heterogeneity of nutritional status between villages was tested using a hierarchical (nested) analysis of variance.	no icc reported	Not done because they report considering between village heterogeneity with hierarchical (nested) analysis of

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
			assistants and one supervisor were recruited and trained to conduct household interviews and collect socio-economic and anthropometric data.		Between-group differences in growth and biochemical status were examined by using repeated-measures analysis of variance. For all variables examined, values indicated that the assumption of compound symmetry was not met; therefore, the Greenhouse- Geisser correction was made (37). This provides a conservative estimate of within-subject effects by correcting the df and corresponding P value while F values remain unaltered		variance. 74 were lost (not sure which groups). six villages to mebendazole (n=115 per cluster) and 7 to placebo (102 per cluster). Tables 3 and four of Rousham 1994 - we calculated se from the ANOVA f-test data

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
Rozelle 2015	112 townships	Anthropometric, cognition, attendance, school performance, hemoglobin	7 counties selected randomly from poorest half of counties in Qiangdongnan. All townships included. All children aged 9-11 years attending primary school within each township were eligible. They randomly selected 20 children from the largest village to participate	Y, for stunting	STATA's multiple linear regression model and its estimation using ordinary least squares (OLS), taking into account the pairing nature of townships within county and data-clustering at the township level.	N	Continuous outcomes not adjusted Proportion stunted adjusted using cluster size of 20 for control and 19 for treatment, and an ICC of 0.02
Shah 1975	Village- 2 project villages, and three control villages	Weight (% reference weight), cure rate	Villages allocated to tetramisole or control	no	Not done, no usable data	no	Not done, no usable data

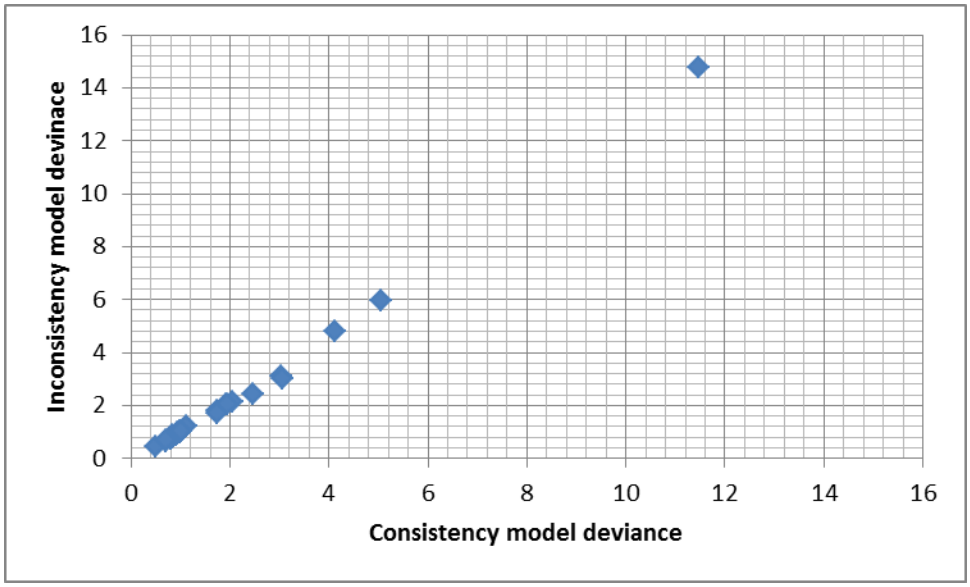
Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
Stoltzfus 1997	schools	weight, height	Randomized 12 schools	no	" All analyses were performed at the individual level and were adjusted for within-school correlations using generalized estimating equations approach (Diggle *et al.*)	no ICC reported	used values reported in the article because they used GEE to consider clustering. For the overall weight gain, we combined the <10 year old and >10 year old groups.
Stoltzfus 2001and 2004	households for iron allocation.	hemoglobin, number stunted, number wasted, number undernourished using WAZ< HAZ cutoffs	Generalized estimating equation approach (17) to account for the intrahousehold clustering introduced by household level randomization of the	no	GEE: Treatment effects on primary outcomes are reported with and without adjustment for baseline values and other important covariates, using the generalized	no	we did not adjust continuous outcomes because GEE considered clustering

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
			iron intervention. Allocation to iron or placebo was carried out by household rather than by child, so that mothers would not be responsible for administering different bottles of supplement to different children within the household. Households were grouped into three strata: those with children 36 mo, those with children 36 mo, and those with children in both age subgroups. Within these strata, households were randomly assigned to		estimating equation approach (17) to account for the intrahousehold clustering introduced by household level randomization of the iron intervention		We adjusted proportion stunted using cluster size of 1.5 (684 children divided by 451 households) and an ICC of 0.02

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
			iron or placebo, in blocks of four. Children were randomly allocated to mebendazole or placebo, stratified by iron allocation and household, in blocks of four. In September 1996, 614 children were assessed				
Wiria 2013	households	BMI (asked for weight and height)	household cluster RCT: 954 households with 4004 subjects were registered. Randomization of households resulted in 1982 people assigned to albendazole treatment and 2022 people to placebo (473 and 481 houses	no	generalized linear mixed models capturing the data correlations induced by clustering within households and repeated evaluations in time of the same subject.: . IQR = Interquartile range. β (beta) and 95 %	no	we did not adjust, data on weight were provided by author and they confirmed this analysis accounted for clustering

Author year	Allocation unit	Outcomes	Method (details)	Did we adjust?	How was clustering accounted for in study?	ICC reported?	How did we adjust for clustering?
			respectively).		confidence interval based on generalized linear mixed models.		with generalized linear mixed models

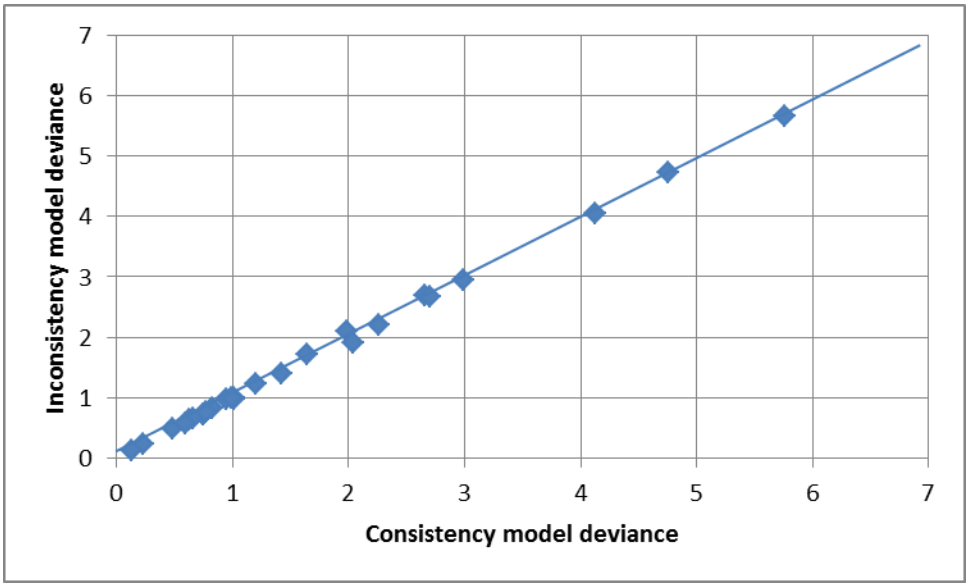
Additional Table 12: Weight Network Meta-analysis, Consistency plot and deviance



information criteria

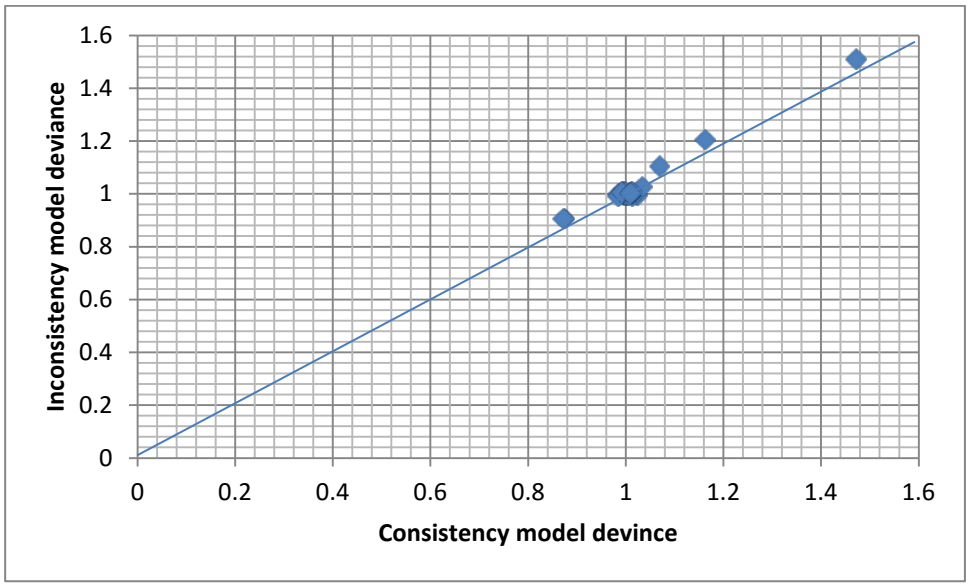
Total Residual Deviance	55.67
Deviance Information Criteria	-31.69

Additional Table 13: Height Network Meta-analysis, Consistency plot



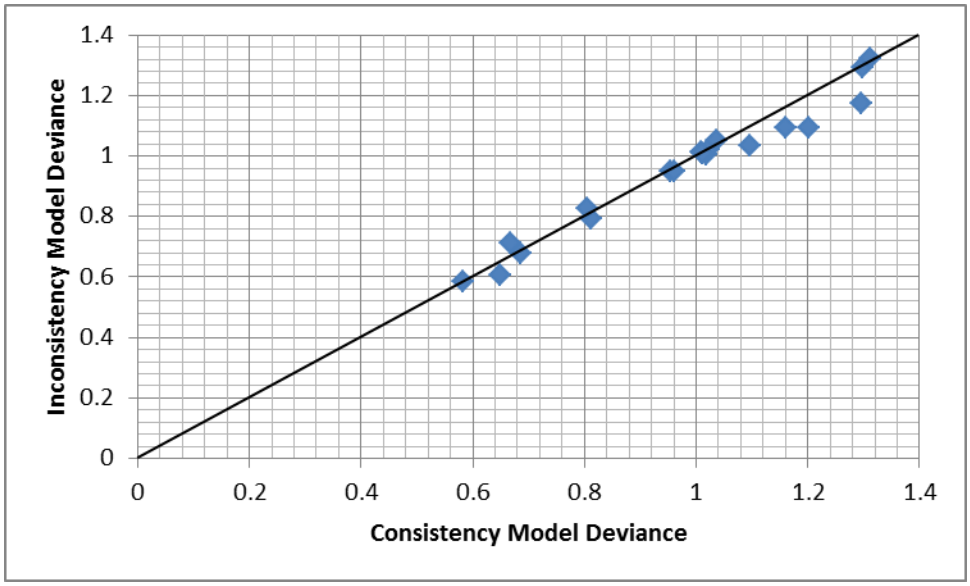
	Total Residual Deviance	43.36 vs. 67 data points
	Deviance Information Criteria	-39.794

Additional Table 14: Weight for height consistency plot



Total Residual Deviance	33.54
Deviance Information Criteria	-7.733

Additional Table 15: Proportion stunted Network Meta-analysis, Consistency plot



Random-Effect Model	Residual Deviance	18.58 vs. 19 data point
	Deviance Information Criteria	133.008

Additional Table 16: Long run outcomes of untreated siblings in Kenya Primary School Deworming Project from Ozier 2016

Outcome	Mean difference (95% CI)	GRADE Certainty
Height (cm)	0.21 [-0.38, 0.80]	Very low
Height for age z-score	0.03 [-0.06, 0.12]	Very low
Stunting (HAZ <-2)	1.01 [0.97, 1.03]	Very low
All cognitive (principal components)	0.21 [0.02, 0.41]*	Very low
Raven's matrices	0.21 [0.05, 0.37]*	Very low
Verbal fluency (animals)	0.20 [0.02, 0.38]*	Very low
Verbal fluency: foods	0.16 [-0.01, 0.33]	Very low
Memory: digit span forwards	0.13 [-0.06, 0.32]	Very low
Memory; digit span backwards	0.02 [-0.15, 0.20]	Very low

Note: Ozier 2016 identified children who were not in school during the Miguel 2004 study in Kenya, born in the years 1995 to 2001, from all of the 75 schools from Miguel 2004 (except for 2 schools which were flooded during the study). This primary analysis is based on children exposed at less than 1 year of age ("treated") compared to children exposed at greater than 1 year of age ("control") which we considered observational for the purposes of rating GRADE certainty. We firther downgraded the study for indirectness since the intervention consisted of mass deworming combined with hygiene promotion (wall charts, regular lectures and teacher training).

Additional Table 17: GRADE evidence profile for mass deworming with albendazole twice per year for soil-transmitted helminths

Date: 2016-01-27
Question: Should Mass deworming with albendazole 400 mg twice per year vs. control be used in children in STH endemic areas?
Settings: L&MICs
Bibliography: Welch et al. 2016

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mass deworming with albendazole 400 mg twice per year	Control	Relative (95% CI)	Absolute		
Weight gain (follow-up one year; measured with: kg; Better indicated by higher values)												
11	randomised trials	no serious risk of bias	serious inconsistency[1]	no serious indirectness	no serious imprecision	none	18740	16690	-	mean 0.09 kg higher (0.04 lower to	⊕⊕⊕O MODERATE	IMPORTANT

										0.2 higher)		
Height gain (follow-up one year; measured with: cm; Better indicated by higher values)												
9	randomised trials	no serious risk of bias	serious inconsistency[2]	no serious indirectness	no serious imprecision	none	3484	3355	-	mean 0.07 cm higher (from 0.1 cm lower to 0.24 cm higher)	⊕⊕⊕O MODERATE	IMPORTANT
Cognitive processing-short-term attention (follow-up one year ,converted to units for WISC IV working memory index, 100 point scale)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2055	2023	-	mean 0.23 points lower, from 0.6 lower to 0.14 more	⊕⊕⊕⊕ HIGH	CRITICAL
School attendance at 1-2 years (measured with percentage; Better indicated by higher values)												
7	randomised trials	no serious risk of	no serious inconsistency	no serious indirectn	no serious imprecision	none	5851	10405	-	mean one % higher (1% lower to 3 %	⊕⊕⊕⊕ HIGH	CRITICAL

		bias		ess						higher)		
Proportion stunted, measured at 1-2 years												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	918/2235 (41.1%)	824/2051 (40.2%)	RR 0.98 (0.88 to 1.08)	8 fewer per 1000 (from 32 more to 48 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Mortality (follow-up 1-5 years)												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	Over one million[3]	2.5 % child mortality[4] 9 % infant mortality[4]	RR 0.95 (0.89 to 1.02)	Child: one fewer per 1000 (from one more to 3 fewer) Infants: 5 fewer per 1000 (from 2 more to 10 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Height in cm (long-term follow-up- 10 years)												
1	Randomised trial	Very serious[5]	no serious inconsistency	Serious[6]	Serious[7]	none	3686	1883	-	MD 0.11 cm lower (0.64 lower to 0.42 higher)	⊕OOO VERY LOW	IMPORTANT
Hours worked (follow-up mean 10 years; Better indicated by higher values)												
1	randomised trial	Very serious[5]	no serious inconsistency	serious[6]	serious[7]	none	3686	1883	-	MD 1.58 higher (0.46 lower to 3.62 higher)	⊕OOO VERY LOW	IMPORTANT
Numeracy and literacy (follow-up 7 to eight years; measured with: Math and English test scores; Better indicated by higher values)												
1	randomised trial	very serious[8]	no serious inconsistency	no serious indirectness	Serious[7]	none	710 total		-	Math: MD 0.3 higher (0.00 lower to 0.60	⊕OOO VERY LOW	IMPORTANT

									higher) English: MD 0.16 higher (0.17 lower to 0.50 higher)		

[1] Heterogeneity with I^2 was 61%, with two studies excluded due to failed baseline diagnostics conducted for all studies (Koroma 1996 and Stephenson 1989) which had standardized differences at baseline $\geq$0.5 (Austin 2009). When included, they led to even higher heterogeneity (I^2 of 93%). With these two studies included, the pooled effect size increases from 0.05 SMD to 0.25 SMD, which is equivalent to 0.44 kg (using a typical SD to convert SMD to kg)

[2] As for weight, two studies with standardized baseline differences of $\geq$0.5 were excluded due to baseline imbalance suggesting failed randomization. If these two studies were included, heterogeneity was high (I^2 of 86%). With these two studies included, the pooled effect size increases to SMD of 0.18 which is equivalent to 0.44 cm

[3] Mortality estimate is driven by one large RCT (DEVTA 2013), which does not report the denominator for mortality, rather the mortality is reported as number of deaths per health worker for approximately one million children aged 1-6 years in the study at any one time

[4] Control group rates for child and infant mortality from Awasthi 2013 study.

[5] Rated down by two levels for risk of bias

[6] Rated down for indirectness because the co-intervention of hygiene promotion was not given to the control group.

[7] Rated down for imprecision

[8] Rated down two levels for risk of bias due to follow-up of 3 % of original sample

Additional Table 18: GRADE Evidence profile Mass deworming for soil-transmitted helminths and shistosomiasis

Date: 2016-01-27
Question: Should Mass deworming with albendazole 400 mg twice per year + praziquantel 40 mg/kg once per year vs. control be used in children in schistosomiasis endemic areas?
Settings: L&MICs
Bibliography: Welch *et al.*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mass deworming with albendazole 400 mg twice per year + praziquantel 40 mg/kg once per year	Control	Relative (95% CI)	Absolute		
Weight (follow-up over one year; measured with: kg; Better indicated by higher values)												

2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	221	217	-	mean 0.21 kg higher (0.14 lower to 0.56 higher)	⊕⊕OO LOW	IMPORTANT
Height (follow-up over one year; measured with: cm; Better indicated by higher values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	221	217	-	mean 0.02 cm lower (0.5 lower to 0.4 higher)	⊕⊕OO LOW	IMPORTANT
Cognitive processing-short-term attention (converted to units for WISC IV working memory index)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2055	2023	-	mean 0.23 points lower, from 0.6 lower to 0.14 more	⊕⊕⊕⊕ HIGH	IMPORTANT

School attendance (measured with percentage; Better indicated by higher values)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	904	3814	-	mean 0 % higher (17 % lower to 18 % higher)	⊕⊕OO LOW	CRITICAL
Proportion stunted (follow-up one year)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	12/127 (9.4%)	40%[6]	RR 0.92 (0.44 to 1.91)	32 fewer per 1000 (from 364 more to 192 fewer)[6]	⊕⊕OO LOW	IMPORTANT
Mortality (follow-up 1-5 years)												
6	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	no serious imprecision	none	Over one million[3]	2.5 % child mortality[7]	RR 0.95 (0.89 to 1.02)	Child: one fewer per 1000 (from one more to 3 fewer)	⊕⊕⊕O MODERATE	CRITICAL

								9 % infant mortality[7]		Infants: five fewer per 1000 (from two more to 10 fewer)		
Long term economic productivity (measured with hours/ week; Better indicated by higher values)												
1	randomised trials	Very serious[8]	no serious inconsistency	serious[9]	serious [10]	none	5,084 (total for both groups)		-	MD 1.58 higher (0.46 lower to 3.62 higher)	⊕OOO VERY LOW	IMPORTANT

Notes on data sources: We chose the direct comparison of albendazole+praziquantel vs. placebo for weight and height (2 studies), with the effect size from network meta-analysis converted to kg using typical standard deviation from included studies for weight and height. For cognition, we use our base case pooled estimate of short-term attention, since we found no difference in effect for one study of treating only children infected with schistosomiasis in our sensitivity analyses. For all other outcomes, we consider the results of primary analyses applicable for this comparison.

[1] Rated down for possible reporting bias because for one study, we obtained the dataset for two out of the five sites of a larger study (Olds 1999)

[2] Rated down for imprecision because the sample size does not meet the optimal information size threshold.

[3] Rated down for lack of allocation concealment, and blinding,

[4] Rated down for imprecision since confidence interval includes null effect

[5] Rated down for imprecision because recommendation would be altered if the lower versus the upper boundary of the CI represented the true underlying effect

[6] Control risk is average of all studies reporting stunting as an outcome.

[7] Rated down for indirectness because no studies of albendazole + praziquantel assessed mortality.

[8] Rated down by two levels for risk of bias.

[9] Rated down for indirectness because the co-intervention of hygiene promotion was not given to the control group.

[10] Study limitations rated down due to followup of 3 per cent of original sample

Additional Table 19: GRADE Evidence Table Mass deworming for schistosomiasis

Date: 2016-01-27
Question: Should mass deworming with praziquantel 40 mg/kg once per year vs. control be used in children in schistosomiasis endemic areas?
Settings: L&MICs
Bibliography: Welch *et al.*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Praziquantel 40 mg/kg once per year	Control	Relative (95% CI)	Absolute		
weight (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	91	91	-	0.32 kg higher (from 0.15 lower to 0.8 higher)	⊕⊕OO LOW	IMPORTANT
height (Better indicated by lower values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	91	91	-	0.02 cm lower (from 0.66 lower to 0.61 higher)	⊕⊕OO LOW	IMPORTANT
School attendance - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL
Cognitive processing - not measured												
0	-	-	-	-	-	none	0	-	-	-		CRITICAL
Proportion stunted - not measured												
0	-	-	-	-	-	none	-	-	-	-		IMPORTANT
Mortality - not measured												
0	-	-	-	-	-	none	-	-	-	-		CRITICAL

Long term years of education completed											
1	observational study	Serious[3]	-	-	-	none	>80,000	-	0.6 more years (from 0.17 lower to 1.11 higher)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded for risk of bias

[2] Downgraded for imprecision - did not meet optimal information size

[3] Makamu 2016 started at “low” certainty because of observational design, and was rated down for risk of bias (moderate risk of bias using IDCG tool).

Additional Table 20: Subgroup analysis for weight and height for albendazole standard vs. placebo

Subgroup		Weight: deworming vs. control (meta-analysis) Pooled estimate (95% CI)	Weight, N studies (participants in treatment/ control)	Height: deworming vs. control (meta-analysis)	Height N studies (participants in treatment/ control)
Age	< two yrs	0.04 (-0.04, 0.11), I^2 = 0%	2 (1408/1227)	0.03 (-0.05, 0.11); I^2 = 0%	2 (1433/1284)
	2-5 yrs	0.10 (-0.04, 0.24), I^2 = 0%	2 (373/347)	0.06 (-0.15, 0.27); I^2 = n/a	1 (166/181)
	>5 yrs	0.06 (-0.07, 0.19), I^2 = 75%	7 (2845/2879)	0.02 (-0.05, 0.10); I^2 = 29%	7 (2845/2879)
	Total	0.05 (-0.02, 0.13), I^2 = 60%	11 (4626/4480)	0.03 (-0.01, 0.07); I^2 = 0%	10 (4444/4344)
	Subgroup differences	P=0.73, I^2 = 0%		P=0.96; I^2 = 0%	
Prevalence	<20%	0.02 (-0.00,	2	0.05 (-0.07,	1 (601/444)

		0.04);	(15516/13442)	0.17);	
	20-50%	I^2 = 0%		I^2 = n/a	4 (2985/3013)
	>50%	0.17 (-0.00, 0.35); I^2 = 84%	4 (2992/3001)	0.01 (-0.04, 0.06); I^2 = 0%	4 (1622/1605)
	Total	0.01 (-0.05, 0.08); I^2 = 0%	5 (1964/1946)	0.01 (-0.06, 0.08); I^2 = 0%	9 (5208/5062)
	Subgroup differences	0.06 (0.00, 0.11); I^2 = 63% P=0.23; I^2 = 32.1%	11 (20472/18389)	0.02 (-0.02, 0.05); I^2 = 0% P=0.84; I^2 = 0%	
Nutritional status	<30 % stunted	0.02 (-0.00, 0.04); I^2 = 0%	2 (607/420)	0.05 (-0.03, 0.13); I^2 = 40%	4 (2589/2621)
	>30 % stunted	0.05 (-0.07, 0.18); I^2 = 0%	5 (17529/15676)	0.06 (-0.06, 0.18); I^2 = 0%	2 (639/476)
	Total	0.02 (-0.00, 0.04); I^2 = 0%	7 (18136/16096)	0.04 (-0.01, 0.10); I^2 = 7%	6 (3228/3097)

	Subgroup differences	P=0.61; I^2 = 0%		P=0.91; I^2 = 0%	

Additional Table 21: Subgroup analysis for weight and height for albendazole >2 per year vs. placebo

Subgroup		Weight: deworming vs. control (meta-analysis) Pooled estimate (95 % CI)	Weight, N studies (participants in treatment/ control)	Height: deworming vs. control (meta-analysis)	Height N studies (participants in treatment/ control)
Prevalence	<20%	-0.02 (-0.13, 0.08); I^2 = n/a	1 (682/ 715)	0.02 (-0.09, 0.12); I^2 = n/a	1 (669/ 705)
	20-50%	0.08 (-0.06, 0.22); I^2 = 0%	2 (398/ 401)	0.17 (0.03, 0.30); I^2 = 0%	2 (397/ 401)
	>50%	0.16 (-0.10, 0.42); I^2 = n/a	1 (116/ 110)	0.08 (-0.18, 0.34); I^2 = n/a	1 (116/ 111)
	Total	0.03 (-0.05, 0.11); I^2 = 0%	4 (1196/ 1226)	0.08 (-0.01, 0.17); I^2 = 11%	4 (1182/ 1217)
	Subgroup differences	P=0.31; I^2 = 15.3%		P=0.26; I^2 = 26.5%	

Additional Table 22: Subgroup analysis for school attendance for any deworming vs. control

Subgroup analysis	Deworming vs. control (meta-analysis) Pooled estimate (95% CI)	N studies
Age		
6 months-5 years	0.06 [-0.01, 0.12] I^2 = Not applicable	1
5 years	0.01 [-0.01, 0.02] I^2 = 47%	7
Total	0.01 [-0.01, 0.02]	
Subgroup differences	Chi^2 = 2.29, df = 1 (P = 0.13), I^2 = 56.3%	8
Prevalence of worms		
<50%	-0.00 [-0.02, 0.02] I^2 = 61%	3
≥50%	0.01 [-0.01, 0.02] I^2 = 61%	5
Total		
Subgroup differences	0.00 [-0.01, 0.02]	
	Chi^2 = 0.40, df = 1 (P = 0.52), I^2 = 0%	8

Additional Table 23: Subgroup analysis for weight and height for any deworming vs. control

Subgroup		Weight: deworming vs. control (meta-analysis) Pooled estimate (95% CI)	Weight, N studies (participants in treatment/ control)	Height: deworming vs. control (meta-analysis)	Height N studies (participants in treatment/ control)
Age	< two yrs	0.01 (-0.05, 0.07); I^2 = 0%	4 (2153/ 1990)	0.03 (-0.03, 0.09); I^2 = 0%	4 (2165/ 2052)
	2-5 yrs	0.04 (-0.03, 0.12); I^2 = 0%	6 (1429/ 1419)	0.02 (-0.08, 0.11); I^2 = 0%	4 (861/ 966)
	> five yrs	0.06 (0.00, 0.11); I^2 = 56%	16 (8133/ 12470)	0.04 (-0.03, 0.11); I^2 = 73%	15 (7991/ 12333)
	Total	0.04 (0.00, 0.08); I^2 = 36%	26 (11715/ 15879)	0.04 (-0.01, 0.09); I^2 = 62%	23 (11017/ 15351)
	Subgroup differences	P=0.59; I^2 = 0%		P=0.93; I^2 = 0%	
Prevalence	<20%	-0.00 (-0.07, 0.06);	7 (17382/ 15343)	0.01 (-0.06, 0.09);	6 (2450/ 2346)

	20-50% >50% Total Subgroup differences	I^2 = 49% 0.13 (0.02, 0.24); I^2 = 67% 0.04 (-0.01, 0.08); I^2 = 2% 0.04 (0.01, 0.08); I^2 = 47% P=0.12; I^2 = 53.7%	7 (3514/3528) 13 (4245/4237) 27 (25141/23108)	I^2 = 27% -0.03 (-0.17, 0.12); I^2 = 83% 0.04 (-0.01, 0.08); I^2 = 0% 0.01 (-0.04, 0.06); I^2 = 55% P=0.69; I^2 = 0%	7 (3506/3540) 10 (3534/3641) 23 (9490/9527)
Nutritional status	<30 % stunted >30 % stunted Total Subgroup differences	0.02 (-0.00, 0.04); I^2 = 0% 0.01 (-0.06, 0.08); I^2 = 50% 0.02 (-0.00, 0.05); I^2 = 15%	10 (21,250/23,656) 8 (4,681/4,542) 18 (25,931/28,198)	0.05 (-0.05, 0.14); I^2 = 83% 0.03 (-0.02, 0.08); I^2 = 25% 0.04 (-0.02, 0.10); I^2 = 73%	9 (6311/10619) 8 (4705/4598) 17 (11016/15217)

		P=0.92; I^2 = 0%		P=0.80; I^2 = 0%	

*Note: this analysis combined all studies of deworming vs. placebo which provided details on the subgroup characteristics. The "deworming" arm was chosen to most closely match deworming twice per year.

Additional Table 24: Weight Sensitivity Cluster Trials: Standardized Mean Difference (SMD) for All Treatment Comparisons-Random Effects Model

Treatment	Reference	MD (95% CrI)
Alben std	PLB	0.03(-0.02,0.07)
Alben HD		-0.09(-0.26,0.08)
Meben HD		0.02(-0.07,0.10)
Alben std + Hygiene		0.04(-0.05,0.13)
Alben + PZQ + HY		-0.03(-0.14,0.07)
Alben std + iron		-0.10(-0.29,0.09)
Meben std		0.08(-0.02,0.19)
Alben HD	Alben std	-0.12(-0.29,0.06)
Meben HD		-0.01(-0.10,0.08)
Alben std + Hygiene		0.01(-0.09,0.11)
Alben + PZQ + HY		-0.06(-0.17,0.05)
Alben std + iron		-0.13(-0.32,0.06)
Meben std		0.06(-0.06,0.17)
Meben HD	Alben HD	0.11(-0.08,0.30)
Alben std + Hygiene		0.13(-0.07,0.32)
Alben + PZQ + HY		0.05(-0.14,0.26)

Alben std + iron		-0.02(-0.27,0.24)
Meben std		0.17(-0.03,0.37)
Alben std + Hygiene	Meben HD	0.02(-0.10,0.14)
Alben + PZQ + HY		-0.05(-0.18,0.08)
Alben std + iron		-0.12(-0.33,0.09)
Meben std		0.07(-0.04,0.17)
Alben + PZQ + HY	Alben std + Hygiene	-0.07(-0.21,0.06)
Alben std + iron		-0.14(-0.35,0.07)
Meben std		0.05(-0.09,0.18)
Alben std + iron	Alben + PZQ + HY	-0.07(-0.28,0.15)
Meben std		0.12(-0.03,0.27)
Meben std	Alben std + iron	0.19(-0.03,0.41)
	Total Residual Deviance	11.72
	Deviance Information Criteria	-36.6

Total Studies	11
2-arm	9
3-arm	2

Additional Table 25: Weight, Sensitivity according to impact on worms > 50 %: Standardized Mean Difference (SMD) for All Treatment Comparisons-Random Effects Model

Treatment	Reference	Network SMD (95% CrI)	Pairwise SMD (95% CI)
Alben std + PZQ	Placebo	0.05(-0.35,0.45)	0.20 (-0.21, 0.61)
Alben HD	Placebo	0.05(-0.64,0.75)	0.08 (-0.06, 0.22)
Meben HD	Placebo	0.07(-0.36,0.64)	0.10 (-0.22, 0.42)
Alben + Hygiene	Placebo	0.04(-0.63,0.69)	0.04 (-0.01, 0.09)
Alben + PZQ + Hygiene	Placebo	-0.03(-0.68,0.62)	-0.04 (-0.11, 0.04)
Alben std	Placebo	0.70(0.02,1.41)	0.38 [-0.31, 1.07]
Alben std + Iron	Placebo	0.03(-0.68,0.72)	0.00 (-0.51, 0.51)
Alben HD	Alben std + PZQ	0.00(-0.80,0.80)	-
Meben HD	Alben std + PZQ	0.02(-0.55,0.72)	-

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10.5 STUDIES WHICH SCREENED FOR INFECTION, INCLUDED IN SENSITIVITY ANALYSES

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11 Appendices

Appendix 1: Initial PRESS form

PRESS EBC Search Submission

Searcher's Name: Jessie Mcgowan **E-mail:** jmcgowan@ottawa.ca

Date submitted: April 19, 2012 **Date needed by:** April 15, 2012

Note to peer reviewers – please enter your information in the Peer Review Assessment area

Remember: this peer review only pertains to your MEDLINE search strategy.

Search question (Describe the purpose of the search)

Question

What are the effects of deworming children (<16 years) in LMICs for soil-transmitted-helminths in conjunction with complementary co-interventions on health outcomes, cognition and school attendance/participation?

PICO format (Outline the PICO for your question, i.e., the Patient, Intervention, Comparison and Outcome)

Population: children under 16 years of ages

Intervention: albendazole (or equivalent for soil-transmitted-helminths in combination with schistosomiasis treatment, food, vitamins, hygiene, sanitation or other cointerventions

Comparison: active or placebo comparison that allows assessment of the effects of the combination of albendazole+cointervention

Outcome: health outcomes (e.g., growth, nutritional status), cognition (achievement scores), school attendance/ participation.

Inclusion criteria (List criteria such as age groups, study designs, to be included)

- Not limited to language of publication
- Not limited to study design
- any article that has albendazole (or equivalent) for soil-transmitted-helminths (all the worms listed) in combination with any other co-intervention (hygiene promotion, sanitation, iron, schoolfeeding, vitamins, etc.).

Exclusion criteria (List criteria such as study designs, to be excluded)

- exclude studies which measure the worm burden, worm prevalence alone since this is not demonstrated to be associated with health or educational outcomes
- exclude albendazole (or equivalent) vs. placebo since this is covered in Paul garner's review
- exclude albendazole + x vs. placebo+x (i.e., if the co-intervention is given in both groups, since this was also included in Paul garner's review)

Was a search filter applied? (Remember this pertains only to the MEDLINE strategy)

Yes X No ☐

If yes, which one?

Cochrane hedge: PUBMED clinical query:

Haynes/ McKibbon *et al*: SIGN (Scottish):

CRD (UK): Robinson and Dickerson:

Other: EPOC search filter for design

MEDLINE search interface used

EBSCO ☐ OVID X PubMED ☐ Other_____

Has the search strategy been adapted (i.e., subject heading and terms reviewed) for other databases? Please check all that apply.

Ageline	☐
AMED	☐
C2-SPCTRE	☐
CINAHL	☐
Cochrane Database of Systematic Reviews (CDSR; Cochrane Reviews)	☐
Cochrane Central Register of Controlled Trials (CENTRAL; Clinical Trials)	x
Cochrane Methodology Register (CMR; Methods Studies)	☐
Cochrane Library (all databases)	☐
Database of Abstracts of Reviews of Effects (DARE; Other Reviews)	☐
Embase	x
ERIC	☐
ICTRP (trials register)	☐
LILACS (Latin American and Caribbean Health Sciences Literature)	x
MEDLINE	x
PsycINFO	☐
PreMEDLINE	x
Other Cochrane Infectious disease register	x
Other Global Health	x

Other LMIC databases

- AFROLIB Database (http://afrolib.afro.who.int/cgi-bin/wxis.exe/iah/?IsisScript=iah/iah.xic&lang=I&base=afrolib)
- 3ie Database of Impact Evaluations (http://www.3ieimpact.org/database_of_impact_evaluations.html)
- BLDS British Library for Development Studies (http://blds.ids.ac.uk/)
- ELDIS (http://www.eldis.org/)
- IDEAS Economics and Finance database (RePEc) http://ideas.repec.org/
- International Clinical Trials Registry Platform - Search Portal: http://www.who.int/trialsearch/
- World Bank - Documents & Reports (http://go.worldbank.org/H1Q3T60M80)
- East View Information Service Online Databases (http://online.eastview.com/index.jsp) – China, Russia and Solviet Union
- Index Medicus for the Western Pacific (WPRIM) (http://wprim.wpro.who.int/SearchBasic.php)
- South African Medical Database (SAMED) (http://www.mrc.ac.za/SamedSearch/)

Other notes or comments that you feel would be useful for the peer reviewer?

- We deliberately chose not to use the EPOC LMIC search filter.
- We started the search using the Cochrane review from Paul Garner: Taylor-Robinson DC, Jones AP, Garner P. Deworming drugs for treating soil-transmitted intestinal worms in children: effects on growth and school performance. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD000371.

Please paste your MEDLINE strategy here:

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 2 2012>

Search Strategy:

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1 exp Helminths/ (46247)

2 (deworm* or de-worm* or whipworm* or whip worm* or hookworm* or hook worm* or roundworm* or round worm* or pinworm* or pin worm*).tw. (2380)

3 (hemint* or geohelminth* or ancylostoma or Necator or Ascaris or Ascaridida or Enterobius or Oxyuroidea or Oxyurida or Trichuris or Trichuroidea or Capillaria or Trichinella or Strongyloid* or Oesophagostomum or Strongylus or ancylostoma or Acanthocephala or Moniliformis or Adenophorea or Enoplida or Secernentea or Ascaridida or Rhabditida or Nematoda or Cestoda or Trematoda or Turbellaria or Platyhelminths or Rotifera).tw. (9714)

4 or/1-3 (49075)

5 Albendazole/ (2211)

6 Mebendazole/ (542)

7 exp Piperazines/ (32245)

8 Levamisole/ (784)

9 exp Pyrantel/ (173)

10 (Albendazole or Mebendazole or Piperazine* or Levamisole or pyrantel or tiabendazole).tw. (5918)

11 or/5-10 (37801)

12 4 and 11 (2211)

13 limit 12 to ("newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to five years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") (619)

14 adolescent/ or exp child/ or exp infant/ (1196631)

15 (child* or paediatric* or pediatric* or youth or infant or adolescent* or school age or preschool or pre-school).tw. (586377)

16 12 and (14 or 15) (648)

17 13 or 16 (648)

18 randomised controlled trial.pt. (226130)

19 random*.ti,ab. (418835)

20 intervention*.ti,ab. (337553)

21 control*.ti,ab. (1389821)

22 evaluat*.ti,ab. (1226805)

23 or/18-22 (2716790)

24 Animals/ (2342515)

25 Humans/ (6471296)

26 24 not (24 and 25) (1533726)

27 23 not 26 (2208290)

28 17 and 27 (354)

Peer Review Assessment

[For peer reviewers only]

Peer reviewer's name: John Eyers

E-mail: johneyers@hotmail.com

Date completed: 20th April 2012

Please select the one most appropriate answer for each element

	Adequate	Adequate with revisions*	Needs revision*
1. Translation of the research question	X		
2. Boolean and proximity operators	X		
3. Subject headings		X	
4. Natural language / free-text			X
5. Spelling, syntax and line numbers		X	
6. Limits and filters	X		
7. Search strategy adaptations	N/A – Medline only		

* Provide an explanation or example for "Adequate with revisions" and "needs revision":

*See my suggestions in red to your search strategy in a separate file

1. In SS3 disease terms, such as trichuriasis, ascariasis, trichinellosis, enterobiasis should be added to the general taxonomic terms (Genera) – such as Ascaris, Trichuris etc. Broad taxonomic terms for non-soil-transmitted helminths are also included such as Trematoda in this search statement. If as indicated in SS1 you want to include all helminths (Exp Helminths/), you should also include disease and species terms for these other helminths,

eg schistosomiasis or Schistosoma* or trematode* in SS3. You have excluded Toxocara (toxocariasis or toxocara*) in your soil-transmitted helminths list – should it be included as children are affected by this organism which can cause significant morbidity?

2. In the section on drugs and therapy, I would add Anthelmintics/ to the MeSH list of drugs (SS5-9) and anthelmint* to the natural language terms (SS10). As for other drugs you have excluded Ivermectin which is also used to treat soil-transmitted helminths, and since you have included eg Trematodes you have not included praziquantel for treatment of schistosomiasis, but I may have misunderstood the Intervention statement in the PICO section – *'albendazole (or equivalent for soil-transmitted-helminths in combination with schistosomiasis treatment, food, vitamins, hygiene, sanitation or other cointerventions'*

3. I have suggested some changes to the children section of the search (SS15)

Other Comments (please limit to 3-5 sentences): n/a

Additional Table 26: Revised PRESS form

PRESS EBC Search Submission

ESS

Searcher's Name: Jessie Mcgowan **E-mail:** jmcgowan@ottawa.ca

Date submitted: April 19, 2012 **Date needed by: April 15, 2012**

Note to peer reviewers – please enter your information in the Peer Review Assessment area

Remember: this peer review only pertains to your MEDLINE search strategy.

Search question (Describe the purpose of the search)

Question

What are the effects of deworming children (<16 years) in LMICs for soil-transmitted-helminths in conjunction with complementary co-interventions on health outcomes, cognition and school attendance/participation?

PICO format (Outline the PICO for your question, i.e., the Patient, Intervention, Comparison and Outcome)

Population: children under 16 years of ages

Intervention: albendazole (or equivalent for soil-transmitted-helminths in combination with schistosomiasis treatment, food, vitamins, hygiene, sanitation or other cointerventions

Comparison: active or placebo comparison that allows assessment of the effects of the combination of albendazole+cointervention

Outcome: health outcomes (e.g., growth, nutritional status), cognition (achievement scores), school attendance/participation.

Inclusion criteria (List criteria such as age groups, study designs, to be included)

- Not limited to language of publication
- Not limited to study design

- any article that has albendazole (or equivalent) for soil-transmitted-helminths (all the worms listed) in combination with any other co-intervention (hygiene promotion, sanitation, iron, schoolfeeding, vitamins, etc.).

Exclusion criteria (List criteria such as study designs, to be excluded)

- exclude studies which measure the worm burden, worm prevalence alone since this is not demonstrated to be associated with health or educational outcomes
- exclude albendazole (or equivalent) vs. placebo since this is covered in Paul garner's review
- exclude albendazole + x vs. placebo+x (i.e., if the co-intervention is given in both groups, since this was also included in Paul garner's review)

Was a search filter applied? (Remember this pertains only to the MEDLINE strategy)

Yes X No ☐

If yes, which one?

Cochrane hedge: PUBMED clinical query:

Haynes/ McKibbon *et al.*: SIGN (Scottish):

CRD (UK): Robinson and Dickerson:

Other: EPOC search filter for design

MEDLINE search interface used

EBSCO ☐ OVID X PubMED ☐ Other_____

Has the search strategy been adapted (i.e., subject heading and terms reviewed) for other databases? Please check all that apply.

Ageline	☐
AMED	☐
C2-SPCTRE	☐
CINAHL	☐
Cochrane Database of Systematic Reviews (CDSR; Cochrane Reviews)	☐
Cochrane Central Register of Controlled Trials (CENTRAL; Clinical Trials)	x
Cochrane Methodology Register (CMR; Methods Studies)	☐
Cochrane Library (all databases)	☐
Database of Abstracts of Reviews of Effects (DARE; Other Reviews)	☐
Embase	x
ERIC	☐
ICTRP (trials register)	☐
LILACS (Latin American and Caribbean Health Sciences Literature)	x
MEDLINE	x
PsycINFO	☐
PreMEDLINE	x
Other Cochrane Infectious disease register	x
Other Global Health	x
The metaRegister of Controlled Trials (mRCT)	x

Other LMIC databases

- AFROLIB Database (http://afrolib.afro.who.int/cgi-bin/wxis.exe/iah/?IsisScript=iah/iah.xic&lang=I&base=afrolib)
- 3ie Database of Impact Evaluations (http://www.3ieimpact.org/database_of_impact_evaluations.html)
- BLDS British Library for Development Studies (http://blds.ids.ac.uk/)
- ELDIS (http://www.eldis.org/)
- IDEAS Economics and Finance database (RePEc) http://ideas.repec.org/
- International Clinical Trials Registry Platform - Search Portal: http://www.who.int/trialsearch/
- World Bank - Documents & Reports (http://go.worldbank.org/H1Q3T60M80)
- East View Information Service Online Databases (http://online.eastview.com/index.jsp) – China, Russia and Solviet Union
- Index Medicus for the Western Pacific (WPRIM) (http://wprim.wpro.who.int/SearchBasic.php)
- South African Medical Database (SAMED) (http://www.mrc.ac.za/SamedSearch/)

Other notes or comments that you feel would be useful for the peer reviewer?

- We deliberately chose not to use the EPOC LMIC search filter.
- We started the search using the Cochrane review from Paul Garner: Taylor-Robinson DC, Jones AP, Garner P. Deworming drugs for treating soil-transmitted intestinal worms in children: effects on growth and school performance. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD000371.

Please paste your MEDLINE strategy here:

Database: Ovid MEDLINE(R) without Revisions <1996 to April Week 4 2012>

Search Strategy:

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1 exp Helminths/ (46381)

2 (deworm* or de-worm* or whipworm* or whip worm* or hookworm* or hook worm* or roundworm* or round worm* or pinworm* or pin worm* or flukes).tw. (3116)

3 (helmint* or geohelminth* or ancylostoma or Necator* or Ascaris or Ascaridida or Ancylostoma or Necator americanus or Enterobius or Oxyuroidea or Oxyurida or Trichuris or Trichuroidea or Capillaria or Trichinella or Strongyloid* or Oesophagostomum or Oesophagostomiasis or Strongylus or Acanthocephala or Moniliformis or Adenophorea or Enoplida or Secernentea or Ascaridida or Rhabditida or Nematoda or Cestoda or Trematod* or Turbellaria or Platyhelminth* or Rotifera or trichuriasis or ascariasis or trichinellosis or or Trichostrongyloidiasis or ancylostomiasis or enterobiasis or nematode* or cestode* or trematode* or ascarid* or Toxocara* or toxocariasis or schistosomiasis or Schistosoma*).tw. (34746)

4 exp Helminthiasis/ (35533)

5 or/1-4 (65257)

6 Albendazole/ (2219)

7 Mebendazole/ (543)

8 exp Piperazines/ (32356)

9 Levamisole/ (786)

10 exp Pyrantel/ (173)

11 Ivermectin/ (2831)

12 exp Anthelmintics/ (19113)

13 (Ivermectin or Albendazole or Mebendazole or Piperazine* or Levamisole or pyrantel or tiabendazole or anthelmint*).tw. (9572)

14 exp Antiplatyhelmintic Agents/ (4233)

15 (Anticestodal or Antiplatyhelmintic or Anti-platyhelmintic or Albendazole or Dichlorophen or Niclosamide or Quinacrine or Bithionol or Diamfenetide or Nitroxinil or Oxyclozanide or Rafoxanide or Schistosomicide* or Antimony Potassium Tartrate or

Antimony Sodium Gluconate or Hycanthone or Lucanthone or Niridazole or Oxamniquine).tw. (3152)

16 or/6-15 (55365)

17 5 and 16 (9423)

18 limit 17 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)") (2028)

19 adolescent/ or exp child/ or exp infant/ (1200007)

20 (child* or paediatric* or pediatric* or youth or infant* or adolescen* or school age* or preschool or pre-school or teen* or schoolchild*).tw. (637932)

21 17 and (19 or 20) (2137)

22 18 or 21 (2137)

23 randomised controlled trial.pt. (226901)

24 random*.ti,ab. (420355)

25 control*.ti,ab. (1394574)

26 intervention*.ti,ab. (338937)

27 evaluat*.ti,ab. (1231245)

28 or/23-27 (2726220)

29 animals/ (2349358)

30 human/ (6490993)

31 29 not (29 and 30) (1537702)

32 23 not 31 (221499)

33 18 and 27 (1521)

Peer Review Assessment

329

[For peer reviewers only]

Peer reviewer's name: John Eyers

E-mail: johneyers@hotmail.com

Date completed: 4th May 2012

Please select the one most appropriate answer for each element

	Adequate	Adequate with revisions*	Needs revision*
1. Translation of the research question	X		
2. Boolean and proximity operators	X		
3. Subject headings		X	
4. Natural language / free-text	X		
5. Spelling, syntax and line numbers	X		
6. Limits and filters	X		
7. Search strategy adaptations	X		

*Provide an explanation or example for "Adequate with revisions" and "needs revision":

Other Comments (please limit to 3-5 sentences): n/a

11.1 SEARCH STRATEGY TRANSLATIONS TO DIFFERENT DATABASES

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, April 2013

Search Strategy:

---

1 flukes.tw. (1471)

2 platyhelminth*.tw. (887)

3 whipworm*.tw. (261)

4 whip worm*.tw. (7)

5 hookworm*.tw. (3001)

6 hookworm*.tw. (3001)

7 hook worm*.tw. (53)

8 roundworm*.tw. (703)

9 round worm*.tw. (119)

10 geohelminth*.tw. (279)

11 ancylostoma*.tw. (1447)

12 Necator*.tw. (867)

13 Ascaris.tw. (5946)

14 Ascaridida.tw. (69)

15 Ancylostoma.tw. (1381)

16 Necator americanus.tw. (540)

17 Trichuris.tw. (2426)

18 Trichuroidea.tw. (18)

19 Adenophorea.tw. (12)

20 Enoplida.tw. (17)

21 Ascaridida.tw. (69)

22 Platyhelminth*.tw. (887)

23 Rotifera.tw. (172)

24 trichuriasis.tw. (336)

25 ascariasis.tw. (1778)

26 ancylostomiasis.tw. (452)

27 ascarid*.tw. (1456)

28 schistosomiasis.tw. (11900)

29 Schistosoma*.tw. (15374)

30 bilharziosis.tw. (171)

31 bilharzia*.tw. (2353)

32 exp Schistosoma/ (13757)

33 or/1-32 (41003)

34 Albendazole/ (3131)

35 Mebendazole/ (1681)

36 exp Piperazines/ (56085)

37 Levamisole/ (3975)

38 exp Pyrantel/ (533)

39 Ivermectin/ (4432)

40 exp Anthelmintics/ (48989)

41 Ivermectin.tw. (3935)

42 Albendazole.tw. (3266)

43 Mebendazole.tw. (1525)

44 Piperazine*.tw. (5729)

45 Levamisole.tw. (3980)

46 pyrantel.tw. (600)

47 tiabendazole.tw. (18)

48 anthelmint*.tw. (6309)

49 *Antiplatyhelmintic Agents/ (218)

50 Anticestodal.tw. (22)

51 Antiplatyhelmintic.tw. (1)

52 Anti-platyhelmintic.tw. (0)

53 Albendazole.tw. (3266)

54 Dichlorophen.tw. (47)

55 Niclosamide.tw. (325)

56 Bithionol.tw. (201)

57 Diamfenetide.tw. (4)

58 Nitroxinil.tw. (7)

59 Oxyclozanide.tw. (65)

60 Rafoxanide.tw. (117)

61 Schistosomicide*.tw. (118)

62 Antimony Potassium Tartrate.tw. (35)

63 Antimony Sodium Gluconate.tw. (1)

64 Hycanthone.tw. (326)

65 Lucanthone.tw. (107)

66 Niridazole.tw. (346)

67 Oxamniquine.tw. (372)

68 Praziquantel/ (3120)

69 Trichlorfon/ (989)

70 metrifonate.tw. (331)

71 Artemisinins/ (3858)

72 (artesunate or artemether).tw. (2405)

73 or/34-72 (115866)

74 (deworm* or de-worm*).tw. (734)

75 exp Anthelmintics/ or Anthelmintic*.tw. (50560)

76 74 or 75 (50949)

77 adolescent/ or exp child/ or exp infant/ (2723799)

78 child*.tw. (927060)

79 paediatric*.tw. (37682)

80 pediatric*.tw. (165163)

81 youth.tw. (30635)

82 infant*.tw. (288702)

83 adolescen*.tw. (158204)

84 school age*.tw. (12650)

85 preschool.tw. (14787)

86 pre-school.tw. (3209)

87 teen*.tw. (20106)

88 schoolchild*.tw. (9950)

89 or/77-88 (2997226)

90 33 and 73 (6526)

91 76 or 90 (51580)

92 89 and 91 (6676)

Database: Embase Classic+Embase <1947 to 2013 April 17>

Search Strategy:

---

1 whipworm*.tw. (356)

2 whip worm*.tw. (14)

3 hookworm*.tw. (4028)

4 hookworm*.tw. (4028)

5 hook worm*.tw. (96)

6 roundworm*.tw. (864)

7 round worm*.tw. (204)

8 pinworm*.tw. (597)

9 pin worm*.tw. (31)

10 flukes.tw. (1719)

11 geohelminth*.tw. (350)

12 ancylostoma.tw. (1722)

13 Necator*.tw. (1145)

14 Ascaris.tw. (8163)

15 Ascaridida.tw. (80)

16 Ancylostoma.tw. (1722)

17 Necator americanus.tw. (747)

18 Enterobius.tw. (1260)

19 Oxyuroidea.tw. (49)

20 Oxyurida.tw. (41)

21 Trichuris.tw. (3043)

22 Trichuroidea.tw. (18)

23 Capillaria.tw. (713)

24 Trichinella.tw. (4062)

25 Strongyloid*.tw. (4724)

26 Oesophagostomum.tw. (779)

337

27 Oesophagostomiasis.tw. (38)

28 Acanthocephala.tw. (675)

29 Adenophorea.tw. (10)

30 Enoplida.tw. (15)

31 Secernentea.tw. (20)

32 Ascaridida.tw. (80)

33 Rhabditida.tw. (168)

34 Cestoda.tw. (1527)

35 Trematod*.tw. (5980)

36 Turbellaria.tw. (210)

37 Platyhelminth*.tw. (980)

38 Rotifera.tw. (190)

39 trichuriasis.tw. (496)

40 ascariasis.tw. (2602)

41 trichinellosis.tw. (1277)

42 Trichostrongyloidiasis.tw. (6)

43 ancylostomiasis.tw. (558)

44 enterobiasis.tw. (633)

45 cestode*.tw. (3468)

46 trematode*.tw. (4332)

47 ascarid*.tw. (2106)

48 schistosomiasis.tw. (15247)

338

49 Schistosoma*.tw. (18458)

50 or/1-49 (67006)

51 Albendazole/ (9094)

52 Mebendazole/ (4966)

53 exp Piperazines/ (286152)

54 Levamisole/ (10932)

55 exp Pyrantel/ (636)

56 Ivermectin/ (7682)

57 exp Anthelmintics/ (105958)

58 Ivermectin.tw. (4395)

59 Albendazole.tw. (4134)

60 Mebendazole.tw. (1927)

61 Piperazine*.tw. (7566)

62 Levamisole.tw. (5166)

63 pyrantel.tw. (723)

64 tiabendazole.tw. (81)

65 anthelmint*.tw. (7784)

66 *Antiplatyhelmintic Agents/ (75)

67 Anticestodal.tw. (26)

68 Antiplatyhelmintic.tw. (1)

69 Anti-platyhelmintic.tw. (0)

70 Albendazole.tw. (4134)

71 Dichlorophen.tw. (67)

72 Niclosamide.tw. (418)

73 Bithionol.tw. (304)

74 Diamfenetide.tw. (4)

75 Nitroxinil.tw. (9)

76 Oxyclozanide.tw. (73)

77 Rafoxanide.tw. (139)

78 Schistosomicide*.tw. (143)

79 Antimony Potassium Tartrate.tw. (54)

80 Antimony Sodium Gluconate.tw. (1)

81 Hycanthone.tw. (447)

82 Lucanthone.tw. (191)

83 Niridazole.tw. (485)

84 Oxamniquine.tw. (447)

85 or/51-84 (389753)

86 (deworm* or de-worm*).tw. (831)

87 anthelmint*.tw. (7784)

88 anthelmintic/ (10575)

89 or/86-88 (14983)

90 adolescent/ or exp child/ or exp infant/ (2525279)

91 child*.tw. (1286310)

92 paediatric*.tw. (57244)

93 pediatric*.tw. (236884)

94 youth.tw. (38046)

95 infant*.tw. (393410)

96 adolescen*.tw. (206928)

97 school age*.tw. (17282)

98 preschool.tw. (18565)

99 pre-school.tw. (4883)

100 teen*.tw. (25542)

101 schoolchild*.tw. (13488)

102 or/91-101 (1814311)

103 50 and 85 (12040)

104 103 or 89 (23484)

105 104 and 102 (2400)

Cochrane Library – CDSR, DARE, CENTRAL, EED, HTA

Search Name: deworming v2 April 18, 2013

Last Saved: 11/03/2013 13:54:30.640

Description:

Search Name: deworming v2 April 18 2013

Last Saved: 18/04/2013 19:02:35.268

Description:

ID	Search
#1	helmint*:ti,ab,kw (Word variations have been searched)
#2	Ancylostoma duodenale
#3	Necator americanus
#4	Ascaris
#5	Enterobius vermicularis
#6	trichuris
#7	Strongyloid*
#8	hookworm*
#9	roundworm*
#10	pinworm*
#11	whipworm*

#12 schistosomiasis

#13 Schistosoma

#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #13

#15 albendazole

#16 mebendazole

#17 piperazine

#18 levamisole

#19 pyrantel

#20 tiabendazole

#21 deworm*:ti,ab or de-worm*:ti,ab

#22 #15 or #16 or #17 or #18 or #19 or #20 or #21

#23 #21 or #22

#24 #23 and #14

#25 deworm

#26 de-worm

#27 deworming

#28 de-worming

#29 anthelmint*

#30 anthelmintic

#31 #25 or #26 or #27 or #28 or #29 or #30

#32 #24 or #31

CINAHL - Ebscohost

S24	S23 or S21
S23	S12 and S22
S22	S20 or S21
S21	"deworm*" or “de-worm" or “anthelmint*” or “anthelmintic”
S20	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S19	(MH "Anthelmintics")
S18	"pyrantel"
S17	"levamisole"
S16	(MH "Ranolazine") OR "piperazines"
S15	"mebendazole"
S14	"albendazole"
S13	(MH "Anthelmintics+") OR (MH "Antiprotozoal Agents+")
S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11	"bilharziosis"
S10	"bilharzia"
S9	(MH "Schistosomiasis") OR "schistosomiasis"

S8	"pinworm" OR (MH "Enterobius") OR (MH "Enterobiasis")
S7	"necator"
S6	"roundworm"
S5	(MM "Hookworm Infections")
S4	"trichuris trichiura"
S3	"whipworm"
S2	(MM "Helminths")
S1	(MM "Trematodes")

LILACS

deworm OR de-worm OR Anthelmintics OR Anthelmintic

ProQuest Social Services Abstracts,

S1 or S2 or S3

S3 (deworm OR de-worming OR de-worm OR deworming OR anthelmintics OR anthelmintic) AND (child OR children OR school OR infant OR preschool OR teenager OR adolescent)

345

S2 flukes or platyhelminth or whipworm or whip worm or hookworm or hook worm or roundworm or round worm or geohelminth or ancylostoma or necator or ascaris or Ascaridida or Ancylostoma or Trichuris or Trichuroidea or Adenophorea or Enoplida or Ascaridida or Platyhelminth or Rotifera or trichuriasis or ascariasis or ancylostomiasis or ascarid or schistosomiasis or Schistosoma or bilharziosis or bilharzias or schistosoma

S1 Albendazole or Mebendazole or Piperazines or Levamisole or Pyrantel or Ivermectin or Anthelmintics or Ivermectin or Albendazole or Mebendazole or

Piperazine or Levamisole or Pyrantel or Tiabendazole or anthelmint or Antiplatyhelmintic Agents or Anticestodal or Antiplatyhelmintic or

Anti-platyhelmintic or Albendazole or Dichlorophen or Niclosamide or

Bithionol or Diamfenetide or Nitroxinil or Oxyclozanide or Rafoxanide or

Schistosomicide or Antimony Potassium Tartrate or Antimony Sodium or Gluconate or Hycanthone or Lucanthone or Niridazole or Oxamniquine or

Praziquantel or Trichlorfon or Metrifonate or Artemisinins or artesunate or artemether

Proquest Econlit,

S1 or S2 or S3

S3 (deworm OR de-worming OR de-worm OR deworming OR anthelmintics OR anthelmintic) AND (child OR children OR school OR infant OR preschool OR teenager OR adolescent)

S2 flukes or platyhelminth or whipworm or whip worm or hookworm or hook worm or roundworm or round worm or geohelminth or ancylostoma or necator or ascaris or Ascaridida or Ancylostoma or Trichuris or Trichuroidea or Adenophorea or Enoplida or Ascaridida or Platyhelminth or Rotifera or trichuriasis or ascariasis or ancylostomiasis or ascarid or schistosomiasis or Schistosoma or bilharziosis or bilharzias or schistosoma

S1 Albendazole or Mebendazole or Piperazines or Levamisole or Pyrantel or Ivermectin or Anthelmintics or Ivermectin or Albendazole or Mebendazole or

Piperazine or Levamisole or Pyrantel or Tiabendazole or anthelmint or Antiplatyhelmintic Agents or Anticestodal or Antiplatyhelmintic or

Anti-platyhelmintic or Albendazole or Dichlorophen or Niclosamide or

Bithionol or Diamfenetide or Nitroxinil or Oxyclozanide or Rafoxanide or

Schistosomicide or Antimony Potassium Tartrate or Antimony Sodium or Gluconate or Hycanthone or Lucanthone or Niridazole or Oxamniquine or

Praziquantel or Trichlorfon or Metrifonate or Artemisinins or artesunate or artemether

Proquest Public Affairs Information Service (PAIS),

S1 or S2 or S3

S3 (deworm OR de-worming OR de-worm OR deworming OR anthelmintics OR anthelmintic) AND (child OR children OR school OR infant OR preschool OR teenager OR adolescent)

S2 flukes or platyhelminth or whipworm or whip worm or hookworm or hook worm or roundworm or round worm or geohelminth or ancylostoma or necator or ascaris or Ascaridida or Ancylostoma or Trichuris or Trichuroidea or Adenophorea or Enoplida or Ascaridida or Platyhelminth or Rotifera or trichuriasis or ascariasis or ancylostomiasis or ascarid or schistosomiasis or Schistosoma or bilharziosis or bilharzias or schistosoma

S1 Albendazole or Mebendazole or Piperazines or Levamisole or Pyrantel or Ivermectin or Anthelmintics or Ivermectin or Albendazole or Mebendazole or

Piperazine or Levamisole or Pyrantel or Tiabendazole or anthelmint or Antiplatyhelmintic Agents or Anticestodal or Antiplatyhelmintic or

Anti-platyhelmintic or Albendazole or Dichlorophen or Niclosamide or

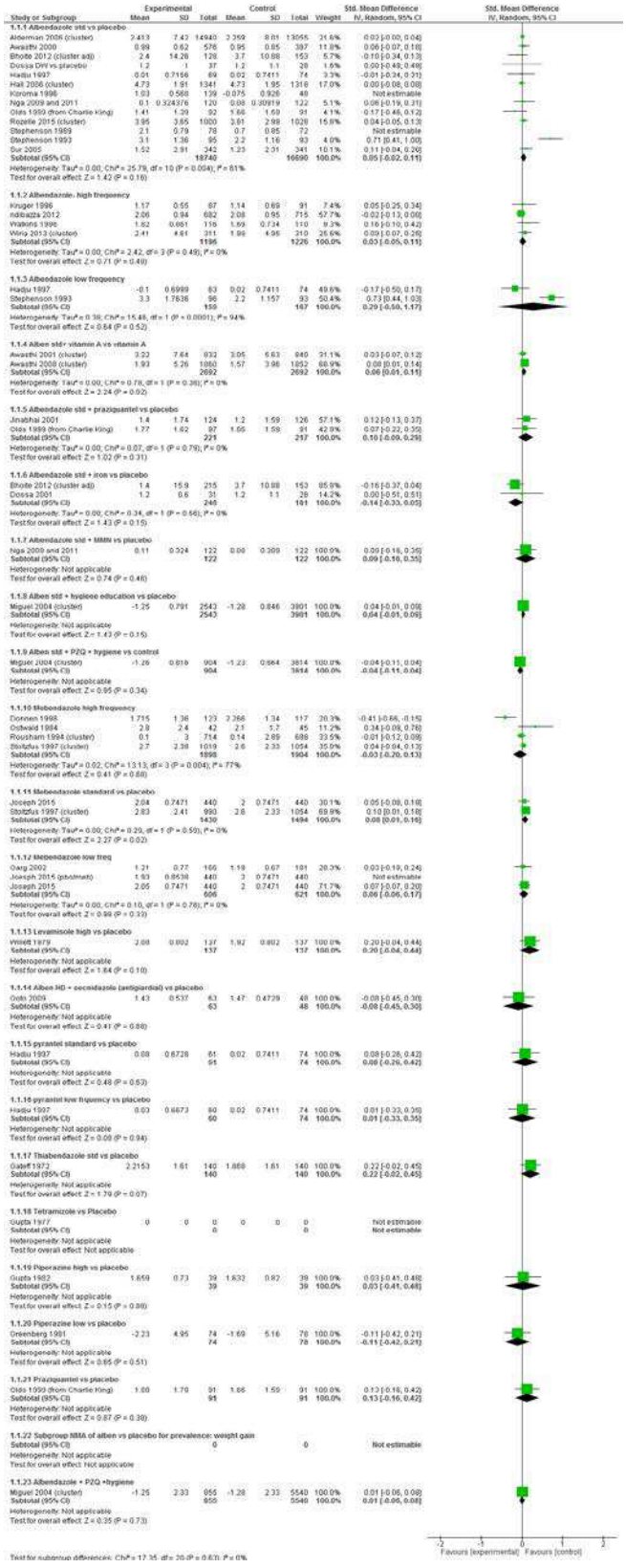
Bithionol or Diamfenetide or Nitroxinil or Oxyclozanide or Rafoxanide or

Schistosomicide or Antimony Potassium Tartrate or Antimony Sodium or Gluconate or Hycanthone or Lucanthone or Niridazole or Oxamniquine or

Praziquantel or Trichlorfon or Metrifonate or Artemisinins or artesunate or artemether

(deworm OR de-worming OR de-worm OR deworming OR anthelmintics OR anthelmintic) AND (child OR children OR school OR infant OR preschool OR teenager OR adolescent)

11.2 : PAIRWISE META-ANALYSIS OF WEIGHT GAIN OR WEIGHT FOR AGE



11.3 COMPARISON OF FULL NETWORK TO PAIRWISE COMPARISONS FOR WEIGHT OR WEIGHT FOR AGE, USING RANDOM EFFECTS

Placebo	0.05 [-0.02, 0.11]	0.03 [-0.05, 0.11]	0.29 [-0.59, 1.17]	-0.05 [-0.22, 0.13]		0.04 [-0.01, 0.09]	0.02 [-0.04, 0.09]	0.13 [-0.16, 0.42]	0.10 [0.01, 0.18]	-0.03 [-0.20, 0.13]	0.03 [-0.18, 0.24]	0.22 [-0.01, 0.44]
0.05(-0.05, 0.16)	Albe n std		0.00 [-0.27, 0.27]	0.05 [-0.15, 0.25]			0.24 [-0.05, 0.52]	-0.29 [-0.58, -0.00]				
0.00(-0.16, 0.18)	-0.05 (-0.24 ,0.15)	Alb en HD										
0.16(-0.10, 0.41)	0.11 (-0.16 ,0.36)	0.15 (-0.16, 0.45)	Alb en LD									
-0.06(-	-0.11 (-	-0.06(-	-0.22(-	Alb en+								

0.30, 0.20)	0.36 ,0.1 5)	0.3 6,0. 24)	0.5 6,0. 15)	iron								
0.35(- 0.05, 0.74)	0.30 (- 0.12 ,0.6 9)	0.3 5(- 0.1 0,0. 77)	0.19 (- 0.2 8,0. 65)	0.41 (- 0.0 7,0. 86)	Al be n+ vit A							
0.04(- 0.25, 0.32)	- 0.01 (- 0.32 ,0.2 8)	0.0 3(- 0.31 ,0.3 6)	- 0.12 (- 0.5 0,0. 27)	0.1 0(- 0.2 9,0. 47)	- 0.3 2(- 0.7 9,0 .18)	Alb en+ hygi ene						
0.15(- 0.10, 0.40)	0.10 (- 0.16 ,0.3 6)	0.15 (- 0.16 ,0.4 4)	- 0.0 1(- 0.3 6,0. 35)	0.21 (- 0.15 ,0.5 6)	- 0.2 0(- 0.6 6,0 .27)	0.11 (- 0.2 6,0. 49)	Alb en+ PZ Q	- 0.0 6 [- 0.3 5, 0.2 2]				
0.23(- 0.11, 0.57)	0.18 (- 0.16 ,0.5 2)	0.2 3(- 0.16 ,0.6 0)	0.0 7(- 0.3 4,0. 49)	0.2 9(- 0.13 ,0.7 0)	- 0.1 2(- 0.6 4,0 .41)	0.19 (- 0.2 5,0. 64)	- 0.0 8(- 0.4 4,0. 28)	PZ Q				
0.06(- 0.21,	0.01 (- 0.29 ,0.2	0.0 5(- 0.2 7,0.	- 0.1 0(- 0.4	0.12 (- 0.2 6,0.	- 0.2 9(- 0.7	0.0 2(- 0.3 8,0.	- 0.0 9(- 0.4	- 0.17 (- 0.6	Me ben std	0.05 [- 0.03,		

0.32)	9)	36)	7,0.27)	47)	5,0.17)	41)	6,0.27)	0,0.25)		0.14]		
-0.04(--0.21, 0.13)	-0.09(-0.30,0.10)	-0.04(-0.29,0.19)	-0.19(-0.51,0.11)	0.02(-0.29,0.31)	-0.39(-0.77,0.00)	-0.07(-0.42,0.25)	-0.19(-0.49,0.11)	-0.27(-0.65,0.11)	-0.09(-0.36,0.17)	Meben HD		
0.03(--0.32, 0.37)	-0.02(-0.39,0.33)	0.03(-0.37,0.40)	-0.13(-0.56,0.30)	0.09(-0.35,0.51)	-0.32(-0.84,0.20)	-0.01(-0.46,0.44)	-0.12(-0.55,0.30)	-0.20(-0.69,0.28)	-0.03(-0.46,0.41)	0.06(--0.32, 0.45)	Meben LD	
0.22(--0.14, 0.57)	0.17(-0.21,0.53)	0.21(-0.19,0.60)	0.06(-0.38,0.50)	0.28(-0.17,0.70)	-0.14(-0.66,0.40)	0.18(-0.28,0.63)	0.07(-0.37,0.50)	-0.01(-0.50,0.47)	0.16(-0.29,0.60)	0.25(--0.14, 0.65)	0.19(--0.31, 0.68)	Thiaben std
0.20(--0.16, 0.56)	0.15(-0.23,0.52)	0.19(-0.21,0.59)	0.04(-0.40,0.49)	0.26(-0.19,0.69)	-0.16(-0.68, 0.38)	0.16(-0.30,0.62)	0.05(-0.40,0.49)	-0.03(-0.53,0.46)	0.14(-0.30,0.59)	0.23(--0.16, 0.64)	0.17(-0.33, 0.67)	-0.02(--0.52, 0.49)
0.04(-	-0.01	0.04(-	-0.12	0.10(-	-0.3	0.00(-	-0.11	-0.19	-0.0	0.08(-	0.01(-	-0.18(

0.48, 0.55)	(-0.54,0.51)	0.52,0.57)	(-0.70,0.46)	0.48,0.67)	1(-0.96,0.33)	0.59,0.58)	(-0.69,0.46)	(-0.82,0.42)	2(-0.60,0.56)	0.47, 0.62)	0.61, 0.63)	-0.81, 0.45)
-0.11(-0.51, 0.30)	-0.16 (-0.58,0.26)	-0.11 (-0.55,0.32)	-0.27(-0.74,0.22)	-0.05(-0.53,0.42)	-0.46(-1.02,0.11)	-0.14 (-0.64,0.35)	-0.26(-0.74,0.22)	-0.34(-0.87,0.18)	-0.17 (-0.65,0.32)	-0.07(-0.50, 0.37)	-0.14(-0.67, 0.39)	-0.33(-0.86, 0.21)
0.21(-0.16, 0.59)	0.16 (-0.21,0.54)	0.21 (-0.20,0.62)	0.05(-0.34,0.46)	0.27(-0.17,0.72)	-0.14(-0.67,0.41)	0.17 (-0.28,0.65)	0.06(-0.38,0.51)	-0.02(-0.52,0.48)	0.15 (-0.30,0.62)	0.25(-0.16, 0.66)	0.18(-0.32, 0.70)	-0.01(-0.52, 0.51)
-0.03(-0.33, 0.26)	-0.08(-0.40,0.22)	-0.04(-0.38,0.29)	-0.19 (-0.57,0.20)	0.03(-0.37,0.40)	-0.39(-0.87, 0.11)	-0.07(-0.48,0.34)	-0.19 (-0.57,0.20)	-0.27(-0.71,0.18)	-0.09(-0.49,0.30)	0.00(-0.33, 0.34)	-0.06(-0.51, 0.39)	-0.25(-0.70, 0.21)
0.09(-0.23, 0.42)	0.04 (-0.29,0.36)	0.09(-0.28,0.45)	-0.07(-0.47,0.34)	0.15 (-0.26,0.55)	-0.26(-0.76,0.25)	0.05(-0.37,0.49)	-0.06(-0.47,0.34)	-0.14 (-0.60,0.32)	0.03(-0.38,0.45)	0.12(-0.23, 0.50)	0.06(-0.41, 0.54)	-0.13(-0.61, 0.35)

-0.08(-0.54, 0.38)	-0.13(-0.60,0.34)	-0.08(-0.58,0.40)	-0.24(-0.77,0.29)	-0.02(-0.55,0.51)	-0.43(-1.04,0.18)	-0.11(-0.66,0.42)	-0.23(-0.76,0.29)	-0.31(-0.88,0.26)	-0.14(-0.66,0.39)	-0.04(-0.53, 0.45)	-0.11(-0.68, 0.47)	-0.29(-0.87, 0.28)
0.47(-0.06, 1.01)	0.42(-0.12,0.97)	0.46(-0.10,1.03)	0.31(-0.27,0.89)	0.53(-0.06,1.12)	0.11(-0.53,0.77)	0.43(-0.17,1.04)	0.31(-0.27,0.91)	0.23(-0.39,0.87)	0.41(-0.18,1.01)	0.50(-0.04, 1.07)	0.44(-0.19, 1.07)	0.25(-0.38, 0.89)
0.00(-0.46, 0.46)	-0.05(-0.51,0.41)	-0.01(-0.49,0.48)	-0.16(-0.67,0.36)	0.06(-0.42,0.54)	-0.35(-0.94,0.26)	-0.04(-0.57,0.50)	-0.15(-0.67,0.37)	-0.23(-0.80,0.33)	-0.06(-0.58,0.47)	0.03(-0.45, 0.53)	-0.03(-0.60, 0.55)	-0.22(-0.79, 0.37)
0.30(-0.04, 0.63)	0.25(-0.11, 0.59)	0.30(-0.09,0.66)	0.14(-0.28,0.56)	0.36(-0.07,0.77)	-0.05(-0.26,0.15)	0.26(-0.18,0.69)	0.15(-0.28,0.56)	0.07(-0.42,0.54)	0.24(-0.17,0.65)	0.33(0.00, 0.66)	0.27(-0.21, 0.74)	0.08(-0.41, 0.57)
0.06(-0.26, 0.39)	0.01(-0.32,0.33)	0.05(-0.32,0.42)	-0.10(-0.50,0.	0.12(-0.29,0.52)	-0.29(-0.80	0.02(-0.41,0.46)	-0.09(-0.50,0.	-0.17(-0.63,0.	0.00(-0.41,0.42)	0.09(-0.26, 0.47)	0.03(-0.44, 0.50)	-0.16(-0.63, 0.33)

			31)		,0.22)		32)	29)			
0.05(-0.42, 0.51)	0.00(-0.48,0.47)	0.04(-0.46,0.53)	-0.11(-0.65,0.42)	0.11(-0.43,0.63)	-0.30(-0.93,0.31)	0.01(-0.53,0.55)	-0.10(-0.64,0.42)	-0.18(-0.76,0.38)	-0.01(-0.55,0.52)	0.08(-0.41, 0.57)	0.02(-0.56, 0.59)	-0.17(-0.75, 0.41)
0.30(-0.22, 0.83)	0.25(-0.29,0.79)	0.29(-0.26,0.85)	0.14(-0.44,0.73)	0.36(-0.23,0.95)	-0.06(-0.70, 0.60)	0.26(-0.33,0.86)	0.14(-0.43,0.73)	0.06(-0.56,0.70)	0.24(-0.34,0.83)	0.33(-0.21, 0.89)	0.27(-0.36, 0.90)	0.08(-0.55, 0.72)

**__Note__: needs to be read side by side with following page for reference. The numbers below the diagonal represent the estimates of effect size from the network meta-analysis, and the numbers above the diagonal represent the effect size estimates from the random effects pairwise analysis of direct comparisons. For example, Albendazole 3-4 times per year vs. placebo was SMD 0.03 [-0.05, 0.11] in direct comparisons in RCTs, and the estimate from the network meta-analysis was: SMD 0.00(-0.16,0.18)

13.3, continued: Weight or weight for age Network analysis compared to pairwise random effects, using SMD

0.20 [-0.04, 0.44]	0.03 [-0.41, 0.48]	-0.11 [-0.41, 0.20]	0.08 [-0.26, 0.42]				0.46 [0.02, 0.91]	0.05 [-0.18, 0.28]	-0.04 [-0.11, 0.04]		0.04 [-0.33, 0.42]	0.29 (-0.15, 0.74)
			-0.10[-0.44, 0.24]					0.00 [-0.47, 0.47]				

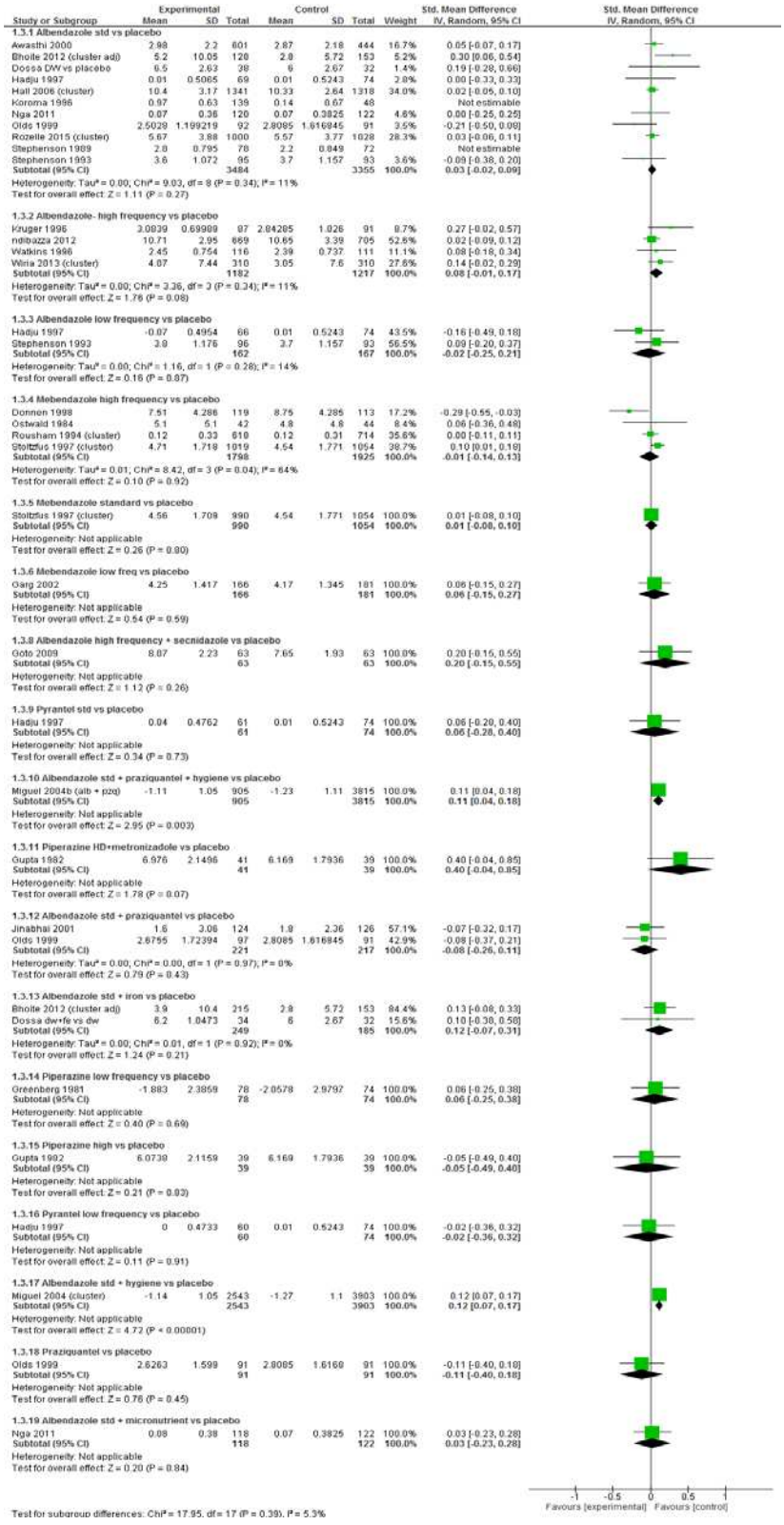
Lev a HD												
-0.16 (-0.79,0.47)	Pip HD						-0.46(-0.90, -0.01)					
-0.30(-0.85,0.24)	-0.15(-0.80,0.51)	Pip LD										
0.01 (-0.50,0.54)	0.17(-0.46,0.81)	0.32 (-0.23,0.87)	Pyrn std									
-0.23(-0.70,0.23)	-0.08(-0.66,0.52)	0.07 (-0.42,0.57)	-0.25(-0.72, 0.22)	Alben + PZQ + hygiene								
-	0.0	0.20	-	0.12(	Alb							

0.11 (-0.59,0.38)	5(-0.56,0.66)	(-0.32,0.72)	0.12(-0.61, 0.37)	-0.31, 0.56)	en+MMN							
-0.27 (-0.86,0.31)	-0.12(-0.80,0.57)	0.03 (-0.58,0.64)	-0.29(-0.89, 0.30)	-0.04(-0.58, 0.50)	-0.17(-0.73,0.40)	Alben HD+ SEC					0.12 [-0.23, 0.47]	
0.27 (-0.38,0.93)	0.42(-0.09,0.95)	0.57 (-0.09,1.25)	0.25(-0.40, 0.91)	0.50(-0.09, 1.11)	0.38(-0.24,1.02)	0.54(-0.15,1.27)	Pip HD + metro					-0.19 [-0.63, 0.24]
-0.20(-0.78,0.39)	-0.04(-0.72,0.66)	0.11(-0.50,0.72)	-0.21(-0.80, 0.37)	0.03(-0.50, 0.58)	-0.09(-0.65,0.47)	0.08(-0.57, 0.74)	-0.47 (-1.16, 0.23)	Iron				
0.10 (-0.39,0.59)	0.26(-0.36,0.88)	0.41 (-0.13, 0.92)	0.09(-0.42, 0.58)	0.33(-0.11, 0.77)	0.21(-0.26,0.67)	0.38(-0.20, 0.95)	-0.17 (-0.79,0.45)	0.30(-0.27,0.86)	Vit A			

-0.14 (-0.62,0.35)	0.02(-0.58,0.63)	0.17 (-0.35,0.69)	-0.15(-0.65, 0.34)	0.09(-0.34, 0.53)	-0.03(-0.40,0.34)	0.14(-0.43, 0.70)	-0.41 (-1.05,0.21)	0.06(-0.51,0.62)	-0.24(-0.70,0.23)	MMN		
-0.15 (-0.74,0.43)	0.01(-0.68,0.69)	0.16 (-0.46,0.77)	-0.16(-0.76, 0.43)	0.08(-0.47, 0.62)	-0.04(-0.62,0.53)	0.13(-0.31, 0.56)	-0.42(-1.14, 0.29)	0.05(-0.62,0.70)	-0.25(-0.84,0.32)	-0.01(-0.59,0.55)	SEC	
0.10 (-0.54,0.74)	0.26(-0.25,0.78)	0.40 (-0.25,1.07)	0.09(-0.56, 0.73)	0.33(-0.26, 0.93)	0.21(-0.41,0.82)	0.37(-0.32, 1.08)	-0.17 (-0.69,0.36)	0.30(-0.40,0.99)	0.00(-0.62,0.62)	0.24(-0.38,0.86)	0.25(-0.44,0.96)	Metro

Random-Effect Model	Residual Deviance	55.67
	Deviance Information Criteria	-31.69

11.4 : HEIGHT OR HEIGHT FOR AGE FOREST PLOT OF RANDOM EFFECTS PAIRWISE META-ANALYSIS



11.5 COMPARISON OF NETWORK META-ANALYSIS COMPARED TO META-ANALYSIS FOR HEIGHT

On the bottom of the diagonal, network meta-analyses for every possible comparison are shown, using network meta-analysis.

Bolded results are statistically significant.

Italicized results are greater than 0.3 SMD, which is equivalent to 0.5 kg, using the typical standard deviation from the included studies

Results from meta-analysis and network meta-analysis can be compared by assessing the result below the diagonal and above the diagonal for a given comparison. For example, Albendazole standard dose (2/ year) vs. placebo has an effect size of 0.03 SMD (-0.02, 0.09) favouring albendazole in meta-analysis, and 0.03 SMD (-0.04, 0.10) favouring albendazole in network meta-analysis

Table E3a

PLCB	0.03 (-0.02,0.09)	0.08 [-0.01, 0.17]	-0.02 [-0.25, 0.21]	0.24 [0.05, 0.43]		0.12 [0.07, 0.17]	-0.39 (-0.98,0.21)	-0.11 [-0.40, 0.18]	0.01(-0.08,0.10)	-0.01 [-0.14, 0.13]	0.06 [-0.15, 0.27]	
0.03(-0.04,0.10)	ALBEN		-0.02 [-0.17, 0.13]	-0.13 [-0.33, 0.07]								
0.08(-0.01,0.20)	0.05 (-0.06,0.19)	ALBEN high										
0.03(-0.18,0.22)	0.00 (-0.21, 0.19)	-0.06 (-0.29, 0.16)	ALBEN low									
0.01 (-0.18,0.20)	-0.02 (-0.20,0.17)	-0.07 (-0.29, 0.14)	-0.01(-0.29,0.26)	ALBEN+ iron								

0.11 (-0.17,0.38)	0.08 (-0.20,0.36)	0.03 (-0.28,0.32)	0.08(-0.25,0.42)	0.10(-0.22,0.44)	ALBEN+vitA							
0.12 (-0.01,0.25)	0.09 (-0.06,0.24)	0.04 (-0.14, 0.19)	0.09(-0.14,0.34)	0.11 (-0.11,0.34)	0.01(-0.28,0.32)	ALBEN+hygiene						
-0.01 (-0.20,0.18)	-0.04 (-0.23, 0.16)	-0.09 (-0.31, 0.12)	-0.03(-0.30,0.24)	-0.02(-0.30,0.24)	-0.11 (-0.45,0.22)	-0.13(-0.36, 0.10)	ALBEN+PZQ					
-0.01 (-0.27,0.25)	-0.04 (-0.30,0.22)	-0.09 (-0.38,0.18)	-0.03(-0.35,0.29)	-0.02(-0.33,0.29)	-0.12 (-0.49,0.27)	-0.13(-0.42, 0.16)	0.01(-0.27,0.27)	PZQ				
-0.03(-0.17,0.10)	-0.06 (-0.22, 0.09)	-0.11(-0.30,0.05)	-0.05(-0.29,0.19)	-0.04(-0.27,0.19)	-0.13 (-0.43,0.16)	-0.15(-0.35, 0.03)	-0.02(-0.25,0.21)	-0.02 (-0.31, 0.27)	MEBEN	0.15 [-0.00, 0.30]		
0.02(-0.0	-0.01 (-	-0.06 (-	-0.01(-	0.01(-0.2	-0.09(-	-0.10(-	0.03(-0.1	0.03 (-0.26	0.05(-0.1	MEBEN high		

9,0.11)	0.14,0.10)	0.23,0.07)	0.23,0.21)	0,0.21)	0.36,0.17)	0.28,0.05)	9,0.24)	,0.30)	0,0.18)			
0.05(-0.18,0.30)	0.03(-0.22,0.28)	-0.03(-0.30,0.23)	0.03(-0.28,0.35)	0.05(-0.25,0.35)	-0.05(-0.42,0.31)	-0.06(-0.33,0.21)	0.06(-0.24,0.37)	0.06(-0.28,0.41)	0.08(-0.19,0.36)	0.04(-0.22,0.31)	MEBEN low	
-0.03(-0.48,0.42)	-0.06(-0.51,0.39)	-0.12(--0.57,0.34)	-0.06(-0.54,0.44)	-0.04(-0.52,0.44)	-0.14(-0.65,0.39)	-0.15(--0.61,0.31)	-0.02(-0.51,0.48)	-0.02(-0.53,0.52)	0.00(-0.47,0.45)	-0.05(-0.50,0.40)	-0.09(-0.59,0.43)	PIP high
0.07(-0.28,0.39)	0.03(-0.31,0.37)	-0.02(-0.37,0.33)	0.04(-0.34,0.42)	0.05(-0.33,0.43)	0.05(-0.33,0.43)	-0.05(-0.42,0.30)	0.07(-0.31,0.45)	0.07(-0.36,0.50)	0.09(-0.27,0.45)	0.04(-0.30,0.40)	0.01(-0.39,0.41)	PIP low
0.12(-0.19,0.43)	0.10(-0.21,0.40)	0.04(-0.29,0.35)	0.10(-0.23,0.42)	0.11(-0.25,0.47)	0.02(-0.38,0.42)	0.00(-0.33,0.33)	0.13(-0.23,0.49)	0.13(--0.26,0.53)	0.15(-0.19,0.49)	0.10(-0.22,0.43)	0.07(-0.32,0.46)	Pyrn
0.11(-0.03,0.25)	0.08(-0.07,0.24)	0.03(-0.16,0.19)	0.08(-0.15,0.33)	0.10(-0.13,0.33)	0.00(-0.30,0.31)	-0.01(--0.20,0.18	0.12(-0.11,0.35)	0.12(--0.17,0.41)	0.14(-0.05,0.34)	0.09(-0.06,0.28)	0.06(-0.23,0.33)	Alben+PZQ+hygie

						)						ne
0.04(-0.20,0.28)	0.01(-0.23,0.26)	-0.04(-0.31,0.22)	0.02(-0.30,0.33)	0.03(-0.26,0.33)	-0.07(-0.43,0.30)	-0.08(-0.35,0.19)	0.05(-0.26,0.36)	0.05(-0.30,0.41)	0.07(-0.21,0.35)	0.02(-0.23,0.29)	-0.02(-0.35,0.34)	Albe n+ MM N
0.21(-0.17,0.58)	0.18(-0.20,0.56)	0.12(-0.26,0.51)	0.17(-0.25,0.60)	0.19(-0.21,0.60)	0.10(-0.35,0.56)	0.09(-0.31,0.48)	0.21(-0.20,0.62)	0.21(-0.24,0.67)	0.23(-0.15,0.63)	0.19(-0.19,0.58)	0.15(-0.29,0.59)	Albe n high + SEC
0.41(-0.06,0.88)	0.38(-0.09,0.85)	0.33(-0.15,0.81)	0.38(-0.11,0.89)	0.40(-0.11,0.90)	0.31(-0.23,0.82)	0.29(-0.19,0.77)	0.43(-0.09,0.92)	0.42(-0.11,0.95)	0.44(-0.04,0.92)	0.39(-0.08,0.87)	0.36(-0.16,0.88)	PIP high + metr o
0.01(-0.38,0.41)	-0.02(-0.41,0.39)	-0.07(-0.48,0.35)	-0.01(-0.44,0.43)	0.00(-0.39,0.41)	-0.09(-0.56,0.39)	-0.11(-0.52,0.31)	0.02(-0.41,0.46)	0.03(-0.45,0.49)	0.04(-0.37,0.46)	-0.01(-0.40,0.41)	-0.04(-0.50,0.42)	Iron
0.10(-0.16,0.35)	0.07(-0.20,0.33)	0.01(-0.27,0.29)	0.07(-0.25,0.39)	0.09(-0.22,0.41)	-0.01(-0.11,0.09)	-0.02(-0.31,0.26)	0.11(-0.22,0.42)	0.11(-0.27,0.46)	0.12(-0.15,0.40)	0.08(-0.17,0.33)	0.04(-0.31,0.39)	Vit A
0.0	0.02	-	0.0	0.0	-	-	0.0	0.05	0.0	0.02	-	MM

5(-0.20,0.29)	(-0.23,0.26)	0.03(-0.31,0.24)	2(-0.29,0.34)	4(-0.27,0.33)	0.06(-0.42,0.31)	0.07(-0.35,0.20)	6(-0.25,0.37)	(-0.30,0.41)	7(-0.21,0.35)	(-0.23,0.29)	0.01(-0.36,0.33)	N
-0.02(-0.41,0.36)	-0.05(-0.44,0.34)	-0.10(-0.51,0.29)	-0.04(-0.48,0.38)	-0.03(-0.46,0.40)	-0.12(-0.60,0.34)	-0.14(-0.55,0.26)	0.00(-0.44,0.42)	-0.01(-0.48,0.44)	0.01(-0.40,0.42)	-0.03(-0.44,0.36)	-0.07(-0.54,0.38)	SEC
0.42(-0.02,0.91)	0.39(-0.05,0.88)	0.34(-0.12,0.83)	0.40(-0.10,0.92)	0.41(-0.07,0.93)	0.32(-0.20,0.86)	0.30(-0.16,0.80)	0.43(-0.06,0.97)	0.43(-0.09,0.99)	0.45(-0.01,0.95)	0.40(-0.05,0.89)	0.38(-0.14,0.90)	Metro

Table E3b, Height, Network meta-analysis continued

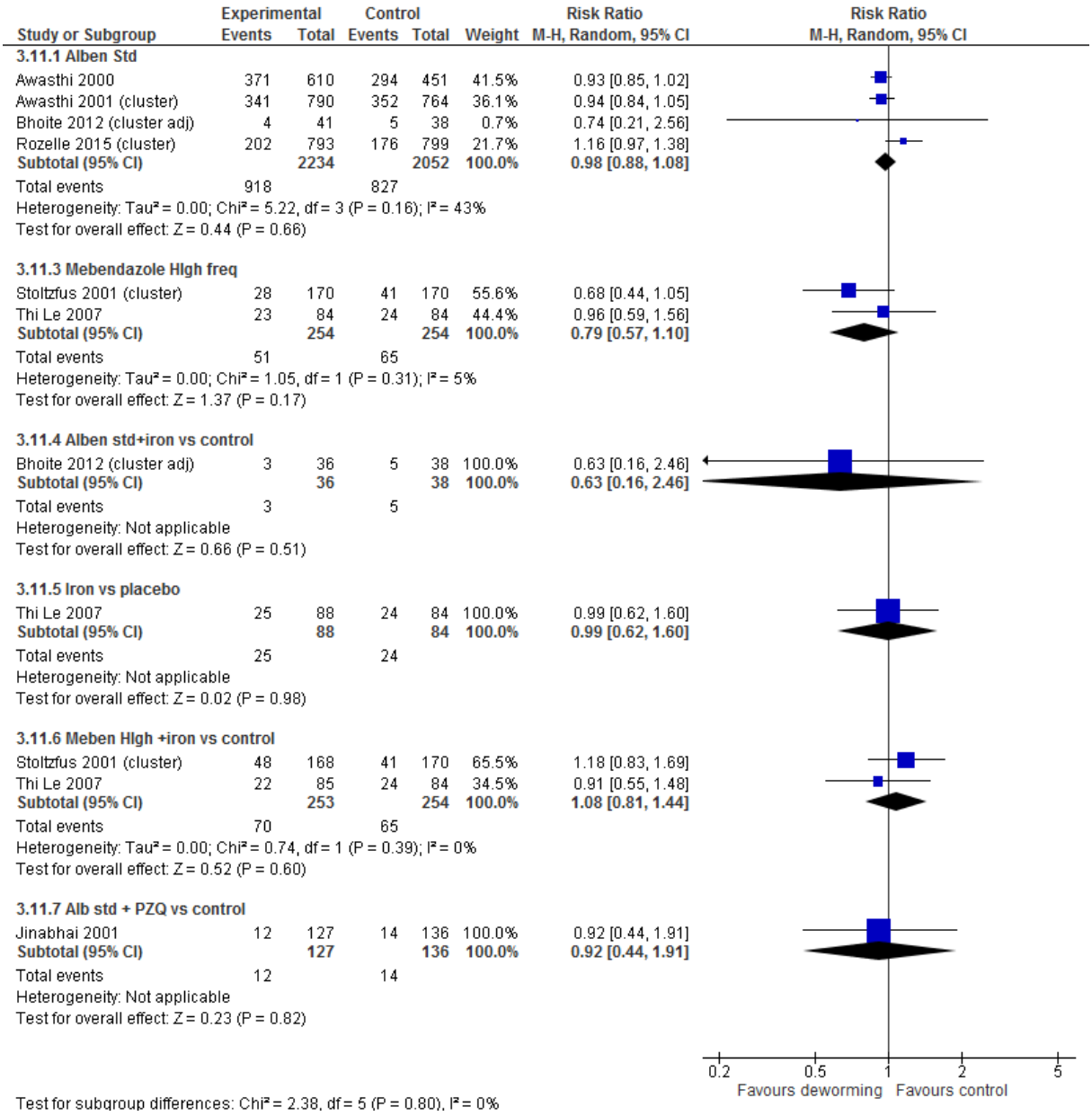
Placebo	-0.05 [-0.49, 0.40]	0.06 [-0.25, 0.38]	0.06 [-0.28, 0.40]	0.11 [0.04, 0.18]	0.01 [-0.24, 0.27]	0.20 [-0.15, 0.55]	0.40 [-0.04, 0.85]	0.2 (-0.86, 1.26)	-0.06 (-0.33,0.20)	0.01 [-0.08, 0.10]	-0.06 [-0.94, 0.82]	0.84 [-0.03, 1.70]
Alben			-0.03 [-0.20, 0.14]		0.00 [-0.22, 0.22]			-0.14 [-0.60, 0.33]		0.03 [-0.22,0.28]		
Alben+iron								0.00 [-0.62, 0.62]				
Alben+vit A									-0.01 [-0.06, 0.04]			
Meben									0.22 [-0.03			

high									, 0.48]			
	PIP HD											0.93 [0.08, 1.79]
	0.10 (-0.44, 0.64)	PIP LD										
	0.15(-0.35, 0.68)	0.06(-0.39,0 .53)	PYRN std									
	0.14(-0.32, 0.61)	0.05(-0.31,0 .41)	-0.02(-0.35,0 .33)	ALBEN std + PZQ+ hygiene								
	0.07 (-0.42, 0.58)	-0.02(-0.43,0 .38)	-0.08(-0.47,0 .31)	-0.07(-0.35,0 .21	ALBEN std+ MMN					0.00 [-0.25 , 0.25]		

				)								
	0.24 (-0.33, 0.81)	0.14(-0.34,0.64)	0.08(-0.39,0.55)	0.10(-0.30,0.49)	0.17(-0.27,0.60)	ALBENHD+SEC					-0.20 [-0.57, 0.18]	
	0.44 (0.00,0.88)	0.34(-0.21,0.94)	0.29(-0.27,0.83)	0.30(-0.19,0.79)	0.36(-0.14,0.89)	0.21(-0.36,0.79)	PIPHD+METRO					
	0.04 (-0.56, 0.65)	-0.05(-0.57,0.45)	-0.11(-0.60,0.40)	-0.10(-0.51,0.33)	-0.02(-0.49,0.42)	-0.19(-0.73,0.35)	-0.39(-1.01, 0.22)	Iron				
	0.13(-0.39, 0.63)	0.04(-0.39,0.45)	-0.03(-0.42,0.35)	-0.01(-0.30,0.28)	0.06(-0.30,0.40)	-0.11(-0.56,0.33)	-0.32(-0.83, 0.21)	0.08(-0.39,0.54)	Vit A			
	0.09 (-0.42, 0.57)	-0.02(-0.42,0.39)	-0.08(-0.46,0.30)	-0.07(-0.34,0.22	0.01(-0.27,0.29)	-0.16(-0.60,0.	-0.36(-0.89, 0.14)	0.03(-0.43,0.49)	-0.05 (-0.39 ,0.31	MMN		

				)		26)			)			
	0.02 (-0.58, 0.59)	-0.09(-0.58,0.43)	-0.14(-0.64,0.34)	-0.12(-0.54,0.28)	-0.06(-0.52,0.39)	-0.22(-0.63,0.16)	-0.43(-1.03, 0.14)	-0.04(-0.58,0.52)	-0.11(-0.58,0.34)	-0.06(-0.53,0.38)	SEC	
	0.46 (0.01,0.91)	0.35(-0.19,0.98)	0.30(-0.24,0.85)	0.31(-0.15,0.81)	0.39(-0.14,0.92)	0.21(-0.34,0.84)	0.02 (-0.45, 0.47)	0.41(-0.18,1.04)	0.33 (-0.18, 0.87)	0.38 (-0.13, 0.91)	0.44 (-0.13,1.05)	MET RO

11.6 : PROPORTION STUNTED, MASS DEWORMING VS. CONTROL PAIRWISE ANALYSIS



11.7 PROPORTION STUNTED, NETWORK META-ANALYSIS COMPARED TO META-ANALYSIS

On the bottom of the diagonal, network meta-analyses for every possible comparison are shown, using network meta-analysis.

Bolded results are statistically significant.

Italicized results are greater than 0.3 SMD, which is equivalent to 0.5 kg, using the typical standard deviation from the included studies

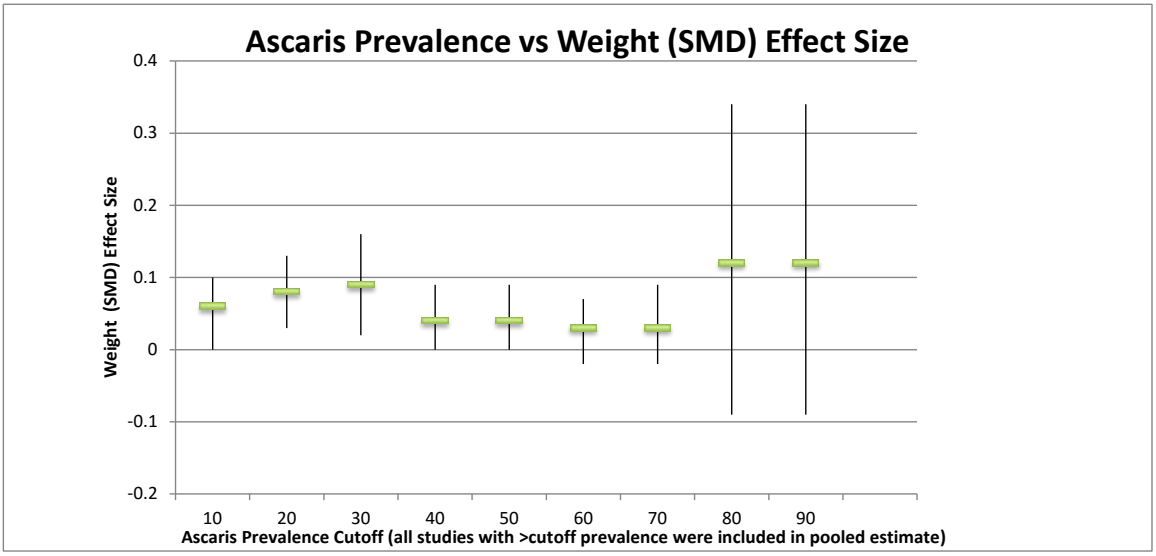
Results from meta-analysis and network meta-analysis can be compared by assessing the result below the diagonal and above the diagonal for a given comparison.

Placebo	1.16 (0.98, 1.39)	1.54 (0.27, 8.69)	1.11 (0.41, 3.06)	1.08 (0.81, 1.44)	0.92 (0.44, 1.91)	
0.97(0.78, 1.18)	Alben std					
0.72(0.16,1.80)	0.74(0.17, 1.87)	Alben + iron				
0.79(0.52, 1.17)	0.81(0.51,1.27)	1.10(0.40, 5.05)	Meben high			
1.07(0.73,1.49)	1.10(0.72,1.63)	1.48(0.54, 6.72)	1.35(0.91,1.98)	Meben high + iron		
0.89(0.41, 1.66)	0.92(0.41, 1.78)	1.24(0.36, 6.15)	1.13(0.47, 2.38)	0.84(0.36, 1.73)	Alben std + PZQ	
0.98(0.66, 1.39)	1.00(0.65, 1.52)	1.35(0.49, 6.20)	1.23(0.83, 1.83)	0.91(0.64, 1.32)	1.09(0.52, 2.58)	Iron

11.8 SENSITIVITY ANALYSES OF PREVALENCE CUTOFFS

Note: Each of these graphs shows meta-analysis of all studies which have a prevalence above the cut-off threshold, and the number of studies and participants is shown below the graph. Therefore, 22 studies with 44,299 participants had >10 % Ascaris baseline prevalence, and the pooled effect of mass deworming on weight (SMD) was about 0.5, with 95 % confidence interval of 0 to 0.1 SMD). For studies with more than one type of deworming, we chose the intervention group which was closest to mass deworming twice per year. For studies with co-interventions, we chose the intervention and comparator arms where co-interventions were similar in both groups (e.g albendazole twice per year + vitamin A vs. vitamin A).

Cut-off thresholds for prevalence of Ascaris and weight

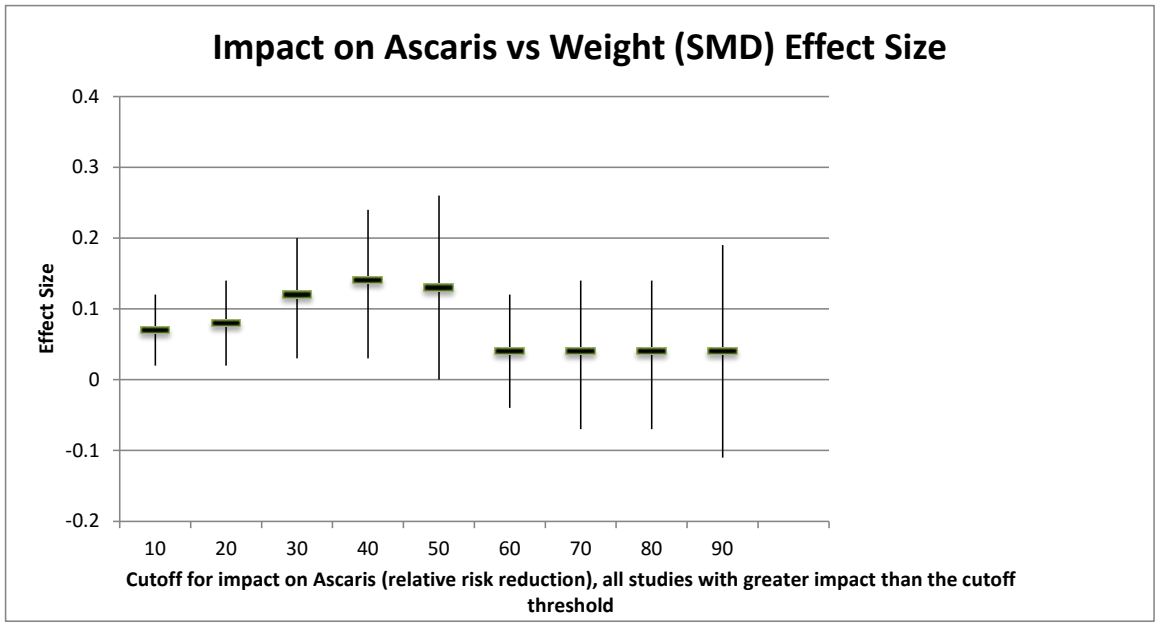


Cutoff Prevalence	Number trials (participants)
10	22 (44,299)
20	20 (15,341)
30	15 (11,136)

40	12 (8,299)
50	12 (8,299)
60	10 (7,342)
70	8 (7,022)
80	2 (369)
90	2 (369)

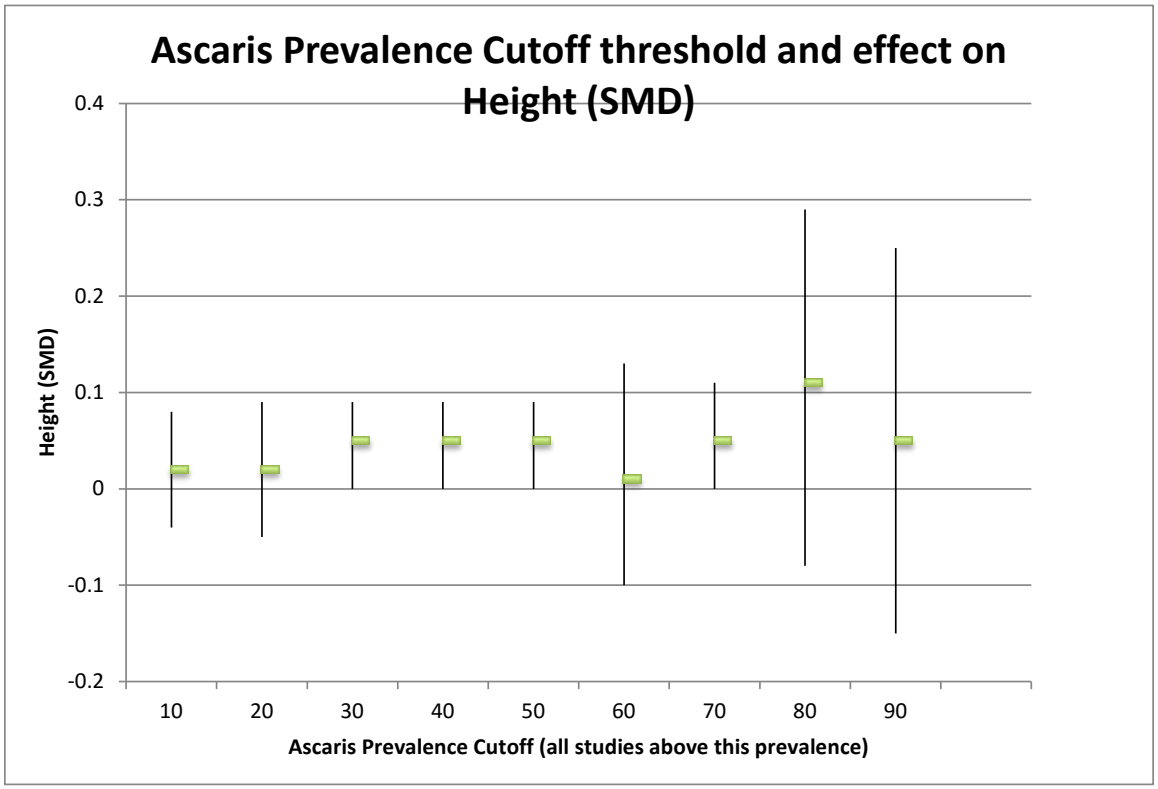
Weight (SMD), Cutoff thresholds for Impact on ascaris (1-relative risk)

Note: As with the previous graph, each point represents meta-analysis of all studies which met the cutoff threshold for impact on ascaris using relative risk reduction. Thus 17 studies had at least a 10 per cent relative risk reduction on ascaris worm burden, and the meta-analysis of these studies showed an effect of 0.07 SMD (95%CI: 0.02, 0.12)



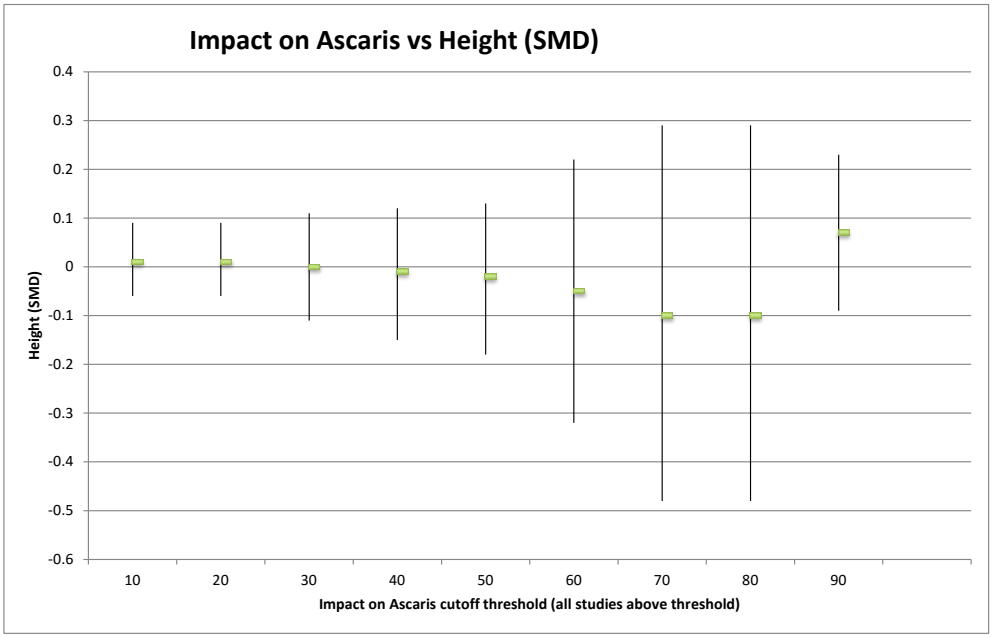
1-RR (impact)	Number studies (participants)
10	17 (13,199)
20	16 (11,121)
30	12 (7,114)
40	11 (5,041)
50	8 (4,463)
60	5 (2,538)
70	4 (1,917)
80	4 (1,917)
90	3 (1,667)

Height, Cut-off threshold for prevalence of ascaris



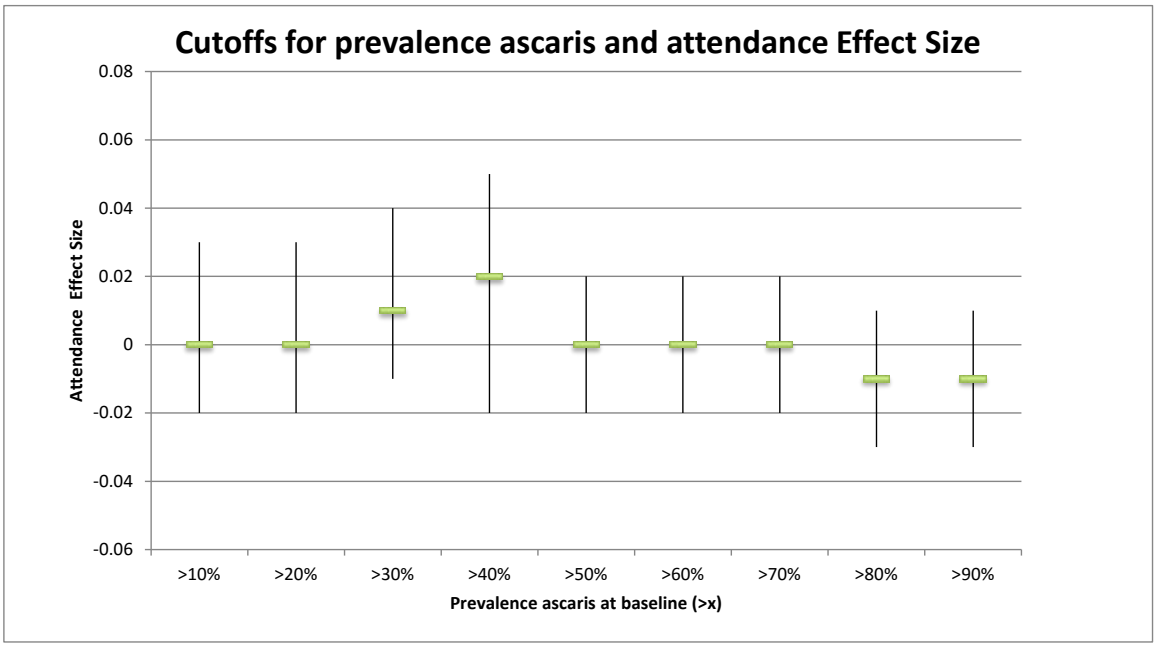
% cutoff prevalence	# studies/ participants
10	19 (15,547)
20	18 (14,502)
30	13 (8,264)
40	11 (7,456)
50	11 (7,456)
60	11(5,911)
70	10 (9,626)
80	4 (1,202)
90	2 (970)

Cut-off threshold for Impact on ascaris and height (SMD)



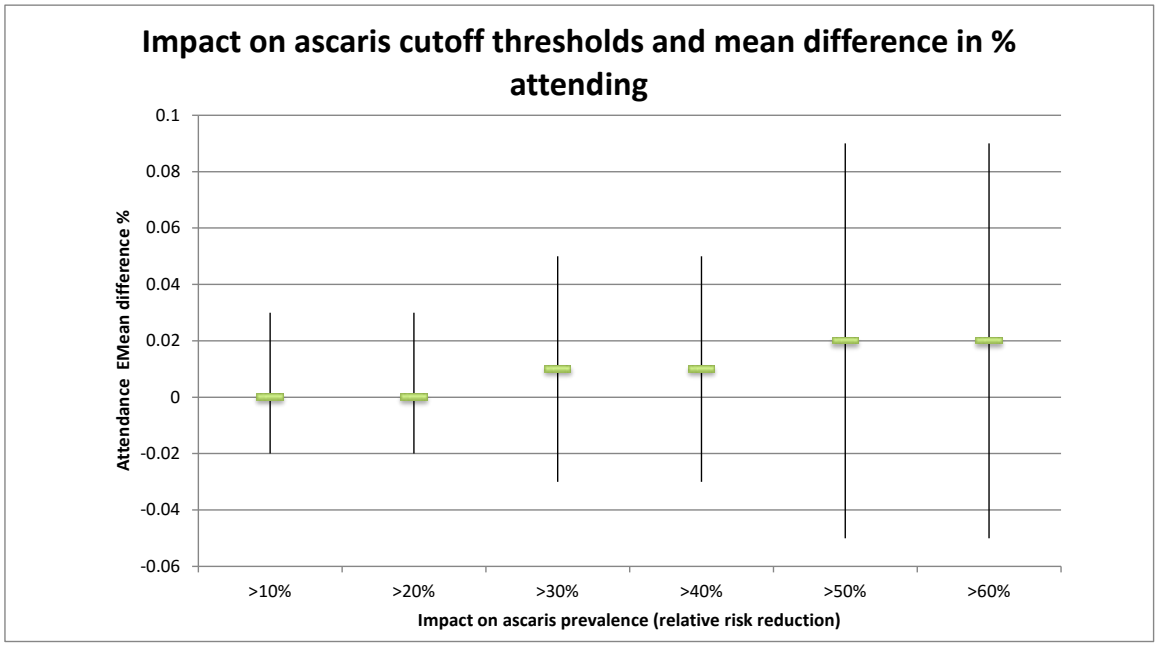
cutoff % impact	number studies (participants)
10	15(10,863)
20	15 (10,863)
30	11(6,774)
40	10(4,701)
50	8(4,396)
60	5(2,466)
70	4 (1,846)
80	4 (1,846)
90	3 (1,596)

Cut-off threshold for prevalence and attendance (MD)



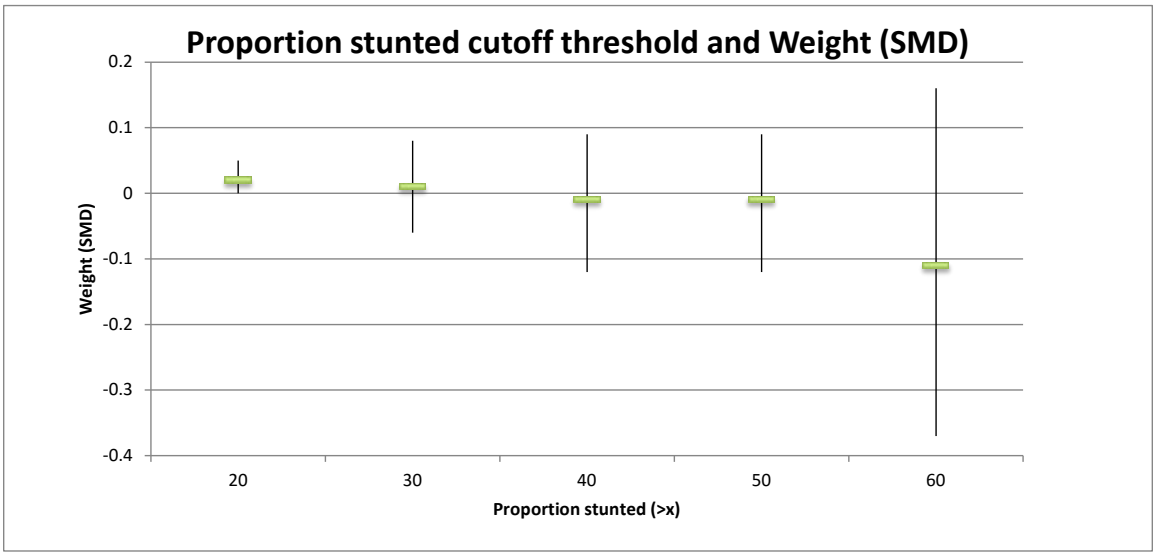
Cutoff	Number studies
>10%	7
>20%	7
>30%	5
>40%	4
>50%	2
>60%	2
>70%	2
>80%	1
>90%	1

Cutoff threshold for impact on ascaris and attendance (mean difference%)



Cutoff	Number studies
>10%	7
>20%	7
>30%	5
>40%	5
>50%	4
>60%	4

Cut-off threshold for proportion of population stunted (below -2HAZ) and weight (SMD)



% cutoff	Number studies (participants)
20	15 (50787)
30	8 (9224)
40	6 (6804)
50	6 (6804)
60	4 (4169)

12 Glossary of abbreviations

Abbreviations:
Alb-std: albendazole 400 mg 2/ year
Alb-LD: Albendazole 400 mg 1/ year
Alb-HD: Albendazole 400 mg >2/ year (3-6)
Sec: secnizadole (antigiardial)
Meb-high: mebendazole >2/ year
MMN: multiple micronutrient fortified biscuit
PZQ: praziquantel once/ year
Metro: metronizadole: antigiardial
Pip: piperazine twice/ year
Leva-high: levamisole >2/ year
Pyrn: pyrantel 2/ year
RCT: randomized controlled trial
CBA: controlled before and after trial
ICC: intra-cluster correlation
SMD: standardized mean difference
CI: confidence interval
STH: soil-transmitted helminthiasis

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