Mass deworming to improve developmental health and wellbeing of children in low-income and middle-income countries: a systematic review and network meta-analysis

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Summary

Background Soil-transmitted helminthiasis and schistosomiasis, considered among the neglected tropical diseases by WHO, affect more than a third of the world's population, with varying intensity of infection. We aimed 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.

Methods We searched 11 databases up to Jan 14, 2016, websites and trial registers, contacted authors, and reviewed reference lists. We included studies published in any language of children aged 6 months to 16 years, with mass deworming for soil-transmitted helminths or schistosomiasis (alone or in combination with other interventions) for 4 months or longer, that reported the primary outcomes of interest. We included randomised and quasi-randomised trials, controlled before–after studies, interrupted time series, and quasi-experimental studies. We screened in duplicate, then extracted data and appraised risk of bias in duplicate with a pre-tested form. We conducted random-effects meta-analysis and Bayesian network meta-analysis.

Findings We included 52 studies of duration 5 years or less with 1 108 541 children, and four long-term studies 8–10 years after mass deworming programmes with more than 160 000 children. Overall risk of bias was moderate. Mass deworming for soil-transmitted helminths compared with controls led to little to no improvement in weight over a period of about 12 months (0·09 kg, 95% credible interval [CrI] −0·09 to 0·28; moderate certainty evidence) or height (0·07 cm, 95% CrI −0·10 to 0·24; moderate certainty evidence), little to no difference in proportion stunted (eight fewer per 1000 children, 95% CrI −48 to 32; high certainty evidence), cognition measured by short-term attention (−0·23 points on a 100 point scale, 95% CI −0·56 to 0·14; high certainty evidence), school attendance (1% higher, 95% CI −1 to 3; high certainty evidence), or mortality (one fewer per 1000 children, 95% CI −3 to 1; high certainty evidence). We found no data on quality of life and little evidence of adverse effects. Mass deworming for schistosomiasis might slightly increase weight (0·41 kg, 95% CrI −0·20 to 0·91) and has little to no effect on height (low certainty evidence) and cognition (moderate certainty evidence). Our analyses do not suggest indirect benefits for untreated children from being exposed to treated children in the community. We are uncertain about effects on long-term economic productivity (hours worked), cognition, literacy, and school enrolment owing to very low certainty evidence. Results were consistent across sensitivity and subgroup analyses by age, worm prevalence, baseline nutritional status, infection status, impact on worms, infection intensity, types of worms (ascaris, hookworm, or trichuris), risk of bias, cluster versus individual trials, compliance, and attrition.

Interpretation Mass deworming for soil-transmitted helminths with or without deworming for schistosomiasis had little effect. For schistosomiasis, mass deworming might be effective for weight but is probably ineffective for height, cognition, and attendance. Future research should assess which subset of children do benefit from mass deworming, if any, using individual participant data meta-analysis.

Funding Canadian Institutes of Health Research and WHO.

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Introduction

WHO recommends mass deworming for soil-transmitted helminths and schistosomiasis in endemic areas, combined with improved sanitation and health education to sustain the effects and reduce reinfection.[1] Mass deworming of children has been described as the most cost-effective strategy to improve educational attendance in endemic helminth countries.[2] Although deworming is inexpensive (US$0·50) per child,[3] the global cost of implementing the WHO recommendations for all children is estimated to be $276 million annually.[4]

A 2015 Cochrane review[5] concluded that mass deworming does not improve child health or school performance; however, concerns have been raised that

Lancet Glob Health 2017; 5: e40–50

This online publication has been corrected. The corrected version first appeared at thelancet.com/lancetgh on May 22, 2018.

See **Comment** pages e2 and e4

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Research in context

Evidence before this study

Previous systematic reviews on mass deworming for soil-transmitted helminths disagree regarding important effects for weight and haemoglobin. An updated Cochrane review in 2015 found little to no effect on haemoglobin, growth, cognition, education, attendance, and mortality. Nonetheless, concerns were raised that this Cochrane review did not consider explanatory factors such as type of worm and baseline nutritional status.

Added value of this study

Our systematic review and network meta-analysis provides new insights into mass deworming for soil-transmitted helminths by taking the following ten factors into account: reinfection; role of baseline nutritional status; that uninfected children in studies might dilute the effects; that only heavily infected children are affected by worms; possibility of different effects by worm type; combinations with co-interventions of hygiene, micronutrients, and other drugs; long-term studies following up to 10 years later; spill-over effects on untreated children across studies; influence of poor learning environments on cognition; and quality of school attendance measures. We found 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. For long-term effects on growth, educational outcomes, and school attendance, our certainty in the evidence is very low. Mass deworming for schistosomiasis might improve weight, might have little to no effect on height (low certainty), probably has little to no effect on cognition and attendance (moderate certainty), and has uncertain effects on school enrolment (very low certainty evidence).

Implications of all the available evidence

Our analyses are based on aggregate level data, which might hide differences in effects at the individual level or interaction between factors. Given over 1 million children have been randomised to mass deworming in these previous studies, future research should take advantage of individual participant data from these studies to assess in which populations and settings—if any—mass deworming is beneficial.

the review did not sufficiently address a number of methodological issues that might have influenced its conclusions.[6–10] Children older than 3 years who are stunted might not be able to catch up on growth.[6] Interaction with food, micronutrients, hygiene promotion, or other deworming drugs such as praziquantel for schistosomiasis might influence effectiveness.[7] Outcome measures for attendance need to be considered in light of validity of on-site versus school records.[7] The types of worms, their prevalence, and appropriateness and intensity of deworming drugs for each worm type need to be considered, as does effect dilution due to uninfected or lightly infected children in the sample.[6] Poor learning environments might contribute to little effects on cognition. Long-term study designs need to be considered.[9,10] Finally, analysis of mass deworming needs to consider the possibility of indirect spill-over effects: untreated children might benefit from exposure to treated children in the same classroom or neighbourhood because of reduced worm burden. Thus, indirect effects could dilute effects in individually randomised trials, making cluster trials more suitable to assess the effectiveness of mass deworming.[7]

For the **Cochrane Handbook** see http://handbook.cochrane.org/

See Online for appendix

We aimed to evaluate the effects of the WHO policy on deworming for soil-transmitted helminths and schistosomiasis on growth, cognition, educational achievement, school attendance, wellbeing, and adverse effects, with or without other co-interventions, in children in endemic helminth countries. We also addressed the concerns about previous reviews.

Methods

Search strategy and selection criteria

We did a systematic review using a causal pathway approach, following an a priori protocol[11] (figure 1). We chose to use both meta-analysis and network meta-analysis, which allowed us to compare effectiveness of interventions that were not compared directly (eg, food, micronutrients, and drug combinations). We used methods described in the Cochrane Handbook and the ISPOR guidelines for network meta-analyses.[12] Our report is guided by the PRISMA Statement for Network Meta-Analyses.[13]

We developed a comprehensive search strategy with our information scientist (JM) for electronic databases and grey literature; this strategy was reviewed with PRESS (Peer Reviewed Electronic Search Strategies)[14] by the information scientist of the Campbell International Development Group. We searched 11 databases up to Jan 14, 2016, with no language restrictions. We also searched websites of relevant organisations, Twitter (#wormwars), screened reference lists, and used SCOPUS to identify studies which cited included studies.[14] We contacted authors for information missing from their original papers. Search strategy details can be found in the appendix (pp 5–6).

Studies had to include mass administration of any drug for chemoprevention of soil-transmitted helminths or schistosomiasis alone or in combination with other deworming drugs or other interventions compared with placebo or other interventions in children aged 6 months to 16 years with no other demographical restrictions. To assess effects in infected children, we expanded our

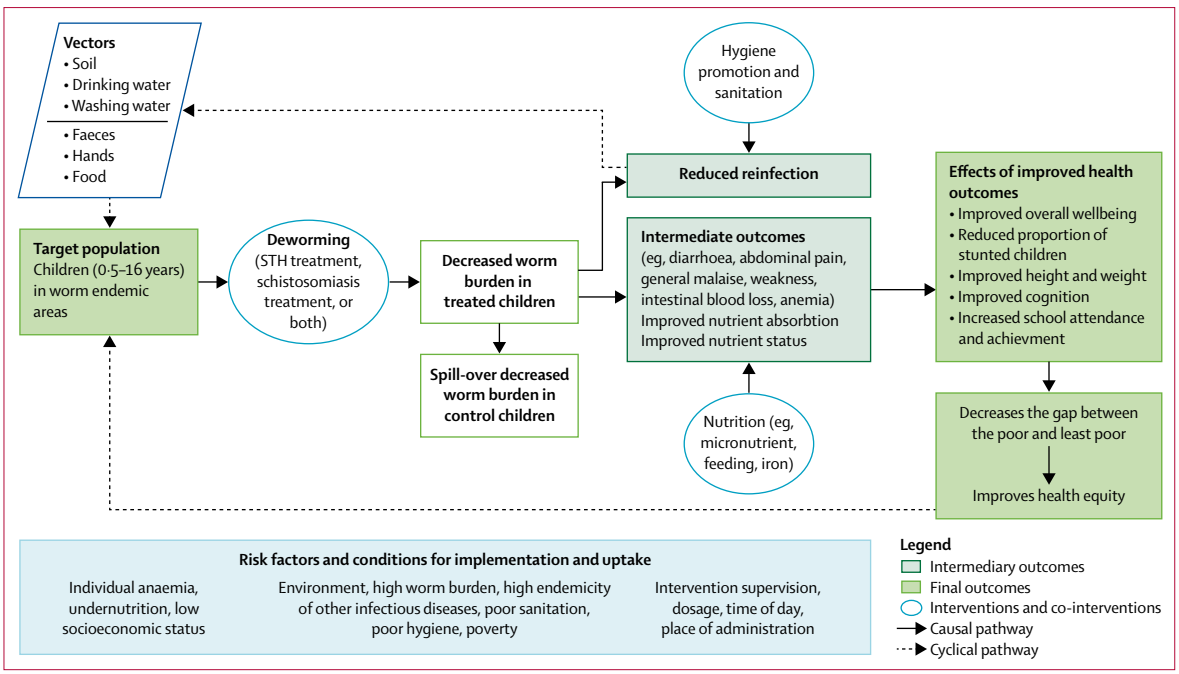

Figure 1: **Logic model showing causal pathways**

protocol's eligibility criteria to include studies that screened for infection. We included randomised and quasi-randomised trials, controlled before–after studies, interrupted time series studies, and quasi-experimental designs that used methods to account for confounding and sample selection bias. Studies had to include one or more of the primary outcomes of growth, cognition, school achievement, school attendance, or adverse effects. Studies had to be at least 4 months' duration, because we considered this the minimum timeframe for differences in our primary outcomes.[11]

We also collected data on haemoglobin, micronutrient status, hygiene practices, worm burden, and other comorbidities; costs and resource use, health equity, and process elements such as how and where drugs were delivered; supervision, compliance, and attrition.

Data extraction

VAW and EG independently screened titles and abstracts, then assessed full-text articles for eligibility and extracted data and assessed risk of bias using a pretested form. We contacted authors for additional information (appendix p 33). We assessed bias using the Cochrane risk of bias tool. For quasi-experimental studies, we used the International Development Coordinating Group's risk of bias tool.[15] We rated the certainty of evidence using the GRADE methods for network meta-analysis[16] and pairwise meta-analysis.[17] GRADE certainty is defined as "the extent of our confidence that the estimates of the effect are correct".[17] Disagreements were resolved by consensus or discussion with a third reviewer, PT.

Statistical analysis

For the continuous outcomes of growth, the effect size of weight (kg) and weight-for-age (WAZ) was analysed as standardised mean differences of change from baseline, using Cohen's *d*, because this increased our sample for exploring heterogeneity more than if we had used either weight or WAZ alone. We also did this for height (cm) and height-for-age (HAZ). Effect sizes for other outcomes, such as weight-for-height, haemoglobin, cognition, school achievement (math and language), and school attendance, were analysed as changes from baseline, as planned in our protocol.[11] We calculated the SD of the change from baseline using a correlation coefficient of 0·9 for weight, height, and haemoglobin and 0·71 for cognition, based on published studies.[18,19] We used end values if only end values were available. We used the variance inflation factor to adjust for unit of analysis issues, based on intraclass correlations from included studies. For cognition, we analysed short-term attention, general intelligence, and development separately.

We did the primary analyses using randomised and quasi-randomised trials because we considered randomised trials at lower risk of bias. The effects of interventions in controlled before–after studies were assessed separately, and were not included in network meta-analyses (except for sensitivity analysis).

We did two levels of analysis: first, meta-analyses of all outcomes for each comparison; and second, network meta-analysis. For the meta-analyses we used Review Manager 5.3, and assessed heterogeneity for each comparison using visual inspection and statistical methods (χ^2 test and I^2). We explored heterogeneity

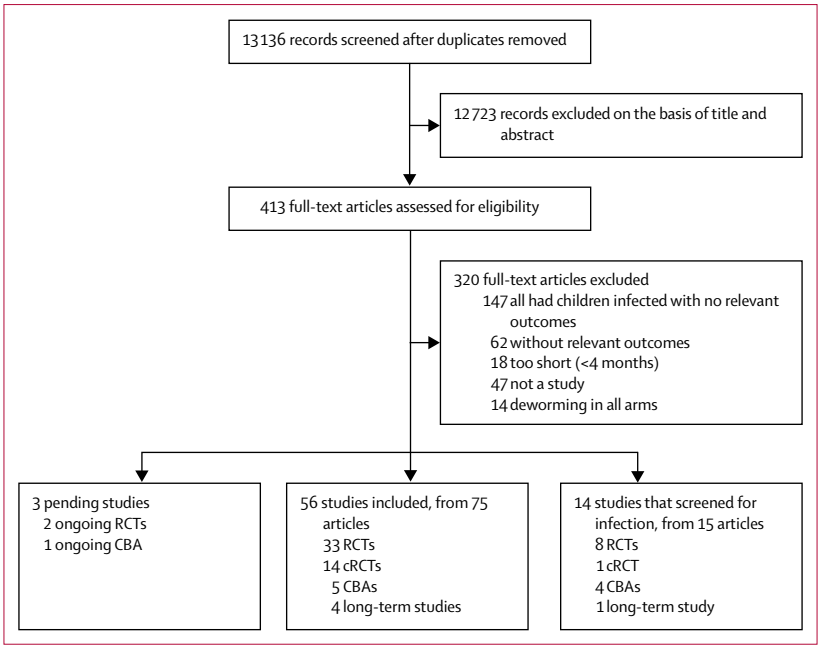

Figure 2: **Study selection**
CBA=controlled before-after study. cRCT=cluster randomised controlled trial.

	Interventions	Total sample size (participants in each arm)	Duration (months)		Mean age or age range (years)
			Treatment	Follow-up	
Albendazole standard (2 doses per year)					
Alderman, 2006*	Albendazole *vs* control	27995 (14940/13055)	36	..	3·7
Awasthi, 2000	Albendazole *vs* placebo	1061 (451/610)	24	..	2·7
Bhoite, 2012	Albendazole *vs* albendazole plus iron *vs* control	496 (128/215/153)	8	6	8–12
Dossa, 2001	Albendazole *vs* albendazole plus iron *vs* iron *vs* placebo	140 (38/34/36/32)	13	..	3–5
Fox, 2005	Albendazole *vs* albendazole plus diethylcarbamazine *vs* diethylcarbamazine *vs* placebo	1292 (328/324/322/318)	6	..	7·7
Hadju, 1997	Albendazole *vs* pyrantel *vs* albendazole LF *vs* pyrantel LF *vs* placebo	330 (69/61/66/60/74)	12	..	8·3
Kruger, 1996	Albendazole plus non-fortified soup *vs* albendazole plus iron-fortified soup *vs* iron-fortified soup plus placebo *vs* non-fortified soup plus placebo	178 (37/50/54/37)	6	5	6–8
Monse, 2013	Albendazole *vs* health education	412 (200/212)	48	..	7·5
Olds, 1999	Albendazole *vs* praziquantel *vs* albendazole plus praziquantel *vs* placebo	1540 (387/380/392/381)	12	..	10·5
Rozelle, 2015	Albendazole plus health education *vs* control	2179 (1084/1095)	12	..	10·6

(Table continues on next page)

using influence analysis, subgroup, and sensitivity analyses. We conducted Bayesian network meta-analysis using WinBUGS[20] according to the routine that accommodates multiarm trials.[21] Consistency between direct and indirect evidence was formally assessed using back-calculation and node-splitting techniques.[22] We used model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic to assess and ensure model convergence. In each network meta-analysis, parameter estimates were obtained based on three chains using 80000 iterations after a burn-in of 40000 iterations for the random-effects model.

We did pre-specified subgroup analysis across age, nutritional status, prevalence of worms, and sex. These subgroup analyses were done using both network meta-analysis and meta-analysis. We assessed indirect effects on untreated children using three methods: assessment of within-study analyses; comparison of control group gains in weight, height, and haemoglobin in cluster and individually randomised trials; and comparison of effects in cluster versus individually randomised trials. Although meta-regressions were planned, data was insufficient. Therefore, we assessed the relationship of weight, height, and attendance with prevalence of each worm (ascaris, hookworm, and trichuris) and impact on each type of worm using weighted least-squares regression. To explore the causal pathway, we also assessed the relationship between attendance outcomes and weight gain. We did pre-planned sensitivity analyses to assess the impact of two studies excluded because of baseline imbalance,[23] risk of bias, type of worm, impact on worm burden, intensity, and study design. We did post-hoc sensitivity analyses to assess the influence of cutoff thresholds for worm prevalence, impact on worms, and nutritional status. We assessed the influence of including studies that screened for infection as a sensitivity analysis. Publication bias was assessed with funnel plots when we had more than ten studies.

Missing values were not imputed for trials. For studies for which we received full datasets, we assumed data were not missing at random; therefore, we used the Cochrane Handbook guidance to impute missing data, based on available data, last observation carried forward for one trial, and single imputation for the other. We assessed the influence of using imputed values with sensitivity analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. VAW, EG, SS, GAW, and AH had full access to all the data in the study and VAW had final responsibility for the decision to submit for publication. This study is registered with the Campbell Collaboration.[11]

Results

The search retrieved 13 136 unique articles (appendix pp 5–6). We included 47 randomised trials and five controlled before–after studies, which included 1 108 541 children (figure 2, table). We found no eligible interrupted time series studies. We included four long-term studies, which collectively followed up more than 160 000 children.[24–27] We received and included additional data from ten studies, including two unpublished studies. We used the corrected dataset for the Kenya Primary School Deworming Project.[28,29] Three unpublished studies are pending publication.

The median age of children was 6·75 years (range 0–18). The studies were in schools, clinics, and communities. Prevalence of ascaris, trichuris, and hookworm ranged from 1% to 95%. None of the studies of mass deworming excluded children on the basis of intensity of infection. No studies reported on the learning environment. Overall risk of bias was moderate, with 40% of studies with high risk of bias for differential attrition and more than 50% of studies with insufficient details to assess blinding (figure 3). Risk of bias for long-term studies was high or moderate. Funnel plots did not suggest publication bias (appendix p 85).

The network geometry was chosen through discussion with the clinicians and policy maker members of the team regarding what was sensible to combine from a clinical and policy perspective. Network meta-analyses for weight (30 trials), height (25 trials), weight-for-height (12 trials), and proportion stunted (seven trials) converged and were consistent. We present meta-analysis only for attendance, short-term cognition, cognitive development, mathematical achievement, and mortality, due to too few studies or failure to converge. For weight, height, and stunting, meta-analysis and network meta-analysis results were consistent (appendix pp 37–56).

Based on our primary analyses and summary of findings table (appendix pp 64–71), mass deworming for soil-transmitted helminths with albendazole twice per year compared with controls probably leads to little to no improvement in weight over a period of about 12 months (0·09 kg, 95% credible interval [CrI] −0·04 to 0·20; moderate certainty evidence) or height (0·07 cm, 95% CrI −0·10 to 0·24; moderate certainty evidence), little to no difference in weight-for-height (0·14, 95% CrI −0·20 to 0·47; high certainty evidence), proportion stunted (eight fewer per 1000 children, 95% CrI −48 to 32; high certainty evidence), performance on short-term attention tasks (unlikely to be influenced by the learning environments; −0·23 points on a 100 point scale, 95% CI −0·56 to 0·14; high certainty evidence), school attendance (1%, 95% CI −1 to 3; high certainty evidence), or mortality (one fewer per 1000 children, 95% CI −3 to 1; high certainty evidence). 12 trials with insufficient data and five controlled before–after studies were consistent with these analyses. Effects of mass deworming for soil-transmitted helminths on long-term (>8 years) economic productivity (hours worked), school enrolment, height,

	Interventions	Total sample size (participants in each arm)	Duration (months)		Mean age or age range (years)
			Treatment	Follow-up	
(Continued from previous page)					
Stephenson, 1993	Albendazole *vs* albendazole LF *vs* placebo	284 (95/96/93)	8·2	..	10·6
Sur, 2005	Albendazole *vs* placebo	702 (351/351)	12	..	2–5
Miguel, 2004*	Albendazole *vs* albendazole plus praziquantel *vs* control	>30 000†	3	..	6–18
Watkins, 1996	Albendazole *vs* placebo	227 (116/111)	6	..	7–12
Albendazole high (>2 doses per year)					
Ndibazza, 2012	Albendazole HF *vs* placebo	2016 (1010/1006)	45	..	1·25–5
Wiria, 2013	Albendazole HF *vs* placebo	4004 (2022/1982)	21	..	5–15
Albendazole low (<2 doses per year)					
Beach, 1999	Albendazole LF *vs* ivermectin *vs* albendazole LF plus ivermectin *vs* placebo	958 (244/240/245/229)	4	..	7·4
Stephenson, 1989	Albendazole LF *vs* placebo	150 (78/72)	6	..	6–16
Koroma, 1996	Albendazole LF *vs* placebo	297 (197/100)	6	..	6–10
Albendazole standard (2 doses per year) plus praziquantel standard (2 doses per year)					
Taylor, 2001	Albendazole plus praziquantel *vs* albendazole plus praziquantel plus iron *vs* albendazole HF plus praziquantel plus iron *vs* albendazole HF plus praziquantel *vs* iron *vs* placebo	428 (60/56/63/57/101/91)	12	..	11·2
Albendazole standard (2 doses per year) plus praziquantel low (1 dose per year)					
Jinabhai, 2001a	Albendazole plus praziquantel LF *vs* placebo	268 (129/139)	4	..	8–10
Albendazole low (1 dose per year) plus praziquantel low (1 dose per year) plus biscuits with vitamin A, iron, and nutrients					
Jinabhai, 2001b	Albendazole LF plus praziquantel LF plus multi-micronutrient fortified biscuits *vs* multi-micronutrient fortified biscuits *vs* albendazole LF plus praziquantel LF plus non-fortified biscuits *vs* vitamin-A-fortified biscuits *vs* non-fortified biscuits	579†	4	..	9·1
Albendazole standard (2 doses per year) plus fortified beverage					
Solon, 2003	Albendazole plus micronutrient-fortified beverage *vs* micronutrient-fortified beverage *vs* albendazole plus non-fortified beverage *vs* non-fortified beverage plus placebo	831 (203/209/213/206)	4	..	9·9
Albendazole high (>2 doses per year) plus iron					
Bobonis, 2006	Albendazole HF plus iron *vs* control	2392 (930/1462)	11	..	3·65

(Table continues on next page)

	Interventions	Total sample size (participants in each arm)	Duration (months)		Mean age or age range (years)
			Treatment	Follow-up	
(Continued from previous page)					
Nga, 2009	Albendazole HF plus multi-micronutrient fortified biscuits *vs* albendazole HF plus non-fortified biscuits *vs* multi-micronutrient fortified biscuits *vs* non-fortified biscuits plus placebo	510 (127/127/128/128)	4	..	6–8
Albendazole standard (2 doses per year) plus vitamin A					
Awasthi, 2001	Albendazole plus vitamin A *vs* vitamin A	2010 (988/1022)	18	..	9·6
Awasthi, 2008	Albendazole plus vitamin A *vs* vitamin A	3935 (1968/1967)	24	..	1–5
Awasthi, 2013	Albendazole plus vitamin A *vs* vitamin A	1 000 000†	60	..	0·5–6
Hall, 2006	Albendazole plus vitamin A *vs* placebo plus vitamin A	2659 (1341/1318)	24	..	6·8
Levamisole high (>2 doses per year)					
Willett, 1979	Levamisole *vs* placebo	341 (166/175)	12	..	3·2
Mebendazole standard (2 doses per year)					
Kloetzel, 1982	Mebendazole *vs* placebo	337 (165/172)	10	..	1–8
Garg, 2002	Mebendazole *vs* placebo	370 (177/193)	6·5	..	2–4
Joseph, 2015	Mebendazole *vs* mebendazole LF plus placebo *vs* placebo plus mebendazole LF *vs* placebo	1760 (440/440/440/440)	12	..	1
Stoltzfus, 1997	Mebendazole *vs* mebendazole HF *vs* control	3605 (1170/1175/1260)	12	..	10
Mebendazole standard (2 doses per year) plus iron					
Ebenezer, 2013	Mebendazole plus iron *vs* placebo	1621 (813/808)	6	6	9·5
Le Huong, 2007	Mebendazole plus non-fortified noodles *vs* mebendazole plus iron-fortified noodles *vs* mebendazole plus iron *vs* iron-fortified noodles plus placebo *vs* non-fortified noodles plus placebo	425 (84/85/84/88/84)	6	..	7·2
Mebendazole high (>2 doses per year)					
Donnen, 1998	Mebendazole HF *vs* vitamin A *vs* control	358 (123/118/117)	18	..	1·9
Kaba, 1978	Mebendazole HF *vs* levamisole HF *vs* mebendazole HF plus levamisole HF	176 (44/45/87)	15	..	6–11
Ostwald, 1984	Mebendazole HF *vs* control	87 (42/45)	5	..	7–10
Rousham, 1994b	Mebendazole HF *vs* placebo	1402 (688/714)	12	..	3·9
Stoltzfus, 2001	Mebendazole HF *vs* mebendazole HF plus iron *vs* iron *vs* placebo	614†	12	..	2·4
Mebendazole high plus pyrantel high (>2 doses per year)					
Lai, 1995	Mebendazole HF plus pyrantel HF *vs* placebo	353 (186/167)	24	..	7·5

(Table continues on next page)

and cognition are unclear owing to very low certainty evidence (appendix p 63).[24–27] Adverse effects were minimal for mass deworming with albendazole (moderate certainty evidence). No studies reported cases of intestinal obstruction. Two studies found effects of deworming were not sustained once deworming was stopped (moderate certainty evidence).

We found little to no difference between any mass deworming treatments for soil-transmitted helminths compared with each other, different frequencies of treatment, or between deworming combined with micronutrients or food (figure 4, appendix p 62).

Mass deworming for schistosomiasis alone might slightly increase weight (0·41 kg, 95% CrI –0·20 to 1·01), lead to little to no increase in height (–0·02 cm, 95% CrI –0·43 to 0·40; low certainty evidence), little to no effect on short-term attention (high certainty evidence), and uncertain effects on school enrolment owing to very low certainty evidence (appendix pp 69–71).[25]

Indirect effects on untreated children were assessed in two studies[28,30] with conflicting results. One cluster trial,[28] reanalysed by an external team,[29] found a within-school indirect effect of 5·6% (SE 2·0) for attendance and 18% (SE 7·0) for hookworm infection and between-school indirect effects for distances between 0 km and 6 km of –1·7% (SE 3·0) for attendance and 15% (SE 11·0) for hookworm infection. These estimates were challenged by the original authors, who calculated post hoc that between-school indirect effects for attendance were statistically significant and important up to 4 km.[31] Another cluster trial[30] found small, non-significant indirect effects for weight and attendance. Indirect effects assessed across included studies showed no benefit to control children in individually randomised trials compared with cluster trials for weight, height, haemoglobin, attendance, or worm burden. These analyses had high heterogeneity (I^2 reported in appendix p 64). Sensitivity analyses using cluster trials only (indirect effects are expected to be smaller due to distance between clusters) were consistent with our main results of little to no effect on weight, height, or attendance (appendix p 77, 80, 83) and the test for subgroup differences compared with individually randomised trials was not significant (appendix p 64).

Considering health equity, all of the studies were in very poor settings and found few effects of mass deworming. One trial[30] found increased effects of deworming on preschool attendance for children with mothers with less than 3 years education (median) compared with mothers with 3 or more years education (low certainty evidence). We are uncertain about the influence of poverty on effects of deworming on long-term mathematical skills and literacy[27] (very low certainty evidence). No other studies assessed effects across socioeconomic status.

Contamination from external sources of deworming was reported only in two cluster trials,[28,32] in which

34% and 5% of control children accessed deworming, respectively.

Subgroup analyses found no clinically important or statistically significant effects across age (<2 years, 2–5 years, and >5 years), prevalence (high, moderate, low), or proportion of children stunted (<30 *vs* ≥30% with HAZ of –2) for weight, height, or attendance. Results were consistent for all prevalence cutoffs from 10–90% and all cutoffs for proportion of children stunted (from 10–60% of population with HAZ ≤–2), suggesting dilution of effect by non-infected children does not explain the small effects (appendix pp 86–92). Subgroup analyses within included studies agreed with these findings, with three exceptions. Within-study analyses suggest no difference in effect of mass deworming between boys and girls for weight and height. Two studies[28,30] found larger effects on attendance for girls than for boys (low certainty evidence). We are uncertain whether mass deworming has different effects for men and women on long-term years of education or hours worked in the past week because of very low certainty evidence (appendix p 66).[24]

Mass deworming was, on average, effective at reducing burden of all worms by comparison with placebo, but effect sizes were highly variable, from 98% risk reduction to 54% increase for some comparisons (appendix p 73). Our weighted least-squares regression found no relationship between baseline ascaris, hookworm, or trichuris, or impact on these worms (assessed as relative risk reduction of each worm type, and which provides an indication of reinfection and possible dilution of effect with uninfected children) and effects on weight, height, or attendance (appendix pp 93–98).

Sensitivity analyses were consistent with primary analyses across different types of worms (≥50% ascaris or ≥50% hookworm), cluster trials compared with individually randomised trials, studies with ≥50% relative risk reduction of worm burden, low risk of bias for allocation concealment, treatment of infected children only, more than 30% of children with moderate to heavy intensity of infection, lower intraclass correlation values, exclusion of unpublished studies, prevalence of schistosomiasis, studies with more than 75% compliance, and studies with less than 2% differential attrition. We found increased effects for weight and height in an influence analysis when two studies with baseline imbalance were included in sensitivity analysis. Effects on school attendance were greater with on-site records than with teacher records. Measures with on-site methods were at risk of bias because of inadequate blinding of 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). (appendix pp 77–84).

We conducted sensitivity analyses to compare mass deworming with studies that screened for infection. Tests for subgroup differences were not significant for weight, height, short-term attention, or attendance, with two exceptions. Treatment of children infected with schistosomiasis increased weight gain by 1·47 kg (95% CI 0·82 to 2·11) compared with the mass deworming effect of 0·18 kg (95% CI –0·22 to 0·58; test for subgroup differences p=0·0009), but not height. Treatment of children infected with soil-transmitted helminths increased weight gain by 0·49 kg (95% CI 0·07–0·90) compared with mass deworming effect of 0·04 kg (95% CI 0·00–0·10; test for subgroup differences p=0·04), but not height. Over the long term, screening

	Interventions	Total sample size (participants in each arm)	Duration (months)		Mean age or age range (years)
			Treatment	Follow-up	
(Continued from previous page)					
Nutrition Enhancement Programme (1 dose per year)					
Linnemayr, 2011	Unspecified deworming plus vitamin A plus iron plus growth promotion plus bed nets plus cooking workshops	4296 (2321/1975)	32·4	..	0–3
Piperazine standard (2 doses per year)					
Greenberg, 1981	Piperazine *vs* placebo	185 (92/93)	11	..	1·5–8
Piperazine high (>2 doses per year)					
Gupta, 1982	Piperazine HF *vs* metronidazole *vs* piperazine HF plus metronidazole *vs* placebo	159 (39/40/41/39)	12	..	2–5·1
Praziquantel (1 dose per year)					
Makamu, 2016	Praziquantel *vs* control	37 385 (4177/33 208)	120	..	7–14
Pyrantel high (>2 doses per year)					
Pust, 1985	Pyrantel HF *vs* palm oil *vs* pyrantel HF plus palm oil *vs* placebo	789 (80/317/92/300)	12	..	1–4·5
Secnidazole (>2 doses per year)					
Goto, 2009	Secnidazole *vs* albendazole plus secnidazole *vs* placebo	410 (141/142/127)	9	..	0·25–1·25
Tetrachloroethylene (1 doses per year)					
Michaelsen, 1985	Tetrachloroethylene *vs* placebo	228 (114/114)	5	..	5–7
Tetramisole standard (2 doses per year)					
Reddy, 1986	Tetramisole *vs* tetramisole plus vitamin A *vs* vitamin A *vs* placebo	360 (75/116/108/61)	12	..	1–5
Tetramisole low (<2 doses per year)					
Shah, 1975	Tetramisole LF *vs* iron-folic acid	325 (165/160)	12	..	1–5
Tetramisole high (>2 doses per year)					
Gupta, 1977	Tetramisole HF *vs* placebo	154 (74/80)	12	..	0·5–2
Tiabendazole high (>2 doses per year)					
Gateff, 1972	Thiabendazole HF *vs* placebo	392 (196/196)	8	..	6–15

HF=high frequency. LF=low frequency. Years followed by a or b refer to separate articles. References in the appendix. *Miguel, 2004 has two long-term follow-up studies (Ozier, 2015 and Baird, 2016), and Alderman, 2006 has one long-term follow-up study (Croke, 2014). †Exact numbers per group not reported.

Table: **Characteristics of included studies**

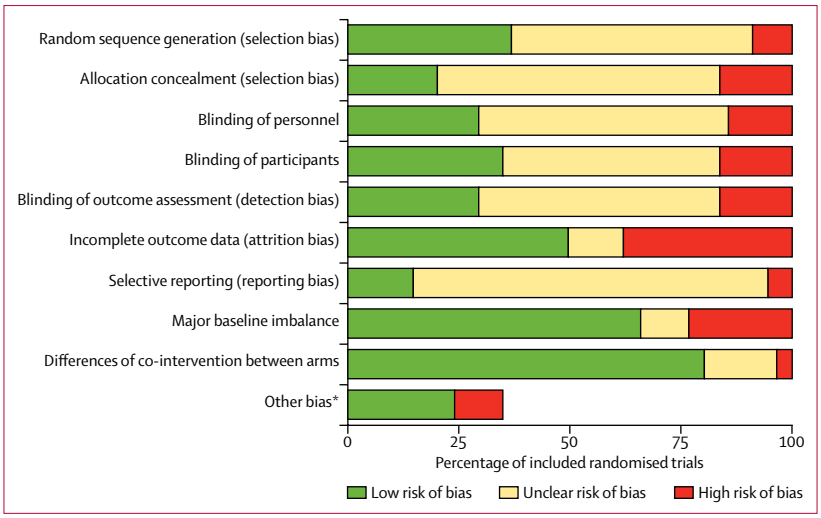

Figure 3: **Risk of bias graph**
Review authors' judgments about each risk of bias item presented as percentages across all included studies.
*Unit analysis errors in cluster randomised trials was judged as high risk of bias.

and treatment of infected children combined with sanitation improvements (eg, latrine building) leads to increased school enrolment, attendance, and improved literacy based on the Rockefeller Hookworm eradication campaign[33] (moderate certainty evidence). Whether mass deworming alone would have these effects without the intensive sanitation interventions is very uncertain.

Discussion

Our review provides novel insight into mass deworming by taking into account ten criticisms of the Cochrane review: reinfection; the influence of poor learning environments on cognition; combinations with co-interventions of hygiene, micronutrients, and other drugs; long-term studies; indirect effects on untreated children across studies; role of baseline nutritional status; that uninfected children in studies might dilute the effects; possibility of different effects by worm type; quality of school attendance measures; and that only heavily infected children are affected by worms. With consideration of these criticisms, we found 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 (figure 1).

Our findings are in line with a Cochrane review[5] of mass deworming for soil-transmitted helminths that found little to no effect for all primary outcomes, even though different approaches were used in our systematic review to explore potential effect modifiers and methodological concerns and 31 additional studies were included. These findings disagree with another review,[34] which found important effects of mass deworming on growth. This discrepancy might be because eight trials have since found little to no effect of mass deworming on weight or height, alongside other methodological reasons described in the Cochrane review.[5]

To our knowledge, our review is the first to assess mass deworming for schistosomiasis. Mass deworming for schistosomiasis might slightly improve weight but has little to no effect on height (low certainty), and probably has little to no effect on cognition and attendance (moderate certainty). We are uncertain about effects on school enrolment owing to very low certainty evidence.[25] Treatment for children infected with schistosomiasis improved weight but not height (low certainty evidence).

The strengths of our review are that we conducted a comprehensive search, identified additional studies, and we found no evidence of publication bias. Furthermore, we reduced bias by using transparent methods, an a priori protocol, duplicate study selection, extraction, data entry, and cross-checking of data and results. We made several methodological decisions and tested the influence of each of these using sensitivity analyses, and all were consistent with our main analyses. We used multiple approaches to assess the relationship of effects to presumed effect modifiers that strengthen our conclusions. We also used network meta-analysis, which provides added information on effects of different frequencies and combinations of interventions (both drug and non-drug).

The limitations of our review are that the analysis of relationships between explanatory variables and outcomes should be interpreted with caution owing to non-normal data and few data points for attendance. However, these analyses were supported by sensitivity analyses exploring the influence of cutoff thresholds. Subgroup and sensitivity analyses are based on aggregate level data, which might hide differences in effects at the individual level or interaction between factors.

We conducted an extensive assessment of effect modification of mass deworming, and found little to no effects of mass deworming for soil-transmitted helminths with or without deworming for schisto-somiasis at the aggregate level. Two moderate quality long-term studies showed an increase in economic productivity (hours worked) and educational enrolment 10 years after deworming.[24,33] But it is uncertain whether these effects are due to deworming or the combined sanitation and hygiene intervention. Mass deworming for schistosomiasis might slightly improve weight and probably has little to no effect on height, cognition, and attendance. 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 policy options

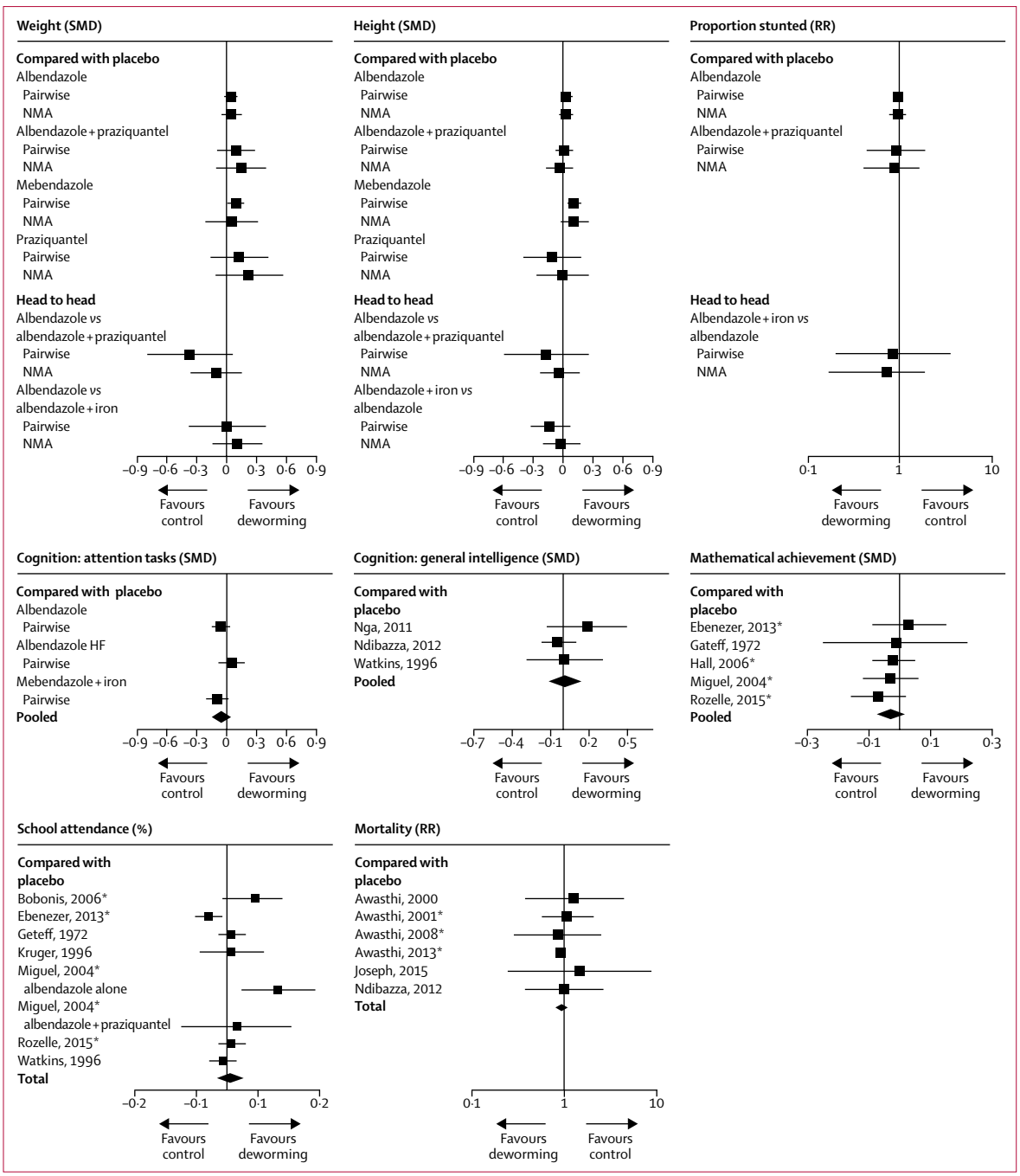

Figure 4: **Network meta-analysis and pairwise meta-analyses for primary outcomes, showing comparability of pairwise and network meta-analyses, as well as comparability in size of effects for single deworming agents, and combinations with other drugs and agents**
SMD=standardised mean difference. NMA=network meta-analysis. RR=relative risk. HF=high frequency. *Cluster trial.

include the need for investment 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 might be effective at improving weight. Because all analyses of effect modification are limited by aggregate level data which might 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.

Contributors

VAW, PT, and HW had the idea for the review, and VAW managed data collection, analysis, and interpretation. GAW and HW planned and interpreted analyses. EG, AH conducted analyses. SSu, CC contributed to data collection and figure development. JM contributed to the search strategy. EK, RF, SA, SSo, SK, ZAB contributed expert knowledge in nutrition, psychometrics and clinical epidemiology.

Declaration of interests

VAW reports grants from the Canadian Institutes of Health Research and WHO during the conduct of the study, a subcontract to SickKids for a grant to conduct individual participant data meta-analysis of deworming for children, and is a co-convenor of Campbell and Cochrane Equity Methods Group. PT reports paid consultancies with Bristol-Myers Squibb, Chelsea, and UCB, reports that Outcomes Measures in Rheumatology (OMERACT), whose Executive Board he serves on in an unpaid capacity, receives support from Actellion, Alderbio, Amgen, Ardea Biosciences, AstraZeneca, Bristol-Myers Squibb, Celgene, Centocor, Cypress/Forest, Eli Lilly, Boehringer Ingelheim, Genentech, Genzyme, Jass Pharmaceuticals, Merck, Novartis, Novo Nordisk, Pfizer, Regeneron, Savient, Takeda, UCB, and reports that the Ontario Biologics Research Initiative (OBRI) Industry Council receives support from Abbott, Roche, Schering Plough/Merck, UCB, and Bristol-Myers Squibb. SK reports that she has a personal relationship with the lead author of one of the studies described in this review. ZAB reports that his institution, SickKids Centre for Global Child Health, Toronto was awarded a grant in December, 2015, to undertake an individual patient data analysis of trials of mass deworming and other interventions for soil transmitted helminths in children, pregnant women, and schistosomiasis. This grant would build on the Campbell and Cochrane reviews on the subject area. EG, AH, GAW, HW, JM, SSu, SA, CC, RF, SSo, and EK have nothing to disclose.

Acknowledgments

We thank our funders, the Canadian Institutes of Health Research and WHO. VAW holds an Ontario Early Researcher Award. PT holds a Canada Research Chair. We thank John Eyers, information scientist at the Campbell International Development Group (London, UK), for reviewing our search strategy. We thank Magnus Nowell, Sam Caldwell, Soshanna Hamilton, Leah Quinlan, Theo Ambie, Manosila Yoganathan, Jessica Trawin, Anna Malinowski, and Miranda Sculthorp (Bruyère Research Institute, Ottawa, ON, Canada) for invaluable research assistance. We gratefully acknowledge the study authors and statisticians who sent us data or answered our queries.

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