

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Welch, VA; Ghogomu, E; Hossain, A; Awasthi, S; Bhutta, ZA; Cumberbatch, C; Fletcher, R; McGowan, J; Krishnaratne, S; Kristjansson, E; Sohani, S; Suresh, S; Tugwell, P; White, H; Wells, GA (2016) Mass deworming to improve developmental health and wellbeing of children in low-income and middle-income countries: a systematic review and network meta-analysis. *Lancet Glob Health*, 5 (1). e40-e50. ISSN 2214-109X DOI: [https://doi.org/10.1016/S2214-109X\(16\)30242-X](https://doi.org/10.1016/S2214-109X(16)30242-X)

Downloaded from: <http://researchonline.lshtm.ac.uk/3319550/>

DOI: [10.1016/S2214-109X\(16\)30242-X](https://doi.org/10.1016/S2214-109X(16)30242-X)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by/2.5/>



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

Vivian A Welch, Elizabeth Ghogomu, Alomgir Hossain, Shally Awasthi, Zulfiqar A Bhutta, Chisa Cumberbatch, Robert Fletcher, Jessie McGowan, Shari Krishnaratne, Elizabeth Kristjansson, Salim Sohani, Shalini Suresh, Peter Tugwell, Howard White*, George A Wells*



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 1108541 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 (0·99 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.

Copyright © The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY license.

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 review⁵ 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

See [Comment](#) pages e2 and e4

*Joint senior authors

Bruyère Research Institute, Ottawa, ON, Canada (V A Welch PhD, E Ghogomu MSc, S Suresh HBSc, P Tugwell MBBS); School of Epidemiology, Public Health and Preventive Medicine (V A Welch, J McGowan PhD, G A Wells PhD), Faculty of Medicine (P Tugwell), and School of Psychology, Centre for Research on Educational and Community Services (E Kristjansson PhD), University of Ottawa, Ottawa, ON, Canada; Cardiovascular Research Methods, University of Ottawa Heart Institute, Ottawa, ON, Canada (A Hossain PhD, G A Wells); Department of Pediatrics, King George's Medical University, Lucknow, India (S Awasthi MD); Research Centre for Global Child Health and Child Health Evaluative Sciences, The Hospital for Sick Children, and Department of Nutritional Sciences, University of Toronto; Division of Epidemiology, Dalla Lana School of Public Health, Toronto, ON, Canada; and Center of Excellence in Women and Child Health, Aga Khan University, Karachi, Pakistan (Prof Z Bhutta MD); Epidemiology Research Institute, Tropical Medicine Research Institute, The University of West Indies, Kingston, Jamaica (C Cumberbatch MSc); Harvard Medical School and Harvard Pilgrim Healthcare Institute, Boston, MA, USA (R Fletcher MD); London School of Hygiene & Tropical Medicine, London, UK (S Krishnaratne MSc); International Operation Canadian Red Cross Society, Ottawa, ON, Canada (S Sohani MBBS);

and Campbell Collaboration,
Oslo, Norway (H White PhD)

Correspondence to:
Dr Vivian Andrea Welch, Bruyere
Research Institute, School of
Epidemiology, Public Health and
Preventive Medicine, University
of Ottawa, Ottawa, ON K1R 6M1,
Canada
vivian.welch@uottawa.ca

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

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 protocol¹¹ (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

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

See Online for appendix

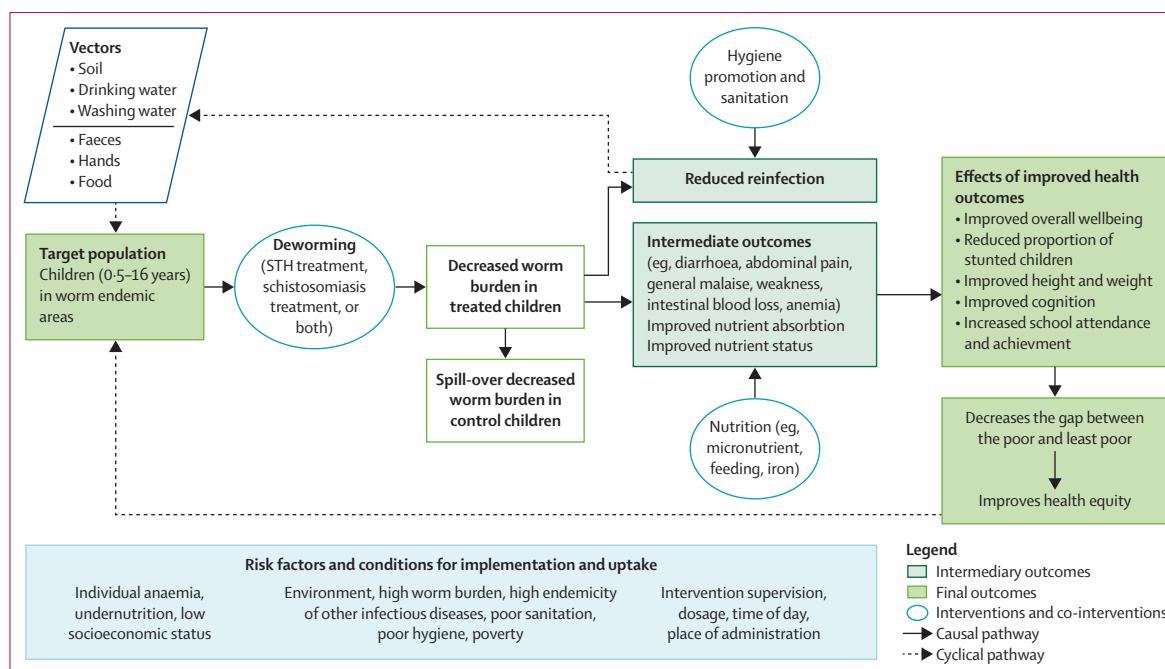


Figure 1: Logic model showing causal pathways

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-analysis¹⁶ 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

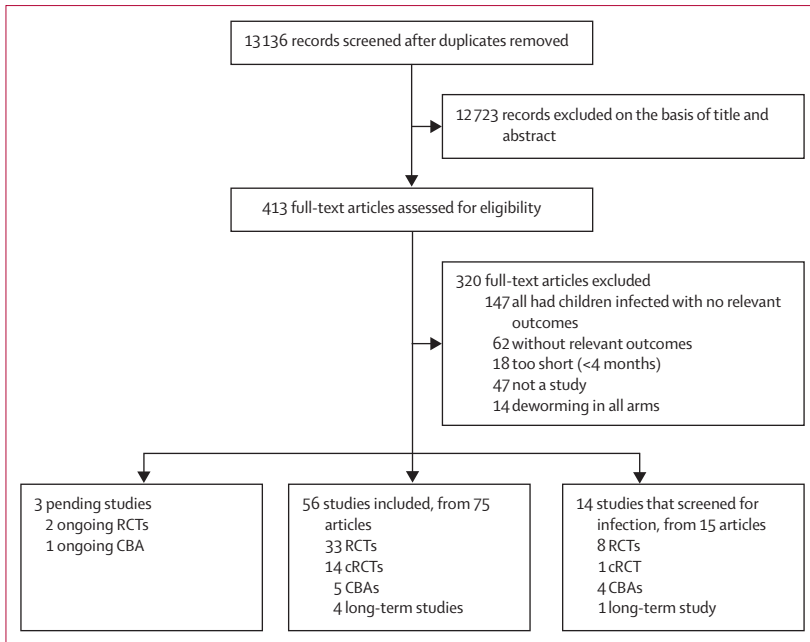


Figure 2: Study selection
CBA=controlled before-after study. cRCT=cluster randomised controlled trial.

| 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 WinBUGS²⁰ 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 80 000 iterations after a burn-in of 40 000 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 intervals [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 weight-for-height (SD 0·14, 95% CrI –0·20 to 0·49; 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

| 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)

soil-transmitted helminths on long-term (>8 years) economic productivity (hours worked), school enrolment,

| 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)

height, 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 0.91), 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 trial³⁰ 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 trial³⁰ 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 literacy²⁷ (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 trichurias, 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

| 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 | Tiabendazole 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 | | | | | |

weight, height, short-term attention, or attendance, with two exceptions. Treatment of children infected with schistosomiasis increased weight gain by 1.1 kg (95% CI 0.6–1.5) compared with mass deworming effect of 0.14 kg (95% CI –0.16 to 0.42; 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

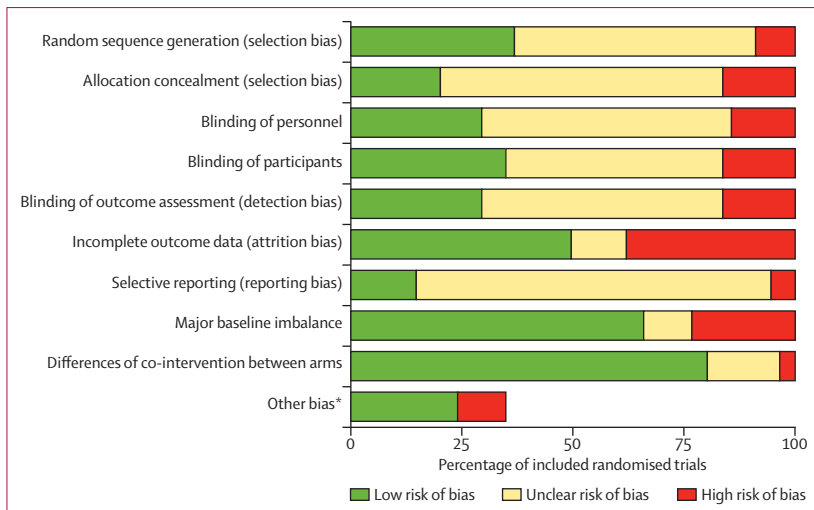


Figure 3: Risk of bias graph

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 campaign³³ (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 review⁹ 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 schistosomiasis 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

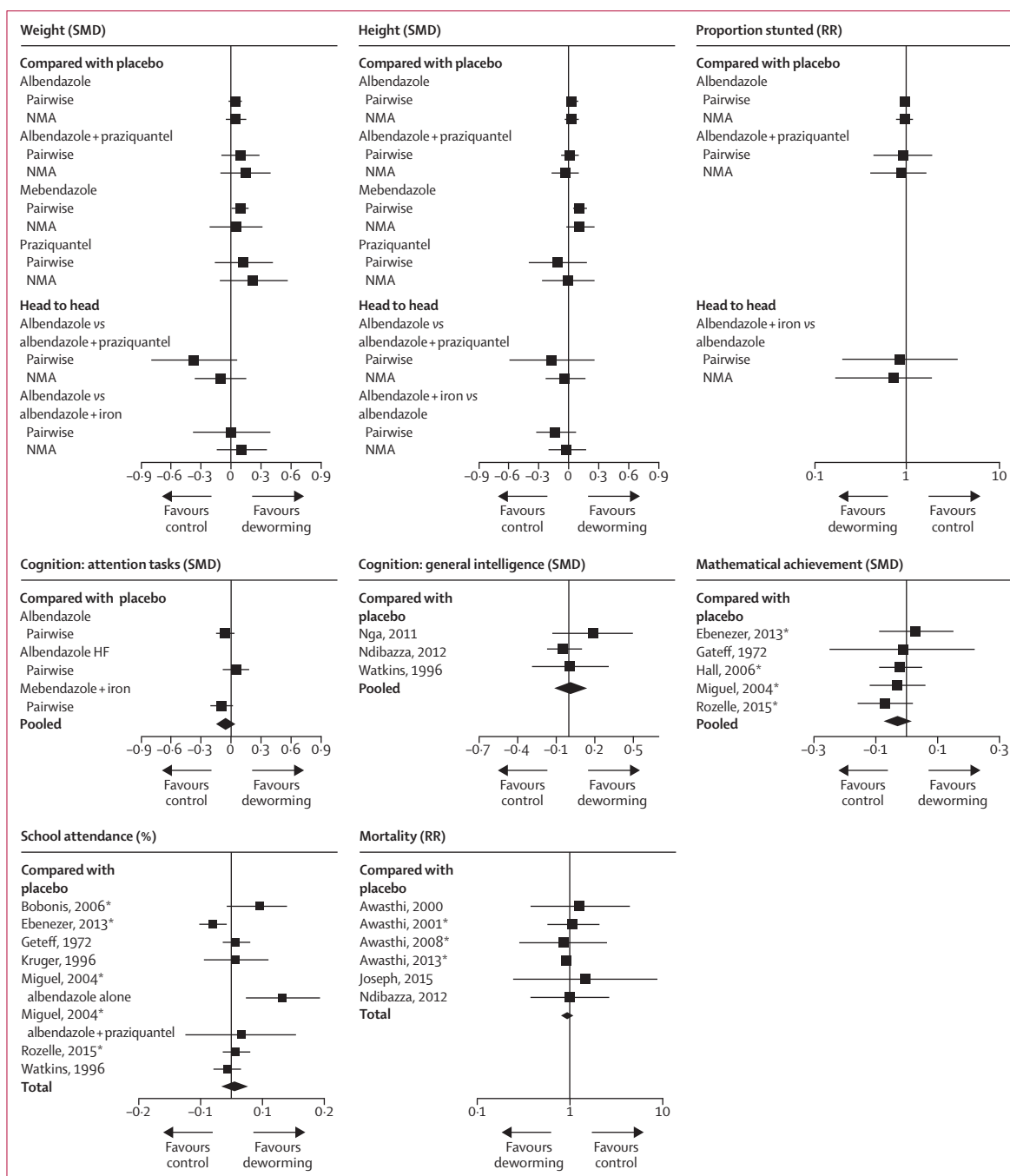


Figure 4: Network meta-analysis and pairwise meta-analyses for primary outcomes, showing comparability of pairwise and network meta-analyses, as well as comparability in size of effects for single deworming agents, and combinations with other drugs and agents
 SMD=standardised mean difference. NMA=network 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, Janssen 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 Sculthorpe (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.

References

- WHO. Helminth control in school-age children. A guide for managers of control programmes, 2nd edn. Geneva: World Health Organization, 2011.
- Evans D, Ghosh A. Prioritizing educational investments in children in the developing world. Santa Monica, CA: RAND Corporation, 2008.
- Givewell. Combination deworming (mass drug administration targeting both schistosomiasis and soil-transmitted helminths). December, 2015. <http://www.givewell.org/international/technical/programs/deworming> (accessed March 15, 2016).
- Hall A, Horton S. Best practice paper: deworming. Copenhagen: Copenhagen Consensus Centre, 2009.
- Taylor-Robinson DC, Maayan N, Soares-Weiser K, Donegan S, Garner P. Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin, and school performance. *Cochrane Database Syst Rev* 2015; 7: CD000371.
- Hotez P, Mistry N, Fenwick A. Should deworming policies in the developing world be reconsidered? Speaking of medicine. *PLOS Blogs*. July 18, 2012. <http://blogs.plos.org/speakingofmedicine/2012/07/18/should-deworming-policies-in-the-developing-world-be-reconsidered/> (accessed Nov 16, 2016).
- Bundy DA, Kremer M, Bleakley H, Jukes MC, Miguel E. Deworming and development: asking the right questions, asking the questions right. *PLoS Negl Trop Dis* 2009; 3: e362.
- Engels D, Savioli L. Evidence-based policy on deworming. *PLoS Negl Trop Dis* 2009; 3: e359.
- Duffo A, Fishbane A, Glennerster R, Kremer M, Madon T, Miguel E. Cochrane's incomplete and misleading summary of the evidence on deworming, innovations for poverty action. *Berkeley Blog*. July 20, 2012. <http://www.poverty-action.org/blog/cochrane%25E2%2580%2599s-incomplete-and-misleading-summary-evidence-deworming> (accessed Nov 16, 2016).
- Montresor A, Addiss D, Albonico M, et al. Methodological bias can lead the Cochrane collaboration to irrelevance in public health decision-making. *PLoS Negl Trop Dis* 2015; 9: e0004165.
- Welch VA, Awasthi S, Cumberbatch C, et al. 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: protocol. Oslo: The Campbell Collaboration, 2013.
- Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on indirect treatment comparisons good research practices: part 2. *Value Health* 2011; 14: 429–37.
- Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; 162: 777–84.
- Sampson M, McGowan J, Lefebvre C, Moher D, Grimshaw J. PRESS: peer review of electronic search strategies. Ottawa: Canadian Agency of Drugs and Technology for Health (CADTH), 2008.
- Hombrados J, Waddington H. Campbell Collaboration International Development Coordinating Group (IDCG) risk of bias tool. Dec 26, 2012. http://www.3ieimpact.org/media/filer_public/2012/12/26/jorge_hombrados_and_hugh_waddington_conference-session12-b_3ie_dhaka_colloquium.pdf (accessed Nov 16, 2016).
- Puhan MA, Schunemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014; 349: g5630.
- Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines 3: rating the quality of evidence—introduction. *J Clin Epidemiol* 2011; 64: 401–06.
- Kristjansson E, Francis DK, Liberato S, et al. Food supplementation for improving the physical and psychosocial health of socio-economically disadvantaged children aged three months to five years: a systematic review. *Cochrane Database Syst Rev* 2015; 5: CD009924.
- Sternberg RJ, Powell C, McGrane P, Grantham-McGregor S. Effects of a parasitic infection on cognitive functioning. *J Exp Psychol Appl* 1997; 3: 67–76.
- Spiegelhalter D, Thomas A, Best N, Lunn D. WinBUGS user manual. Version 1.4. Cambridge: Institute of Public Health, 2003.
- Leicester and Bristol University. Multi-parameter evidence synthesis research. <http://www.bristol.ac.uk/social-community-medicine/projects/mpes/> (accessed Nov 16, 2016).
- Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. Report by the Decision Support Unit. Sheffield: Decision Support Unit, 2011.
- Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; 28: 3083–107.
- Baird S, Hamory Hicks J, Kremer M, Miguel E. Worms at work: long run impacts of a child health investment. *Q J Econ* 2016; published online July 19. DOI:10.1093/qje/qjw022.
- Makamu F, Azam M, Kazianga H. Returns to controlling a neglected tropical disease schistosomiasis control program and education outcomes in Nigeria. 2016. <https://www.aea-net.org/conference/2016/retrieve.php?pdfid=1185> (accessed Nov 16, 2016).
- Ozier O. Exploiting externalities to estimate the long-term effects of early childhood deworming. Washington, DC: World Bank Group, 2015.
- Croke K. The long run effects of early childhood deworming on literacy and numeracy: evidence from Uganda. Cambridge, MA: Harvard School of Public Health, 2014.
- Miguel E, Kremer M. Worms: identifying impacts on education and health in the presence of treatment externalities. *Econometrica* 2004; 72: 159–217.

-
- 29 Aiken AM, Davey C, Hargreaves JR, Hayes RJ. Re-analysis of health and educational impacts of a school-based deworming programme in western Kenya: a pure replication. *Int J Epidemiol* 2015; **44**: 1572–80.
- 30 Bobonis GJ, Miguel E, Puri-Sharma C. Anemia and school participation. *J Hum Resour* 2006; **41**: 692–721.
- 31 Hicks JH, Kremer M, Miguel E. Estimating deworming school participation impacts and externalities in Kenya: a Comment on Aiken et al. Washington, DC: International Initiative for Impact Evaluation (3ie), 2014.
- 32 Alderman H, Konde-Lule J, Sebuliba I, Bundy D, Hall A. Effect on weight gain of routinely giving albendazole to preschool children during child health days in Uganda: cluster randomised controlled trial. *BMJ* 2006; **333**: 122.
- 33 Bleakley H. Disease and development: evidence from hookworm eradication in the American south. *Q J Econ* 2007; **122**: 73–117.
- 34 Hall A, Hewitt G, Tuffrey V, de Silva N. A review and meta-analysis of the impact of intestinal worms on child growth and nutrition. *Matern Child Nutr* 2008; **4** (suppl 1): 118–236.