

Mass deworming for improving health and cognition benefits of children in endemic helminth areas: a systematic review and individual participant data network meta-analysis

Vivian A Welch, Michelle F Gaffey, Elizabeth Ghogomu, Paul Arora, Simon Cousens, Alomgir Hossain, Rehana A Salam, Peter Tugwell, Zulfiqar Bhutta, George A Wells

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TITLE OF THE REVIEW

Mass deworming for improving health and cognition benefits of children in endemic helminth areas: a systematic review and individual participant data network meta-analysis

BACKGROUND

Soil transmitted helminths and schistosomes affect millions of children worldwide. Mass deworming is applied globally to reduce the consequences of helminth infection. Systematic reviews and meta-analyses based on aggregate results of the effect of mass deworming on health and education outcomes are conflicting with some showing benefit (Hall, Hewitt, Tuffrey, & de, 2008) and others not (Taylor-Robinson, Maayan, Soares-Weiser, Donegan, & Garner, 2015). Debate has ensued about whether these conflicting results are due to the influence of variations in effect across individual-level characteristics such as whether children are infected or not and intensity of infection (Bundy, Kremer, Bleakley, Jukes, & Miguel, 2009; Hotez et al., 2007; Montresor et al., 2015) as well as setting characteristics such as the sanitation environment and rapidity of reinfection (Campbell, 2016).

A recent Campbell review and network meta-analysis led by our group (VW, PT, GAW, ZB), with 47 randomized trials and >1 million children, found little to no overall effect on growth and school attendance. Because our analysis used network meta-analysis, we were able to explore the size of effect with different types and frequency of drugs and their combination with food or micronutrients; none of which contributed to larger effects. Our review also did not find larger effects in subgroups of children at the aggregate level across characteristics such as age, baseline nutritional status, prevalence or intensity of infection that are postulated to be important (Welch et al., 2016). These analyses were conducted at the study level, rather than using data for each individual child, which limits the power to detect effect modification by individual participant characteristics. This review was therefore unable to identify whether mass deworming was more effective for children with certain characteristics. There was substantial unexplained heterogeneity between studies, with some studies finding larger effects than others, and no single individual-level, setting-level or methodology characteristic explaining this variation. Thus, we concluded that our analysis of effect modifiers may have been limited by the aggregate level nature of the data.

There would be value in conducting an Individual Participant Data (IPD) meta-analysis to explore the question of whether mass deworming is more effective for subgroups of children defined by characteristics such as infection intensity and status, age or nutritional status. This understanding could help to develop targeted strategies to reach these children better with deworming, guide policy regarding deworming and contribute to improved acceptance of deworming by parents and communities.

This review has been developed with an advisory board of experts in parasitology, nutrition and infectious diseases (Robert Black, Sue Horton, Celia Holland, Deirdre Hollingsworth and Peter Tugwell). We decided not to assess spill-over effects since the only study which

described and assessed spillover effects and collected infection intensity data, has already been replicated using the original data (Miguel 2004, Aiken 2014), and we do not expect any other cluster randomized trial to contain data about the distance between clusters that could allow these calculations. We also decided not to assess cognitive outcomes such as short-term attention because the comparison of studies of mass deworming with studies which selected and treated infected children found no difference in effects on short-term attention (e.g. digit recall) for treatment of infected children, suggesting little variation due to intensity of infection for attention outcomes (Welch et al. 2016).

The primary objective is to explore whether the effects of deworming on anaemia, growth and cognition vary with child-level and study-level characteristics, specifically: intensity of infection (as assessed by egg count), infection status (including species of worm), age, socioeconomic status, sex, nutritional status; population level prevalence and intensity as well as water and sanitation environment.

OBJECTIVES

1. To what extent do the effects of deworming on anaemia, growth and cognition vary with individual child-level characteristics: age, sex, infection status, socio-economic status, nutritional status, intensity of infection?
2. To what extent do the effects of deworming on anaemia, growth and cognition vary with environment-level characteristics: prevalence, intensity, water and sanitation?

EXISTING REVIEWS

1. Hall, A., Hewitt, G., Tuffrey, V., & de, S. N. (2008). A review and meta-analysis of the impact of intestinal worms on child growth and nutrition. *Matern Child Nutr*, 4, Suppl1, 118-236.
2. Taylor-Robinson, D. C., Maayan, N., Soares-Weiser, K., Donegan, S., & Garner, P. (2015). Deworming drugs for soil-transmitted intestinal worms in children: effects on nutritional indicators, haemoglobin, and school performance (Review). *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD000371. DOI: 10.1002/14651858.CD000371.pub6.
3. Croke, K., Hicks, J.H., Hsu, E., Kremer, M. & Miguel, E. (2016). Does mass deworming affect child nutrition? Meta-analysis, cost-effectiveness, and statistical power (No. 22382). The National Bureau of Economic Research.
4. Welch, V., Ghogomu, E., Hossain, A., Awasthi, S., Bhutta, Z., Cumberbatch, C., . . . White, H. (2016). 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. *Campbell Systematic Reviews* 2016:7. doi: 10.4073/csr.2016.7

The above reviews analysed data at the study-level and found conflicting effects of deworming on health and education outcomes in children as well as no effects in subgroups of children across characteristics such as age, baseline nutritional status, prevalence or intensity of infection. This review will analyse individual participant data to assess effect modification of mass deworming for children and explore whether there are any subgroups of children and settings that would benefit from mass deworming.

INTERVENTION

Deworming using any drugs for soil transmitted helminths or schistosomiasis with or without co-interventions such as food, micronutrients, iron or hygiene interventions. Eligible drugs include (but are not limited to) albendazole, praziquantel, levamisole, ivermectin, diethyl carbamazine, pyrantel, piperazine, mebendazole, hycanthone and tetramisole.

We will include studies with combined approaches to parasite elimination such as albendazole and praziquantel. Also, because deworming may be used in combination with iron, food or hygiene promotion, we will include studies with multiple component interventions. We will include studies using a mass drug administration (e.g. at schools or community clinics), and we will also include studies where children with infections were identified and dewormed. We will control for infection intensity in the analytic models.

We will exclude studies with non-drug only interventions such as hygiene, food, micronutrients, or iron.

Comparators: Placebo, control, or other active interventions (e.g. vitamin A, iron, hygiene promotion).

POPULATION

Children aged 6 months to 16 years. Children below 6 months are rarely treated because they are not exposed to worms.

We will exclude studies with less than 100 participants because of the time and effort required for each dataset and the information gained from smaller studies will be small compared to larger datasets. We will not exclude studies on the basis of attrition rate from the study.

OUTCOMES

The primary health outcomes are:

- weight
- height

- serum ferritin
- haemoglobin

The primary cognition outcomes are:

- short-term attention tasks (e.g. digit recall),
- cognitive development.

We will include studies which report weight, haemoglobin, serum ferritin, cognition, or height.

STUDY DESIGNS

We will include:

- randomised controlled trials and
- quasi-randomised trials

For the purpose of determining whether specific individual-level and environment-level characteristics are associated with greater effects of deworming, there is sufficient evidence from over 70 randomized trials with over 100,000 children to include only randomized and quasi-randomized trials. We will include studies reported in abstract form at a conference as well as unpublished studies. We will seek full datasets from all studies and carry out the same methods for data checking and quality for all studies. We will analyse data from studies which report infection intensity since the primary objective of this review is to assess effect modification across intensity of infection.

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Aiken, A. M., Davey, C., Hargreaves, J. R. & Hayes, R. J. (2014). Reanalysis of health and educational impacts of a school-based deworming program in western Kenya: Part 1, pure replication, 3ie Replication Paper 3, part 1. Washington, DC: International Initiative for Impact Evaluation (3ie)

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REVIEW AUTHORS

Lead review author: The lead author is the person who develops and co-ordinates the review team, discusses and assigns roles for individual members of the review team, liaises with the editorial base and takes responsibility for the on-going updates of the review.

Name: Vivian A Welch

Title:
Director, Methods Centre, Bruyère
Research Institute;
Assistant Professor

Affiliation:
School of Epidemiology, Public
Health and Preventive Medicine,
University of Ottawa

Address:
304b - 85 Primrose Avenue,

City, State, Province or County:
Ottawa, Ontario

Postal Code: K1R 6M1

Country: Canada

Phone:
613-562-6262 ext 2904

Email:
Vivian.welch@uottawa.ca

Co-author(s):

Name: Michelle F Gaffey

Title:
Researcher
PhD Candidate

Affiliation:
Hospital for Sick Children, and
University of Toronto

Address:
555 University Avenue

City, State, Province or County:
Toronto, Ontario

Postal Code:
M5G 1X8

Country:
Canada

Phone:
416-813-7654 ext 328532

Email:
michelle.gaffey@sickkids.ca

Name: Elizabeth Ghogomu

Title:
Research Associate

Affiliation:
Bruyère Research Institute,
University of Ottawa

Address:
213 - 85 Primrose Avenue,

City, State, Province or County:
Ottawa, Ontario

Postal Code: K1R 7G5

Country: Canada

Phone:
613-562-6262 ext 2962

Email:
cmmsg@uottawa.ca

Name: Paul Arora

Title:
Epidemiologist
Assistant Professor

Affiliation:
Public Health Agency of Canada in
the National Public Health
Laboratory and Dalla Lana School
of Public Health, University of
Toronto

Address:
11th flr, 180 Queen St. West.

City, State, Province or County:
Toronto, Ontario

Postal Code: M5V 3LZ

Country: Canada

Phone:
(416) 952-6268

Email:
paul.arora@utoronto.ca

Name: Simon Cousens

Title:
Mathematician/statistician
Professor

Affiliation:

London School of Hygiene and
Tropical Medicine (LSHTM)

Address:
Room 116-LSHTM Keppel Street

City, State, Province or County:
London

Postal Code: WC1E 7HT

Country: UK

Phone:
+44 (20) 7927 2422

Email:
simon.cousens@lshtm.ac.uk

Name: Alomgir Hossain

Title:
Biostatistician

Affiliation:
Cardiovascular Research Methods
Centre
University of Ottawa Heart
Institute

Address:
40 Ruskin Street

City, State, Province or County:
Ottawa, Ontario

Postal Code: K1Y 4W7

Country: Canada

Phone:
1-613-798-5555 ext 10633

Email:
AHossain@ottawaheart.ca

Name: Rehana A Salam

Title:

Affiliation:
University of Adelaide

Address:

City, State, Province or County:

Postal Code:

Country: Australia

Phone:

Email: rehana.salam@aku.edu

Name: Peter Tugwell

Title:
Director, Co-director,
Professor

Affiliation:
Center for Global Health, WHO
Collaborating Centre for
Knowledge Translation and Health
Technology Assessment in Health
Equity, Bruyère Research Institute
School of Epidemiology, Public
Health and Preventive Medicine,
University of Ottawa

Address:
302 - 85 Primrose Avenue,

City, State, Province or County:
Ottawa, Ontario

Postal Code: K1R 6M1

Country: Canada

Phone:
613-562-6262 ext 2908

Email:
tugwell.bb@uottawa.ca

Name: George A Wells

Title:
Director, Professor

Affiliation:
Cardiovascular Research Methods
Centre
University of Ottawa Heart
Institute; School of Epidemiology,
Public Health and Preventive
Medicine, University of Ottawa

Address:
40 Ruskin Street

City, State, Province or County:
Ottawa, Ontario

Postal Code: K1Y 4W7

Country: Canada

Phone:
(613) 798-5555, Ext. 18640

Email:
gawells@ottawaheart.ca

Name: Zulfiqar Bhutta

Title:
Co-Director, Centre for Global
Child Health; Professor

Affiliation:
The Hospital for Sick Children

Address:
555 University Avenue

City, State, Province or County:
Toronto, Ontario

Postal Code:
M5G 1X8

Country:
Canada

Phone:
416-813-7654 ext 328532

Email:
Zulfiqar.bhutta@SickKids.ca

*George Wells and Zulfiqar Bhutta as joint last authors

ROLES AND RESPONSIBILITIES

- Content: Zulfiqar Bhutta and Michelle Gaffey have child health and nutritional expertise
- Systematic review methods: Paul Arora, Elizabeth Ghogomu, Vivian Welch, Peter Tugwell have methodological expertise
- Statistical analysis: Simon Cousens, Alomgir Hossain, George Wells have statistical expertise
- Information retrieval: Vivian Welch has information retrieval expertise. We will use the search strategy developed for the Campbell review of deworming for children, developed by Jessie McGowan (information scientist) and reviewed by John Evers (Campbell information scientist)

FUNDING

We have funding from the Bill and Melinda Gates Foundation.

The deliverable deadlines for the review are here below:

	Feb 201 7	Ma r	Apri l	Ma y	Ju n	Ju l	Au g	Sep t	Oc t	No v	De c	Jan 201 8
Title registered	X											
Protocol development	X	X										
Protocol submission		X										
Searching and screening		X	X									
Data extraction			X	X	X							
Synthesis				X	X	X	X	X				
Interpretation and write up						X	X	X	X	X	X	
publication											X	X

POTENTIAL CONFLICTS OF INTEREST

Vivian Welch, Elizabeth Ghogomu, Alomgir Hossain, Peter Tugwell, and George Wells were authors of a prior aggregate-level Campbell Deworming review.

PRELIMINARY TIMEFRAME

- Date you plan to submit a draft protocol: March 2017

- Date you plan to submit a draft review: August 2017

AUTHOR DECLARATION

Authors' responsibilities

By completing this form, you accept responsibility for preparing, maintaining, and updating the review in accordance with Campbell Collaboration policy. The Coordinating Group will provide as much support as possible to assist with the preparation of the review.

A draft protocol must be submitted to the Coordinating Group within one year of title acceptance. If drafts are not submitted before the agreed deadlines, or if we are unable to contact you for an extended period, the Coordinating Group has the right to de-register the title or transfer the title to alternative authors. The Coordinating Group also has the right to de-register or transfer the title if it does not meet the standards of the Coordinating Group and/or the Campbell Collaboration.

You accept responsibility for maintaining the review in light of new evidence, comments and criticisms, and other developments, and updating the review every five years, when substantial new evidence becomes available, or, if requested, transferring responsibility for maintaining the review to others as agreed with the Coordinating Group.

Publication in the Campbell Library

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Form completed by: Vivian Welch

Date: 20 July 2017