11-1-2020

Maternal Hookworm Infection and Its Effects on Maternal Health: A Systematic Review and Meta-Analysis.

Tara E Ness

Vedika Agrawal

Kathryn Bedard

Lara Ouellette

Timothy A Erickson

See next page for additional authors

Am. J. Trop. Med. Hyg., 103(5), 2020, pp. 1958–1968
doi:10.4269/ajtmh.20-0503

Maternal Hookworm Infection and Its Effects on Maternal Health: A Systematic Review and Meta-Analysis

Tara E. Ness,[1]* Vedika Agrawal,[2] Kathryn Bedard,[1] Lara Ouellette,[3] Timothy A. Erickson,[1,4] Peter Hotez,[1,4,5,6,7] and Jill E. Weatherhead[1,2,4]

[1]*Department of Pediatrics, Baylor College of Medicine, Houston, Texas;* [2]*Department of Medicine, Baylor College of Medicine, Houston, Texas;* [3]*Texas Medical Center Library, Houston, Texas;* [4]*National School of Tropical Medicine, Baylor College of Medicine, Houston, Texas;* [5]*Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, Texas;* [6]*Hagler Institute for Advanced Study at Texas A&M University, College Station, Texas;* [7]*Department of Biology, Baylor University, Waco, Texas*

Abstract. Hookworm is an intestinal parasite that infects nearly 230 million people, with another 5.1 billion at risk, especially in poverty-stricken tropical and subtropical regions. Pregnancy is an especially vulnerable time for hookworm infection because of its effect on both maternal and subsequently fetal health. A systematic review and meta-analysis was conducted. The meta-analysis was performed on the association between maternal hookworm and maternal anemia, as well as maternal hookworm coinfection with malaria. The prevalence of hookworm ranged from 1% to 78% in pregnant women, whereas malaria prevalence ranged from 11% to 81%. Pregnant women with hookworm infection were more likely to have anemia (combined odds ratio [cOR] 2.55 [2.20, 2.96], $P < 0.001$). In addition, pregnant woman with hookworm were more likely to have malaria coinfection (cOR 1.60 [1.38, 1.86], $P < 0.001$). Other effects on maternal and child health were investigated and summarized without systematic review or meta-analysis because of the limited study numbers. Despite current deworming recommendations in pregnant women, heavy hookworm burden, coinfection with malaria, and subsequent anemia persist. Although this is likely due, in part, to a lack of implementation of preventive chemotherapy, additional interventions such as health education, proper waste management, or linking malaria and soil-transmitted helminth treatment and prevention programs may also be needed. Further investigations on maternal–child outcomes as a result of hookworm infection during pregnancy will highlight public health interventional targets to reduce morbidity in pregnant women and children globally.

Hookworm is a common helminthic parasite, infecting nearly 230 million people globally, particularly in subtropical and tropical areas of poverty. During pregnancy, hookworm can affect the mother and may also affect the developing fetus, making it an important time for targeted public health interventions. We conducted a review and analysis of research published on hookworm infection during pregnancy over the last 10 years to provide an updated perspective on the prevalence and current impact of infection. The prevalence of hookworm during pregnancy ranged from 1% to 78%, showing that even with current deworming recommendations, hookworm infection persists in some regions likely because of inadequate implementation. The results showed pregnant women with hookworm infection were more likely to have anemia than pregnant women without hookworm infection (combined odds ratio [cOR] 2.55 [2.20, 2.96], $P < 0.001$). In addition, pregnant women with hookworm infection were more likely to have malaria coinfection (cOR 1.60 [1.38, 1.86], $P < 0.001$) than pregnant women without hookworm infection. Anemia during pregnancy is concerning as it has been associated with increased incidence of low birth weight, premature birth, and maternal mortality. The impact of maternal hookworm on infant cognitive development, infant birth outcomes, infant vaccine response, and maternal coinfection with HIV represents critical areas of further research.

INTRODUCTION

Soil-transmitted helminths (STHs), including *Trichuris trichiura*, *Ascaris lumbricoides*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*) are parasitic worms infecting more than 1 billion people living in areas of extreme poverty and rank among the most common infectious agents of humans.[1] Hookworms infect nearly 230 million people globally living in areas of extreme poverty and lacking appropriate sanitation and access to clean water, especially in tropical and subtropical climates. They parasitize the gastrointestinal tract causing blood loss that can result in anemia and severe morbidity, estimated at 4 million disability-adjusted life years (DALYs) worldwide.[1,2] As such, hookworm exhibits the highest disease burden among all STHs.

Hookworm larvae enter into the human host from soil by penetrating the skin and migrating through blood vessels to the heart and then lungs. There, they penetrate the pulmonary alveoli, ascend to the pharynx, and are swallowed by the host to reside in the small intestines. Adult worms develop from the larvae and embed themselves into the intestinal wall, causing anemia through their ingestion of the host's blood. Although mild anemia may be asymptomatic, it can also cause weakness, fatigue, shortness of breath, tachycardia, and poor concentration. In addition to anemia, high worm burdens of the two main human hookworm species, *A. duodenale* and *N. americanus*, can lead to abdominal pain, diarrhea, loss of appetite, weight loss, and fatigue.[3] In children, chronic hookworm infection and anemia also result in cognitive and physical growth delays,[4] whereas adults with hookworm exhibit declines in work performance and productivity.[5] In so doing, hookworm infection reinforces poverty in low- and middle-income countries.[6]

There is also increasing evidence for the disproportionate impact of hookworm infection and anemia on girls and women.[7] Pregnancy is a particularly vulnerable time period for women to be infected as infection with these helminths has the potential to negatively affect maternal health and may have an

* Address correspondence to Tara E. Ness, Pediatric House Staff Office, Abercrombie Bldg., 6621 Fannin St., Houston, TX 77030. E-mail: tara.ness@bcm.edu

impact on the developing fetus. A previous systematic review and meta-analysis conducted over 10 years ago in 2008, before implementation of widespread deworming protocols, demonstrated hookworm infection during pregnancy is specifically associated with low hemoglobin (Hb) levels in pregnant women.[8] As a result of the poor outcomes associated with hookworm during pregnancy, in 2002, the WHO supported treatment of hookworm using benzimidazoles (albendazole and mebendazole) during pregnancy in areas where the prevalence of hookworm and *T. trichiura* infection exceeded 20–30%.[9] Although the safety of benzimidazole use during pregnancy was not clear at that time, a recent systematic review has shown that adverse effects, even during the first trimester, are unlikely.[10]

This study aimed at evaluating the impact of hookworm during pregnancy on maternal and child outcomes in the current WHO-recommended era of routine treatment of hookworm during pregnancy. Over the past 10 years, there has been a modest decline in hookworm by 28.5%[1] which may be due, in part, to hookworm treatment in high-risk groups living in endemic regions. However, this systematic review and meta-analysis demonstrates the persistence of hookworm and anemia as well as hookworm and malaria coinfection in pregnant women. The findings highlight the urgency of implementing the new 2017–2018 WHO recommendations for providing preventive chemotherapy for pregnant women after the first trimester in regions where hookworm prevalence is greater than or equal to 20% and the prevalence of anemia is greater than 40% among pregnant women.[11,12] This review includes studies impacted by the 2002 recommendation to treat hookworm during pregnancy, but likely not yet affected by the 2017–2018 recommendations to implement preventative chemotherapy to pregnant women in endemic areas.

METHODS

Study design. Before the beginning of the review, the research question, types of participants, types of studies, and inclusion/exclusion criteria were outlined, and a protocol was developed. The protocol was registered in the PROSPERO registry of systematic reviews (registration number: CRD42018084942). A preliminary, non-systematic search was conducted on January 1, 2018 using PubMed to identify potential outcomes related to maternal hookworm infection specifically: the impact of maternal hookworm on maternal anemia and the impact of maternal hookworm on maternal coinfection with malaria. Outside of these two outcomes, studies highlighting other maternal (i.e., C-reactive protein [CRP]/inflammation and non-malarial coinfection) and infant (birth weight, infant anemia, and infant development) outcomes did not have enough study numbers for a robust systematic review and meta-analysis. The non-systematic review study results are summarized under "Other Results" but are otherwise not included in the systematic review or meta-analysis. A systematic review was subsequently performed on the impact of maternal hookworm on maternal anemia and the impact of maternal hookworm on maternal coinfection with malaria. The inclusion criteria were human studies involving pregnant women who were diagnosed during their pregnancy with hookworm via diagnostic stool examination and were also tested for anemia and/or malaria during their pregnancy. Studies in all languages were included. We limited the search from 2008 to current to capture those studies not included within the previous review published in 2008 and to provide a more up-to-date representation of the epidemic after implementation of the 2002 WHO guidelines for treatment of pregnant women with STH.

Comprehensive search. A comprehensive and structured search was completed by a trained medical librarian to determine the effects of hookworm infection during pregnancy on maternal health, specifically regarding the conditions of anemia and malaria. Using Medline Ovid (Medline on OvidSP) as the standard and foundational database, three overarching concepts were explored and developed: hookworm infections, pregnancy and maternal health, and anemia/malaria. Each concept was expounded on using both controlled and natural languages. Our search terms included "hookworm," "helminths," "*Ancylostoma*," or "*Necator*" in combination with "pregnancy" or "maternal" plus "anemia" or "malaria." Medical Subject Headings (MeSH) terms were identified, and keywords were pulled along with various synonyms. The keywords were searched using the title, abstract, and keyword fields within the Medline Ovid database. Once each concept was thoroughly built, the three concepts were added together to create one comprehensive search. The search results were restricted from 2008 to current.

The search was approved by T. E. N. and J. E. W. and then translated to Embase and the Cochrane Library. The only gray literature included was that through the Embase database. The final searches were all run on January 25, 2019 in each database. The results were uploaded to the EndNote citation manager for de-duplication. De-duplication was completed on January 28, 2019 both internally and externally. It should be noted that the searches were run during a government shutdown, which may have affected the content and timing of updates of the databases. A search rerun and update was conducted on August 5, 2019 with de-duplication completed internally and externally. There was no government shutdown to affect the outcome of the updated results. This resulted in a total of 516 independent studies, which included the gray literature such as conference abstracts. Our PRISMA diagram is shown in Figure 1. Our MeSH terms are provided under Supplemental Materials.

Search coverage. Medline Ovid* MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily (1946 to August 2, 2019).

Embase* (1947 to August 5, 2019).

Cochrane Library* (including Cochrane Database of Systematic Reviews, and Cochrane CENTRAL (trials) through August 5, 2019).

Study selection. We included cross-sectional cohort, case series, and randomized control trials in our review. Conference abstracts were considered and were included when complete data were available, either within the abstract itself or through communication with the authors. We did not include other reviews but screened the studies they used and their references for any additional studies that were not captured by our search strategy. Studies were excluded if they did not investigate the impact of hookworm infection during pregnancy or did not indicate Hb levels. In addition, studies were excluded if they reported "helminth infection" and did not have additional information on hookworm, specifically. Search

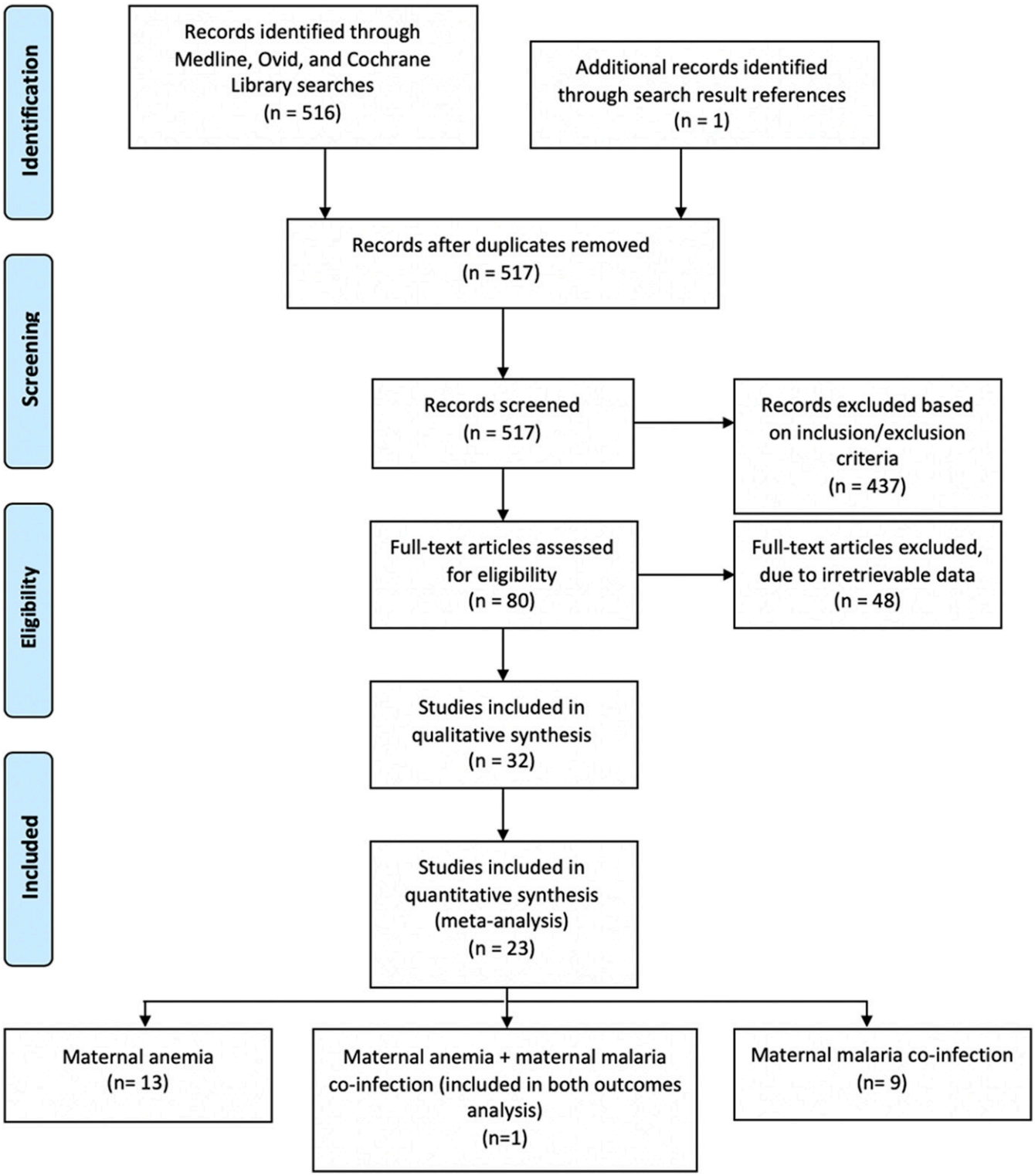

FIGURE 1. PRISMA flow diagram of study selection. This figure appears in color at www.ajtmh.org.

results were reviewed in a non-blinded fashion by T. E. N. and V. A., and abstracts and full articles were reviewed when relevance was not definitive. No disagreements arose between the reviewers. Before performing the meta-analysis with selected studies, T. E. N. and J. E.W. evaluated each study based on the quality of data and appropriateness of the study for inclusion with the appraisal tool for cross-sectional studies (AXIS),[13] including the diagnostic methods used for hookworm, anemia, and malaria diagnosis, definition of data variables (such as Hb level for determining anemia), study population, study limitations, statistical analysis, and ethical considerations.

Data collection and analysis. Data were extracted by T. E. N. and J. E. W., which included the study setting, study design, number of individuals in the study, hookworm prevalence, method of hookworm diagnosis, definition of anemia (when available), malaria prevalence (when available), and the number of individuals with and without the outcome of interest (anemia or malaria). When data necessary for meta-analysis were not readily available, an email was sent to the study authors requesting the additional information needed. If there was no response, a follow-up email was sent either to the main author or an additional author when contact details were available.

Prevalence of hookworm in the study population was noted when available. When prevalence of hookworm was not explicitly stated, it was calculated by the authors based on the data that were presented within the study. Data were input into RevMan, and references were organized in Mendeley. Hookworm infection was designated as "presence" or "absence" of human hookworm species (*A. duodenale* and/or *N. americanus*) based on stool studies (stool microscopy) unless otherwise noted. Maternal anemia was defined based on the individual study criteria, however, in most cases was based on the WHO definition of Hb < 11. Maternal malaria infection was designated as "present" or "absent" based on the presence of malaria parasite on blood smears. Studies varied in their adjustment for different variables; as a result, comparisons were made without any adjustments. A "pooled" or cOR was created for our two outcomes (maternal anemia or maternal coinfection with malaria) to describe the overall effect when all studies were considered. The analysis was performed using a fixed-effects model (Mantel–Haenszel method) in RevMan for the production of cORs, CIs, tests of heterogeneity, and production of forest plots. RevMan was used to produce the funnel plots to also assess for publication bias in the included studies. In addition, an Egger's analysis was completed to investigate overall bias in the meta-analysis.

RESULTS

A comprehensive literature search returned 516 studies (Figure 1). Four hundred thirty-seven studies were excluded because they did not meet the inclusion criteria (did not involve pregnant human individuals, were not related to hookworm infection, hookworm infection was not diagnosed during pregnancy, or were editorials or reviews on the subject). Forty-eight articles addressed the topic of interest but did not report raw data that could be used for analysis, and the data were unable to be obtained from the studies' authors after at least two email inquiries. Eleven review articles were noted in the systematic review and excluded from the analysis based on not meeting the inclusion criteria; however, these were screened for additional studies potentially missed by the systematic review.[14–24] Based on this approach, one new study that met the inclusion criteria was identified from a review and incorporated into the meta-analysis.[16,25] From the search, contact with authors, and screening of studies used in relevant reviews, 32 total studies reflecting 32 cohorts were included in our qualitative analysis. Nine studies were excluded from the quantitative meta-analysis on maternal anemia and hookworm infection after using the AXIS tool assessing study quality and appropriateness of data. One study was excluded because of the hookworm data not being fully published per study authors,[26] and eight studies were excluded because of having unclear definitions of anemia or having a definition of anemia that was not consistent with the WHO definition and our other included studies (Hb < 11).[27–34] One of these studies already excluded on the basis of anemia definition also had patient self-report as the method of hookworm diagnosis[31] and so was not used in the maternal malaria and hookworm coinfection meta-analysis. After these exclusions, 23 studies were included for meta-analysis, 13 of which investigated hookworm during pregnancy and maternal anemia, nine of which investigated maternal malaria coinfection and one study which investigated both outcomes. The 32 studies for qualitative analysis have their characteristics described in the tables but are not otherwise included in the meta-analysis, including the calculation of cORs or production of forest plots.

Study characteristics. Studies investigating hookworm during pregnancy during the study period were conducted in Africa (Ethiopia, Gabon, Ghana, Malawi, Nigeria, Tanzania, and Uganda), South America (Peru), Asia (Bangladesh, Nepal, Thai–Burmese border, and Vietnam) and Oceania (Papua New Guinea). Table 1 shows hookworm prevalence data as well as the study period and method of stool processing and hookworm diagnosis, arranged alphabetically by the T. E. N. Prevalence was lowest in Tanzania at 0.3% and highest in Vietnam at 78%. Within the country of Ethiopia, which had the most studies performed, prevalence ranged from 9% to 29%.

No clear trend in prevalence was identified based on the geographical location or study publication date. Fifteen studies (10 investigating anemia and five investigating malaria coinfection) had hookworm prevalence over 20% in pregnant women, meeting the new WHO's 2017 recommendation for routine deworming in pregnant women in these areas if anemia prevalence is > 40%.

Hookworm and maternal anemia association. Twenty-three studies presented data on hookworm occurrence and maternal anemia during pregnancy representing 18,419 pregnant women. Studies were conducted in Bangladesh, Ethiopia, Ghana, Kenya, Nigeria, Papua New Guinea, Peru, Nepal, Tanzania, Uganda, and Vietnam. Ethiopia had the most studies conducted on the topic, nine in total. Study characteristics are summarized in Table 2.

Using the data extracted from the 14 identified studies as determined by the AXIS tool criteria for meta-analysis,[25,36,38,41,42,44,45,47–50,52,53,55] a cOR and forest plot was generated (Figure 2). Pregnant women with hookworm infection were more likely to have anemia (cOR 2.55 [2.20, 2.96], $P < 0.001$) than pregnant women without hookworm, which was demonstrated in nine of the 14 studies. The I^2 value of 89% indicates considerable heterogeneity, and the Eggers analysis showed a P-value > 0.05 ($P = 0.103$), indicating there is not substantial bias in the 14 studies. The funnel plot is available under Supplemental Materials showing no substantial bias.

As previously mentioned, the most recent WHO guidelines recommend routine preventive chemotherapy in pregnant women after the first trimester in areas with a prevalence of hookworm greater than 20% and anemia prevalence > 40%.[11,12] A subset analysis of the impact of maternal hookworm infection on anemia in regions above and below this guideline cutoff was performed. As expected in areas with

TABLE 1
Prevalence of hookworm in studies included in systematic review and meta-analysis

Study	Country	Hookworm (%)	Study period	Stool processing and diagnostics for hookworm
Adegnika[35]	Gabon	27	April 2003–July 2004	Kato–Katz
Agu[27]	Nigeria	17	April 2011–July 2011	Wet mount
Aikawa[28]	Vietnam	21	July 2003 and January 2004	Formalin–ether concentration
Baingana[36]	Uganda	67	March 2009–June 2009	Formol–diethyl ether concentration
Boel[37]*	Thai–Burmese border	69	1996	Formalin–ethyl acetate sedimentation
Boel[37]*	Thai–Burmese border	55	2007	Formalin–ethyl acetate sedimentation
Bolka[38]	Ethiopia	11	June–July 2018	Formalin–ether concentration
Ebuy[29]	Ethiopia	29	July–August 2016	Wet mount
Ekejindu[39]	Nigeria	27	Unclear	Sodium chloride flotation
Fairley[40]	Kenya	32	2000–2005	Formol–ether method
Feleke[41]	Ethiopia	19	November 2014–May 2015	Formalin/filtration concentration
Fuseini[25]	Ghana	7	August–November 2005	Stool microscopy
Getachew[42]	Ethiopia	25	August–September 2001	McMaster concentration
Getachew[43]†	Ethiopia	25	August–September 2001	McMaster concentration
Gyorkos[44]	Peru	46	April–July 2004	Kato–Katz
Hailu[45]	Ethiopia	22	February 2017–June 2017	Formol–ether concentration
Hillier[46]	Uganda	45	April 2003–November 2005	Kato–Katz
Kumera[47]	Ethiopia	11	July and August 2016	Formaldehyde–ether sedimentation
Lebso[48]	Ethiopia	15	May–June 2015	Wet mount
Lindstrom[30]	Bangladesh	1	January–December 2002	Stool analysis
Mahande[31]	Tanzania	0 (0.3)	2000–2011	Patient self-report
Makhoul[32]	Nepal	29	2005–2006	Kato–Katz
Melku[49]	Ethiopia	9	March 2012–April 2012	Wet mount
Mengist[50]	Ethiopia	18	November 2015–January 2016	10% Formalin (fresh specimens) and formalin–ether concentration (preserved)
Mutuku[26]	Kenya	9	2013–2014	Ritchie's concentration
Ndyomugyenyi[33]	Uganda	5	January 2003–May 2004	Kato–Katz
Ojurongbe[51]	Nigeria	2	October 2012–May 2013	Direct saline and formol–ether concentration
Phuanukoonnon[52]	Papua New Guinea	18	April 2008–September 2009	Direct mount with saline
Tay[34]	Ghana	8	April–July 2012	Formol–ether concentration
Thi Tran[53]	Vietnam	35	January 2014–December 2016	Kato–Katz
Thigpen[54]	Malawi	14	November 2002–September 2004	Kato–Katz
van Eijk[55]	Kenya	40	July 2003	Modification of formol–ether and ethyl acetate concentration and Kato–Katz
Yatich[56]	Ghana	4	November–December 2006	Kato–Katz

Data are rounded to the nearest percentile to allow for uniformity.
* This study includes data from two cross-sectional analyses performed in 1996 and 2007, respectively.
† Getachew 2012 and 2013 published on same cohort with same location and hookworm prevalence.

hookworm prevalence greater than 20%, pregnant women with hookworm infection were more likely to have anemia than pregnant women without hookworm (cOR of 1.71 [1.42, 2.05], $P < 0.001$). Interestingly, in areas with hookworm prevalence less than 20%, pregnant women with hookworm infection had increased risk of having anemia with a cOR of 6.07 [4.66, 7.91], $P < 0.001$. Two studies, with different definitions of anemia, reported intensity of infection with regard to maternal anemia, and both showed increasing crude and adjusted odds ratios with increasing intensity of hookworm infection as determined by eggs per gram of stool.[32,44]

Hookworm and maternal malaria coinfection. Eleven studies presented data on the association of maternal hookworm during pregnancy and coinfection with malaria, providing a total of 12,993 pregnant women. These studies took place in Ethiopia, Gabon, Ghana, Kenya, Malawi, Nigeria, Tanzania, the Thai–Burmese border, and Uganda. The malaria prevalence in these studies ranged from 11% to 81%. Study characteristics are summarized in Table 3.

Using the data extracted from 10 of these studies after using the AXIS tool, a cOR and forest plot was generated (Figure 3). Pregnant women with hookworm infection were more likely to have malaria (cOR 1.60 [1.38, 1.86], $P < 0.001$) than pregnant women without hookworm infection. The I^2 value of 8% indicates minimal heterogeneity, and the Egger's analysis had a P-value > 0.05 ($P = 0.462$), indicating there is not substantial bias within the studies. A funnel plot is available under Supplementary Materials and did not show any bias. Although the overall effect was significant, only five of the studies showed a significant effect on their individual study level.

Other results. In the preliminary review of the topic of hookworm during pregnancy, several studies identifying additional effects of maternal hookworm (i.e., infant outcomes and maternal coinfection with HIV) were identified; however, insufficient studies were available to perform a systematic review and meta-analysis. Despite the exclusion from the systematic review and meta-analysis, these studies highlight critical areas of future research on hookworm during pregnancy. Two studies investigated the association between maternal hookworm infection and maternal HIV status.[57,58] One study found that hookworm infection was associated with a higher mean HIV viral load during pregnancy,[57] whereas the other showed an inverse association between hookworm and HIV viral load in pregnant women.[58] Despite the lower HIV viral loads in hookworm coinfection in the Woodburn et al.[57] study, this study still demonstrated a lower CD4 count in HIV and hookworm coinfected pregnant women, suggesting an important impact of HIV and hookworm on the immunologic health of pregnant women. One study aimed at evaluating the effect of hookworm infection during pregnancy on overall

TABLE 2
Characteristics of studies investigating hookworm and maternal anemia during pregnancy

Study	Location	Study type	Population	Anemia definition	Anemia prevalence (%)
Agu[27]	Nigeria	Cross-sectional	226 pregnant women	Hb < 10 g/dL	40
Aikawa[28]	Vietnam	Cross-sectional	886 pregnant women (666 with stool available)	Hb < 10 g/dL	13
Baingana[36]	Uganda	Cross-sectional	151 pregnant women	Hb < 11 g/dL	28
Bolka[38]	Ethiopia	Cross-sectional	352 pregnant women	Hb < 11 g/dL	31
Ebuy[29]	Ethiopia	Unmatched case–control	164 pregnant women (88 cases and 176 controls)	Hb < 7 g/dL cases, 11–15.5 g/dL controls	NA
Feleke[41]	Ethiopia	Cross-sectional	550 pregnant women	Hb < 11 g/dL	34
Fuseini[25]	Ghana	Cross-sectional	300 pregnant women	Hb < 11 g/dL	64
Getachew[42]	Ethiopia	Cross-sectional	388 pregnant women	Hct < 33%*	54
Gyorkos[44]	Peru	Prospective cohort	1,042 pregnant women	Hb < 11 g/dL	31
Hailu[45]	Ethiopia	Cross-sectional	743 pregnant women	Hb < 11 g/dL	11
Kumera[47]	Ethiopia	Cross-sectional	234 pregnant women	Hb < 11 g/dL	47
Lebso[48]	Ethiopia	Cross-sectional	507 pregnant women	Hb < 11 g/dL	17
Lindstrom[30]	Bangladesh	Cross-sectional	740 pregnant women	Not stated	27
Mahande[31]	Tanzania	Cross-sectional	6,533 pregnant women	Not stated	2
Makhoul[32]	Nepal	Cross-sectional	3,003 pregnant women	Hb < 8 g/dL	4
Melku[49]	Ethiopia	Cross-sectional	302 pregnant women	Hb < 11 g/dL in first and third trimester Hb < 10.5 g/dL second trimester	17
Mengist[50]	Ethiopia	Cross-sectional	372 pregnant women	Hb < 11 g/dL	17
Mutuku[26]	Kenya	Prospective cohort	378 pregnant women	Hb < 11 g/dL	72
Ndyomugyenyi[33]	Uganda	Cross-sectional	832 pregnant women	Hb < 100 g/L (10 g/dL)	21
Phuanukoonnon[52]	Papua New Guinea	Cross-sectional	201 pregnant women	Hb < 11 g/dL	7
Tay[34]	Ghana	Cross-sectional	375 pregnant women	Not stated	66
Thi Tran[53]	Vietnam	Cross-sectional	216 pregnant women	Hb < 11 mg/mL	8
van Eijk[55]	Kenya	Cross-sectional	390 pregnant women	Hb < 11 g/dL	52

NA = not applicable.
* Per WHO, Hct < 33% is equal to Hb < 11 g/dL.

inflammation by measuring CRP. This particular study showed a positive association between maternal hookworm infection during pregnancy and CRP, possibly explained by tissue damage and inflammation.[59] However, other investigations have shown hookworm may downregulate the immune response via suppression of tumor necrosis factor α-regulated pro-inflammatory pathways.[60] Several studies investigated infant vaccine response in regard to maternal hookworm infection; however, the results were mixed, with most studies not showing a change in infant antibody levels in response to vaccination.[61–64] Of the studies investigating infant birth outcomes, one showed maternal hookworm infection was associated with low infant birth weight[65]; one showed an association with preterm delivery, low birth weight, small for gestational age, and/or infant anemia[51]; and one showed that maternal infection with hookworm was associated with reduced low birth weight in the infant compared with that without infection.[66] An additional study found maternal hookworm infection was associated with infant anemia,[67] and another showed an association with hookworm at the

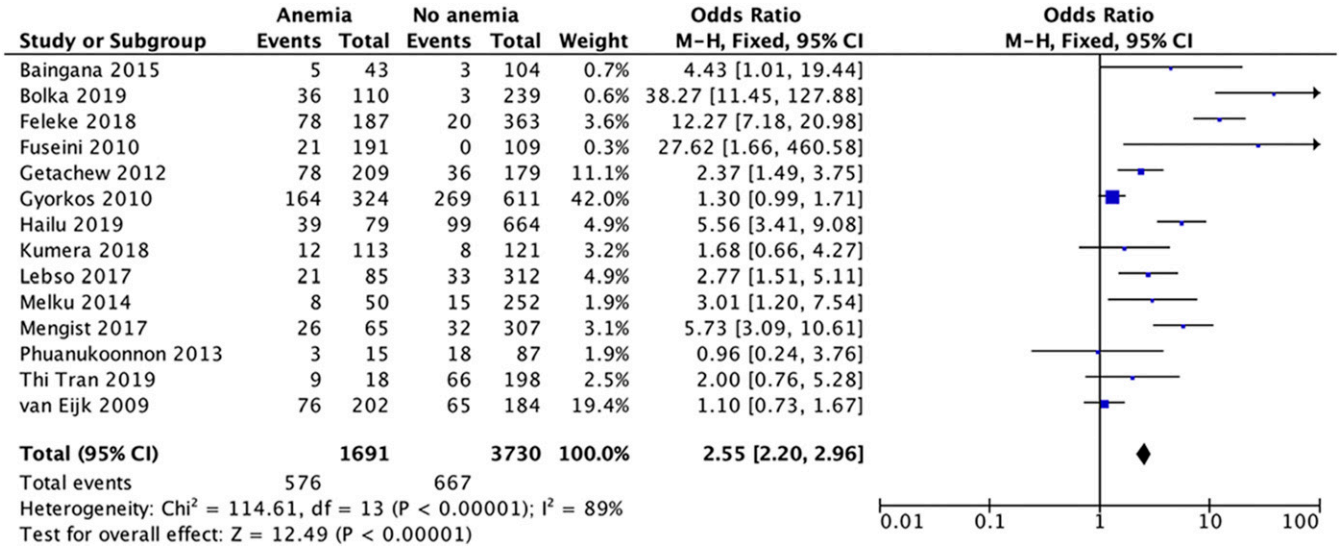

FIGURE 2. Forest plot of studies investigating maternal hookworm and anemia. This figure appears in color at www.ajtmh.org.

TABLE 3
Characteristics of studies investigating maternal hookworm and malaria coinfection

Study	Location	Study type	Population	Malaria prevalence (%)
Adegnika[35]	Gabon	Prospective cohort	340 pregnant women	25
Boel[37*]	Thai–Burmese border	Cross-sectional	829 pregnant women	27
Boel[37*]	Thai–Burmese border	Cross-sectional	829 pregnant women	20
Ekejindu[29]	Nigeria	Cross-sectional	100 pregnant women	81
Fairley[40]	Kenya	Cross-sectional	695 pregnant women	43
Fuseini[25]†	Ghana	Cross-sectional	300 pregnant women	58
Getachew[43]	Ethiopia	Cross-sectional	388 pregnant women	12
Hillier[46]	Uganda	Cross-sectional	2,507 pregnant women	11
Mahande[32]†	Tanzania	Cross-sectional	6,533 pregnant women	13
Ojurongbe[51]	Nigeria	Cross-sectional	200 pregnant women	30
Thigpen[54]	Malawi	Randomized control trial	848 pregnant women	38
Yatich[56]	Ghana	Cross-sectional	746 pregnant women	36

Prevalence data are rounded to the nearest percentile to allow for uniformity.
* This one study includes data from two cross-sectional analyses performed in 1996 and 2007.
† Studies were included both in anemia and malaria coinfection tables.

first antenatal care visit and lower gross motor scores and cognitive performance at 1 year of age.[68] Although most studies assessed did show an impact of maternal hookworm infection on other aspects of maternal and child health, more studies are required to critically assess the global association between hookworm infection during pregnancy and these maternal and child outcomes.

DISCUSSION

This systematic review and meta-analysis reviewed studies published between January 2008 and August 2019. The included studies were conducted after the WHO's 2002 recommendation to treat pregnant women with hookworm infection after the first trimester but before or at the time of publication of the more recent WHO guidelines for preventive chemotherapy in areas where hookworm prevalence is > 20% and anemia prevalence is > 40% among pregnant women.[11,12] These WHO recommendations were created with the goal to reduce worm burden as a means to reduce hookworm-induced morbidity, particularly in high-risk populations such as pregnant women. In the past 10 years, the prevalence of hookworm has decreased by 28.5% globally.[1] Despite this modest decline in prevalence among all at-risk individuals, the current study, conducted during the same time period, discovered persistent hookworm-associated morbidity in the form of maternal anemia and maternal coinfection with malaria. This persistence of hookworm-induced morbidity highlights the critical need to implement routine deworming in pregnant women after the first trimester in high-prevalent areas as outlined by the WHO. Since introducing protocols to implement preventive chemotherapy to pregnant women, it is estimated that only 10–23% of eligible pregnant women have received appropriate preventive therapy.[69,70] Importantly, a sub-analysis within the current study demonstrated detrimental effects of maternal hookworm infection on anemia in areas where the prevalence of hookworm is less than 20% (under the WHO cutoff), suggesting these areas would benefit from expanded recommendations. Administration of preventive chemotherapy in pregnant women improves maternal outcomes, including reductions in maternal morbidity and mortality due to anemia; neonatal morbidity, including infant birth weight; and HIV viral load in individuals coinfected with HIV.[58,71–75] Although inclusive of all helminths, it is estimated more than 600,000 DALYs are lost in girls and women of reproductive age because of STHs.[76] In addition to its recommendations in 2017 for pregnant women, the WHO recommended that deworming be available and accessible to nonpregnant girls and women of reproductive age in all endemic areas, and identified updating the global epidemiology, intensity, morbidity, and disease burden of helminths in this population as one of their research priorities.[77] This study builds on previous research showing the adverse effects of hookworm infection during pregnancy and provides an

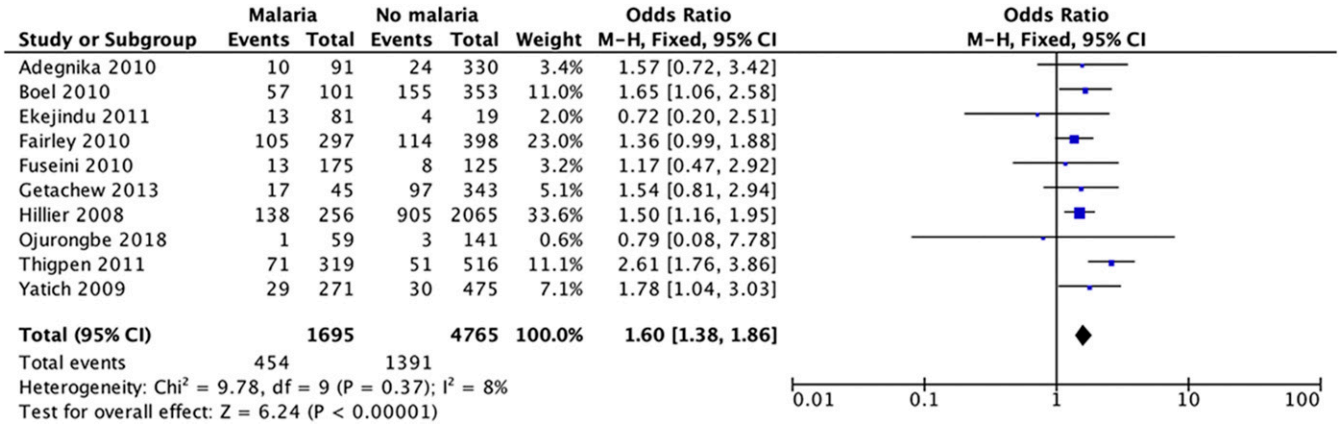

FIGURE 3. Forest plot of studies investigating maternal hookworm and malaria coinfection. This figure appears in color at www.ajtmh.org.

important reflection of currently used public health strategies to reduce hookworm-associated morbidity, specifically in the health of women of childbearing age.

A systematic review and meta-analysis conducted 10 years earlier (2008) showed a significant association between intensity of maternal hookworm infection and mean maternal Hb.[8] However, in comparison to the work of Brooker et al., the current study included articles with lower prevalence of hookworm infection, with 17 of the 32 included studies in areas having hookworm prevalence below 20%, than Brooker et al., which had only three of their 13 studies with prevalence below 20%. This is in agreement with general global modest declines in the prevalence of hookworm over the past 10 years observed in the most recent Global Burden of Disease Study,[1] as a result of poverty reduction measures under the auspices of Millennium Development Goals, implementation of preventive chemotherapy policies, or both. Despite these public health gains, the current meta-analysis builds on the results of the previous study by showing that maternal hookworm infection remains associated with maternal anemia. Furthermore, this study demonstrates endemic areas that do not meet the prevalence threshold of preventive chemotherapy administration in pregnant women implemented by the WHO remain at risk of anemia associated with hookworm. Maternal anemia has significant health impacts on the lives of the women and children including declines in health and even maternal deaths,[78] hypertensive disorders during pregnancy,[79] preterm birth,[80] low birth weight and preterm delivery,[81–83] increased risk of infant anemia,[84] and other poor pregnancy outcomes such as polyhydramnios and gestational diabetes.[83]

The current study showed a significant association between maternal hookworm infection and coinfection with malaria, which was not evaluated in the previous meta-analysis. Other studies, however, have revealed high levels of hookworm and malaria coinfections in Africa, often leading to synergies in terms of low Hb levels and anemia.[21,85,86] Coinfection of hookworm and malaria, which both lead to severe anemia particularly in pregnant women, has severe consequences on the health outcomes of women and children and, thus, requires further public health attention. This includes the opportunity for linking preventive chemotherapy for hookworm with malaria control programs, including intermittent preventive therapy during pregnancy, or for the development of multivalent vaccines that simultaneously target malaria and hookworm.[87,88]

An additional non-systematic review on maternal and infant effects of hookworm infection during pregnancy was summarized in this review. Despite exclusion from the systematic review and meta-analysis due to lack of sufficient studies, these studies are mentioned to emphasize the critical deficit in knowledge related to maternal hookworm infection and maternal and child outcomes. Two studies evaluated the association between HIV and hookworm but had conflicting results in regard to HIV viral load. However, despite the conflicting results regarding the impact of hookworm on viral load, both studies noted reduced CD4 counts in pregnant women with both HIV and hookworm infection. These data suggest coinfection of HIV with hookworm during pregnancy may place women at greater risk of poor immunologic recovering. Several studies also addressed the impact of maternal hookworm infection on infant vaccination response and, however, did not arrive at a clear consensus. Outcomes including infant developmental, maternal coinfection with HIV, and infant anemia as a result of hookworm infection during pregnancy are public health targets that require further investigation.

Although the systematic review search criteria generated a significant number of studies to perform the meta-analysis, several relevant studies which could have provided increased depth to the analysis were excluded because of lack of complete and/or detailed data sets. Attempts were made to contact the corresponding authors in these situations; however, the data were excluded if unable to obtain additional information. Although the reviewers were not blinded, this limitation was unlikely to lead to significant inclusion bias as two separate reviewers assessed each study independently. The analysis did not adjust for confounding variables because of the heterogeneity of both collected and reported variables of the included studies, which could affect the results of the meta-analysis. However, individual studies that were included did not show a significant decrease in association of exposure and outcome with these variables so was unlikely to substantially affect the outcome of the meta-analysis. This systematic review included articles that reported only hookworm infection or lack of infection, instead of intensity of infection, which has been shown to impact the likelihood of anemia. Including studies which identified intensity of infection instead of the presence of infection would have likely impacted the meta-analysis results. However, only two studies investigating maternal anemia also reported intensity of hookworm infection in relation to anemia,[32,44] although they had differing definitions of anemia (Hb < 11 versus Hb < 8), so the studies were not able to be combined for a meta-analysis. In alignment with the previously published Booker et al. meta-analysis from 2008, both studies showed increasing crude and adjusted odds ratios for anemia with increasing intensity of hookworm infection.

Hookworm infection in pregnant women remains an important global health issue associated with maternal anemia and concurrent parasitic infections, such as malaria. Despite increased recognition of this global health issue, hookworm infection, coinfection with malaria, and subsequent anemia persist. Now supported by the WHO, the need for preventive chemotherapy in women of childbearing age and pregnant women needs to be implemented to at-risk populations rapidly. However, the process of reaching at-risk women remains stunted, with still only 10–20% of at-risk pregnant women receiving preventive chemotherapy at this time. Alternative approaches to this global health threat include utilization of a new human hookworm vaccine under development either alone or jointly administered with a new malaria vaccine, which might lead to significant benefit specifically for pregnant women.[89] Further investigation on maternal–child outcomes of hookworm infection during pregnancy is warranted specifically focusing on areas with minimal research including infant growth and development and long-term morbidity in women. This study highlights important knowledge gaps in the understanding of hookworm infection during pregnancy and provides important directions for further scientific investigations.

Received May 18, 2020. Accepted for publication June 23, 2020.

Published online August 24, 2020.

Note: Supplemental figures appear at www.ajtmh.org.

Acknowledgments: We thank Roger Soll, Gautham Suresh, and Mohan Pammi, at Texas Children's Hospital who provided a workshop on performing systematic reviews and provided guidance during the

production of this manuscript. We would also like to thank Patricia E. Bryan at Texas Children's Hospital who assisted in data management.

Disclosure: P. H. is a patent holder and lead investigator on vaccines against hookworm both in clinical trials and in development.

Authors' addresses: Tara E. Ness, Vedika Agrawal, Kathryn Bedard, and Jill E. Weatherhead, Department of Pediatrics, Baylor College of Medicine, Houston, TX, E-mails: tara.ness@bcm.edu, vedika.agrawal@bcm.edu, kathryn.bedard@bcm.edu, and weatherh@bcm.edu. Lara Ouellette, Texas Medical Center Library, Liaison, Houston, TX, E-mail: lara.ouellette@library.tmc.edu. Timothy A. Erickson, Department of Pediatrics, Baylor College of Medicine, Section of Pediatric Tropical Medicine, Houston, TX, E-mail: timothy.erickson@bcm.edu. Peter Hotez, Department of Pediatrics, Baylor College of Medicine, Houston, TX, and Department of Pediatrics, Texas Children's Hospital, Houston, TX, E-mail: hotez@bcm.edu.

REFERENCES

1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet 392:* 1789–1858.
2. Bartsch SM, Hotez PJ, Asti L, Zapf KM, Bottazzi ME, Diemert DJ, Lee BY, 2016. The global economic and health burden of human hookworm infection. *PLoS Negl Trop Dis 10:* e0004922.
3. Centers for Disease Control and Prevention, 2013. *Parasites-Hookworm*. Available at: https://www.cdc.gov/parasites/hookworm/gen_info/faqs.html. Accessed September 10, 2019.
4. Majid MF, Kang SJ, Hotez PJ, 2019. Resolving "worm wars": an extended comparison review of findings from key economics and epidemiological studies. *PLoS Negl Trop Dis 13:* e0006940.
5. Lenk EJ, Redekop WK, Luyendijk M, Rijnsburger AJ, Severens JL, 2016. Productivity loss related to neglected tropical diseases eligible for preventive chemotherapy: a systematic literature review. *PLoS Negl Trop Dis 10:* e0004397.
6. Hotez P, 2008. Hookworm and poverty. *Ann N Y Acad Sci 1136:* 38–44.
7. Hotez PJ, 2018. Empowering girls and women through hookworm prevention. *Am J Trop Med Hyg 98:* 1211–1212.
8. Brooker S, Hotez PJ, Bundy DA, 2008. Hookworm-related anaemia among pregnant women: a systematic review. *PLoS Negl Trop Dis 2:* e291.
9. World Health Organization, 2002. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. *Report of a WHO Expert Committee*. WHO Technical Report Series 912. Geneva, Switzerland: World Health Organization.
10. Gyorkos TW, St-Denis K, 2019. Systematic review of exposure to albendazole or mebendazole during pregnancy and effects on maternal and child outcomes, with particular reference to exposure in the first trimester. *Int J Parasitol 49:* 541–554.
11. World Health Organization, 2017. *Preventive Chemotherapy to Control Soil-Transmitted Helminth Infections in at-Risk Population Groups*. Available at: http://www.who.int/elena/titles/full_recommendations/deworming/en/. Accessed September 10, 2019.
12. World Health Organization, 2016. *WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience*. Available at: https://www.who.int/reproductivehealth/publications/maternal_perinatal_health/anc-positive-pregnancy-experience/en/. Accessed September 10, 2019.
13. Downes MJ, Brennan ML, Williams HC, Dean RS, 2016. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open 6:* e011458.
14. Ababiya T, Gabriel T, 2014. Prevalence of anemia among pregnant women in Ethiopia and its management: a review. *Int Res J Pharm 5:* 737–750.
15. Adegnika AA, Kremsner PG, 2012. Epidemiology of malaria and helminth interaction: a review from 2001 to 2011. *Curr Opin HIV AIDS 7:* 221–224.
16. Blackwell AD, 2016. Helminth infection during pregnancy: insights from evolutionary ecology. *Int J Womens Health 8:* 651–661.
17. Campbell SJ, Nery SV, Doi SA, Gray DJ, Soares Magalhães RJ, McCarthy JS, Traub RJ, Andrews RM, Clements ACA, 2016. Complexities and perplexities: a critical appraisal of the evidence for soil-transmitted helminth infection-related morbidity. *PLoS Negl Trop Dis 10:* e0004566.
18. Haider BA, Humayun Q, Bhutta ZA, 2009. Effect of administration of antihelminthics for soil transmitted helminths during pregnancy. *Cochrane Database Syst Rev 2:* CD005547.
19. Imhoff-Kunsch B, Briggs V, 2012. Antihelminthics in pregnancy and maternal, newborn and child health. *Paediatr Perinat Epidemiol 26 (Suppl 1):* 223–238.
20. Khambalia AZ, Aimone AM, Zlotkin SH, 2011. Burden of anemia among indigenous populations. *Nutr Rev 69:* 693–719.
21. Naing C, Whittaker MA, Nyunt-Wai V, Reid SA, Wong SF, Mak JW, Tanner M, 2013. Malaria and soil-transmitted intestinal helminth co-infection and its effect on anemia: a meta-analysis. *Trans R Soc Trop Med Hyg 107:* 672–683.
22. Roberts T, Gravett CA, Velu PP, Theodoratou E, Wagner TA, Zhang JSF, Campbell H, Rubens CE, Gravett MG, Rudan I, 2011. Epidemiology and aetiology of maternal parasitic infections in low- and middle-income countries. *J Glob Health 1:* 189–200.
23. Salam RA, Haider BA, Humayun Q, Bhutta ZA, 2015. Effect of administration of antihelminthics for soil-transmitted helminths during pregnancy. *Cochrane Database Syst Rev 6:* CD005547.
24. Thayer WM, Clermont A, Walker N, 2017. Effects of deworming on maternal and child health: a literature review and meta-analysis for the lives saved tool. *Am J Trop Med Hyg 97:* 470.
25. Fuseini G, Edohsup D, Kalifasup BG, Hamidsup AW, Knight D, 2010. Parasitic infections and anaemia during pregnancy in the Kassena-Nankana district of Northern Ghana. *J Public Health Epidemiol 2:* 48–52.
26. Mutuku FM, Malhotra I, LaBeaud AD, Muinde J, Mzungu E, Mungai PL, Mukoko D, King CL, King CH, 2014. Marked changes in maternal parasitic infections in Kwale county (2006–2014). *Am J Trop Med Hyg 91:* 329.
27. Agu PU, Ogboi JS, Akpoigbe K, Okeke T, Ezugwu E, 2013. Impact of Plasmodium falciparum and hookworm infections on the frequency of anaemia in pregnant women of rural communities in Enugu, South East Nigeria. *Pan Afr Med J 14:* 27.
28. Aikawa R, Jimba M, Nguen KC, Binns CW, 2008. Prenatal iron supplementation in rural Vietnam. *Eur J Clin Nutr 62:* 946–952.
29. Ebuy Y, Alemayehu M, Mitiku M, Goba GK, 2017. Determinants of severe anemia among laboring mothers in Mekelle city public hospitals, Tigray region, Ethiopia. *PLoS One 12:* e0186724.
30. Lindström E, Hossain MB, Lönnerdal BO, Raqib R, El Arifeen S, Ekström EC, 2011. Prevalence of anemia and micronutrient deficiencies in early pregnancy in rural Bangladesh, the MINIMat trial. *Acta Obstet Gynecol Scand 90:* 47–56.
31. Mahande AM, Mahande MJ, 2016. Prevalence of parasitic infections and associations with pregnancy complications and outcomes in northern Tanzania: a registry-based cross-sectional study. *BMC Infect Dis 16:* 78.
32. Makhoul Z, Taren D, Duncan B, Pandey P, Thomson C, Winzerling J, Muramoto M, Shrestha R, 2012. Risk factors associated with anemia, iron deficiency and iron deficiency anemia in rural Nepali pregnant women. *Southeast Asian J Trop Med Public Health 43:* 735–746.
33. Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P, 2008. Malaria and hookworm infections in relation to haemoglobin and serum ferritin levels in pregnancy in Masindi district, western Uganda. *Trans R Soc Trop Med Hyg 102:* 130–136.
34. Tay SC, Nani EA, Walana W, 2017. Parasitic infections and maternal anaemia among expectant mothers in the Dangme East District of Ghana. *BMC Res Notes 10:* 3.
35. Adegnika AA, Ramharter M, Agnandji ST, Ateba Ngoa U, Issifou S, Yazdanbahksh M, Kremsner PG, 2010. Epidemiology of parasitic co-infections during pregnancy in Lambaréné. *Gabon Trop Med Int Health 15:* 1204–1209.
36. Baingana RK, Enyaru JK, Tjalsma H, Swinkels DW, Davidsson L, 2015. The aetiology of anaemia during pregnancy: a study to evaluate the contribution of iron deficiency and common

infections in pregnant Ugandan women. *Public Health Nutr 18:* 1423–1435.
37. Boel M et al., 2010. Complex interactions between soil-transmitted helminths and malaria in pregnant women on the Thai-Burmese border. *PLoS Negl Trop Dis 4:* e887.
38. Bolka A, Gebremedhin S, 2019. Prevalence of intestinal parasitic infection and its association with anemia among pregnant women in Wondo Genet district, Southern Ethiopia: a cross-sectional study. *BMC Infect Dis 19:* 483.
39. Ekejindu IM, Okeke EK, Akah B, Okpala E, Ezeagwuna DA, Onwurah O, 2011. Malaria and hookworm co-infection among pregnant and non-pregnant women in a semi-urban area in Anambra State, Nigeria. *World J Med Sci 6:* 33–35.
40. Fairley JK, Malhotra I, Mungai P, Muchiri E, King CL, King CH, 2010. The effects of maternal helminth infection and co-infection with malaria on birthweight and subsequent growth in offspring in a population on the coast of Kenya. *Am J Trop Med Hyg 83:* 147.
41. Feleke BE, Feleke TE, 2018. Pregnant mothers are more anemic than lactating mothers, a comparative cross-sectional study, Bahir Dar, Ethiopia. *BMC Hematol 18:* 2.
42. Getachew M, Yewhalaw D, Tafess K, Getachew Y, Zeynudin A, 2012. Anaemia and associated risk factors among pregnant women in Gilgel Gibe dam area, Southwest Ethiopia. *Parasit Vectors 5:* 296.
43. Getachew M, Tafess K, Zeynudin A, Yewhalaw D, 2013. Prevalence soil transmitted helminthiasis and malaria co-infection among pregnant women and risk factors in Gilgel Gibe dam Area, Southwest Ethiopia. *BMC Res Notes 6:* 263.
44. Gyorkos TW, Gilbert NL, Larocque R, Casapia M, 2010. Hookworm and *Trichuris* infections associated with anemia during pregnancy. *Am J Trop Med Hyg 83:* 354–355.
45. Hailu T, Kassa S, Abera B, Mulu W, Genanew A, 2019. Determinant factors of anaemia among pregnant women attending antenatal care clinic in Northwest Ethiopia. *Trop Dis Travel Med Vaccines 5:* 13.
46. Hillier SD et al., 2008. *Plasmodium falciparum* and helminth coinfection in a semiurban population of pregnant women in Uganda. *J Infect Dis 198:* 920–927.
47. Kumera G, Haile K, Abebe N, Marie T, Eshete T, 2018. Anemia and its association with coffee consumption and hookworm infection among pregnant women attending antenatal care at Debre Markos Referral Hospital, Northwest Ethiopia. *PLoS One 13:* e0206880.
48. Lebso M, Anato A, Loha E, 2017. Prevalence of anemia and associated factors among pregnant women in Southern Ethiopia: a community based cross-sectional study. *PLoS One 12:* e0188783.
49. Melku M, Addis Z, Alem M, Enawgaw B, 2014. Prevalence and predictors of maternal anemia during pregnancy in Gondar, Northwest Ethiopia: an institutional based cross-sectional study. *Anemia 2014:* 108593.
50. Mengist HM, Zewdie O, Belew A, 2017. Intestinal helminthic infection and anemia among pregnant women attending antenatal care (ANC) in East Wollega, Oromia, Ethiopia. *BMC Res Notes 10:* 440.
51. Ojurongbe O, Okorie PN, Opatokun RL, Ojurongbe TA, Mabayoje VO, Olowe OA, Adeyeba OA, 2018. Prevalence and associated factors of *Plasmodium falciparum* and soil transmitted helminth infections among pregnant women in Osun state, Nigeria. *Afr Health Sci 18:* 542–551.
52. Phuanukoonnon S, Michael A, Kirarock WS, Pomat WS, van den Biggelaar AH, 2013. Intestinal parasitic infections and anaemia among pregnant women in the highlands of Papua New Guinea. *Papua New Guinea Med J 56:* 119–125.
53. Thi Tran KA, Cao B-L, Que A-T, LE T-A, 2019. Soil-transmitted helminth infection and its association with anemia and zinc deficiency among women in Nghe An Province, Vietnam. *Iranian J Parasitol 14:* 180–182.
54. Thigpen MC, Filler SJ, Kazembe PN, Parise ME, Macheso A, Campbell CH, Newman RD, Steketee RW, Hamel M, 2011. Associations between peripheral *Plasmodium falciparum* malaria parasitemia, human immunodeficiency virus, and concurrent helminthic infection among pregnant women in Malawi. *Am J Trop Med Hyg 84:* 379–385.
55. Van Eijk AM, Lindblade KA, Odhiambo F, Peterson E, Rosen DH, Karanja D, Ayisi JG, Shi YP, Adazu K, Slutsker L, 2009. Geohelminth infections among pregnant women in rural western Kenya; a cross-sectional study. *PLoS Negl Trop Dis 3:* e370.
56. Yatich NJ et al., 2009. Malaria and intestinal helminth co-infection among pregnant women in Ghana: prevalence and risk factors. *Am J Trop Med Hyg 80:* 896–901.
57. Woodburn PW, Muhangi L, Hillier S, Ndibazza J, Namujju PB, Kizza M, Ameke C, Omoding NE, Booth M, Elliott AM, 2009. Risk factors for helminth, malaria, and HIV infection in pregnancy in Entebbe, Uganda. *PLoS Negl Trop Dis 3:* e473.
58. Webb EL, Kyosiimire-Lugemwa J, Kizito D, Nkurunziza P, Lule S, Muhangi L, Muwanga M, Kaleebu P, Elliott AM, 2012. The effect of anthelminthic treatment during pregnancy on HIV plasma viral load; results from a randomised, double blinded, placebo-controlled trial in Uganda. *J Acquir Immune Defici Syndr 60:* 307–313.
59. González-Fernández D, del Carmen Pons E, Rueda D, Sinisterra OT, Murillo E, Scott ME, Koski KG, 2017. C-reactive protein is differentially modulated by co-existing infections, vitamin deficiencies and maternal factors in pregnant and lactating indigenous Panamanian women. *Infect Dis Poverty 6:* 94.
60. Loukas A, Prociv P, 2001. Immune responses in hookworm infections. *Clin Microbiol Rev 14:* 689–703.
61. Nash S, Mentzer AJ, Lule SA, Kizito D, Smits G, van der Klis FR, Elliott AM, 2017. The impact of prenatal exposure to parasitic infections and to anthelminthic treatment on antibody responses to routine immunisations given in infancy: secondary analysis of a randomised controlled trial. *PLoS Negl Trop Dis 11:* e0005213.
62. Malhotra I, McKibben M, Mungai P, McKibben E, Wang X, Sutherland LJ, Muchiri EM, King CH, King CL, LaBeaud AD, 2015. Effect of antenatal parasitic infections on anti-vaccine IgG levels in children: a prospective birth cohort study in Kenya. *PLoS Negl Trop Dis 9:* e0003466.
63. Kizito D, Tweyongyere R, Namatovu A, Webb EL, Muhangi L, Lule SA, Bukenya H, Cose S, Elliott AM, 2013. Factors affecting the infant antibody response to measles immunisation in Entebbe-Uganda. *BMC Public Health 13:* 619.
64. Elliott AM et al., 2010. Effects of maternal and infant co-infections, and of maternal immunisation, on the infant response to BCG and tetanus immunisation. *Vaccine 29:* 247–255.
65. Yatich NJ et al., 2010. The effect of malaria and intestinal helminth coinfection on birth outcomes in Kumasi, Ghana. *Am J Trop Med Hyg 82:* 28–34.
66. Fairley JK, Bisanzio D, King CH, Kitron U, Mungai P, Muchiri E, King CL, Malhotra I, 2013. Birthweight in offspring of mothers with high prevalence of helminth and malaria infection in coastal Kenya. *Am J Trop Med Hyg 88:* 48–53. Erratum in: Am J Trop Med Hyg 2014;91(6): 1284.
67. McClure EM, Meshnick SR, Mungai P, Malhotra I, King CL, Goldenberg RL, Hudgens MG, Siega-Riz AM, Dent AE, 2014. The association of parasitic infections in pregnancy and maternal and fetal anemia: a cohort study in coastal Kenya. *PLoS Negl Trop Dis 8:* e2724.
68. Mireku MO, Boivin MJ, Davidson LL, Ouédraogo S, Koura GK, Alao MJ, Massougbodji A, Cot M, Bodeau-Livinec F, 2015. Impact of helminth infection during pregnancy on cognitive and motor functions of one-year-old children. *PLoS Negl Trop Dis 9:* e0003463.
69. Mupfasoni D, Mikhailov A, Mbabazi P, King J, Gyorkos TW, Montresor A, 2018. Estimation of the number of women of reproductive age in need of preventive chemotherapy for soil-transmitted helminth infections. *PLoS Negl Trop Dis 12:* e0006269.
70. Bangert M, Bancalari P, Mupfasoni D, Mikhailov A, Gabrielli AF, Montresor A, 2019. Provision of deworming intervention to pregnant women by antenatal services in countries endemic for soil-transmitted helminthiasis. *PLoS Negl Trop Dis 13:* e0007406.
71. Ivan E, Crowther NJ, Mutimura E, Rucogoza A, Janssen S, Njunwa KK, Grobusch MP, 2014. Effect of deworming on disease progression markers in HIV-1–Infected pregnant women on antiretroviral therapy: a longitudinal observational study from Rwanda. *Clin Infect Dis 60:* 135–142.

72. Larocque R, Casapia M, Gotuzzo E, MacLean JD, Soto JC, Rahme E, Gyorkos TW, 2006. A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. *Trop Med Int Health 11:* 1485–1495.
73. Torlesse H, Hodges M, 2001. Albendazole therapy and reduced decline in haemoglobin concentration during pregnancy (Sierra Leone). *Trans R Soc Trop Med Hyg 95:* 195–201.
74. Urassa DP, Nystrom L, Carlsted A, 2011. Effectiveness of routine antihelminthic treatment on anaemia in pregnancy in Rufiji District, Tanzania: a cluster randomised controlled trial. *East Afr J Public Health 8:* 176–184.
75. Christian P, Khatry SK, West KP, Jr., 2004. Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal. *Lancet 364:* 981–983.
76. Montresor A, Trouleau W, Mupfasoni D, Bangert M, Joseph SA, Mikhailov A, Fitzpatrick C, 2017. Preventive chemotherapy to control soil-transmitted helminthiasis averted more than 500 000 DALYs in 2015. *Trans R Soc Trop Med Hyg 111:* 457–463.
77. World Health Organization, 2018. *Reaching Girls and Women of Reproductive Age with Deworming: Report of the Advisory Group on Deworming in Girls and Women of Reproductive Age*, Bellagio, Italy: Rockefeller Foundation Bellagio Center, WHO.
78. Parks S, 2019. Maternal anaemia and maternal, fetal, and neonatal outcomes in a prospective cohort study in India and Pakistan. *BJOG 126:* 737–743.
79. Chen C, Grewal J, Betran AP, Vogel JP, Souza JP, Zhang J, 2018. Severe anemia, sickle cell disease, and thalassemia as risk factors for hypertensive disorders in pregnancy in developing countries. *Pregnancy Hypertens 13:* 141–147.
80. Xiong X, Buekens P, Alexander S, Demianczuk N, Wollast E, 2000. Anemia during pregnancy and birth outcome: a meta-analysis. *Am J Perinatol 17:* 137–146.
81. Allen LH, 2000. Anemia and iron deficiency: effects on pregnancy outcome. *Am J Clin Nutr 71 (Suppl 5):* 1280S–1284S.
82. Rasmussen S, Øian P, 1993. First-and second-trimester hemoglobin levels: relation to birth weight and gestational age. *Acta obstetricia gynecologica Scand 72:* 246–251.
83. Lin L, Wei Y, Zhu W, Wang C, Su R, Feng H, Yang H, Gestational Diabetes Mellitus Prevalence Survey (GPS) Study Group, 2018. Prevalence, risk factors and associated adverse pregnancy outcomes of anaemia in Chinese pregnant women: a multicentre retrospective study. *BMC Pregnancy Childbirth 18:* 111.
84. Colomer J, Colomer C, Gutierrez D, 1990. Anaemia during pregnancy as a risk factor for infant iron deficiency: report from the Valencia Infant Anaemia Cohort (VIAC) study. *Paediatr Perinat Epidemiol 4:* 196–204.
85. Brooker S, Akhwale W, Pullan R, Estambale B, Clarke SE, Snow RW, Hotez PJ, 2007. Epidemiology of plasmodium-helminth co-infection in Africa: populations at risk, potential impact on anemia, and prospects for combining control. *A J Trop Med Hyg 77 (Suppl 6):* 88–98.
86. Brooker S, Clements AC, Hotez PJ, Hay SI, Tatem AJ, Bundy DA, Snow RW, 2006. The co-distribution of *Plasmodium falciparum* and hookworm among African schoolchildren. *Malar J 5:* 99.
87. Hotez PJ, Molyneux DH, 2008. Tropical anemia: one of Africa's great killers and a rationale for linking malaria and neglected tropical disease control to achieve a common goal. *PLoS Negl Trop Dis 2:* e270.
88. Hotez PJ, Strych U, Bottazzi ME, 2019. Neglected parasitic infections and the syndemic anemia vaccines for Africa. Bets UAK, ed. *Curious 2018: Future Insights in Science and Technology*. Cham, Switzerland: Springer, 75–85.
89. Bartsch SM, Hotez PJ, Hertenstein DL, Diemert DJ, Zapf KM, Bottazzi ME, Bethony JM, Brown ST, Lee BY, 2016. Modeling the economic and epidemiologic impact of hookworm vaccine and mass drug administration (MDA) in Brazil, a high transmission setting. *Vaccine 34:* 2197–2206.