MASS DEWORMING FOR SOIL-TRANSMITTED HELMINTHS AND SCHISTOSOMIASIS AMONG PREGNANT WOMEN: A SYSTEMATIC REVIEW AND INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

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Thesis Abstract

Background

Soil transmitted helminthiasis (STH) and schistosomiasis during pregnancy can cause active and debilitating disease with adverse birth outcomes. A recent estimation suggests that approximately 688 million girls and women of reproductive age (WRA) are at risk of helminth infections; including 140 million pregnant and lactating women and another 108 million adolescent girls. Mass deworming is regarded as the most effective means of controlling morbidity and mortality with STH and schistosomiasis; however there are various factors that could potentially modify its effectiveness including baseline nutritional status, worm burden and concomitant interventions. Currently, it is difficult to establish whether mass deworming during pregnancy has beneficial effects under certain conditions and limited effects under others.

Objectives

1. To conduct a systematic review and meta-analysis on the impact of deworming during pregnancy.

2. To conduct a systematic review and meta-analysis on the impact of interventions other than deworming; including water, sanitation and hygiene (WASH) interventions.

3. To conduct an individual participants data (IPD) meta-analysis to identify the factors that explain variation in the effect estimates of mass deworming.

4. To discuss the current guidelines on mass deworming, the challenges and the economic perspective of mass deworming for WRA.

Methods

To achieve the aforementioned objectives, following methodology was adopted:

1. A systematic review and meta-analysis evaluating the effectiveness of mass deworming during pregnancy.
2. A systematic review and meta-analysis evaluating the effectiveness of WASH interventions during pregnancy.
3. An IPD meta-analysis to explore whether the effect of mass deworming during pregnancy varies with individual characteristics, intensity of infection, socioeconomic status, sanitation environment and co-interventions.

Results

1. Findings from the systematic review assessing mass deworming during pregnancy suggest that it does not have any impact on maternal anaemia; however it significantly reduced the prevalence of STH and schistosomiasis. There was no impact of mass deworming during pregnancy on haemoglobin, birth weight, low birth weight (LBW), preterm birth, perinatal mortality, stillbirths, neonatal mortality and congenital abnormalities.
2. Findings from the systematic review on interventions other than mass deworming among pregnant women and WRA suggest that the data are too scarce and of low quality to inform best practice.
3. The IPD component of the thesis captured majority of the existing data (70% of the total potential participant population).
4. Findings from the IPD analysis suggest that mass deworming during pregnancy is associated with reducing anaemia with no apparent impact on infection intensity, LBW and preterm birth. These analyses were limited by the availability of data for the impact by subgroups and effect modification. Further studies accounting for maternal baseline worm intensities, concomitant iron/folic acid supplementation and antenatal care coverage could change these findings.

Conclusion

Mass deworming remains the recommended strategy to prevent and treat STH and schistosomiasis; however deworming alone is insufficient to achieve improvements in all maternal and newborn health outcomes. It is essential to address other factors such as poor sanitation, food insecurity and malnutrition. There is a need to support and promote open data policy for future IPDs to test new hypothesis.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Chapter 1: Literature Review and Conceptual Framework

Epidemiology of Soil Transmitted Helminthiasis

The term 'helminth' means parasitic worms and soil transmitted helminthiasis (STH) are a group of diseases caused by infection with four intestinal parasites: *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whip worm), *Necator americanus* (hookworm) and *Ancylostoma duodenale* (hookworm) (WHO, 2015). STH is transmitted through the eggs present in the faeces of an infected person which contaminate the soil in areas with poor water and sanitation facilities. Eggs of *Ascaris* and *Trichuris* mature in soil and infect other people when ingested through contaminated hands or food while the larvae of hookworms penetrate the skin of the person walking barefoot on contaminated soil.

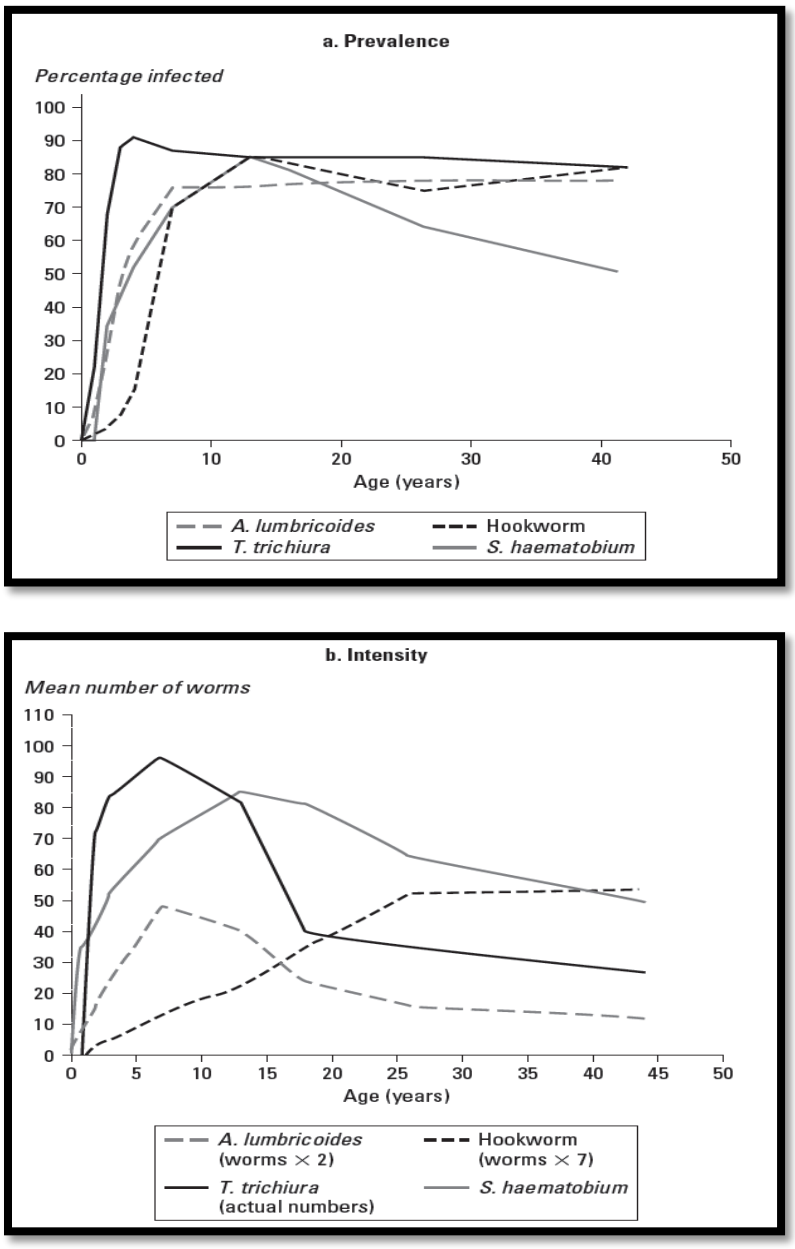
Around 25% of the world's population (roughly about 1.5 billion people) is infected with one or more of STH with a disproportionately higher burden in low- and middle- income countries (LMICs) (Chan, Medley, Jamison, & Bundy, 1994). An estimated 438.9 million people were infected with hookworm in 2010; 819 million with roundworms and 464.6 million with whipworm. STH altogether, contributed to a total of 4.98 million years lived with disability (YLDs) (Pullan, Smith, Jasrasaria, & Brooker, 2014). Of these YLDs, 65% were attributable to hookworm, 22% to roundworm and the remaining 13% to whipworm. In terms of geographical distribution, around 67% of STH occurred in Asia contributing to 68% of the YLDs (Pullan et al., 2014). Even within LMICs, the disease disproportionally affects the most marginalised population groups and appears to be predominantly affecting the poorest populations with lack of clean water, hygiene and sanitation facilities (Pullan, Smith, Jasrasaria, & Brooker, 2014; WHO 2019). Over 267 million preschool-age children and 568 million school-age children live in STH endemic areas and an estimated 4 million pregnancies a year are complicated by maternal hookworm infection alone (D. Bundy, Chan, & Savioli, 1995; WHO, 2005). An age related pattern is observed for the prevalence and intensity of STH and schistosomiasis (Figure 1.1). Roundworm and whipworm reaches maximum prevalence (prevalence of a parasite species is defined as the percentage of hosts infected by that species) before five years of age, while maximum prevalence of hookworm and schistosome infections is usually attained in adolescence or in early adulthood. High intensity (intensity of the infection is defined as the mean number of parasite eggs, oocysts or larvae per infected host) infestation with round worm and whip worm are common among children aged 5 to 10 years, while hookworm infections reaches maximum intensity from 20 to 25 years of age (Bethony et al., 2006; Hotez & Cerami, 1983; Hotez et al., 2006).

Epidemiology of Schistosomiasis

Schistosomiasis is also a parasitic disease caused by blood flukes of the genus *Schistosoma*. Six species of schistosomes are responsible for infection in humans: *Schistosoma mansoni*, *S.haematobium, S. japonicum, S. intercalatum, S. guineensis and S. mekongi; S. haematobium* and *S. mansoni* are predominant causes of disease (WHO, 2015). When infected persons' faeces containing parasite eggs are released in fresh water, these eggs hatch and the subsequent larvae infect susceptible snail hosts. Parasites undergo asexual multiplication in snails and release another larval stage into water. These larvae penetrate the skin during contact with infested water and infect the human host during domestic, occupational and recreational contact with water.

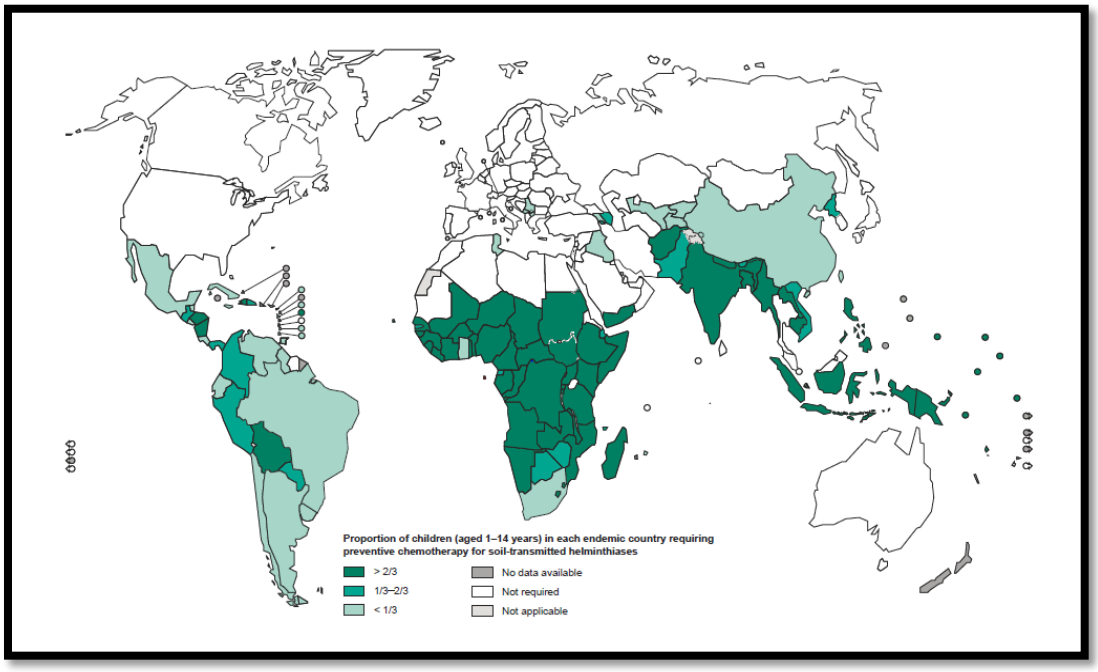
The distribution of schistosomiasis is focal, since transmission depends on specific snail hosts and human activities and the endemicity changes with the environment, water development schemes, migration, control interventions and snail host distribution. An estimated 249 million people required preventive chemotherapy for schistosomiasis in 2012, 93% of them in sub-Saharan Africa (WHO, 2015). Figure 1.2 and Figure 1.3 depicts the worldwide distribution of STH and schistosomiasis respectively.

Figure 1.1: Age-associated prevalence and intensity (faecal egg count) profiles of STH and Schistosomiasis infections



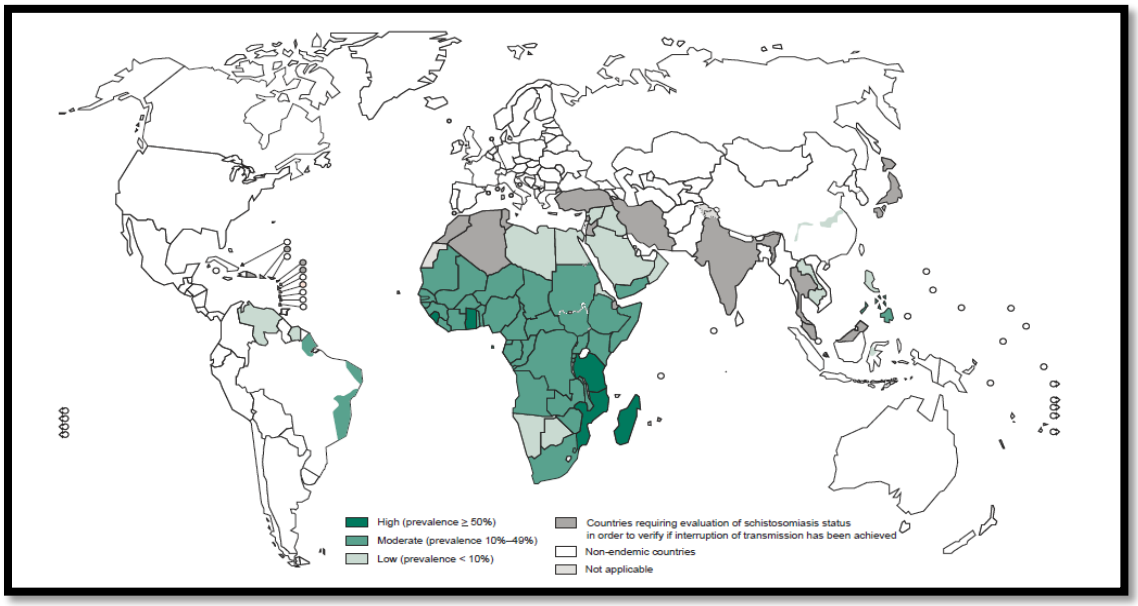
Source: Hotez, P.J., et al., Helminth infections: soil-transmitted helminth infections and schistosomiasis. 2 ed. Disease Control Priorities in Developing Countries. 2006, Washington: World Bank

Figure 1.2: Worldwide distribution of STH



Source: World Health Organization. Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected diseases 2015. World Health Organization, 2015

Figure 1.3: Worldwide distribution of Schistosomiasis



Source: World Health Organization. Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected diseases 2015. World Health Organization, 2015

Why is it a Public Health Concern?

STH and schistosomiasis are a major public health concern since these parasites feed on blood and hence contribute to anaemia (P. Hotez & Cerami, 1983; Torlesse & Hodges, 2000). Anaemia is one of the most common side effects of infection with STH or schistosomes, due to blood loss in the intestine or urinary tract. STH may also lead to haemorrhage by releasing anticoagulant compounds, thereby leading to iron-deficiency anaemia. Although iron-deficiency anaemia is multifactorial, hookworm infection is an important contributory factor in endemic areas, especially among women of reproductive age (WRA). An analysis on anaemia epidemiology based on data from the Global Burden of Diseases, Injuries and Risk Factors (GBD) 2010 Study suggested that hookworm and schistosomiasis were among the top ten causes of anaemia among females in 2010 (Kassebaum et al., 2014). It is the leading cause of pathological blood loss in tropical and subtropical regions (Pawlowski, Schad, & Stott, 1991). Additionally, STH and schistosomiasis often occur with co-infections in areas where malnutrition is already prevalent (Martin, Blackwell, Gurven, & Kaplan, 2013).

Infection during pregnancy leads to an added demand for nutrients that are critical for fetal growth and development (Abrams & Miller, 2011; Blackwell, Snodgrass, Madimenos, & Sugiyama, 2010). Hookworms, in particular, along with other STH and *schistosomes,* have been associated with reductions in haemoglobin and iron deficiency during pregnancy (Gyorkos, Gilbert, Larocque, & Casapía, 2011; Larocque, Casapia, Gotuzzo, & Gyorkos, 2005; Muhangi et al., 2007; Ndyomugyenyi, Kabatereine, Olsen, & Magnussen, 2008q; Nurdia, Sumarni, Hakim, & Winkvist, 2001). Schistosomiasis could also lead to hepatic fibrosis and the associated increased risk of oesophageal varices among pregnant women at approximately the same rates as non-pregnant individuals. Women in LMICs are especially prone to these infections and their consequences since they may be pregnant or lactating for as much as half of their reproductive lives ("Report of the WHO informal consultation on hookworm infection and anaemia in girls and women," 1994). Estimates indicate that over 50% of the pregnant women residing in LMICs have iron-deficiency anaemia (Mason, 2000; WHO, 1997). There is a direct association between the intensity of STH infection, blood loss and consequent anaemia, especially for hookworms (Bundy et al., 1995; Chan et al., 1994; Larocque et al., 2005). The association between anaemia during pregnancy and adverse pregnancy outcomes, including low birth weight (LBW), preterm birth, perinatal mortality and infant survival have already been documented (Rahman et al., 2016; Sifakis & Pharmakides, 2000). Furthermore, the chances of favourable pregnancy outcomes are reduced by 30% to 45% in anaemic mothers, with their infants having less than one half of normal iron reserves (Rahman et al., 2016).

'Deworming': The Treatment as per the Existing Guidelines

Mass deworming (also called preventive chemotherapy, is the process of treating large numbers of people in areas with a high prevalence of these conditions) along with the water, sanitation and hygiene (WASH) interventions are generally accepted as effective measures to prevent and treat STH and Schistosomiasis (WHO, 2017). The World Health Organization (WHO) recommends mass deworming for STH and Schistosomiasis depending on prevalence of worm infection. Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for pregnant women, after the first trimester, living in areas where both:

(i) the baseline prevalence of hookworm and/or *T. trichiura* infection is 20% or higher among pregnant women, and

(ii) anaemia is a severe public health problem, with a prevalence of 40% or higher among pregnant women, in order to reduce the worm burden of hookworm and *T. trichiura* infection (WHO, 2017).

For schistosomiasis, annual treatment with praziquantel in high risk communities (>50%) and once every two years in medium risk (>10% and <50%) is recommended and women can be treated with praziquantel at any stage of pregnancy and lactation (WHO, 2006). In addition to deworming; education on health and hygiene and provision of adequate sanitation is also recommended. Table 1.1 summarises the existing deworming guidelines by the WHO.

Deworming is regarded as the most effective means of controlling morbidity and mortality with STH and Schistosomiasis. Preventive chemotherapy (either alone or in combination) has been used as a public heath tool for preventing morbidity due to infection usually with more than one helminth at a time since many of the anthelminthic drugs are broad spectrum. In 1994, the WHO convened an informal consultation on hookworm infection and anaemia in girls and women, which promoted the use of anthelminthic drugs in pregnancy after the first trimester in areas where these infections are endemic and where anaemia is prevalent, but it also recommended evaluation of the long-term safety, particularly in terms of birth outcomes (WHO, 1994). Deworming during pregnancy is often accompanied with iron supplementation to reduce anaemia.

Table 1.1: Existing Deworming Guidelines by the World Health Organisation

	Parasite Species	Common Name	At-risk Population	Recommended Treatment	Additional Control Strategies
Soil Transmitted Helminths	*Ascaris lumbricoides*	Roundworm	Preschool and school-age children; women of childbearing age (including pregnant women in the 2nd and 3rd trimesters and lactating women); adults at high risk in certain occupations (e.g. tea-pickers and miners)	Albendazole 400mg Or Mebendazole 500 mg	Education on health and hygiene Provision of adequate sanitation Nutrition interventions
	Ancylostoma duodenale Necator americanus	Hookworms			
	Trichuris trichiura	Whipworm			
Schistosomes	*Schistosoma japonicum Schistosoma mansoni Schistosoma mekongi*	Intestinal blood flukes	School-age children; adults considered to be at risk, from specific groups (pregnant and lactating women; groups with occupations involving contact with infested water, such as fishermen, farmers, irrigation workers, or women in their domestic tasks) to entire communities living in endemic areas	Praziquantel 40mg/kg	
	Schistosoma haematobium	Urinary blood fluke			

Existing Evidence on the Interventions

Currently, no vaccines are licensed for STH and schistosomiasis; and deworming with anthelminthic drugs is endorsed as an effective strategy for the prevention and control along with appropriate WASH interventions and education (WHO, 1994, 2017). A Cochrane review evaluating the impact of deworming given after the first trimester of pregnancy (including four trials with 4265 participants) suggested that a single dose of anthelminthic in the second trimester of pregnancy was not associated with any impact on maternal anaemia in the third trimester (risk ratio (RR): 0.94; 95% Confidence Interval (CI): 0.81, 1.10; 3266 participants; four trials; low quality evidence). The review did not find any impact on LBW (RR 1.00; 95% CI: 0.79, 1.27; 3255 participants; three trials; moderate quality evidence); preterm birth (RR 0.88; 95% CI 0.43 to 1.78; 1318 participants; two trials, moderate quality evidence); and perinatal mortality (RR 1.09; 95% CI 0.71 to 1.67; 3385 participants; two trials; moderate quality evidence) (Salam, Haider, Humayun, & Bhutta, 2015). The review concludes that the existing evidence is insufficient to recommend use of anthelminthic drugs for pregnant women. Furthermore, the review conclusions stated that there is a need for more robust, large scale

randomised controlled trials to establish the benefit of anthelminthic treatment during pregnancy. There are no existing systematic review on schistosomiasis treatment in pregnancy, however, an existing Cochrane review evaluating the impact of drugs to treat schistosomiasis in general population (including 52 trials) suggested that praziquantel 40 mg/kg is effective as the standard treatment for *S. mansoni* infection while oxamniquine, a largely discarded alternative (due to a lack of current consensus on the optimal dosing regimen) also appeared to be effective (Danso-Appiah, Olliaro, Donegan, Sinclair, & Utzinger, 2013). Another Cochrane review evaluating the effectiveness of drugs (including 30 trials with 8165 participants) for urinary schistosomiasis in general population suggested that praziquantel 40 mg/kg was the most studied drug for treating urinary schistosomiasis, and had the strongest evidence base (Kramer, Zhang, Sinclair, & Olliaro, 2014). The review concluded that there is a need for future research on the combination of drugs to treat schistosomiasis using rigorous, adequately powered trials with standardized outcome measures.

For interventions other than deworming, existing literature highlights the lack of high quality evidence (Grimes et al., 2014; Strunz et al., 2014). One review (including 36 studies) suggested that availability of sanitation was associated with reduced infection with STH (odds ratio (OR): 0.49, 95% CI: 0.40, 0.60; 13 studies); while use of sanitation had a non-significant impacts on whipworm (OR: 0.54, 95% CI: 0.28, 1.02; 5 studies), hookworm (OR: 0.63, 95% CI: 0.37, 1.05; 5 studies), and roundworm (OR: 0.78, 95% CI: 0.60, 1.00; 8 studies). Sanitation availability and use combined was associated with reduced prevalence of STH (OR: 0.51, 95% CI: 0.44, 0.61; 15 studies), roundworm (OR: 0.54, 95% CI: 0.43, 0.69; 32 studies), whipworm (OR: 0.58, 95% CI: 0.45, 0.75; 24 studies) and hookworm (OR: 0.60, 95% CI: 0.48, 0.75; 24 studies) (Ziegelbauer et al., 2012). Another review including 94 studies suggested that use of treated water was associated with lower odds of overall STH infection (OR: 0.46, 95% CI: 0.36, 0.60; 3 studies) (Strunz et al., 2014). Piped water access was associated with lower odds of roundworm (OR: 0.40, 95% CI: 0.39, 0.41; 4 studies) and whipworm infection (OR: 0.57, 95% CI: 0.45, 0.72; 3 studies), but not any STH infection (OR: 0.93, 95% CI: 0.28, 3.11; 5 studies). Access to sanitation was associated with decreased likelihood of infection with any STH (OR: 0.66, 95% CI: 0.57, 0.76; 8 studies), whipworm (OR: 0.61, 95% CI: 0.50, 0.74; 7 studies), and roundworm (OR 0.62, 95% CI 0.44, 0.88; 6 studies), but not with hookworm infection (OR: 0.80, 95% CI: 0.61, 1.06; 6 studies). Wearing shoes was associated with reduced odds of hookworm infection (OR: 0.29, 95% CI: 0.18, 0.47; 5 studies) and infection with any STH (OR: 0.30, 95% CI: 0.11, 0.83; 3 studies). Hand washing, both before eating (OR: 0.38, 95% CI: 0.26, 0.55; 3 studies) and after defaecating (OR: 0.45, 95% CI: 0.35, 0.58; 3 studies), was associated with lower odds of roundworm infection. Soap use or even availability was significantly associated with lower infection with any STH (OR: 0.53, 95% CI: 0.29, 0.98; 3

studies), as was hand washing after defaecation (OR: 0.47, 95% CI: 0.24, 0.90; 5 studies) (Strunz et al., 2014).

One systematic review evaluated the impact of community based packaged delivery of interventions including health education to promote general hygiene and sanitation along with drug administration, iron and β-carotene supplementation, snail control, constructing latrines, eliminating cattle from the residential areas, staff training, and community mobilization (Salam, Maredia, Das, Lassi, & Bhutta, 2014). The findings from this review were based on 32 studies and suggested that community based interventions (CBIs) are associated with reduced prevalence of STH (RR: 0.45, 95% CI: 0.38, 0.54) and schistosomiasis (RR: 0.40, 95% CI: 0.33, 0.50). CBIs were also associated with improved mean haemoglobin (standard mean difference (SMD): 0.34, 95% CI: 0.20, 0.47) and reduced anaemia prevalence (RR: 0.90, 95% CI: 0.85, 0.96). However, there was no clear impact on ferritin, height, weight, LBW or stillbirths. A recent feasibility modelling study suggested that the most important determining factors in the control of STH were underlying intensity of STH transmission, current implementation of control programmes for neglected tropical diseases, and whether countries receive large-scale external funding and have strong health systems. However it will require a collaborative approach including a clean environment, appropriate delivery platforms and strong political will (Brooker, Nikolay, Balabanova, & Pullan, 2015). Table 1.2 summarises the evidence on existing interventions.

Table 1.2: Summary of the Existing Evidence

Interventions	Review Details	Outcome
Deworming for STH in pregnant women (Salam et al., 2015)	4 trials, 4265 participants	Maternal anaemia: RR: 0.94, 95% CI: 0.81 to 1.10; 3266 participants; 4 trials Low birth weight: RR: 1.0, 95% CI: 0.79 to 1.27; 1290 participants; 3 trials Preterm birth: RR: 0.88, 95% CI: 0.43 to 1.78; 1318 participants; 2 trials Perinatal mortality: RR: 1.09, 0.71 to 1.67; 3385 participants; 2 trials
Deworming for STH in children with known infection (Welch et al., 2016)	45 trials: one trial had over one million children, and the remaining included 67,672 participants	Haemoglobin: RR: 0.1, 95% CI: -0.65 to 0.86; 247 participants; 2 trials Weight gain: 0.2 to 1.3 kg higher; 627 participants; 5 trials
Deworming for STH in children through community deworming programs (Welch et al., 2016)		Weight gain: SMD: 0.08, 95% CI: -0.11 to 0.27; 38392 participants; 10 trials Height: SMD: 0.02, 95% CI: -0.14 to 0.17; 7057 participants; 7 trials Haemoglobin: SMD: 0.02, 95% CI: -0.08 to 0.04; 3595 participants; 7 trials Mortality: RR: 0.95, 95% CI: 0.89 to 1.92; 1005135 participants; 3 trials
Availability of sanitation (Ziegelbauer et al., 2012)	36 studies (including 1 trial)	A. lumbricoides: OR: 0.46, 95% CI: 0.33 to 0.64; 24 studies T. trichiura: OR: 0.56, 95% CI: 0.46 to 0.70; 19 studies Hookworm: OR: 0.58, 95% CI: 0.45 to 0.76; 19 studies
Use of sanitation (Ziegelbauer et al., 2012)		T. trichiura: OR: 0.54, 95% CI: 0.28 to 1.02; 5 studies Hookworm: OR: 0.63, 95% CI: 0.37-1.05; 5 studies A. lumbricoides: OR: 0.78, 965% CI: 0.60 to 1.0; 8 studies
Sanitation availability and use (Ziegelbauer et al., 2012)		T. trichiura: OR: 0.58, 95% CI: 0.45 to 0.75; 24 studies Hookworm: OR: 0.60, 95% CI: 0.48 to 0.75; 24 studies A. lumbricoides: OR: 0.54, 95% CI: 0.43 to 0.69; 32 studies
Piped water use (Strunz et al., 2014)	94 studies (including 5 trials)	STH infection: OR: 0.93, 95% CI: 0.28 to 3.11; 5 studies A. lumbricoides: OR: 0.40; 95% CI: 0.39 to 0.41; 4 studies T. trichiura: OR: 0.57, 95% CI: 0.45 to 0.72; 3 studies
Treated water use (Strunz et al., 2014)		STH infection: OR: 0.46, 95% CI: 0.36 to 0.60; 3 studies
Wearing shoes (Strunz et al., 2014)		Hookworm: OR: 0.29, 95% CI: 0.18 to 0.47; 5 studies STH infection: OR: 0.30, 95% CI: 0.11 to 0.83; 3 studies
Soap availability/use (Strunz et al., 2014)		STH infection: OR: 0.53, 95% CI: 0.29 to 0.98; 3 studies
Hand washing before eating (Strunz et al., 2014)		A. lumbricoides: OR: 0.38, 95% CI: 0.26 to 0.55; 3 studies
Hand washing after defaecation (Strunz et al., 2014)		A. lumbricoides: OR: 0.45, 95% CI: 0.35 to 0.58; 3 studies STH infection: OR: 0.47, 95% CI: 0.24 to 0.90; 5 studies
Sanitation access (Strunz et al., 2014)		STH infection: OR: 0.66, 95% CI: 0.57 to 0.76; 8 studies T. trichiura: OR: 0.61, 95% CI: 0.50 to 0.74; 7 studies A. lumbricoides: OR: 0.62, 95% CI: 0.44 to 0.88; 6 studies Hookworm: OR: 0.80, 95% CI: 0.61 to 1.06; 6 studies

Research and Implementation Gaps

While WASH and deworming are generally accepted as effective interventions to disrupt STH and schistosomiasis transmission, there is a great deal of heterogeneity in reported effect estimates from the existing systematic reviews. Furthermore, the effectiveness of mass deworming in improving various maternal and child health outcomes is a current source of debate (Turner et al., 2015). Critical appraisal of existing studies suggests that these studies fail to account for various factors that could modify the effectiveness of deworming including nutritional status, type of infection, worm burden and other concomitant interventions (Barry, Simon, Mistry, & Hotez, 2013; Turner et al., 2015). I joined the author team of the Cochrane systematic review evaluating deworming in the second trimester of pregnancy in 2015 (the protocol for this review was first published in 2005; and the review was first published in 2009. The most recent update of this review in 2015 concluded that there was insufficient evidence to recommend deworming in pregnancy with no impact on maternal anaemia, LBW, preterm birth and perinatal mortality (Salam, Haider, Humayun, & Bhutta, 2015). However this review focused only on STH and did not assess the effectiveness of deworming based on baseline morbidity and nutritional status. The review also did not report worm burden. The most recent Campbell systematic review and network meta-analysis with 47 randomised trials and over one million children, found little to no overall effect on growth, attention and school attendance (Welch et al., 2016). These reviews were conducted at the study level, rather than using data for each individual participant, limiting the power to detect effect modification by individual participant characteristics. Such characteristics could potentially modify the effect of deworming including baseline nutritional status, type of STH infection, treatment protocol, worm burden and concomitant interventions (such as iron supplementation) (Barry et al., 2013; Turner et al., 2015).

Despite the availability of more recent global estimates on the burden and interventions for STH and schistosomiasis, additional research is needed to understand the factors that explain the variation in the effect estimates of recommended interventions to prevent transmission. Various factors that could potentially modify the effectiveness of deworming include baseline nutritional status (anaemia and body mass index (BMI)), type of STH infection, treatment protocol, worm burden (particularly intensity of infection) and concomitant interventions (such as iron supplementation and co-administration of other drugs such as praziquantel for schistosomiasis). Currently, it is difficult to establish whether deworming during pregnancy has beneficial effects under certain conditions and limited effects under others, and there exists a possibility that it is only beneficial in women with very high parasite burdens, dietary insufficiencies, or both (Blackwell, 2016). Importantly, there has been no comprehensive study of these potential sources of heterogeneity in

the effects of WASH and mass drug administration (MDA) on transmission of STH. Moreover, all intestinal worms are not the same; not all intestinal worms respond to the same deworming medication; and not all infested individuals exhibit the disease. Additionally, STH infections are not always symptomatic and not all who receive MDA will benefit equally and hence there is a need to understand potential targeting of such programs for the age groups at risk (for example pregnant women, adolescents and WRA) (Anderson, Turner, Truscott, Hollingsworth, & Brooker, 2015). A recent systematic review has also highlighted the scarcity of cost related data for STH programs, which is of prime importance in planning treatment frequency and targeting for STH and schistosomiasis interventions (Turner et al., 2015). Reinfection depends on the prevalence and intensity of infection as well as environmental factors such as the WASH practices in the community.

Existing studies fail to account for various underlying host and environmental factors that modify the effectiveness of deworming. An objective assessment of sources of heterogeneity in existing studies as well as subsets of subjects with varied risks and responses is required to move the field forward. An individual participant data (IPD) meta-analysis would explore the question of whether mass deworming during pregnancy is more effective for subgroups of women defined by characteristics such as nutrition status and infection intensity. IPD meta-analysis refers to analysing data for each participant in the existing studies (Tierney, Pignon, et al., 2015; Tierney, Vale, et al., 2015). The term IPD refers to analysing data recorded for each participant in contrast to the aggregate study data in meta-analysis. The advantage of an IPD analysis over aggregate meta-analysis is that it has the potential to improve the quality of both the data and the analyses and consequently the reliability of the results (Tierney, Vale, et al., 2015). Furthermore, it also provides an opportunity to re-analyse the data for a range of other possibilities for example, investigating the treatment effects varying by participant characteristics which is not possible with the aggregate data (Riley, Lambert, & Abo-Zaid, 2010). An IPD approach could allow the evaluation of variation in effect estimates by various individual, socio-demographic and environmental factors in pregnant women that could potentially modify the effectiveness of deworming during pregnancy. This understanding could help develop targeted strategies to reach pregnant women with deworming and guide future deworming policies.

Conceptual Framework to Guide the Research

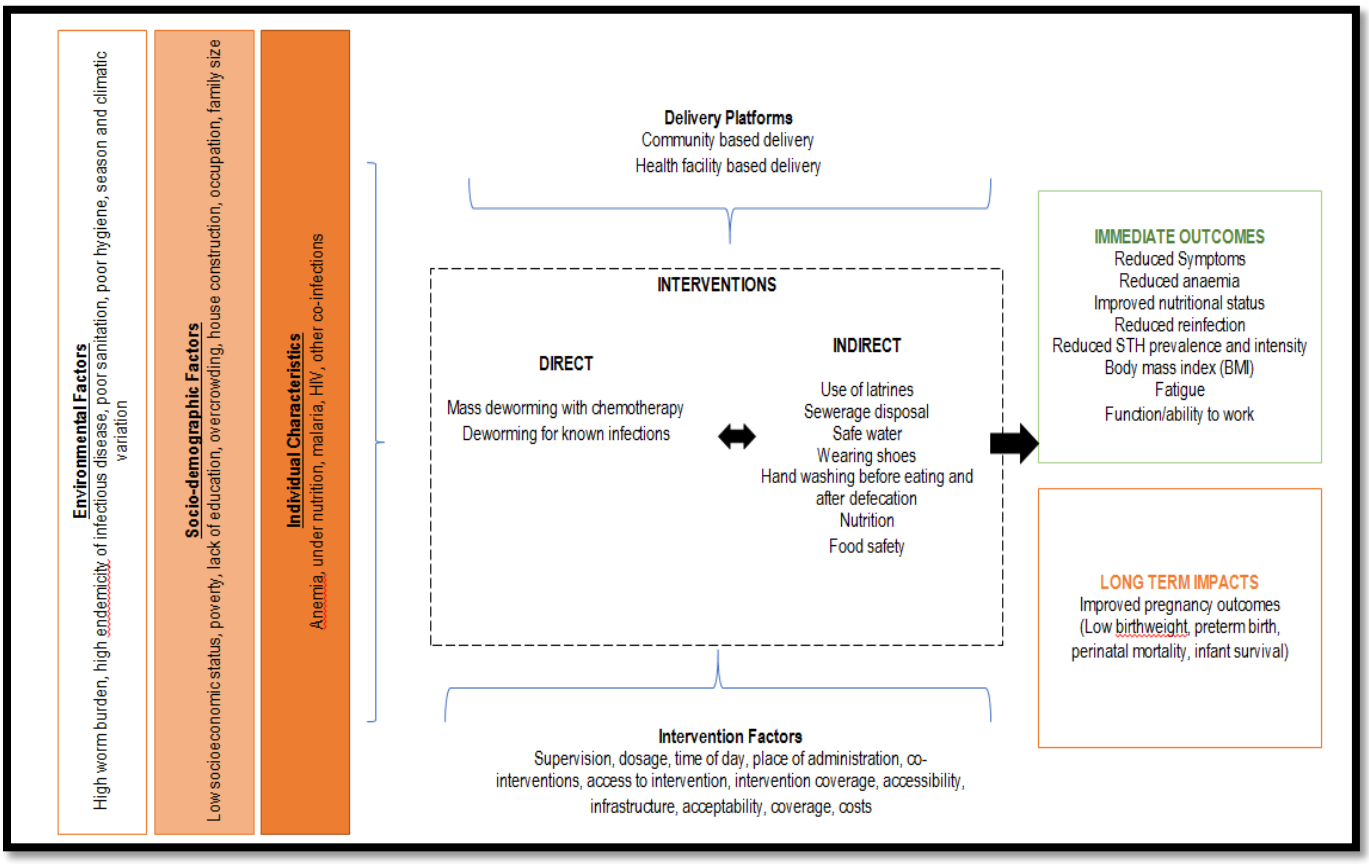
To guide the research, a conceptual framework was devised (Figure 1.4). The conceptual framework focuses on the direct (deworming) and indirect interventions (use of latrines, sewerage disposal, safe water, wearing shoes, hand washing before eating and after defecation, nutrition, food safety) for maternal STH and

schistosomiasis. Around these direct and indirect interventions to prevent and control STH and schistosomiasis, there are various environmental, socio-demographic, individual and intervention factors that could potentially have an impact on the direct and indirect interventions. The environmental factors include high worm burden, high endemicity of infectious disease, poor sanitation, poor hygiene, season and climatic variation. Among the socio-demographic factors are low socioeconomic status, poverty, lack of education, overcrowding, house construction, occupation and family size. The individual factors that could potentially have an impact include maternal anaemia, baseline under-nutrition and other infections (including malaria, human immunodeficiency virus (HIV) or any other co-infections). The factors specific to intervention include supervision, dosage, time of day, place of administration, co-interventions, access to intervention, intervention coverage, accessibility, infrastructure, acceptability, coverage and costs.

The framework also highlights various delivery platforms to target women for STH and schistosomiasis prevention and management. These platforms mainly include community-based or health-facility based delivery mechanisms. Community based delivery of interventions comprise of interventions administered at the community level by lay community members who have received basic training. Infectious diseases control programmes are increasingly setting up community-based delivery strategies and interventions that utilize groups of trained, community-based volunteers when health facilities or staff are not available. Health facility based delivery utilises primary, secondary or tertiary care facilities to target the delivery of interventions. In the context of pregnant women, these facilities include antenatal care clinics.

Finally the framework highlights the desired outcomes including reduced symptoms, reduced anaemia, improved nutritional status, reduced reinfection, reduced STH prevalence and intensity, BMI, fatigue and ability to work. These outcomes then lead to impacts including improved pregnancy outcomes, LBW, preterm birth, perinatal mortality and infant survival as a result of successful prevention and management of maternal STH and schistosomiasis.

Figure 1.4: Conceptual Framework



Research Objectives

Based on the highlighted research gaps, it is important to characterise factors that modify the effect of maternal deworming and WASH interventions on STH and schistosomiasis transmission and to quantify the effect of deworming efforts in this specific sub-population. This will be done through a global systematic review of existing studies using IPD meta-analysis. The broad objective of this research is to use IPD meta-analysis to explore whether the effect of deworming among pregnant women vary with individual characteristics (nutritional status, anaemia), intensity of infection (as assessed by egg count), infection status (including species of worm), socioeconomic status, sanitation environment and co-interventions. Specific objectives are as follows:

1. To conduct a systematic review and meta-analysis on the impact of mass deworming during pregnancy for STH and schistosomiasis on maternal, birth and newborn health outcomes.
2. To conduct a systematic review and meta-analysis on the impact of WASH interventions for STH and schistosomiasis on maternal, birth and newborn health outcomes.
3. To conduct an IPD meta-analysis to identify the factors that explain the variation in the effect estimates of recommended interventions for STH and schistosomiasis.
4. To discuss the current guidelines on mass deworming, the challenges and the economic perspective of mass deworming for WRA.

Chapter 2: Systematic review and meta-analysis to assess the impact of mass deworming during pregnancy on maternal, birth and newborn health outcomes

Abstract

Background

Mass deworming is recommended as an effective strategy to prevent and treat soil transmitted helminthiases (STH) and schistosomiasis. However there is a great deal of heterogeneity in the existing evidence and the effectiveness of mass deworming in improving various maternal and newborn health outcomes is a current source of debate. Furthermore, the long-term safety of mass deworming during pregnancy, particularly in terms of birth outcomes, remains less rigorously evaluated. The aim of this review is to evaluate the impact of mass deworming during pregnancy on maternal, birth and newborn health outcomes.

Methods

We conducted a systematic review and meta-analysis of mass deworming using any drug or a combination of drugs during pregnancy for STH and schistosomiasis compared to no mass deworming. We used a comprehensive search strategy to identify eligible studies regardless of date of publication, language, or publication status till March 2018. We assessed the quality of the included studies using the Cochrane risk of bias assessment tool and summarised the quality of evidence according to the outcomes as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria.

Findings

A total of 16 studies (31 papers) including 45,710 pregnant women were included in this review; nine of the included studies were randomised controlled trials. Findings suggest that mass deworming during pregnancy does not have any impact on maternal anaemia (risk ratio (RR): 0.97, 95% confidence interval (CI): 0.89 to 1.05; six trials; 6696 participants; moderate quality evidence). Mass deworming during pregnancy significantly reduced the prevalence of *Ascaris* (RR: 0.24, 95% CI: 0.19 to 0.29; three trials; 2328 participants; moderate quality evidence), *S.japonicum* (RR: 0.30, 95%CI: 0.21 to 0.42; one trial; 370 participants; moderate quality evidence) and *S.mansoni* (RR: 0.25, 95% CI: 0.16 to 0.38; one trial; 1003 participants; moderate quality evidence). There was no impact on any of the other outcomes including hookworm prevalence (RR: 0.35, 95% CI: 0.11 to 1.10; five trials; 3299 participants; low quality evidence), *Trichuris* (RR: 0.68, 95% CI: 0.50 to 0.92; four trials; 2690 participants; moderate quality evidence), haemoglobin (Hb) (mean difference (MD) 0.08 g/dL, 95% CI: -0.07 to 0.24; five trials; 5704 participants; low quality evidence); birth weight (MD: 0.00 kg, 95% CI: -0.07 to 0.07; four trials; 3651 participants; moderate quality evidence); low birth weight

(LBW) (RR: 1.04, 95% CI: 0.84 to 1.29; four trials; 3625 participants; moderate quality evidence); preterm birth (RR: 0.80, 95% CI: 0.49 to 1.30; three trials; 1781 participants; moderate quality evidence); perinatal mortality (RR: 1.09, 95% CI: 0.71 to 1.67; two trials; 3385 participants; moderate quality evidence); stillbirths (RR: 1.83, 95% CI: 0.99 to 3.37; three trials; 3866 participants; moderate quality evidence); neonatal mortality (RR: 0.69, 95% CI: 0.39 to 1.22; three trials; 3822 participants; moderate quality evidence) and congenital abnormalities (RR: 1.09, 95% CI: 0.79 to 1.49; four trials; 4212 participants; moderate quality evidence). Subgroup analysis could not be conducted due to the limited number of studies included in the review and since an individual participant data analysis (IPD) was already planned to follow.

Interpretation

Mass deworming during pregnancy is associated with reducing worm burden; however there was no impact on any other maternal or pregnancy outcomes.

Introduction

The World Health Organization (WHO) identifies three population groups at high risk for soil transmitted helminthiases (STH) and schistosomiasis including school-age children, preschool children, and girls and women of reproductive age (WRA) (WHO, 2006). A recent estimation suggests that an estimated 688 million girls and WRA are at risk of STH infection; including 140 million pregnant and lactating women and another 108 million adolescent girls (Mupfasoni et al., 2018). Table 2.1 specifies the numbers and percentages of subgroups of women at risk. Approximately 40 million WRA are infected with schistosomiasis (Friedman, Mital, Kanzaria, Olds, & Kurtis, 2007; Nour, 2010). Geographically, the WHO South-East Asia and African regions have the highest numbers of each WRA subgroup, accounting for 74.7% of all STH at-risk WRA (Mupfasoni et al., 2018).

Table 2.1: Subgroups of WRA at risk of STH infection in 2015 (Mupfasoni et al., 2018)

Subgroup	Number at risk of STH infection	Percentage at risk of STH infection
Adolescent girls (15-19 years)	108 269 000	15.7
Pregnant women (15-49 years)	69 463 000	10.1
Lactating women (15-49 years)	69 463 000	10.1
Non-pregnant, non-lactating adult women (20-49 years)	440 947 000	64.1
Total	**688 142 000**	**100**

STH and schistosomiasis during pregnancy causes active and debilitating disease with adverse effects on birth outcomes and the infant's developing immune system (Bustinduy, Stothard, & Friedman, 2017; Freer, Bourke, Durhuus, Kjetland, & Prendergast, 2017; Sanya, Nkurunungi, Andia Biraro, Mpairwe, & Elliott, 2017). STH (including *Ascaris lumbricoides*, *Trichuris trichiura* and the hookworms (*Ancylostoma duodenale* and *Necator americanus*)) and *schistosomes (*including *S.haematobium, S.mansoni, and S. japonicum)* have been associated with reductions in haemoglobin and iron deficiency during pregnancy. Evidence suggests a direct association between the intensity of infection, blood loss and consequent adverse pregnancy outcomes including low birth weight (LBW), preterm birth, perinatal mortality and infant survival (Bundy et al., 1995; Chan et al., 1994; Gyorkos et al., 2011; Larocque et al., 2005; Muhangi et al., 2007; Ndyomugyenyi et al., 2008q; Nurdia et al., 2001). Women suffer considerably from female genital schistosomiasis that causes infertility, preterm labour, anaemia, menstrual disorders, and dyspareunia (Freer et al., 2017; Nour, 2010).

Currently, mass deworming is recommended as an effective strategy to prevent and treat STH and schistosomiasis. The most recent recommendations by the WHO on deworming among pregnant women (WHO, 2017) recommends preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), as a public health intervention for pregnant women including pregnant adolescent girls after the first trimester (in the second or third trimester), living in areas where both:

(i) the baseline prevalence of hookworm and/or *T. trichiura* infection is ≥ 20% among pregnant women, and

(ii) where anaemia is a severe public health problem, with a prevalence of ≥ 40% among pregnant women.

For schistosomiasis, annual treatment with praziquantel in high risk communities (>50%) and once every two years in medium risk communities (>10% and <50%) is recommended. Women can be treated with praziquantel at any stage of pregnancy and lactation (WHO, 2006).

Deworming drugs such as levamisole, mebendazole, albendazole, praziquantel and pyrantel have been reported to be efficacious with minimal side-effects but data about their use in pregnancy are scarce (WHO, 1994, 2018). Adverse events associated with deworming in girls and women themselves have rarely been published, and usually only within the context of specific research studies (Keiser & Utzinger, 2008; Ndyomugyenyi, Kabatereine, Olsen, & Magnussen, 2008). However, no serious adverse events have been reported (Ndyomugyenyi et al., 2008a). Along with the concerns related to undue exposure to deworming drugs during pregnancy as a result of routine mass deworming and the potential adverse effects on the foetus, there is lack of evidence supporting the health benefits of treating during pregnancy on birth outcomes. More recently, issues related to limited efficacy profiles of albendazole, mebendazole, levamisole, and pyrantel pamoate have been raised with some evidence supporting co-administration of a some deworming drugs (Moser, Schindler, & Keiser, 2017; Palmeirim et al., 2018). Although mass deworming is regarded as the most effective means of controlling morbidity and mortality with STH and schistosomiasis; the long-term safety when administered during pregnancy, particularly in terms of birth outcomes has not been rigorously evaluated (WHO, 1994, 2018). Therefore, the aim of this review is to assess the impact of mass deworming for STH and schistosomiasis during pregnancy on maternal, birth and newborn health outcomes.

Objective

The objective of this systematic review and meta-analysis is to assess the impact of mass deworming during pregnancy for STH and schistosomiasis on maternal, birth and newborn health outcomes.

Methodology

Criteria for considering studies for this review

Types of studies

We included primary studies using experimental or quasi-experimental study designs that allow for causal inferences. We included randomised controlled trials (RCTs), quasi randomised studies and controlled before after studies (CBA). We also included case-control and cross-sectional studies reporting associations between mass deworming during pregnancy and on maternal, birth and newborn health outcomes. We excluded case reports and case-series.

Types of participants

Participants were pregnant women receiving preventive or therapeutic deworming drugs for STH and schistosomiasis.

Types of interventions

We included mass deworming using any drug or a combination of drugs (including levamisole, mebendazole, albendazole, praziquantel and pyrantel) for STH and schistosomiasis with or without co-interventions compared to placebo or control (no mass deworming). Co-interventions could be food provision, micronutrient supplementation, iron and/or folic acid supplementation, hygiene interventions or education. We included studies where the co-interventions were similar in the intervention and control groups to assess the impact of mass deworming.

Types of outcome measures

The following primary and secondary outcomes were reported; however we did not use the list of outcomes as a criterion for inclusion:

-Primary outcomes:

- Maternal anaemia at term (defined as haemoglobin (Hb) less than 11 g/dL)
- Maternal infection intensity (as defined and reported by the study authors)

-Secondary outcomes:

- Maternal Hb at term
- Maternal ferritin at term
- Maternal anthropometric measures (including maternal weight, body mass index (BMI), gestational weight gain etc.)
- Birth weight
- Low birth weight (LBW) (defined as birth weight less than 2500 grams)
- Preterm birth (defined as birth before 37 weeks of gestation)
- Perinatal mortality (includes foetal death after 28 weeks of gestation and infant death that occurs at less than seven days of life)
- Stillbirth (defined as a baby born with no signs of life at or after 28 weeks' gestation)
- Congenital anomalies (defined as structural or functional anomalies (e.g. metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life)
- Infant mortality (defined as the number of deaths among children under one year of age occurring among the live births in a given geographical area during a given year, per 1,000 live births occurring among the population of the given geographical area during the same year)

Search methods for identification of studies

We used a comprehensive search strategy to identify eligible studies regardless of the date of publication, language, or publication status till March 2018. The search strategy is attached as Appendix 1.

Electronic searches

We searched the following electronic databases: MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin-American and Caribbean System on Health Sciences Information (LILACS), Excerpta Medica dataBASE (EMBASE), the Cochrane Library, Global Health CABI and Centre for Agriculture and Biosciences (CAB) Abstracts. We searched websites of relevant organizations such as the WHO Neglected Tropical Diseases, World Bank and World Food Program.

Searching other resources

We also contacted authors of studies and members of the study's advisory board for any unpublished studies or grey literature reporting eligible studies. We checked the reference lists of relevant studies and reviews. We also searched for trials registered with ClinicalTrials.gov.

Data collection and analysis

Selection of studies

Two reviewers independently assessed potential study eligibility using predefined screening criteria. Any studies considered obviously irrelevant from screening the titles and/or abstracts were excluded at the first level. Any uncertainties at the first level screening were re-assessed on the basis of full text in the second level of screening. For any discrepancies, study's advisory group was contacted for the final decision. Any disagreements were resolved through discussion until a consensus was reached.

Data extraction and management

We extracted data from included studies on the following:

- Background: time period when study took place, type of publication (e.g. full-text journal article, abstract, conference paper, thesis) and study country or countries.
- Population and study setting: population age and setting.
- Methods: study design, description of study arms, unit of allocation, sample or cluster size per study arm (for individually or cluster randomised trials respectively), start and end date, duration of follow up.
- Participants: total number randomised, baseline characteristics, number of withdrawals, socio-demographic data (if available).
- Intervention group details: number randomised to group, description of intervention, co-interventions, duration and follow-up, timing and delivery of intervention. In case of studies with multiple intervention arms, we described all arms, while we reported the arms that met the inclusion criteria.
- Comparison group details: number randomised to group, description of comparison, duration and follow-up, timing and delivery.

- Outcomes: measurement tool, total number in intervention and comparison groups, change indicated at each time point. In case if multiple measures are reported for the same outcome construct, we used the one pre-specified in protocol.

- Any other information deemed relevant.

Assessment of risk of bias in included studies

We assessed the quality of the included studies using the Cochrane risk of bias assessment tool for the RCTs. The quality of the RCTs was assessed based on selection bias, performance bias, detection bias, attrition bias and reporting bias (Higgins, Altman, & Sterne, 2011). For non-randomised studies, we used the Cochrane Effective Practice and Organisation of Care (EPOC) group criteria for risk of bias assessment (EPOC, 2015). Quality of non-randomised studies was assessed based on random sequence generation, allocation concealment, baseline outcome measurements similar, baseline characteristics similar, incomplete outcome data, knowledge of the allocated interventions adequately prevented during the study, protection against contamination, selective outcome reporting and other risk of bias. We summarised the quality of evidence according to the outcomes as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (Walker, Fischer-Walker, Bryce, Bahl, & Cousens, 2010). A grade of "high", "moderate", "low" and "very low" were used for grading the overall evidence indicating the strength of an effect on specific health outcome based on methodological flaws within the component studies, consistency of results across different studies, generalizability of research results to the wider patient base and how effective the treatments have shown to be (Balshem et al., 2011).

Measures of treatment effect

For each outcome, data were converted to the same format (e.g. means and standard deviations for continuous data), including appropriate conversion of scales such that an increase/decrease always indicates improvement or deterioration of an indicator. Dichotomous and continuous outcomes were analysed separately. For dichotomous outcomes, results were presented as summary risk ratios (RRs) with 95% confidence intervals (CI), whenever possible, in order to compare risk of the outcome between intervention and control groups. Continuous outcome data were presented as either a mean difference (MD), if outcomes were measured on the same scale, or a standardized mean difference (SMD), if outcomes were measured on different scales, with 95% CI.

Unit of analysis issues

Separate meta-analysis was conducted for studies with separate study designs (RCTs and non-randomised studies). Special attention was given to cluster-randomised trials to ensure that clustering has been appropriately accounted for within the analysis of the primary study, such that study precision is not over or under-estimated within our analysis. We did not make any adjustments if authors had appropriately adjusted for cluster design already.

One trial (Urassa et al., 2011) was cluster-randomised trial. We used the intra-cluster correlation coefficient (ICC) and the variance inflation factor to adjust the standard errors appropriately. Subsequently, effect sizes and standard errors were meta-analysed by using the generic inverse method (GIV).

In order to take into account potential sources of dependency, we grouped studies in terms of their location, population and the intervention being evaluated (for e.g. different drugs) to ensure that there was no double counting of evidence when synthesizing results across studies. If there were multiple papers that described the same trial, these were combined and coded as a single study.

For trials that included multiple intervention arms, we selected one pair (intervention and control) that satisfied the inclusion criteria of the review and excluded the rest. If more than two intervention groups met the eligibility criteria, then these groups were combined into a single pair-wise comparison group and data were disaggregated into corresponding subgroups, or these arms were separated into different forest plots to ensure that there is no double counting of participants.

Dealing with missing data

Where data were incomplete or in a form that could not be converted with the information available, we contacted the corresponding author for clarification or to obtain missing data. If authors accounted for missing data (i.e. multiple imputations), we used the adjusted data within our analysis.

Assessment of heterogeneity

Clinical and methodological heterogeneity was explored by assessing the similarities and differences in included studies' participants, interventions, outcomes, and methods. Statistical heterogeneity was assessed by visually inspecting forest plots, calculating the I^2 statistic (>50% indicated substantial heterogeneity) and conducting a Chi^2 test, where a p-value <0.1 was considered statistically significant. Sources of heterogeneity was explored using sub-group analysis (where possible).

Assessment of reporting bias

If the number of studies was sufficient (>10), funnel plots were used to visually assess publication bias. This kind of bias is unlikely if data forms a symmetric inverted funnel shape around the mean effect estimate.

Data synthesis

Statistical analysis was carried out using Review Manager 5.3. For RCTs, we followed intention to treat (ITT) analysis. For comparable interventions and outcomes, we presented the synthesis of quantitative evidence through meta-analysis. Fixed effects meta-analysis was used where there was sufficient similarity between studies' populations and methods, such that it was reasonable to assume that studies are estimating the same treatment effect. Where there was enough heterogeneity between studies to expect that underlying treatment effects differ between studies, random effects meta-analyses was used. For random effects analyses, the DerSimonian and Laird method was applied to incorporate a measure of variation (Tau^2) among intervention effects from different studies. For interpretation of results, overall effect estimates that had an associated p-value <0.05 were deemed statistically significant. Non-significant findings were also reported. Where possible, interaction tests were used to determine if there was a relevant difference in effect across sub-groups. We also examined the subgroups' confidence intervals; non-overlapping intervals indicated a statistically significant difference between groups.

Subgroup analysis and investigation of heterogeneity

Depending on data availability, exploratory sub-group analyses was planned on the primary outcomes for the following variables, selected based on their potential to impact the intervention effect:

- Baseline infection intensity (light versus moderate versus heavy)
- Baseline nutritional status (anaemic versus non-anaemic, low BMI versus normal BMI)
- Co-interventions

An individual participant data analysis was also planned to follow this systematic review. The findings are reported in the following chapters.

Sensitivity analyses

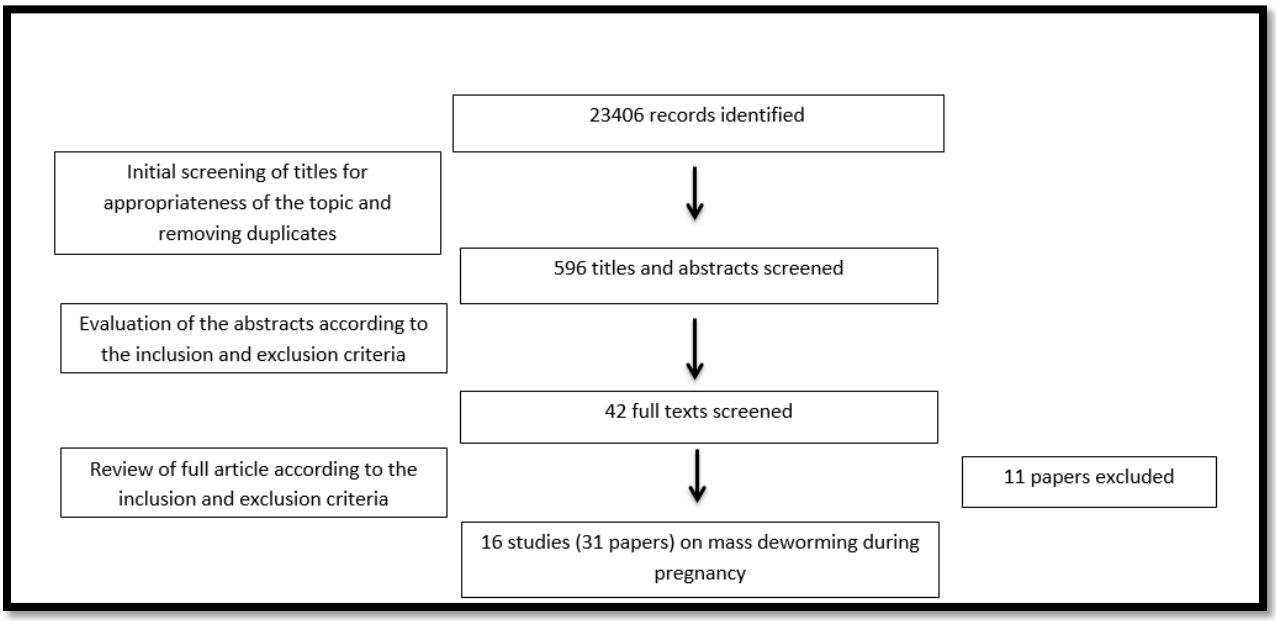
Sensitivity analyses was conducted to determine whether the removal of studies with high risk of bias or the removal of non-randomised studies significantly impact findings.

Results

Search results

Figure 2.1 provides a search flow diagram. We identified a total of 23,406 record through the search strategy provided in Appendix 1. A total of 31 papers (Abel, Rajaratnam, Kalaimani, & Kirubakaran, 2000; Ács, Bánhidy, Puhó, & Czeizel, 2005; Adam, Elwasila, & Homeida, 2005; Atukorala, De Silva, Dechering, Dassenaeike, & Perera, 1994a; Christian, Khatry, & West Jr, 2004; De Silva, Sirisena, Gunasekera, Ismail, & De Silva, 1999; Deepti & Nandini, 2015; Elliott et al., 2007; Elliott, Mpairwe, et al., 2005; Elliott, Namujju, et al., 2005; Gyorkos et al., 2011; Gyorkos, Larocque, Casapia, & Gotuzzo, 2006; Renée Larocque et al., 2006; Liabsuetrakul et al., 2009; Millard et al., 2014; Tehalia 2011; Mpairwe et al., 2011; Nampijja et al., 2012; Juliet Ndibazza et al., 2012; J Ndibazza et al., 2010; Ndyomugyenyi et al., 2008a; Olveda et al., 2016; Torlesse & Hodges, 2000, 2001; Tweyongyere et al., 2009; Tweyongyere et al., 2011; Tweyongyere et al., 2008; Tweyongyere et al., 2013; Urass, Nystrom, & Carlstedt, 2011; Villar, Dala, & Cardona, 1998; Webb et al., 2012; Webb et al., 2011) based on 16 studies were included based on the eligibility criteria. Appendix 2 provides reasons for exclusion for the excluded studies.

Figure 2.1: Search Flow Diagram



Characteristics of studies

A total of 16 studies including 45,710 pregnant women were included in this review. Nine of the included studies were RCTs while seven were non-randomised studies. Studies were conducted in Hungary, India, Nepal, Pakistan, Philippines, Peru, Sierra Leone, Sri Lanka, Sudan, Tanzania, Thailand and Uganda between 1994 and 2016. The deworming drugs provided in these studies included albendazole, mebendazole, praziquantel or a combination of these. A majority of the studies provided mass deworming for STH only; while only two studies (Adam et al., 2005; Olveda et al., 2016) provided deworming for schistosomiasis; one study (Elliott, Mpairwe, et al., 2005) targeted both STH and schistosomiasis. The sample size ranged from 25 pregnant women to 22843 pregnant women. The most common co-intervention was iron/folic acid supplementation while other interventions included food supplementation, anti-malarial drug administration and education. Table 2.2 summarises deworming drugs and the co-interventions used in each study while table 2.3 describes the characteristics of included studies.

Table 2.2: Number of studies providing each of the deworming drugs and co-interventions

Deworming Drugs	Co-interventions					
	None	Iron Supplement	Iron Folate	Food Supplement	Antimalarial	Education
Albendazole	5	2	2	-	1	-
Mebendazole	3	2	1	1	-	1
Praziquantel	2	-	-	-	-	-
Pyrantal Pamoate	1	-	-	-	-	-
Ivermectin	-	1	-	-	-	-
Albendazole+Praziquantel	1	-	-	-	-	-
Ivermectin+Albendazole	-	1	-	-	-	-
Albendazole+Mebendazole	1	-	-	-	-	-

Table 2.3: Characteristics of included studies

Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
Elliott 2005 (Elliott et al., 2007; Elliott, Mpairwe, et al., 2005; Elliott, Namujju, et al., 2005; Renée Larocque et al., 2006; Millard et al., 2014; Mpairwe et al., 2011; Nampijja et al., 2012; Juliet Ndibazza et al., 2012; J Ndibazza et al., 2010; Tweyongyere et al., 2009; Tweyongyere et al., 2011; Tweyongyere et al., 2008; Tweyongyere et al., 2013; Webb et al., 2012; Webb et al., 2011)	Randomised Controlled Trial	Entebbe Hospital, Uganda between June-August, 2002.	2507 participants	-Albendazole (400 mg) -Praziquantel (40 mg/kg) -Albendazole and praziquantel	Placebo	Maternal education Household economic index Trimester at treatment Parity Place of delivery HIV status Malaria parasites Active syphilis Worm prevalence Anaemia	Infection Infantile eczema Maternal and perinatal outcomes Immune responses (BCG, tetanus, pertussis, hep B, measles, diphtheria, polio, haemophilus) Co-infections (malaria, pneumonia, diarrhoea, TB, measles, HIV) Anaemia (haemoglobin concentration) Growth and development (birth weight, weights, height, head circumference, MUAC, intellectual function) Worm prevalence Mortality
Larocque 2006 (Gyorkos et al., 2011; Gyorkos et al., 2006; Renée Larocque et al., 2006)	Randomised Controlled Trial	Health centres in the Iquitos region of Peru	1042 participants	Single dose of mebendazole (500 mg) plus a daily iron supplement (60 mg elemental iron, ferrous sulphate)	Single dose placebo plus a daily iron supplement (60mg elemental iron, ferrous sulphate)	Gestational age Environment (Urban/rural) Schooling Primigravida Housing Flooring Toilet facility	Mean infant birth weight (LBW and VLBW) Maternal anaemia in third trimester Infection prevalence Stillbirth Early neonatal death Term birth Miscarriage

Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
						Water use STH prevalence STH intensities Anaemia Haemoglobin	Malformations
Ndyomugyenyi 2008 (Ndyomugyenyi et al., 2008a)	Randomized Controlled Trial	Masindi district, western Uganda	832 participants	Group A (n = 198) received ivermectin Group B (n = 194) received albendazole (a single dose of 400 mg) Group C (n = 199) received a combination of ivermectin and albendazole, and all women in addition received the routine antenatal care package with iron supplements	Group D (n = 241) was a reference group without any intervention	Weight Height Hb Gestational age	Maternal Hb in third trimester Birth weight LBW Abortion Stillbirths Neonatal death Preterm birth Cure rate Mean parasite density Neonatal anaemia Neonatal mean Hb
Torlesse 2001 (Torlesse & Hodges, 2000, 2001)	Randomised Controlled Trial	Antenatal clinics in peri-urban and 6 in rural areas in Sierra Leone	184 participants	Albendazole, 2 x 200 mg, single dose, at first antenatal visit in second trimester. Daily iron-folate supplements	2 tablets containing calcium with vitamin D were used as the control for	Hb	Worm prevalence Anaemia Iron deficiency anaemia Cure rate Egg reduction rate

Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
				comprised of 36 mg iron	albendazole. Calciferol tablets (1.25 as ferrous gluconate and 5 mg folic acid started at first antenatal visit in second trimester for entire duration of pregnancy. mg), 1 daily, were chosen as the control for iron-folate supplements		
Urassa 2011 (Urassa et al., 2011)	Cluster Randomised Controlled Trial	Rufiji district, Tanzania	3080 participants	Single dose Albendazole (400mg) (given at term and 4 months later) Daily iron folate supplements (36mg iron; 5mg folate)	Placebo	Parity Gestational age Distance of facility from residence Knowledge of anaemia Knowledge of malaria Hb Anaemia	Haemoglobin Serum ferritin concentration during pregnancy Anaemia

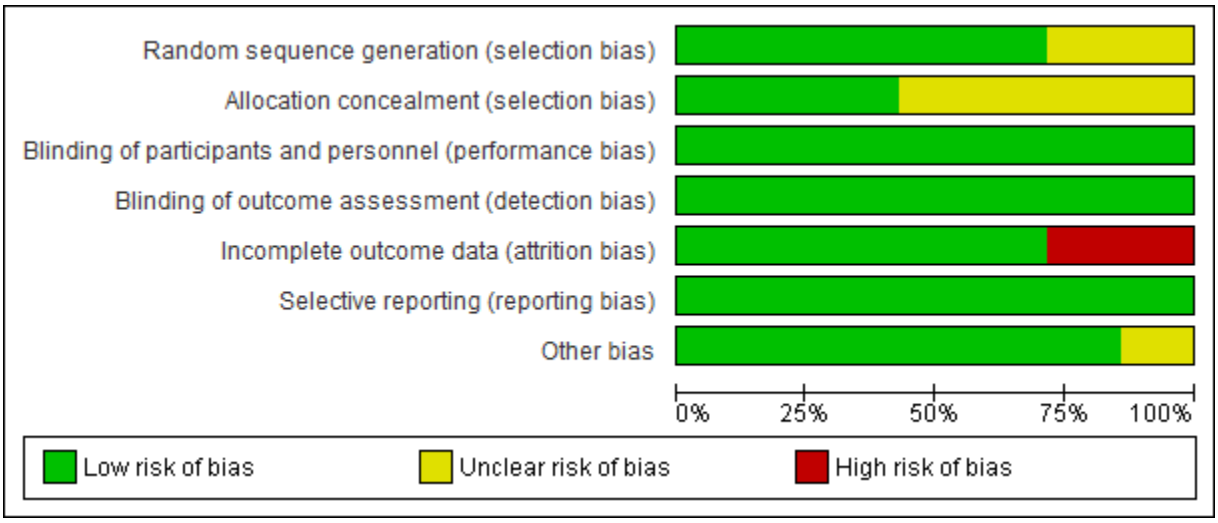
Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
				Sulphadoxine pyramethamine			
Deepti 2015 (Deepti & Nandini, 2015)	Randomised Controlled Trial	India	500 participants	-Albendazole -Mebendazole -Albendazole and mebendazole	Placebo	Education Socio-economic status Hb Baseline infestation	Maternal anaemia Worm intensity Worm prevalence Birth weight Low birth weight
Tehalia 2011 (Tehalia 2011)	Randomised Controlled Trial	Not specified	Not specified	Single dose albendazole with iron supplementation 400 mg	Chewable antacid tablet with iron supplementation		Maternal anaemia
Villar 1998 (Villar et al., 1998)	Randomised Controlled Trial	Not specified	156 pregnant women	Single dose of Pyrantel Pamoate (11mg/kg)	No treatment		Congenital anomalies SGA
Atukorala 1994 (Atukorala et al., 1994a)	Controlled before-after study	Plantation sector of SriLanka	195 pregnant women	Anthelminthic therapy in addition to iron-folate supplements	Iron-folate supplements	Socio-demographic variables	BMI Hb Serum transferrin Serum ferritin
Abel 2000 (Abel et al., 2000)	Controlled before-after study	Rural Vellore district in India	828 pregnant women	Iron supplementation, deworming, and information, education and communication	No intervention	Anaemia Hb Iron deficiency	Anaemia Hb Iron deficiency
Christian 2004 (Christian et al., 2004)	Prospective cohort	30 village development communities in	4998 pregnant women	Albendazole administered twice during pregnancy	No intervention		Anaemia Hb Birthweight Infant mortality

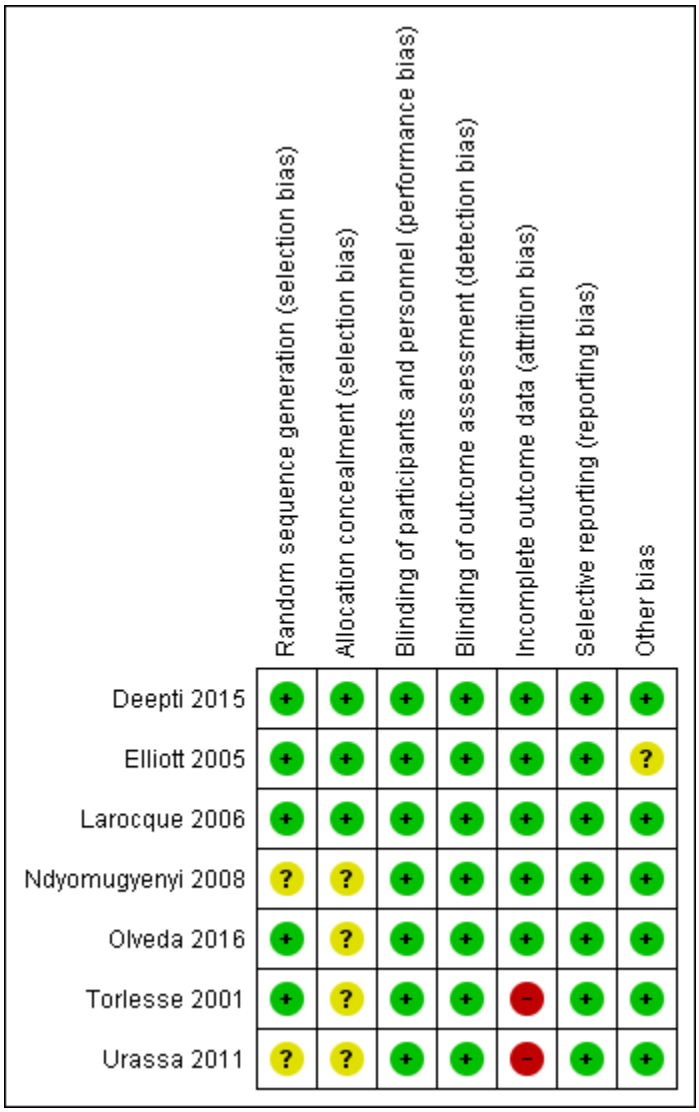
Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
		Sarlahi district, Nepal					
de Silva 1999 (De Silva et al., 1999)	Cross-sectional survey	Sri Lanka	7087 pregnant women	Mebendazole	No intervention		Birth defects
Acs 2005 (Ács et al., 2005)	Case-control study	Hungary	22 843 pregnant women	Mebendazole	No intervention		Anaemia Threatened abortion Congenital anomaly
Adam 2005 (Adam et al., 2005)	Prospective cohort	Sudan	25 pregnant women	Single oral dose of Praziquantel, at 40 mg/kg	No control group		Abortion Stillbirth Congenital anomalies
Liabsuetrakul 2009 (Liabsuetrakul et al., 2009)	Prospective cohort	Four southernmost provinces of Thailand	1063 pregnant women	400 mg of albendazole	No control group	Worm intensity	Cure rate
Olveda 2016 (Olveda et al., 2016)	Randomised Controlled Trial	Villages in northeastern Leyte, Philippines	370 pregnant women	over-encapsulated praziquantel (total dose 60 mg/kg given as two split doses)	Placebo	Socio-economic status Height Weight Baseline prevalence	Birth weight LBW SGA Maternal Hb Newborn Hb Maternal weight gain Treatment success Cure rate Maternal adverse events Congenital anomaly Fetal death Abortion

Quality of Studies

The quality of the included RCTs was assessed using the Cochrane risk of bias assessment criteria. Out of the nine RCTs included in the review; risk of bias was assessed for seven trials since and the information available for two trials (Tehalia, 2011; Villar et al., 1998) was not sufficient and the authors could not be contacted for clarification. The included RCTs were judged to be of good quality except two studies rated to be at high risk of attrition bias, and one study lacked allocation concealment. Figure 2.2 depicts the risk of bias for the included RCTs.

Figure 2.2: Risk of Bias for the Included Trials





Quality of non-randomised studies was assessed using the EPOC criteria. All the studies were judged to be at overall high risk of bias mainly due to the lack of random sequence generation and allocation concealment due to the design limitation. Majority of the studies were also judged to be at high risk for similarity in baseline outcome measurements, similarity in baseline characteristics, incomplete outcome data, lack of prevention of knowledge of the allocated interventions and lack of protection against contamination. Table 2.4 depicts the risk of bias for non-randomised studies.

Table 2.4: Risk of bias for non-randomised studies

Risk of Bias Judgements	Studies						
	Atukorala 1994	Abel 2000	Christian 2004	de Silva 1999	ACS 2005	Adam 2005	Liabbsuetrakul 2009
Random sequence generation							
Allocation concealment							
Baseline outcome measurements similar							
Baseline characteristics similar							
Incomplete outcome data							
Knowledge of the allocated interventions prevented							
Protection against contamination							
Selective outcome reporting							
Other risk of bias							

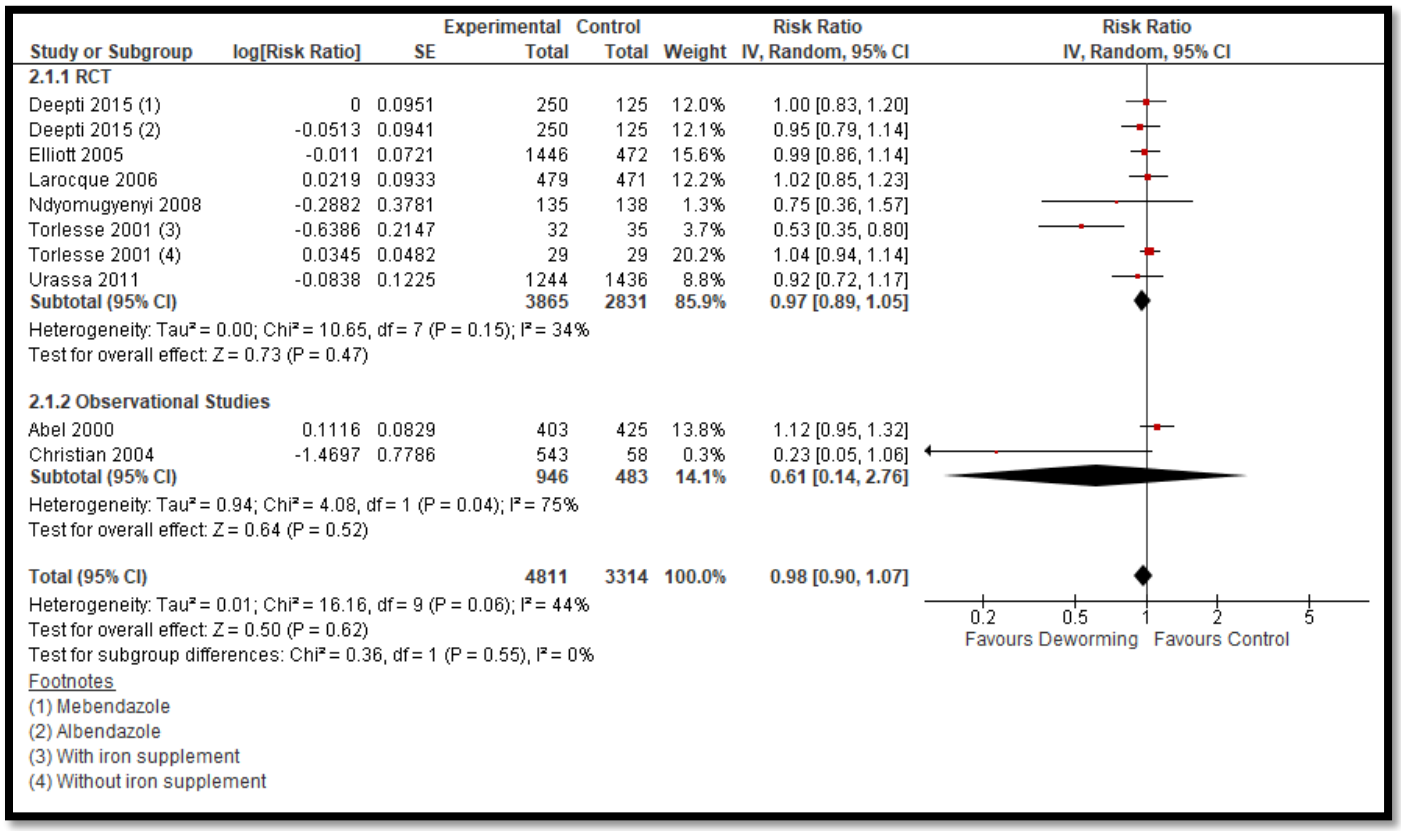
*Red boxes denote high risk; green boxes denote low risk

Primary Outcomes

Maternal Anemia

Eight studies with 8096 pregnant women; including six RCT (Deepti & Nandini, 2015; Elliott, Mpairwe, et al., 2005; Renee Larocque et al., 2005; Ndyomugyenyi et al., 2008a; Torlesse & Hodges, 2000; Urass et al., 2011) and two non-randomised studies (Abel et al., 2000; Christian et al., 2004) reported maternal anemia suggesting no important impact of mass deworming on maternal anemia in both RCTs (RR: 0.97, 95% CI: 0.89-1.05) and non-randomised study (RR: 0.61, 95% CI: 0.14-2.76) subgroups. The outcome was judged to be of 'moderate' quality due to high risk of attrition bias in one of the studies. Figure 2.3 depicts the forest plot for the impact of mass deworming on maternal anemia.

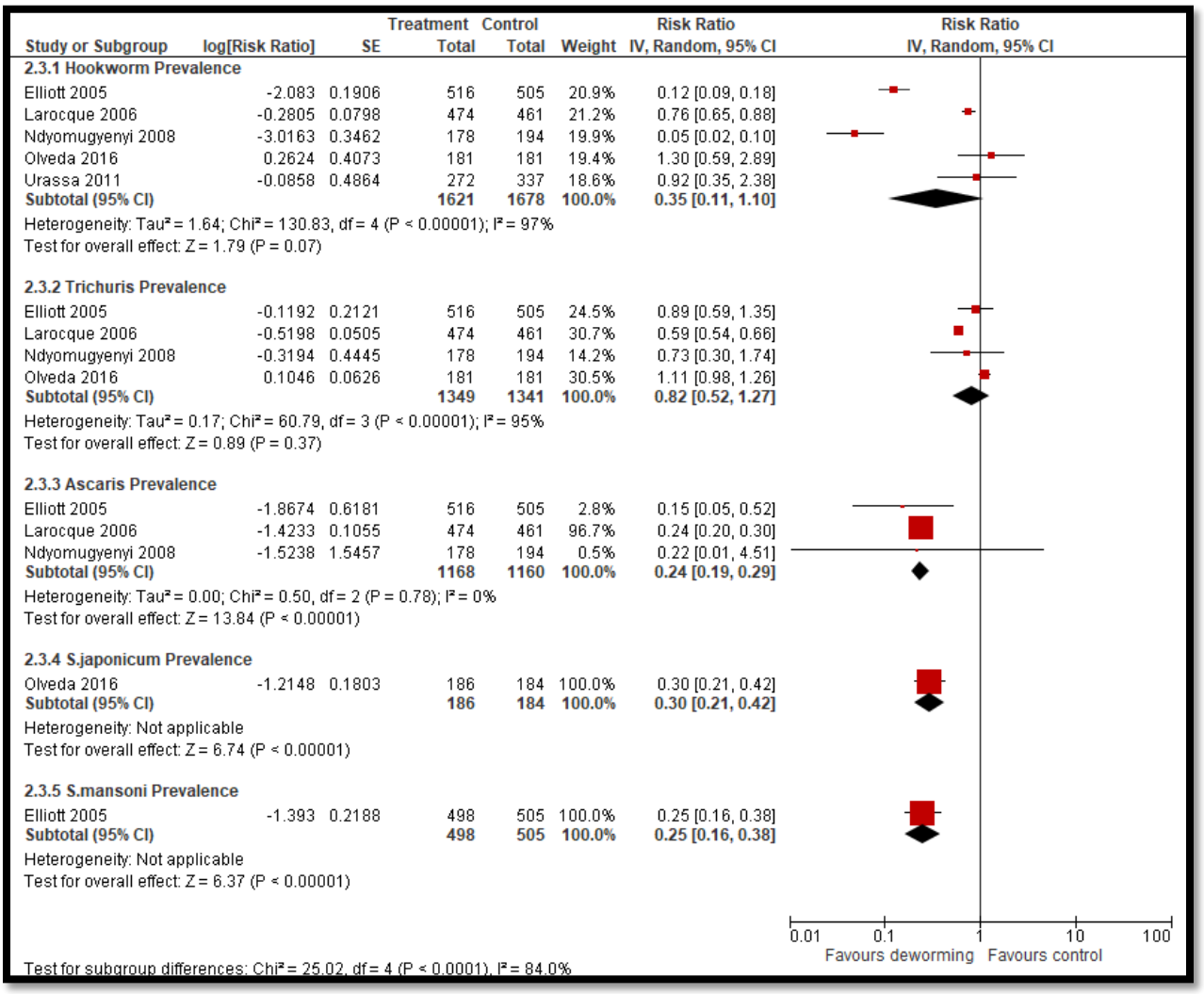
Figure 2.3: Forest plot for the impact of mass deworming during pregnancy on maternal anaemia



Worm Prevalence

Five studies (Elliott, Mpairwe, et al., 2005; Larocque et al., 2005; Ndyomugyenyi et al., 2008; Olveda et al., 2016; Urassa et al., 2011) including 3307 pregnant women reported the impact of mass deworming during pregnancy on worm prevalence. All studies were RCTs. Mass deworming reduced the prevalence of *Ascaris* (RR: 0.24, 95% CI: 0.19-0.29), *S.japonicum* (RR: 0.30, 95%CI: 0.21-0.42) and *S.mansoni* (RR: 0.25, 95% CI: 0.16-0.38). There was no effect on the prevalence of hookworm (RR: 0.35, 95% CI: 0.11-1.10) and *Trichuria* (RR: 0.82, 95% CI: 0.52-1.27). The outcome was rated to be of 'low' quality for hookworm prevalence; and 'moderate' quality for *Trichuria* and *Ascaris* prevalence, due to high heterogeneity and high risk of selection bias in one of the studies. Figure 2.4 depicts the forest plot for the impact of mass deworming on worm prevalence.

Figure 2.4: Forest plot for the impact of mass deworming on worm prevalence

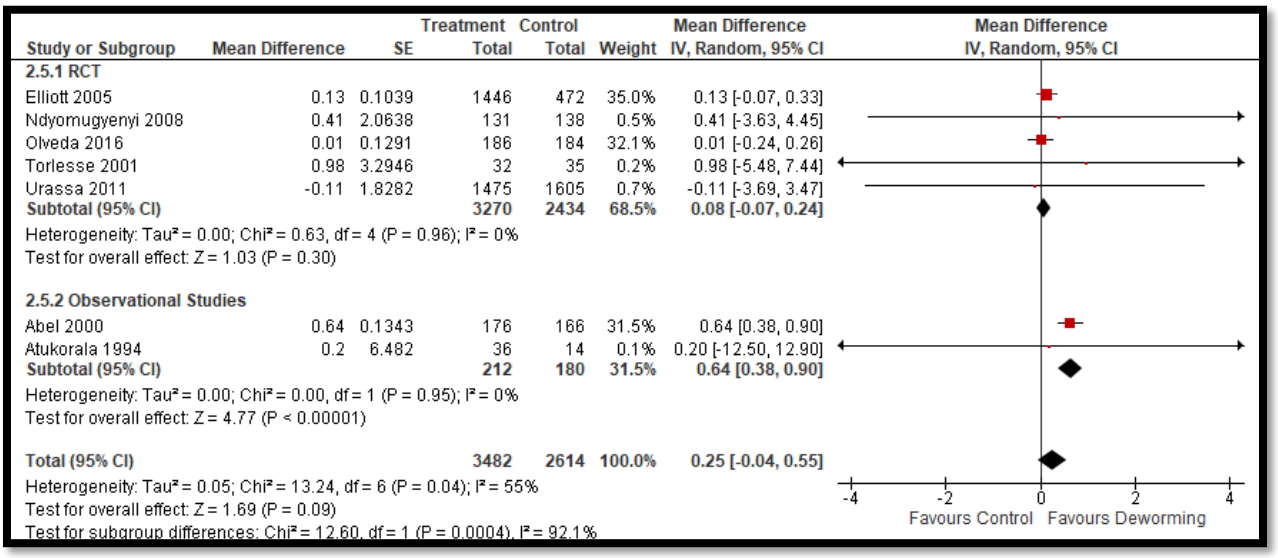


Secondary Outcomes

Haemoglobin

Seven studies with 5138 pregnant women; including five RCTs (Elliott, Mpairwe, et al., 2005; Ndyomugyenyi et al., 2008a; Olveda et al., 2016; Torlesse & Hodges, 2000; Urassa et al., 2011) and two non-randomised studies (Abel et al., 2000; Atukorala et al., 1994) reported maternal Hb suggesting a non-significant impact from RCTs (MD: 0.08 g/dL, 95% CI: -0.07-0.24), but a significant improvement in Hb from non-randomised studies (MD: 0.64 g/dL, 95% CI: 0.38-0.90). Figure 2.5 depicts the forest plot for the impact of mass deworming during pregnancy on maternal Hb.

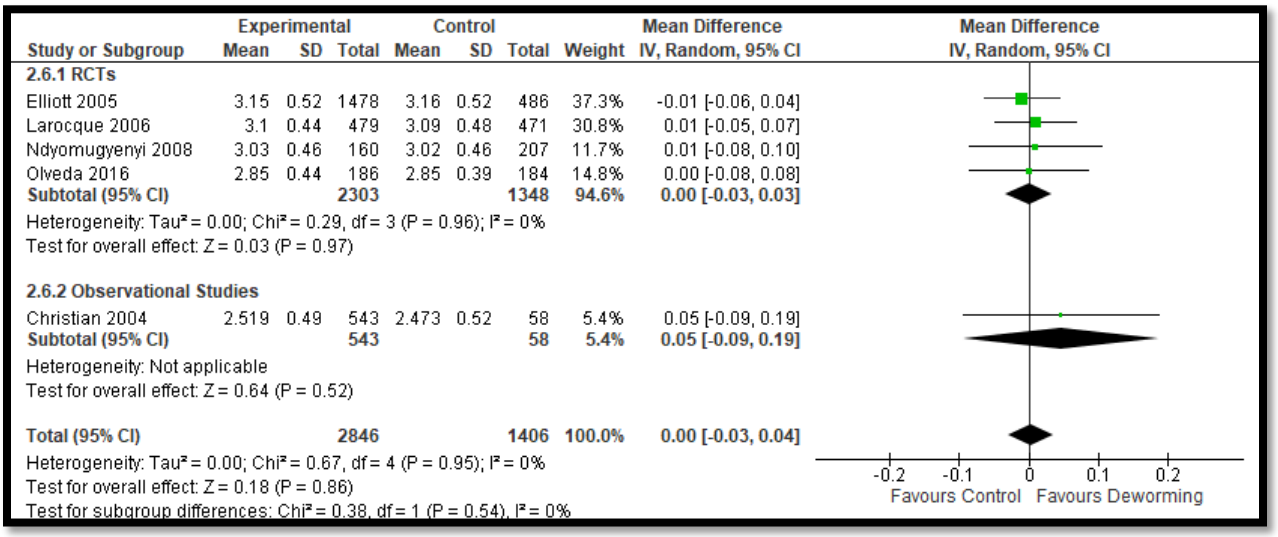
Figure 2.5: Forest plot for the impact of mass deworming during pregnancy on maternal Hb



Birth weight

Five studies with 3280 pregnant women; including four RCTs (Abel et al., 2000; Elliott, Mpairwe, et al., 2005; Larocque et al., 2005; Ndyomugyenyi et al., 2008a; Olveda et al., 2016) and one non-randomised study (Christian et al., 2004) reported data on birth weight suggesting no impact from RCT (MD: 0.00 kg, 95% CI: -0.03-0.03) and non-randomised studies (MD: 0.05 kg, 95% CI: -0.09-0.19). Figure 2.6 depicts the forest plots for the impact of mass deworming during pregnancy on birth weight.

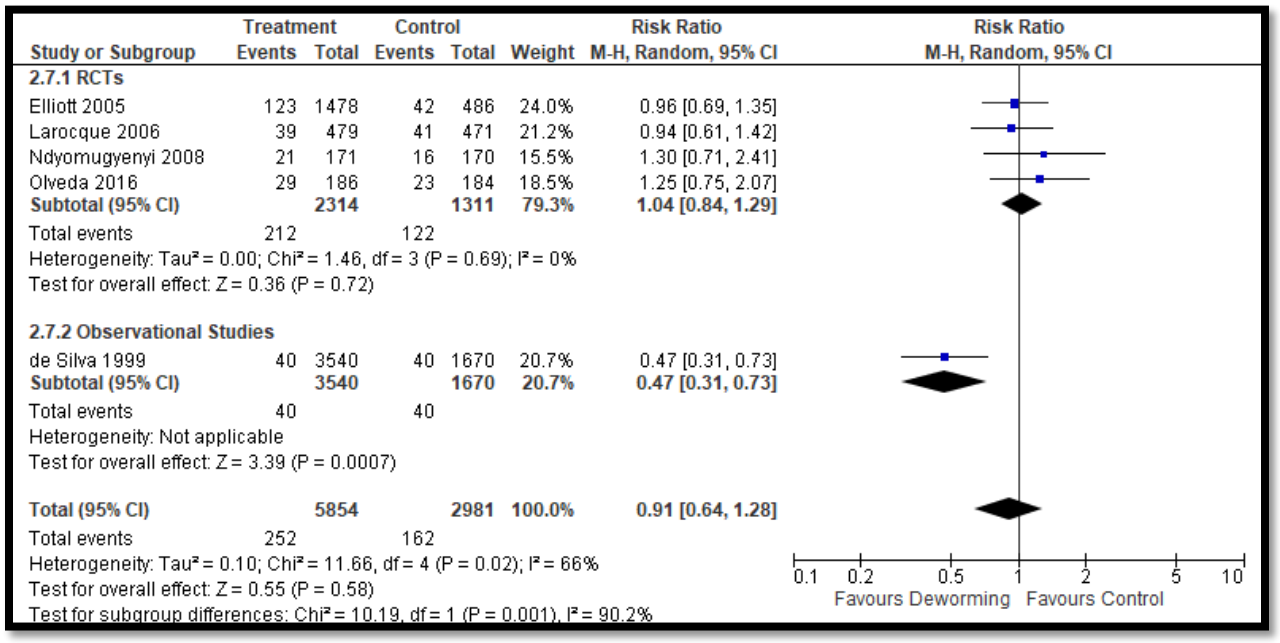
Figure 2.6: Forest plot depicting the impact of mass deworming on birth weight



LBW

Five studies with 8835 pregnant women; including four RCTs (Elliott, Mpairwe, et al., 2005; Larocque et al., 2005; Ndyomugyenyi et al., 2008a; Olveda et al., 2016) and one non-randomised study (De Silva et al., 1999) reported data on LBW suggesting non-significant impact from RCTs (RR: 1.04, 95% CI: 0.84-1.29) while a significant reduction in LBW from non-randomised study (RR: 0.47, 95% CI: 0.31-0.73). The outcome was judged to be of 'moderate' quality due to high risk of selection bias in one of the studies. Figure 2.7 depicts the forest plot for the impact of mass deworming during pregnancy on LBW.

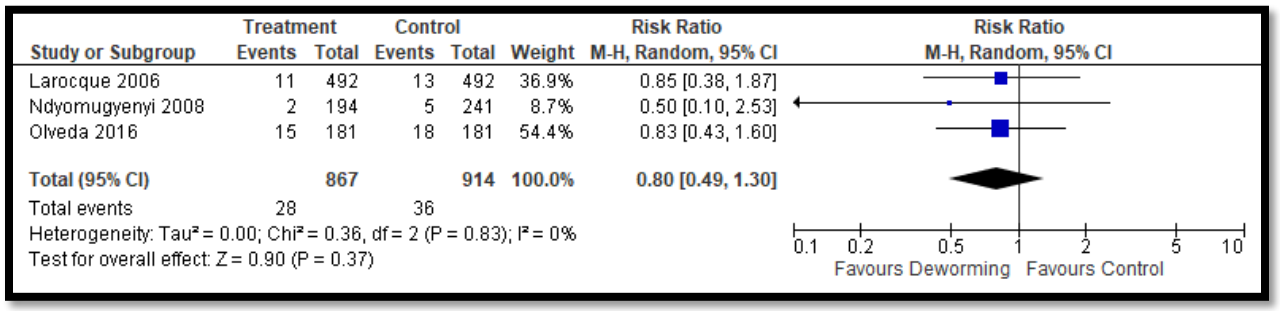
Figure 2.7: Forest plot depicting the impact of mass deworming during pregnancy on LBW



Preterm Birth

Three RCTs (Larocque et al., 2005; Ndyomugyenyi et al., 2008a; Olveda et al., 2016) with 1318 pregnant women reported preterm birth showing a non-significant impact of mass deworming during pregnancy on preterm birth (RR: 0.80, 95% CI: 0.49-1.30). The outcome was judged to be of 'moderate' quality due to high risk of selection bias in one of the studies. Figure 2.8 depicts the forest plot for the impact of mass deworming on preterm birth.

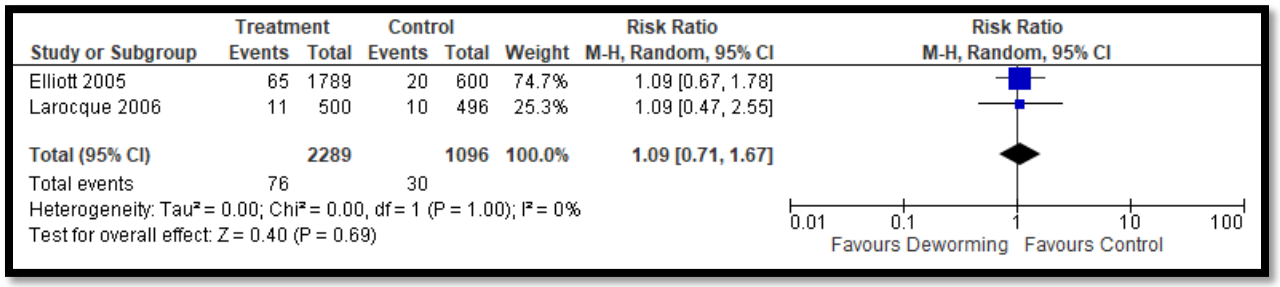
Figure 2.8: Forest plot depicting the impact of mass deworming during pregnancy on preterm birth



Perinatal Mortality

Two RCTs (Elliott, Mpairwe, et al., 2005; Larocque et al., 2005) with 3385 pregnant women reported data on perinatal mortality suggesting no clear impact on perinatal mortality (RR: 1.09, 95% CI: 0.71-1.67); . Figure 2.9.

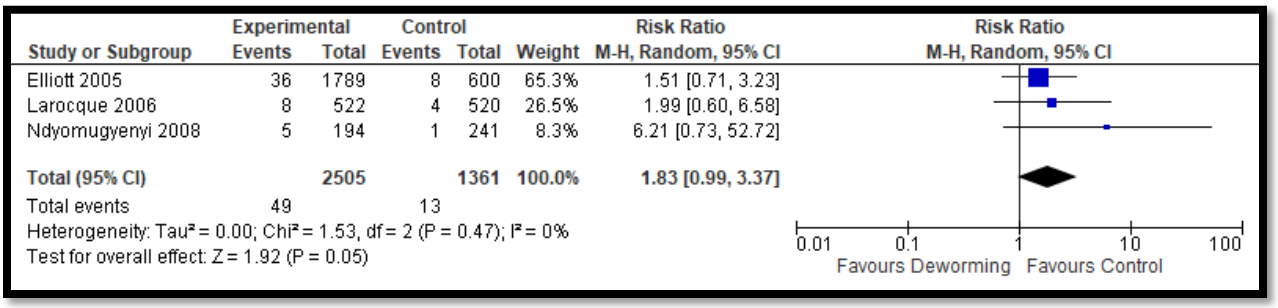
Figure 2.9: Forest plot for the impact of mass deworming during pregnancy on perinatal mortality



Stillbirth

Three RCTs (Elliott, Mpairwe, et al., 2005; Larocque et al., 2005; Ndyomugyenyi et al., 2008a) with 2671 pregnant women reported data on stillbirths suggesting slight increase in stillbirth (RR: 1.83, 95% CI: 0.99-3.37). Figure 2.10 depicts the forest plot for the impact of mass deworming on stillbirths.

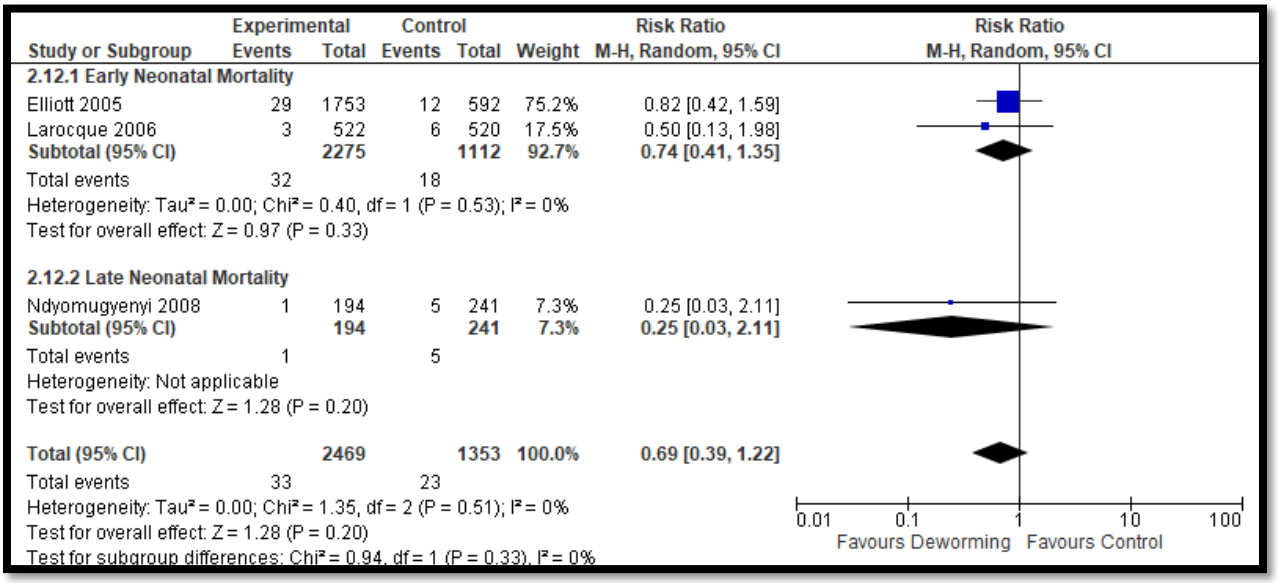
Figure 2.10: Forest plot for the impact of mass deworming on stillbirths



Neonatal Mortality

Three RCTs (Keiser & Utzinger, 2008; J Ndibazza et al., 2010; Torlesse & Hodges, 2000) with neonates reported data on neonatal mortality suggesting no impact on either early (RR: 0.74, 95% CI: 0.41-1.35) or late neonatal mortality (RR: 0.25, 95% CI: 0.03, 2.11). Figure 2.11 depicts the forest plot for the impact of mass deworming during pregnancy on neonatal mortality.

Figure 2.11: Forest plot for the impact of mass deworming during pregnancy on neonatal mortality



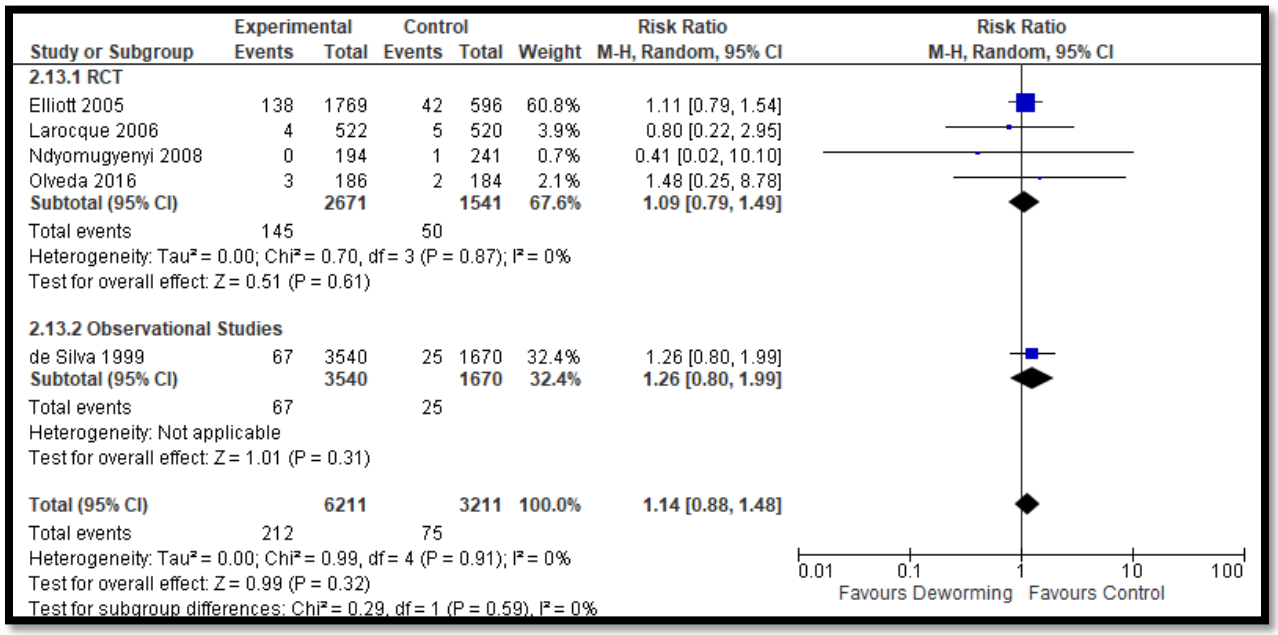
Infant Mortality

One non-randomised study (Christian et al., 2004) with 1147 infants reported data on infant mortality suggesting no impact of maternal deworming on infant mortality (RR: 1.06, 95% CI: 0.7-1.62).

Congenital Anomalies

Five studies with 8239 pregnant women; including four RCTs (Elliott, Mpairwe, et al., 2005; Renee Larocque et al., 2005; Ndyomugyenyi et al., 2008; Olveda et al., 2016) and one non-randomised study (De Silva et al., 1999) reported data suggesting no impact of mass deworming during pregnancy on congenital anomalies from RCTs (RR: 1.09, 95% CI: 0.79-1.49) and non-randomised study (RR: 1.26, 95% CI: 0.8-1.99). Figure 2.12 depicts the forest plot for the impact of mass deworming on congenital anomalies.

Figure 2.12: Forest plot for the impact of mass deworming during pregnancy on congenital anomalies



Summary of the Findings

Table 2.5 reports the summary of the findings according to the GRADE criteria. Outcomes were rated to be of moderate to low quality owing to study limitations and high heterogeneity.

Table 2.5: Summary of the findings table (RCTs only)

Mass Deworming versus Control for STH and Schistosomiasis during Pregnancy

Patient or population: Pregnant women in second or third trimester of pregnancy
Settings: Antenatal clinics and community mainly in low-middle-income countries
Intervention: Any deworming drug versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Mass deworming versus control				
Maternal anaemia in third trimester (< 11 g/dL)	Study population 455 per 1000	395 per 1000 (81 to 1000)	RR 0.97 (0.89 to 1.05)	6696 (6 studies)	⊕⊕⊕⊖ moderate[1]	
Hookworm prevalence	Study population 419 per 1000	170 per 1000 (45 to 352)	RR 0.35 (0.11 to 1.10)	3299 (5 studies)	⊕⊕⊖⊖ low[2]	
***Trichuris* prevalence**	Study population 423 per 1000	314 per 1000 (45 to 779)	RR 0.82 (0.52 to 1.27)	2690 (4 studies)	⊕⊕⊕⊖ moderate[3]	
***Ascaris* prevalence**	Study population 300 per 1000	72 per 1000 (0 to 170)	RR 0.24 (0.19 to 0.29)	2328 (3 studies)	⊕⊕⊕⊖ moderate[3]	
LBW (birth weight < 2500 grams)	Study population 93 per 1000	92 per 1000 (81 to 156)	RR 1.04 (0.84 to 1.29)	3625 (4 studies)	⊕⊕⊕⊖ moderate[3]	
Preterm birth (birth before 37 weeks of gestation)	Study population 39 per 1000	32 per 1000 (10 to 83)	RR 0.80 (0.49 to 1.30)	1781 (3 studies)	⊕⊕⊕⊖ moderate[3]	

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

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

Footnotes
[1] Downgraded by 1 for high risk of attrition bias in Torlesse 2001 and Urassa 2011.
[2] Downgraded by 2 for high risk of attrition bias in Urassa 2011 and high heterogeneity $I^2 = 98\%$
[3] Downgraded by 1 for unclear risk of selection bias in Ndyomugyenyi 2008.

Discussion and Conclusions

This review summarises findings from 16 studies (31 papers) including 45,710 pregnant women. Nine of the included studies were RCTs while seven studies were non-randomised studies. The majority of the included studies targeted STH while two studies targeted schistosomiasis alone. Findings suggest that among the primary outcomes of the review; mass deworming during pregnancy does not have any impact on maternal anaemia; however mass deworming during pregnancy significantly reduced the prevalence of *Ascaris*, *S.japonicum* and *S.mansoni*. There was no impact on the prevalence of hookworm, *Trichuris* and any of the secondary outcomes including Hb, birth weight, LBW, preterm birth, perinatal mortality, stillbirths, neonatal mortality and congenital anomalies. The quality of the included trials was reasonable while the non-randomised studies were judged to be of low quality. The quality of evidence according to GRADE criteria ranged from low to moderate. All the studies were conducted in low-middle-income countries except one study conducted in Hungary. Planned subgroup analysis could not be conducted due to the limited number of studies included in the review; however an individual participant data analysis (IPD) was planned to explore the findings further from this systematic review.

These findings are consistent with the existing three systematic reviews on mass deworming during pregnancy (Brooker, Hotez, & Bundy, 2008; Imhoff-Kunsch & Briggs, 2012; Salam et al., 2015). The review by (Brooker et al., 2008) only included hookworm studies suggesting that there is insufficient data to quantify the benefits of deworming. This review however also recommended increased coverage of anthelminthic treatment among pregnant women. The review by (Imhoff-Kunsch & Briggs, 2012) evaluated deworming for STH and concluded that there was no clear benefit of deworming on maternal, newborn and child health outcomes, however the review suggested that there may be a public health benefit to alleviate the burden of STH infections in pregnant women. Finally, the Cochrane review by (Salam et al., 2015) evaluating deworming for STH concluded that the evidence was insufficient to recommend use of deworming drugs for STH among pregnant women. This review focused on RCTs only and did not measure worm prevalence as an outcome. Our systematic review collates the most recent evidence on mass deworming for STH and schistosomiasis during pregnancy suggesting that the intervention is effective in reducing the worm burden; however there is little impact on any other maternal, birth or newborn health outcomes.

Despite of the comprehensive evaluation of the effectiveness of mass deworming during pregnancy for STH and schistosomiasis in this review; there are some limitations and questions that remain beyond the scope of this exercise and still remain unanswered. Firstly, the number of trials included in the existing evidence

base is very small; that is only seven trials; of which only one trial assessed the effectiveness of mass deworming for schistosomiasis. Secondly, the analysis is limited in scope to make inferences for concurrent administration of iron supplementation, variable periods of follow-up, different baseline prevalence (and intensities) of infections; owing to the small sample size. Thirdly, all the included studies provided preventive mass deworming (deworming drugs administered to the entire population disregarding their infection status with the intent of providing treatment benefit to those who are infected and uninfected persons are treated because the program is applied to the whole population for logistical and cost reasons); and hence measuring the benefits of the intervention on the entire treated group therefore might not be appropriate as benefits might only accrue to those infected and not to those uninfected. Fourthly, the prevalence and intensity of STH and schistosomiasis infections varied greatly across the included studies. Finally, other interventions (including water, sanitation and hygiene interventions) also need to be evaluated along with deworming for the control of morbidity. There is a need to critically appraise the existing studies in order to account for various factors that could modify the effectiveness of mass deworming including nutritional status, type of infection, worm burden and other concomitant interventions (Barry et al., 2013; Turner et al., 2015). Since systematic reviews are conducted at the study level, rather than using data for each individual participant, the power of the systematic reviews to detect effect modification by individual participant characteristics is limited. Currently, it is difficult to establish whether deworming during pregnancy has beneficial effects under certain conditions and limited effects under others and there exists a possibility that it is only beneficial in women with very high parasite burdens, dietary insufficiencies, or both (Blackwell, 2016). An IPD meta-analysis was planned to explore the question of whether mass deworming during pregnancy is more effective for subgroups of women defined by characteristics such as nutrition status and infection intensity. Findings from this planned IPD meta-analysis are reported in the coming chapters.

Chapter 3: Systematic review and meta-analysis to assess the effectiveness of interventions other than deworming for pregnant women and women of reproductive age on maternal, birth and newborn health outcomes

Abstract

Background

Mass deworming with anthelminthic drugs is endorsed as an effective strategy for the prevention and control of soil transmitted helminthiases (STH) and schistosomiasis. However, deworming alone offers only a short term control unless augmented by additional control interventions (including water, sanitation and hygiene interventions) to break the infection transmission cycle. Furthermore, there are concerns related to drug resistance associated with the scale-up of periodic mass deworming campaigns.

Methods

We conducted a systematic review and meta-analysis to assess the effectiveness of interventions other than deworming (based on our conceptual framework) for pregnant women and women of reproductive age (WRA) on maternal, birth and newborn health outcomes. We used a comprehensive search strategy to identify eligible studies regardless of date of publication, language, or publication status till March 2018.

Findings

From a total of 2324 records identified; seven studies fulfilled the eligibility criteria and were included in this review. One study was a quasi-experimental study; one prospective cohort study; while five studies were cross-sectional. Two studies included pregnant women while all other studies included WRA. Studies were conducted in Bangladesh, China, Kenya, Rwanda, Tanzania and Vietnam. None of the included studies reported any of the pre-defined primary or secondary outcomes and meta-analysis could not be conducted due to the study design limitations and heterogeneity in the studies. Findings from one quasi-experimental study suggested that health education related to schistosomiasis prevention and treatment was significantly associated with reductions in the rate of infested water exposure and infection rate. Data from other included cross-sectional studies suggested that STH and schistosomiasis prevalence is significantly associated with geophagy during pregnancy, hand washing, consuming piped water and availability of latrine.

Interpretation

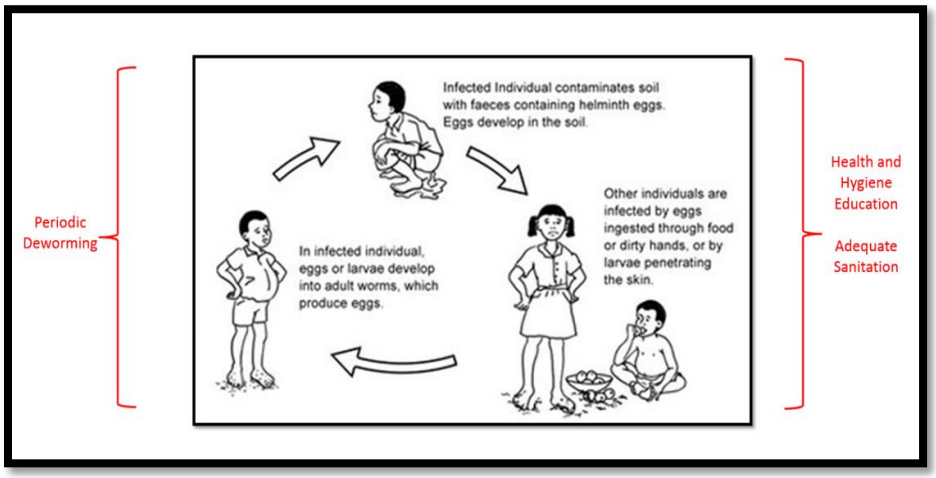
This review suggests that the existing evidence pertaining to interventions other than deworming among pregnant women and WRA on maternal, birth and newborn health outcomes is scarce and of low quality.

Introduction

Recent data from the Global Burden of Diseases (GBD) Study suggests that soil transmitted helminthiasis (STH) infections (including ascariasis, trichuriasis, and hookworm infections) accounted for 1.75 billion prevalent cases; while schistosomiasis alone accounted for 291 million prevalent cases in 2013 (Herricks et al., 2017). Ascariasis, trichuriasis, and hookworm infections alone are accountable for more than three-quarters of the total prevalence of neglected tropical diseases (NTD). Moreover, over the last two decades, there has been no substantial reduction in the prevalence of schistosomiasis and only a modest impact on hookworm and trichuriasis has been observed (Herricks et al., 2017). Among adolescent and adult women, schistosomiasis and hookworm infection still remain the leading causes of disability adjusted life years (DALYs) (Kassebaum et al., 2014). Furthermore, DALYs for schistosomiasis may have been even higher if female genital schistosomiasis is taken into consideration (Herricks et al., 2017).

STH is transmitted through the eggs present in the faeces of an infected person which contaminate the soil in areas with poor water and sanitation facilities. These eggs mature in soil and infect other people when ingested through contaminated hands or food or penetrate the skin of the person walking barefoot on contaminated soil. Schistosomiasis is transmitted when infected persons' faeces containing parasite eggs are released in fresh water, these eggs hatch and the subsequent larvae infect susceptible snail hosts. These larvae undergo asexual multiplication in snails and release another larval stage into water which penetrate the skin during contact with infested water and infect the human host during domestic, occupational and recreational contact with water. Figure 3.1 depicts the transmission cycle for STH.

Figure 3.1: Transmission cycle for STH



Currently, no vaccines are licensed for STH and schistosomiasis; and mass deworming with anthelminthic drugs is endorsed as an effective strategy for the prevention and control along with appropriate water, sanitation and hygiene (WASH) interventions and education (WHO, 1994, 2017). Deworming treatment alone offers only a short term control unless augmented by additional control interventions to break the transmission cycle. Deworming drugs kill the adult parasites within the human host but do not prevent rapid reinfection if the host contacts an environment contaminated with infective stages of the parasites. Therefore, there exists a risk that the prevalence of infection will return to pre-treatment levels within six to 12 months of a single round of deworming (Campbell, Savage, & Gray, 2014; Freeman et al., 2013; Jia, Melville, Utzinger, King, & Zhou, 2012). Furthermore, there are concerns related to drug resistance associated with the scale-up of periodic mass deworming campaigns (Moser et al., 2017; Palmeirim et al., 2018).

A massive burden of disease is associated with insufficient hygiene, sanitation, and water supply and this is largely preventable with proven, cost-effective interventions (Bartram & Cairncross, 2010). Inadequate WASH is estimated to be responsible for 4% of deaths and 5.7% of disease burden worldwide, primarily driven by its role in the transmission of diarrhoeal disease and helminthiases (Prüss, Kay, Fewtrell, & Bartram, 2002). Geographically, the prevalence of the STH and schistosomiasis is especially high in the large middle-income countries in Oceania, Southeast Asia, and South Asia; countries where WASH facilities are highly inadequate (Herricks et al., 2017; WHO). The WHO identifies girls and women of reproductive age (WRA) amongst the most vulnerable population groups for STH and schistosomiasis (WHO, 2006); however these groups remains the most neglected groups for WASH facilities especially in poor resource settings (Giné-Garriga, Flores-Baquero, de Palencia, & Pérez-Foguet, 2017). A recent feasibility modelling study suggested that it is possible to stop STH transmission; however it will require a collaborative approach including a clean environment, appropriate delivery platforms and strong political will (Brooker et al., 2015).

The existing data evaluating the impact of WASH interventions on STH schistosomiasis is scarce; of low quality; and on general population groups rather than the population groups vulnerable to the disease (Grimes et al., 2014; Salam et al., 2014; Strunz et al., 2014; Ziegelbauer et al., 2012). Furthermore, the existing reviews fail to assess the impact of WASH interventions during pregnancy in addition to mass deworming and its impact on maternal, newborn and health outcomes. The aim of this review, therefore is to assess the effectiveness of interventions other than deworming (including WASH interventions) on maternal, birth and newborn health outcomes.

Objective

To evaluate the effectiveness of interventions other than deworming (including WASH interventions) for WRA on maternal, birth and newborn health outcomes.

Methodology

Criteria for considering studies for this review

Types of studies

We included primary studies using experimental or quasi-experimental study designs that allow for causal inferences. We aimed to include randomised controlled trials (RCTs), quasi randomised studies and controlled before after studies (CBA); however we did not find any eligible RCTs. We also included case-control and cross-sectional studies reporting associations between WASH interventions and maternal, birth and newborn health outcomes. We excluded case reports and case-series.

Types of participants

Participants were WRA receiving interventions other than deworming (including WASH interventions and education) for STH and schistosomiasis prevention and management. For the studies including WRA as a subset of the total study population, we only included such studies if the results were separately provided for the WRA subgroup.

Types of interventions

We included any intervention other than deworming compared to no intervention. Interventions could include WASH interventions like use of latrines, sewage disposal, safe water, wearing shoes, hand washing before eating and after defecation, nutrition and food safety, and education. We excluded studies that only reported associations between participant knowledge of the WASH strategies and outcomes of interest. Studies assessing the efficacy of different methods to assess exposures to risk factors were also excluded.

Types of outcome measures

The following primary and secondary outcomes were reported. However we did not use the list of outcomes as a criterion for inclusion, that is, we included studies if they fulfilled the eligibility criteria and did not report any of the following outcomes of interest.

-Primary outcomes:

- Maternal anaemia at term (defined as haemoglobin (Hb) less than 11 g/dL)

- Maternal infection intensity (as defined and reported by the study authors)

-Secondary outcomes:

- Maternal Hb at term
- Maternal ferritin at term
- Maternal anthropometric measures (including maternal weight, body mass index (BMI), gestational weight gain etc.)
- Birth weight
- Low birth weight (LBW) (defined as birth weight less than 2500 grams)
- Preterm birth (defined as birth before 37 weeks of gestation)
- Perinatal mortality (includes foetal death after 28 weeks of gestation and neonatal death that occurs at less than seven days of life)
- Stillbirth (defined as a baby born with no signs of life at or after 28 weeks' gestation)
- Congenital anomalies (defined as structural or functional anomalies (e.g. metabolic disorders) that occur during intrauterine life and can be identified prenatally, at birth or later in life)
- Infant mortality (defined as the number of deaths among children under one year of age occurring among the live births in a given geographical area during a given year, per 1,000 live births occurring among the population of the given geographical area during the same year)

Search methods for identification of studies

We used a comprehensive search strategy to identify eligible studies regardless of date of publication, language, or publication status till March 2018. The search strategy is attached as Appendix 3.

Electronic searches

We searched the following electronic databases: MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin-American and Caribbean System on Health Sciences Information (LILACS), Excerpta Medica dataBASE (EMBASE), the Cochrane Library, Global Health CABI and Centre for Agriculture

and Biosciences (CAB) Abstracts. We searched websites of relevant organizations such as the WHO Neglected Tropical Diseases, World Bank and World Food Program.

Searching other resources

We also contacted authors of studies and members of the study's advisory board for any unpublished studies or grey literature reporting eligible studies. We checked reference lists of relevant studies and reviews. We also searched for trials registered with ClinicalTrials.gov.

Data collection and analysis

Selection of studies

Two reviewers independently assessed potential study eligibility using predefined screening criteria. Any studies considered obviously irrelevant from screening the titles and/or abstracts were excluded at the first level. Any uncertainties at the first level screening were re-assessed on the basis of full text in the second level of screening. For any discrepancies, study's advisory group was contacted for the final decision. Any disagreements were resolved through discussion until a consensus was reached.

Data extraction and management

We extracted data from included studies on the following:

- Background: time period when study took place, type of publication (e.g. full-text journal article, abstract, conference paper, thesis) and study country or countries.
- Population and study setting: population age and setting.
- Methods: study design, description of study arms, unit of allocation, sample or cluster size per study arm (for individually or cluster randomised trials respectively), start and end date, duration of follow up.
- Participants: total number randomised, baseline characteristics, number of withdrawals, socio-demographic data (if available).
- Intervention group details: number randomised to group, description of intervention, co-interventions, duration and follow-up, timing and delivery of intervention. In case of studies with multiple intervention arms, we described all arms, while we reported the arms that met the inclusion criteria.

- Comparison group details: number randomised to group, description of comparison, duration and follow-up, timing and delivery.
- Outcomes: measurement tool, total number in intervention and comparison groups, change indicated at each time point. In case if multiple measures are reported for the same outcome construct, we used the one pre-specified in protocol.
- Any other information deemed relevant.

Assessment of risk of bias in included studies

We assessed the quality of the included studies using the Cochrane risk of bias assessment tool for the RCTs. The quality of the RCTs was assessed based on selection bias, performance bias, detection bias, attrition bias and reporting bias (Higgins et al., 2011). For non-randomised studies, we used the Cochrane Effective Practice and Organisation of Care (EPOC) group criteria for risk of bias assessment (EPOC, 2015). Quality of non-randomised studies was assessed based on baseline outcome measurements similar, baseline characteristics similar, incomplete outcome data, knowledge of the allocated interventions adequately prevented during the study, protection against contamination, selective outcome reporting and other risk of bias. We summarised the quality of evidence according to the outcomes as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (Guyatt et al., 2011). A grade of "high", "moderate", "low" and "very low" were used for grading the overall evidence indicating the degree of certainty of an effect on specific health outcome based on methodological flaws within the component studies, consistency of results across different studies, generalizability of research results to the wider patient base and how effective the treatments have been shown to be (Balshem et al., 2011).

Measures of treatment effect

For each outcome, data were converted to the same format (e.g. means and standard deviations for continuous data), including appropriate conversion of scales such that an increase/decrease always indicates improvement or deterioration of an indicator. Dichotomous and continuous outcomes were analysed separately. For dichotomous outcomes, results were presented as summary risk ratios (RRs) or odds ratio (OR) with 95% confidence intervals (CI), whenever possible, in order to compare risk of the outcome between intervention and control groups. Continuous outcome data were presented as either a mean difference (MD), if outcomes were measured on the same scale, or a standardized mean difference (SMD), if outcomes were measured on different scales, with 95% CI.

Unit of analysis issues

In order to take into account potential sources of dependency, we grouped studies in terms of their location, population and the intervention being evaluated to ensure that there was no double counting of evidence when synthesizing results across studies. If there were multiple papers that described the same study, these were combined and coded as a single study.

For studies that included multiple intervention arms, we planned to select one pair (intervention and control) that satisfied the inclusion criteria of the review and exclude the rest. If more than two intervention groups met the eligibility criteria, then we planned to combine these groups into a single pair-wise comparison group and combined data were disaggregated into corresponding subgroups, or these arms were separated into different forest plots to ensure that there is no double counting of participants. However, we did not come across any such study.

Dealing with missing data

Where data were incomplete or in a form that could not be converted with the information available, we contacted the corresponding author for clarification or to obtain missing data. If authors accounted for missing data (i.e. multiple imputations), we used the adjusted data within our analysis.

Assessment of heterogeneity

Clinical and methodological heterogeneity was explored by assessing the similarities and differences in included studies' participants, interventions, outcomes, and methods. Statistical heterogeneity was assessed by visually inspecting forest plots, calculating the I^2 statistic (>50% indicated substantial heterogeneity) and conducting a Chi^2 test, where a p-value <0.1 was considered statistically significant. Sources of heterogeneity was explored using sub-group analysis (where possible).

Assessment of reporting bias

If the number of studies was sufficient (>10), funnel plots were used to visually assess publication bias. This kind of bias is unlikely if data forms a symmetric inverted funnel shape around the mean effect estimate.

Data synthesis

We planned to conduct meta-analysis using Review Manager 5.3, for comparable interventions and outcomes. However, due to limitation in the study design and heterogeneity in the included studies, we could not conduct meta-analysis for this review and have reported the findings narratively. For interpretation of results, overall effect estimates that had an associated p-value <0.05 were deemed statistically significant. Non-significant findings were also reported.

Subgroup analysis and investigation of heterogeneity

Depending on data availability, we planned an exploratory sub-group analyses on the primary outcomes for the various types of interventions; however due to limited number of studies included in this review, we could not conduct any subgroup analysis.

Sensitivity analyses

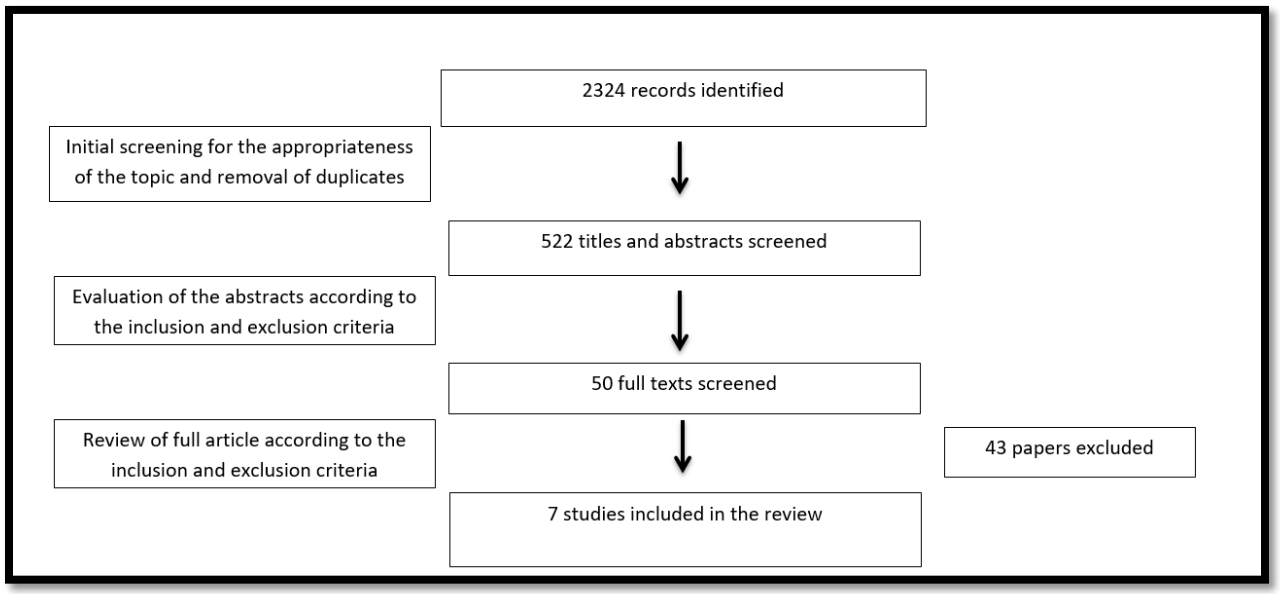
Sensitivity analyses was planned to be conducted to determine whether the removal of studies with high risk of bias or the removal of non-randomised studies significantly impact findings. However, we could not conduct any sensitivity analysis due to the limited number of studies included in this review.

Results

Search results

A total of 2324 records were identified using the search strategy specified in Appendix 3. Seven papers fulfilled the eligibility criteria and were included in the review. Majority of the studies were excluded since they did not provide data on WRA. Figure 3.2 depicts the search flow diagram and Appendix 4 provides reasons for exclusion for the excluded studies.

Figure 3.2: Search Flow Diagram



Characteristics of studies

A total of seven studies were included: one quasi-experimental study (Guanghan et al., 2000); one prospective cohort study (Luoba et al., 2005); and five cross-sectional surveys (Benjamin-Chung et al., 2015; Ivan et al., 2013; Nguyen, Nguyen, Nguyen, & Le, 2006; Sera et al., 2007; Stothard et al., 2008). Two studies

(Ivan et al., 2013; Luoba et al., 2005) included pregnant women while all others included WRA. Studies were conducted in Bangladesh, China, Kenya, Rwanda, Tanzania and Vietnam. None of the included studies reported the pre-defined primary or secondary outcomes. We could not conduct meta-analysis due to the study design limitations and heterogeneity in the studies and hence the findings were narratively summarised. Characteristics of the included studies are summarised in table 3.1.

Findings

One quasi-experimental study (Guanghan et al., 2000) assessed the impact of health education for schistosomiasis control in a heavily endemic area of Poyang Lake region in China. The study included 559 participants including children and adults; findings were reported separately for children, adult women and men. Health education was implemented in the experimental group and the results were compared to a control area without health education. Health education comprised of anti-schistosomiasis knowledge, showing video tapes about schistosomiasis control, exhibiting the samples of *Schistosomiasis japonica* and pasting up pictures about schistosomiasis control. Training on techniques for preventing infection with *S. japonicum* and how to wear appliances and smear medicine for protection was also provided. Findings from this study suggests that health education for schistosomiasis prevention and management led to increased anti-schistosomiasis knowledge among WRA along with reduction in the rate of infested water exposure (6.7% in the intervention group compared to 11.5% in the control group) and infection rate (7.1% in the intervention group compared to 21.1% in the control group). The study concluded that health education regarding schistosomiasis prevention is potentially effective in reducing infection *S. japonicum* among WRA.

Two studies; one prospective cohort and one cross-sectional survey, assessed the association between geophagy and reinfection with STH among pregnant women and WRA. The prospective cohort study was conducted among 827 pregnant women in Nyanza Province in western Kenya (Luoba et al., 2005). This study assessed the effect of earth-eating (geophagy) during pregnancy on STH reinfection after treatment. The women were recruited at a gestational age of 14 to 24 weeks and followed up to 6 months postpartum. After deworming of the infected women with mebendazole (500 mg, single dose) at 32 weeks gestation, the women were reassessed for infection post-partum. The re-infection rate for hookworm was found to be 14.8%, for *T. trichiura* 6.6%, and for *A. lumbricoides* 5.2% at three months postpartum, and 16%, 5.9% and 9.4% at six months postpartum. The study concluded that geophagy is associated with re-infection with STH among pregnant and lactating women and that intensities built up more rapidly among geophagous women. Another cross-sectional survey was conducted among 970 women from Pemba Island, Zanzibar, Tanzania that assessed association between geophagy and STH prevalence (Sera et al., 2007). This study suggested

that neither the prevalence nor the intensity of infection with *Ascaris, Trichuris* or hookworm differed significantly by geophagy status.

Four studies were cross-sectional surveys. One cross-sectional study was conducted among 980 HIV-infected pregnant females from health centers in rural and peri-urban locations in the central and eastern provinces of Rwanda (Ivan et al., 2013). The prevalence of any STH infections was found to be 34.3% among pregnant women. Findings suggest that hand washing was associated with reduced infection with any STH (OR: 0.29, 95% CI: 0.19 to 0.46) as well as with infections with *Trichuris* (OR: 0.52, 95% CI: 0.33 to 0.8) and hookworm (OR: 0.2, 95% CI: 0.1 to 0.4). Consuming piped water compared to river water was associated with significant reductions in *Ascaris* prevalence (OR: 0.30, 95% CI: 0.16 to 0.53); as well as any STH infection (OR: 0.23, 95% CI: 0.14 to 0.38). Findings from this study suggest that HIV-positive pregnant women would benefit from the scaling up of de-worming programs alongside health education and hygiene interventions.

Another cross-sectional survey in 100 villages in rural Bangladesh assessed exposures to self-reported deworming consumption in the past six months, access to a hygienic latrine, and household flooring material among 532 WRA (Benjamin-Chung et al., 2015). The prevalence of any infection among WRA in this study was 30.3%, prevalence of *Ascaris* was 11.8%, prevalence of hookworm was 6.4% and prevalence of *Trichuris* was 18.2%. Another study utilized the nationwide survey data from Vietnam to assess the risk factors for STH infection among 5127 women (Nguyen et al., 2006). About 76% women were found to be infected with one or more STH species; 36% with hookworm, 59% with *Ascaris lumbricoides* and 28% with *Trichuris trichiura*. Hookworm infection was found to be associated with a lack of a closed latrine (OR: 2.1; 95% CI: 1.4 to 3.1). This study concluded that WRA, especially rural farmers, should be included among the high priority groups for STH control programs through mass deworming and improving sanitation. Another cross-sectional study conducted across 10 Ungujan villages in Zanzibar among 322 mothers and their pre-school children suggested that among mothers, the mean prevalence for ascariasis was found to be 6.7%, for trichuriasis was 11.9% and for hookworm was 1.9% (Stothard et al., 2008). Findings from this study suggested that access to a household latrine was a significantly associated protective factor for any STH infection (OR: 0.56; 95% CI: 0.32 to 0.99). The study concluded that intervention efforts should be stepped up and greater efforts placed upon improving household sanitation.

Table 3.2 summarizes the associations between various WASH exposures and worm burden from the included studies.

Table 3.1: Characteristics of the included studies

Serial No	Study ID	Study Design	Country/Setting	Sample Size	Intervention/Exposure	Control Group	Outcomes Reported
1.	Benjamin-Chung 2015 (Benjamin-Chung et al., 2015)	Cross-sectional survey	Rural Bangladesh	1630 participants from 100 villages including 532 WRA	Exposure to: self-reported deworming consumption in the past six months, access to a hygienic latrine, and household flooring material		Prevalence of STH Access to hygienic latrines
2.	Guanghan 2000 (Guanghan et al., 2000)	Quasi experimental study	Heavy endemic area of Poyang Lake including two natural villages, Lotun and Taojia, located in Xinjian county of Jiangxi Province, were selected as field sites in China	543 participants with 204 WRA	Health education for schistosomiasis control including education based on anti-schistosomiasis knowledge by showing video-tape about schistosomiasis control, exhibiting the samples of schistosomiasis japonica and pasting up the pictures about schistosomiasis control and lecturing the technique of protecting from infection with *S.japonicum* and setting an example for how to wear appliances and smear medicine for protecting from infection with *S.japonicum.* A single course of anti-schistosomiasis was also provided.	No health education	Anti-schistosomiasis knowledge Anti-schistosomiasis attitude and value concept Infested water exposure Infection rates
3.	Ivan 2013 (Ivan et al., 2013)	Cross-sectional survey	Health centres in rural and peri-urban locations in the central and eastern provinces of Rwanda	Pregnant females with HIV (n=980) were recruited	Exposure to: education, employment, hand washing, piped/river water, wearing shoes and dietary supplements		Prevalence of helminthic infection Prevalence of malaria Prevalence of helminthic and malaria co-infection Association of helminthic infection with water, shoe

							wearing and hand washing
4.	Luoba 2005 (Luoba et al., 2005)	Prospective cohort	Two locations of Usigu Division, Bondo District, Nyanza Province, western Kenya	827 pregnant women	Exposure to geophagy-earth-eating habit		Prevalence of helminthic infection Intensity of helminthic infection Reinfections associated with geophagy
5.	Nguyen 2006 (Nguyen et al., 2006)	National survey	Vietnam	5127 non-pregnant women	Exposure to geographic area, occupation, education and place of defecation		Prevalence of helminthic infection Association of helminthic infections with risk factors
6.	Stothard 2008 (Stothard et al., 2008)	Cross-sectional survey	10 villages on Unguja Island representative of urban, semi-urban and rural environments in Zanzibar	Mothers (n=322) and their pre-school children (n=359)	Exposure to knowledge about STH, household latrine, access to local health services, received STH treatment ever, received Vitamin A supplement ever, child immunizations, wear shoes/sandals, play on the ground, have ever passed blood in stool, have ever passed worms in stool		Prevalence of helminthic infection Infection intensity
7.	Sera 2007 (Sera et al., 2007)	Cross-sectional survey	Northern area of Pemba Island, Zanzibar, Tanzania	970 pregnant women	Exposure to geophagy during current pregnancy, age, urban or rural residence, ownership by household of four durable goods (bicycle, radio, home lit by electric and/or glass lanterns and a metal roof), presence of pit toilet in the home and whether the woman had received formal education		Prevalence and intensity of helminthic infection Association of helminthic infection with pit toilet in the household

Table 3.2: Associations between WASH exposures and worm burden

Study	Worm Species	Prevalence by Exposure Prevalence Ratio (PR) or Odds Ratio (OR) or Percentage Prevalence (PP) with 95% CI					
		Access to Hygienic Latrine	**Finished Floor**	**Piped Water**	**Hand Washing**	**Geophagy**	**Other Place of Defecation**
Benjamin-Chung 2015 (Benjamin-Chung et al., 2015)	*Ascaris*	PR: 0.91 (0.67, 1.24)	PR: 0.56 (0.32, 0.97)				
	Hookworm	PR: 0.73 (0.43, 1.24)	PR: 0.48 (0.16, 1.45)				
	Trichuris	PR: 1.03 (0.84, 1.27)	PR: 0.98 (0.72, 1.33)				
Ivan 2013 (Ivan et al., 2013)	*Ascaris*			OR: 0.30 (0.16, 0.53)	OR: 0.52 (0.33, 0.80)		
	Hookworm	Not Reported					
	Trichuris				OR: 0.20 (0.10, 0.40)		
Luoba 2005 (Luoba et al., 2005)	*Ascaris*					PP: 6.0 (4.0, 9.0)	
	Hookworm					PP: 9.6 (5.3, 13.9)	
	Trichuris					PP: 3.4 (1.2, 5.6)	
Nguyen 2006 (Nguyen et al., 2006)	*Ascaris*	NR					
	Hookworm						2.1 (1.4, 3.1)
	Trichuris						

Discussion and Conclusions

This review summarizes findings from seven studies with 8962 participants. Except for one quasi-experimental study and one prospective cohort all other studies were cross-sectional surveys. We could not conduct meta-analysis due to the study design limitations and heterogeneity between the included studies. Results from the included studies were summarized narratively. Findings from one quasi-experimental study suggested that health education related to schistosomiasis prevention and treatment was significantly associated with reductions in the rate of infested water exposure and infection rate. Data from other cross-sectional studies suggested that STH and schistosomiasis prevalence was significantly associated with hand washing, consuming piped water and availability of latrines. This review suggests that despite the proven role of water, sanitation and hygiene measures in prevention of STH and schistosomiasis, the existing evidence is scarce and of low quality. This systematic review has some limitations: firstly only one study assessed causal inference between intervention and outcome since all other studies were cross-sectional surveys. There are many factors that could confound the relationship between WASH access or practices and STH and schistosomiasis prevalence, including socioeconomic status, age, gender and mass deworming programs in the study region that were not accounted for in the included studies. Secondly, meta-analysis could not be conducted due to limited number of studies and study design limitations.

These findings are consistent with the existing systematic reviews in wider population groups (Grimes et al., 2014; Strunz et al., 2014; Ziegelbauer et al., 2012) suggesting that availability of sanitation, use of sanitation, use of treated water, access to piped water, wearing shoes, hand washing (both before eating and after defaecating) and soap use or even availability is significantly associated with reduced STH and schistosomiasis prevalence. Community based packaged delivery of interventions including health education to promote general hygiene and sanitation along with drug administration, iron and β-carotene supplementation, snail control, constructing latrines, eliminating cattle from the residential areas, staff training, and community mobilization have also been found to be associated with reduced prevalence of STH and schistosomiasis, improved mean haemoglobin and reduced anaemia prevalence with no clear impact on ferritin, height, weight, LBW or stillbirth (Salam et al., 2014). However, the existing reviews have assessed these interventions in general population groups and not specifically among pregnant women or WRA.

Improvements of WASH infrastructure and appropriate health-seeking behavior are necessary for achieving sustained control, elimination, or eradication of STH and schistosomiasis. A recent feasibility modelling study suggested that a collaborative approach including clean environment, appropriate delivery platform and

strong political will have the potential to break the STH transmission cycle (S. J. Brooker et al., 2015). Moreover, in order to improve drug compliance for *schistosomiasis* there is an urgent need for intensive health education campaigns before conducting mass drug administration (MDA) in order to provide disease specific information and counter the prevailing misconceptions about transmission, prevention, treatment, and drug side-effects (Inobaya et al., 2018). Despite this acknowledgement, very few programs to control STH and schistosomiasis have specific WASH focused-interventions, targets and approaches and the number further dwindles when it comes to targeting WRA and pregnant women. WHO has recently published a new Global Strategy: 'Water, Sanitation and Hygiene for accelerating and sustaining progress on Neglected Tropical Diseases' focusing on cross-cutting actions that benefit disease control for NTDs and strengthen health systems (Boisson et al., 2016). Increased attention towards WASH for STH and schistosomiasis has a great potential to catalyze synergies with integrated NTD control programs, while jointly elevating awareness of WASH and NTDs. Additional high-quality implementation research is needed to explore the potential of integrated WASH interventions alongside mass deworming programs.

Research Priorities

Following are the key research priorities when considering WASH intervention for reducing the burden of STH and schistosomiasis along with deworming:

-To understand the relative importance of STH and schistosomiasis transmission and implications for effective WASH interventions.

-To assess the access and coverage of WASH interventions among vulnerable population groups followed by rigorously evaluating the effectiveness of conventional WASH interventions on transmission.

-To evaluate the relative effectiveness of combined WASH and deworming versus deworming alone on transmission in different settings and for different populations.

-To evaluate whether WASH interventions can improve maternal and neonatal health outcomes in context of STH and schistosomiasis.

-To design and evaluate behavior change interventions to increase WASH uptake.

-To design and evaluate behavior change interventions that improve the sustainability of other hygiene behaviors (e.g. personal and domestic hygiene) in endemic populations.

Chapter 4: An individual participant data (IPD) meta-analysis to identify the factors that explain the variation in the effect of mass deworming during pregnancy

Abstract

Background

Mass deworming is recommended as an effective strategy to prevent and treat soil-transmitted helminthiases (STH) and schistosomiasis. However there is a great deal of heterogeneity in the existing evidence and the effectiveness of mass deworming in improving various maternal and newborn health outcomes is a current source of debate. Critical appraisal of existing studies suggests that these studies fail to account for various factors that could modify the effectiveness of deworming including nutritional status, type of infection, worm burden and concomitant interventions. Currently, it is difficult to establish whether mass deworming during pregnancy has beneficial effects under certain conditions and limited effects under others.

Objective

The objective of the review is to use individual participant data (IPD) meta-analysis to explore whether the effect of mass deworming during pregnancy varies with individual characteristics (nutritional status, anaemia), intensity of infection (as assessed by egg count), infection status (including species of worm), socioeconomic status, sanitation environment and co-interventions.

Search methods

We developed a search strategy with an information scientist to search MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin-American and Caribbean System on Health Sciences Information (LILACS), Excerpta Medica dataBASE (EMBASE), the Cochrane Library, Internet Documents in Economics Access Service (IDEAS), Google Scholar, Web of Sciences, Social Services Abstracts, the World Health Organization (WHO) Global Health Library, Global Health CABI and CAB Abstracts till March 2018. We also searched grey literature, websites, contacted authors and screened references of relevant systematic reviews.

Selection criteria

We included individually randomised controlled trials; cluster randomised controlled trials and quasi-randomied studies providing preventive or therapeutic deworming drugs for STH and schistosomiasis during pregnancy.

Data collection and analysis

We contacted all eligible study authors to invite them to join our investigators' collaborative group and share their individual participant data. We used a data sharing agreement. All IPD were assessed for completeness, compared to published reports and entered into a common data spreadsheet. Risk of bias was assessed using the Cochrane Risk of Bias tool. Overall quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methods. This review was registered as a protocol in the Campbell Collaboration Library.

Results

We screened 23,406 records and identified a total of 16 studies on mass deworming during pregnancy; out of which seven trials with 8515 participants were deemed to be eligible for IPD. Trial authors were contacted for all seven trials deemed eligible for the IPD. Out of the seven trials, we received data from three trials; data from two trials were no longer available (trialists were not able to retrieve the data); one trialist refused to share the data while one could not be contacted due to severe health conditions. This IPD analyzed the majority of the existing data; out of 8515 potential IPD participants; data were captured for 5957 (70%) participants.

Findings from this IPD suggest that mass deworming during pregnancy reduces maternal anaemia by 23% (risk ratio (RR): 0.77, 95% confidence interval (CI): 0.73-0.81; three trials; 5216 participants; moderate quality evidence). Mass deworming during pregnancy did not have any impact on any of other outcomes including *Trichiura* infection (RR: 0.69, 95% CI: 0.42-1.13; two trials; 2867 participants; moderate quality evidence), hookworm infection (RR: 0.52, 95% CI: 0.18-1.47; two trials; 2867 participants; moderate quality evidence), low birth weight (LBW) (RR: 0.89, 95% CI: 0.67-1.18; two trials; 2267 participants; moderate quality evidence) and preterm birth (RR: 0.69, 95% CI: 0.47-1.03; two trials; 2707 participants; moderate quality evidence). Due to limited availability of the data on the pre-defined effect modifiers, we could only assess for effect modification by baseline *Trichiura* infection, maternal anaemia at baseline and maternal body mass index (BMI) at baseline. There was no evidence of effect modification by *Trichiura* intensity at baseline, maternal anemia at baseline and maternal BMI at baseline. However these findings should be interpreted with caution due to small sample sizes.

The quality of evidence is rated as moderate for our findings. Further studies accounting for maternal baseline worm intensities, concomitant iron/folic acid supplementation and antenatal care coverage could change our findings.

Interpretation

Our analyses suggest that mass deworming during pregnancy is associated with reducing anaemia with no apparent impact on any other maternal or pregnancy outcomes. Our analyses were limited by the availability of data for the impact by subgroups and effect modification and thus there is a need to assess mass deworming for STH and schistosomiasis during pregnancy in large scale programmatic settings along with an attempt to measure various individual and environmental factors that could potentially affect its impact. There is also a need to support and promote open data for future IPDs.

Introduction

The World Health Organization (WHO) identifies three population groups at high risk for soil transmitted helminthiases (STH) and schistosomiasis including school-age children, preschool children, and girls and women of reproductive age (WRA) (WHO, 2006). A recent estimation suggests that approximately 688 million girls and WRA are at risk of STH infection; including 140 million pregnant and lactating women and another 108 million adolescent girls (Mupfasoni et al., 2018). Approximately 40 million WRA are infected with schistosomiasis (Friedman et al., 2007; Nour, 2010). Geographically, the WHO South-East Asia and African regions have the highest numbers of WRA subgroups, accounting for 74.7% of all STH at-risk WRA (Mupfasoni et al., 2018). STH and schistosomiasis during pregnancy causes active and debilitating disease with adverse effects on birth outcomes and the infant's developing immune system (Bustinduy et al., 2017; Freer et al., 2017; Sanya et al., 2017).

The WHO recommends mass deworming for STH and schistosomiasis depending on prevalence of worm infection. Preventive chemotherapy (deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), is recommended as a public health intervention for pregnant women. For schistosomiasis, annual treatment with praziquantel in high risk communities (>50%) and once every two years in medium risk communities (>10% and <50%) is recommended and women can be treated with praziquantel at any stage of pregnancy and lactation. In addition to deworming; education on health and hygiene and provision of adequate sanitation is also recommended.

Mass drug administration (MDA) along with the water, sanitation and hygiene (WASH) interventions are generally accepted as effective measures to prevent and treat STH and schistosomiasis. However, findings from existing studies are conflicting and the effectiveness of MDA in improving various maternal and child health outcomes is a current source of debate (Turner et al., 2015). Findings from the systematic review detailed in Chapter 2 suggests that mass deworming during pregnancy is associated with reducing worm burden with no impact on any other maternal or pregnancy outcomes including anaemia, haemoglobin (Hb), birth weight, low birth weight (LBW), preterm birth, perinatal mortality, stillbirths, neonatal mortality and congenital abnormalities. An existing Cochrane review of deworming using anthelminthics in the second trimester of pregnancy including four trials and 4265 participants concluded that there was insufficient evidence to recommend mass deworming in pregnancy (Salam et al., 2015). There was no impact of a single dose of anthelminthic in the second trimester of pregnancy on maternal anaemia in the third trimester, LBW, preterm birth and perinatal mortality. This review did not assess the impact of deworming on worm burden

and intensity. A recent Campbell systematic review and network meta-analysis with 47 randomised trials and over one million children, found little to no overall effect on growth, attention and school attendance (Welch et al., 2016). However, these reviews were conducted at the study level, rather than using data for each individual participant, which limits the power to detect effect modification by individual participant characteristics that could potentially modify the effect of deworming (Barry et al., 2013; Turner et al., 2015).

There are various factors that could potentially modify the effectiveness of deworming including baseline nutritional status (anemia and body mass index (BMI)), type of STH infection, treatment protocol, worm burden (particularly intensity of infection) and concomitant interventions (such as iron supplementation and other drugs such as praziquantel for schistosomiasis). Individual participant data (IPD) meta-analysis refers to analyzing data for each participant in the existing studies (Tierney, Pignon, et al., 2015; Tierney, Vale, et al., 2015).The advantage of an IPD analysis over aggregate meta-analysis is that it has the potential to improve the quality of both the data and the analyses and consequently the reliability of the results (Tierney, Vale, et al., 2015). Furthermore, it also provides an opportunity to re-analyze the data for the range of other possibilities for example, investigating the treatment effects varying by participant characteristics which is not possible with the aggregate data (Riley et al., 2010). An IPD approach will allow the evaluation of variation in effect estimates by various individual, socio-demographic and environmental factors in pregnant women that could potentially modify the effectiveness of deworming during pregnancy. IPD meta-analysis explores the question of whether mass deworming during pregnancy is more effective for subgroups of women defined by characteristics such as nutrition status and infection intensity. This understanding could help to develop targeted strategies to reach pregnant women with deworming and guide policy regarding mass deworming.

Objective

The objective of the review is to use IPD meta-analysis to explore whether the effects of deworming among pregnant women vary with individual characteristics (nutritional status, anaemia), intensity of infection (as assessed by egg count), infection status (including species of worm), socioeconomic status, sanitation environment and co-interventions.

Methodology

The protocol was published with the Campbell Collaboration (Salam et al., 2018) on Jun 12, 2018 and reported according to the preferred reporting items for systematic reviews and meta-analyses for protocols (PRISMA-P) (Moher et al., 2015). Results of the review are reported using the Preferred Reporting items for

Systematic Reviews and Meta-analyses of individual patient data (PRISMA-IPD) Statement (Stewart et al., 2015).

Criteria for considering studies for this review

We included studies that met the following eligibility criteria:

Types of studies

We included individually randomised controlled trials (RCT); cluster RCTs and quasi randomised studies as these were the most appropriate design for the IPD meta-analysis. No language or date restrictions were applied.

Types of participants

Participants were pregnant women receiving preventive or therapeutic deworming drugs for STH and schistosomiasis.

Types of interventions

We included mass deworming using any drug or a combination of drugs (including levamisole, mebendazole, albendazole, praziquantel and pyrantel) for STH and schistosomiasis with or without co-interventions compared to placebo or control (no mass deworming). Co-interventions could be food provision, micronutrient supplementation, iron and/or folic acid supplementation, hygiene interventions or education. We included studies where the co-interventions were similar in the intervention and control groups to assess the impact of mass deworming.

Types of outcome measures

The following primary and secondary outcomes were reported; however we did not use the list of outcomes as a criterion for inclusion of studies in the review:

-Primary outcomes:

- Maternal anaemia at term (haemoglobin less than 11 g/dL)
- Maternal infection intensity (as reported by the study authors)

-Secondary outcomes:

- Maternal haemoglobin (Hb) at term
- Maternal ferritin

- Maternal anthropometric measures (height and weight)
- Maternal body mass index (BMI)
- Birth weight
- LBW (less than 2500 g)
- Preterm birth (birth before 37 weeks of gestation)
- Perinatal mortality (includes fetal death after 28 weeks of gestation and infant death that occurs at less than seven days of life)
- Stillbirth
- Congenital anomalies
- Infant mortality

Duration of follow-up

We did not restrict inclusion based on the duration of follow-up.

Types of settings

The settings included any area where STH or schistosomes are endemic. These could include studies conducted in either community settings or facility settings including hospitals, antenatal clinics, primary healthcare centres etc.

Search methods

We conducted the search in the following databases till March 2018: MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Latin-American and Caribbean System on Health Sciences Information (LILACS), Excerpta Medica dataBASE (EMBASE), the Cochrane Library, Internet Documents in Economics Access Service (IDEAS), Google Scholar, Web of Sciences, Social Services Abstracts, the World Health Organization (WHO) Global Health Library, Global Health CABI and CAB Abstracts. We also searched grey literature in OpenGrey and websites of relevant organizations such as the World Bank, World Food Program and International Food Policy Research Institute. We also contacted authors of studies and members of our advisory board for any unpublished studies or grey literature reporting eligible studies. We checked reference lists of relevant studies and reviews. We also searched for trials registered with

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (http://www.who.int/trialsearch/).

Titles and abstracts were screened in duplicate by two reviewers. We pilot-tested the screening criteria at both title and abstract screening stage and full text stage. We used the PRISMA flow diagram to report eligibility of studies. We retrieved full text of all studies which pass this first level screening. The full text reviews were also done in duplicate by two reviewers, and agreement was reached by consensus. Disagreements were resolved by consultation with a third reviewer. No language or date limits were applied. The search strategy is attached as Appendix 5.

Description of methods used in primary research

RCTs of mass deworming include two-arm trials as well as factorial trials, with women allocated either individually or by cluster-randomisation.

Details of study coding categories and quality assessment

We extracted the study characteristics including details of the populations, setting, socio-demographic characteristics, interventions, comparators, outcomes and study design in duplicate. Risk of bias was assessed at the study as well as the outcome level. At the study level, two independent reviewers performed quality appraisal for each study using the Cochrane risk of bias tool which assessed selection bias, performance bias, detection bias, attrition bias and reporting bias (Higgins et al., 2011). Disagreements were resolved by discussion or consultation with a third reviewer. At the outcome level, we summarized the quality of evidence according to the outcomes as per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (Walker et al., 2010). A grade of “high”, “moderate”, “low” and “very low” was used for grading the overall evidence indicating the strength of an effect on specific health outcome based on methodological flaws within the component studies, consistency of results across different studies, generalizability of research results to the wider patient base and how effective the treatments have shown to be (Balshem et al., 2011). The two reviewers discussed ratings and reached consensus. Disagreements were resolved by consulting a third reviewer. We developed a summary of findings table to show the effects for the primary outcomes of maternal anaemia and infection intensity; as well as the secondary outcomes of preterm birth, LBW and perinatal mortality since these outcomes assess long-term effects, particularly in terms of birth outcomes.

Data collection and analysis

Trialists of the included trials provided IPD by electronic transfer where possible or other means as needed. The individual trial data were recoded as required and checked with respect to range, internal consistency, missing values, outliers, errors and consistency with published reports. Trial details such as randomisation methods and intervention details were cross-checked against published reports, trial protocols and data collection sheets. Inconsistencies or missing data were discussed with the individual trialists and attempts were made to resolve any problems by consensus. We did not exclude any study based on the way the outcomes were reported.

Data were entered into a flat spread-sheet with the same fields for every study. We considered the missing values for each variable as missing at random (MAR). We planned to use multiple imputation to impute the missing values for covariates at baseline (individual participant level variables) and outcome variables (primary and secondary outcomes). Imputation was planned be done using Proc MI in SAS/STAT (SAS Institute Inc., Cary, NC, USA). We planned to assess the robustness of the results by running a separate model excluding imputed data (i.e. complete case analysis). However, we restricted our analysis to conventional complete case analyses, that is, removing subjects with a missing value from the analyses, since the missing data were considered to be non-trivial. Studies with missing data on more than 50% of outcome or covariate data were planned to be included in the complete case analysis only; however none of the studies were missing more than 50% of outcome or covariate data.

Descriptive characteristics of each study were presented, with details on the participant characteristics, environment, worm species, prevalence, intensity of infection, geographic location, interventions, comparator, outcomes and risk of bias assessment. Following data items were collected:

-Individual Level:

- Infection intensity with *Ascaris, Trichuris,* hookworm and schistosomes (across four levels of none, light, moderate and heavy, using the WHO cutoffs for each helminth)
- Anaemia status (using WHO cutoffs by age and altitude of non-anaemic, mild (100-109 g/l), moderate (70-99 g/l) and severe (lower than 70 g/l)
- Under-nutrition (BMI<18.5 kg/m^2)

- Socioeconomic status (as defined by trial authors): We assessed whether the measurement of socioeconomic status can be compared across study settings and time.
- Deworming drug used.

-Environmental Level:

- WASH practices (as defined by trial authors)
- Population level infection intensity (using WHO cut-offs for each worm-type, as above)

We calculated the standardised difference between the published data and the IPD received from authors for baseline characteristics and baseline outcome assessment. For outcome variables, we replicated the effect measures reported in study publications and calculated the standardised difference between the IPD received and the study report (Austin, 2009).

The comparison of interest for the pairwise analysis included (but not restricted to) any deworming drug versus no deworming. We planned to conduct pair-wise comparisons for one deworming drug versus other deworming drug or a combination of deworming drugs, however we could not perform such analysis due to limited data. We conducted a one-stage IPD meta-analysis using random-effects multilevel meta-regression models to examine the interactions between the covariates and the treatment. The one-stage approach analyses the IPD from all studies simultaneously, for example, in a hierarchical regression model with random effects. The choice of one-stage IPD was pre-specified as it avoids the use of approximate normal sampling distributions, known within-study variances, and continuity corrections that plague the two-stage approach with an inverse variance weighting (Burke, Ensor, & Riley, 2017). Network meta-analysis is a common approach to synthesize the efficacy of multiple treatments, and to compare their relative efficacy, however, we did not plan to conduct network meta-analysis based on our previous experience with limited number of studies in the domain (Salam et al., 2015). We conducted pairwise analyses for each comparison of interest by entering all IPD data into a multilevel model, with each study as one cluster. We expected considerable heterogeneity between studies for each outcome; therefore, we used a random effects model.

Where IPD was not available for all trials, we used a two-part model with one part based on IPD data and the second part based on aggregate data from studies which did not provide IPD (Fisher, Copas, Tierney, & Parmar, 2011; Riley et al., 2008; Riley & Steyerberg, 2010). We accounted for clustering as above by nesting

clusters within studies. We accounted for the pre-defined covariates of infection intensity, baseline anaemia, baseline nutritional status, socioeconomic status and maternal education in the model.

Measures of treatment effects

We separately analyzed the dichotomous and continuous outcomes. For dichotomous outcomes, we presented the results as summary risk ratios (RRs) with 95% confidence intervals (CI). We presented continuous outcome data as either a mean difference (MD), if outcomes have been measured on the same scale, or a standardised mean difference (SMD), if outcomes have been measured on different scales, with 95% CI.

Assessment of clinical and methodological heterogeneity within treatment comparisons

Heterogeneity across trials in terms of subject characteristics, trial methodologies and treatment protocols was assessed using visual plots, tables and homogeneity statistics. We assessed heterogeneity using visual inspection of forest plots for pairwise analyses as well as statistical tests of heterogeneity (I^2). In addition to I^2, we also assessed between-study variance (variation across study findings beyond random sampling error) by the variance of the distribution of the true study effects, commonly denoted as $\tau 2$.

Publication bias

We planned to generate a funnel plot for comparisons and outcomes with >10 studies. We planned to use Egger's test for asymmetry and visual inspection to assess the presence of publication bias and/or selective reporting. However, none of the comparisons or outcomes included >10 studies and hence we could not assess for publication bias.

Subgroup analyses

Where sufficient data were available, sub-group analyses were planned to be conducted to assess effects across both individual-level as well as environment-level characteristics. We compared the results of models with subgroup analyses by assessing the size of quantitative or qualitative differences in effects, the statistical significance of tests for interactions, assessing between-study variance and assessing the goodness of fit of the models using the likelihood ratio. Before conducting subgroup analyses, we assessed the distribution of each variable. If there were insufficient participants in some categories, the levels were combined. The individual and environment level effect modifiers specified above were planned to be assessed (data permitting).

Sensitivity analyses

Where sufficient data were available, we planned to conduct sensitivity analyses to assess robustness of results when restricted to studies at low risk of bias for sequence generation, allocation concealment and blinding of participants. We planned to assess whether results were robust to excluding imputed data (i.e. complete case analysis).

Data Management

Data were transferred to SAS as a common platform for all studies, using a common data dictionary. We checked IPD data for consistency immediately upon receiving datasets for outlier individuals (e.g. with duplicate participant IDs, unrealistic date ranges). We compared the IPD from authors with the aggregate data reported in the articles. Any missing or unusual data were flagged for discussion with the trial author or statistician. We asked for clarification from the authors to establish reasons for any discrepancies, and address them if possible. Any requests for authors were discussed when the data were provided, such as clarification of trial risk of bias, conduct or eligibility criteria. We also ran the same statistical analysis as the authors to check for consistency with the published paper (Stewart et al., 2015). We requested statements of ethics approval from each study and we did not include data from studies that had not received ethics approval. We requested that all data be transferred without any identifiers.

Results

Search results

We searched all databases up to March, 2018. Figure 4.1 provides a search flow diagram. We identified a total of 23,406 records through the search strategy provided in Appendix 5. A total of 31 papers (Abel et al., 2000; Ács et al., 2005; Adam et al., 2005; Atukorala et al., 1994a; Christian et al., 2004; De Silva et al., 1999; Deepti & Nandini, 2015; Elliott et al., 2007; Elliott, Mpairwe, et al., 2005; Elliott, Namujju, et al., 2005; Gyorkos et al., 2011; Gyorkos et al., 2006; Renée Larocque et al., 2006; Liabsuetrakul et al., 2009; Millard et al., 2014; Tehalia, 2011c; Mpairwe et al., 2011; Nampijja et al., 2012; Juliet Ndibazza et al., 2012; J Ndibazza et al., 2010; Ndyomugyenyi et al., 2008a; Olveda et al., 2016; Torlesse & Hodges, 2000, 2001; Tweyongyere et al., 2009; Tweyongyere et al., 2011; Tweyongyere et al., 2008; Tweyongyere et al., 2013; Urass et al., 2011; Villar et al., 1998; Webb et al., 2012; Webb et al., 2011) based on 16 studies assessed mass deworming during pregnancy. These 16 studies were assessed for IPD eligibility and seven studies with 8515 participants were identified to be eligible for IPD. Table 4.1 details the study eligibility for IPD. Major reasons for exclusion from IPD included:

(i) study design not being appropriate (mainly cross-sectional and case control studies) and;

(ii) only abstracts were available with insufficient information and the trialists could not be contacted.

Figure 4.1: Search Flow Diagram

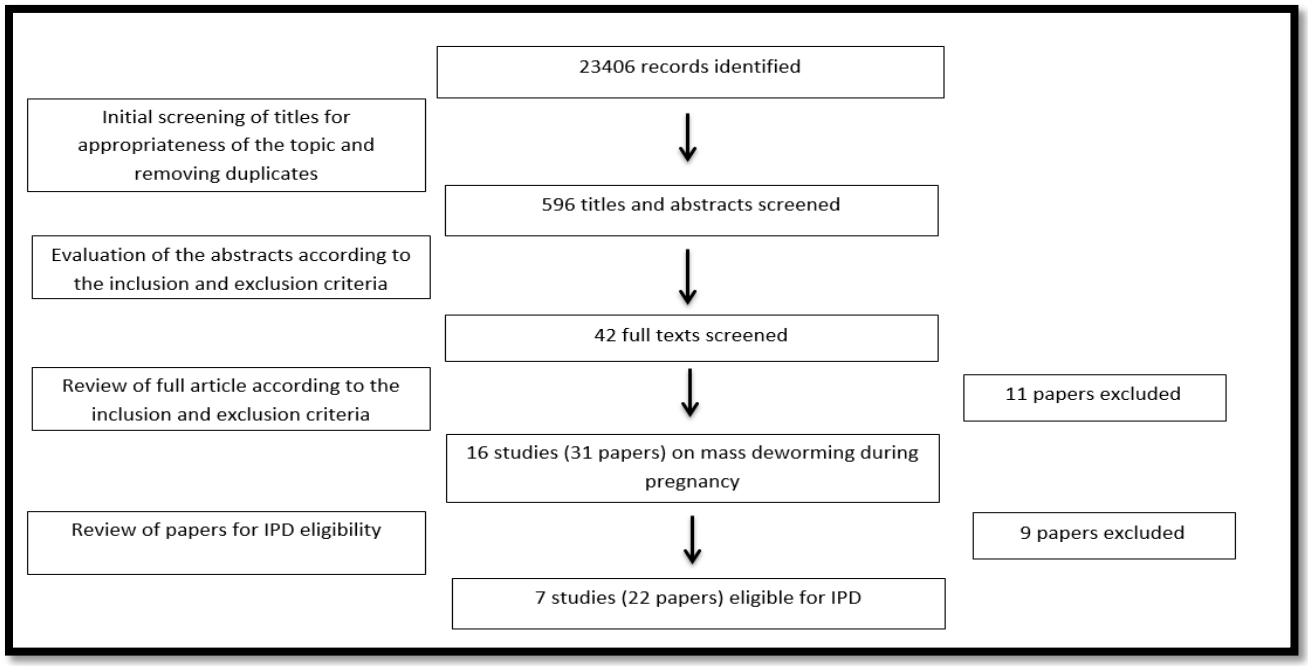


Table 4.1: Eligibility for IPD

Study ID	Study Design	Eligibility for IPD	Reason for Exclusion
Elliott 2005 (J Ndibazza et al., 2010)	Randomised Controlled Trial	Yes	
Larocque 2006 (Renée Larocque et al., 2006)	Randomised Controlled Trial	Yes	
Ndyomugyenyi 2008 (Ndyomugyenyi et al., 2008a)	Randomised Controlled Trial	Yes	
Torlesse 2001 (Torlesse & Hodges, 2001)	Randomised Controlled Trial	Yes	
Urassa 2011 (Urass et al., 2011)	Randomised Controlled Trial	Yes	
Deepti 2015 (Deepti & Nandini, 2015)	Randomised Controlled Trial	Yes	
Tehalia 2011 (Tehalia 2011)	Randomised Controlled Trial		Only abstract available with insufficient information
Villar 1998 (Villar MA, 1998)	Randomised Controlled Trial		Only abstract available with insufficient information
Olveda 2016 (Olveda et al., 2016)	Randomised Controlled Trial	Yes	
Atukorala 1994 (Atukorala, De Silva, Dechering, Dassenaeike, & Perera, 1994d)	Before-after study		This was a before-after study
Abel 2000 (Abel et al., 2000)	Before-after study		This was a before-after study
Christian 2004 (Christian et al., 2004)	Prospective Cohort		This was a cohort study
de Silva 1999 (De Silva et al., 1999)	Cross-sectional survey		This was a cross-sectional study
ACS 2005 (Ács et al., 2005)	Case-control study		This was a case-control study
Adam 2005 (Adam et al., 2005)	Prospective cohort		This was a cohort study
Liabsuetrakul 2009 (Liabsuetrakul et al., 2009)	Prospective cohort		This was a cohort study

Characteristics of studies

A total of seven studies including 8515 pregnant women were eligible for IPD. All of these studies were RCTs. Studies were conducted in India, Philippines, Peru, Sierra Leone, Tanzania and Uganda between 2001 and 2016. The deworming drugs provided in these studies included albendazole, mebendazole, praziquantel, ivermectin or a combination of these. The majority of the studies provided mass deworming for STH only; while one study (Olveda, Acosta et al. 2016) provided deworming for schistosomiasis alone; and one study (Elliott, Mpairwe et al. 2005) targeted both STH and schistosomiasis. Sample sizes ranged from 184 pregnant women to 3080 pregnant women. The most common co-intervention was iron/folic acid supplementation while other interventions included food supplementation, anti-malarial drug administration and education. Maternal and birth outcomes were assessed in the third trimester and at the time of delivery in all the included studies. Table 4.2 describes the characteristics of studies eligible for IPD. Out of the seven studies, three trials were subsequently included in the IPD (Elliott, Mpairwe et al. 2005, Urassa, Nystrom et al. 2011, Olveda, Acosta et al. 2016) and further description is provided in the following sections.

Table 4.2: Characteristics of IPD Eligible Studies

Serial no	Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
1.	Elliott 2005	Randomised Controlled Trial	Entebbe Hospital, Uganda between June-August, 2002.	2507 participants	-Albendazole (400 mg) and placebo, -Praziquantel (40 mg/kg) and placebo -Albendazole and praziquantel	Placebo and placebo	Maternal education Household economic index Trimester at treatment Parity Place of delivery HIV status Malaria parasites Active syphilis Helminth prevalence (Hookworm, schistosomes, *Trichuris*, Ascaris lumbricoides) Anemia	Infection Infantile eczema Immune responses in mothers and infants Maternal and perinatal outcomes Immune responses (BCG, tetanus, pertussis, Hep B, measles, diphtheria, polio, haemophilius) Co-infections (malaria, pneumonia, diarrhoea, TB, measles, HIV) Anemia (haemoglobin concentration) Growth and development (birth weight, weights, height, head circumference, MUAC, intellectual function) Worm infection Mortality
2.	Larocque 2006	Randomised Controlled Trial	Health centres in the Iquitos region of Peru	1042 participants	Single dose of mebendazole (500 mg) plus a daily iron supplement (60 mg elemental iron, ferrous sulphate)	Single dose placebo plus a daily iron supplement (60mg elemental iron, ferrous sulphate)	Gestational age Environment (Urban/rural) Schooling Primigravida Housing Flooring Toilet facility	Mean infant birth weight (LBW and VLBW) Maternal anaemia in third trimester measured by (1) mean Hb and (2) Hb < 11 g/dL Infection prevalence Stillbirth Early neonatal death

Serial no	Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
							Water use STH prevalence (hookworm, *Trichuris, Ascaris*, co-infection with hookworm/*Trichuris*) STH intensities Anemia Hemoglobin	Term birth Miscarriage Malformations
3.	Ndyomugyenyi 2008	Randomised Controlled Trial	Masindi district, western Uganda	832 participants	Group A (n = 198) received ivermectin Group B (n = 194) received albendazole (a single dose of 400 mg) Group C (n = 199) received a combination of ivermectin and albendazole, and Women in addition received the routine antenatal care package with iron supplements	Group D (n = 241) was a reference group without soil-transmitted helminths.	Weight Height Hb Gestational age	Maternal Hb in third trimester Birth weight LBW Abortion Stillbirths Neonatal death Preterm birth Cure rate Mean parasite density Neonatal anemia Neonatal mean Hb

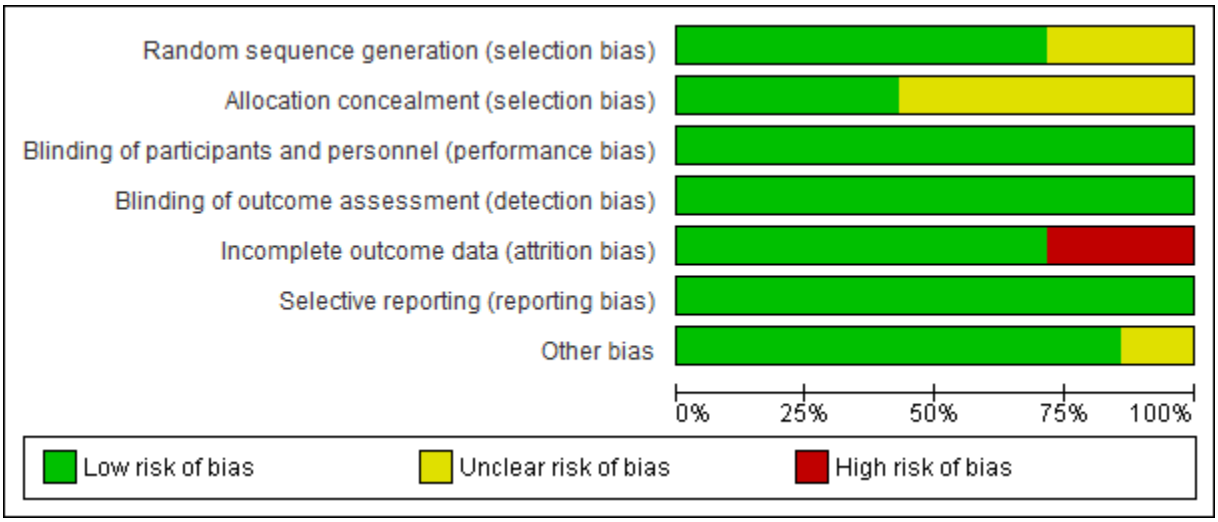
Serial no	Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
4.	Torlesse 2001	Randomised Controlled Trial	Antenatal clinics in peri-urban and 6 in rural areas in Sierra Leone	184 participants	Albendazole, 2 x 200 mg, single dose, at first antenatal visit in second trimester. Daily iron-folate supplements comprised 36 mg iron	2 tablets containing calcium with vitamin D were used as the control for albendazole. Calciferol tablets (1.25 as ferrous gluconate and 5 mg folic acid started at first antenatal visit in second trimester for entire duration of pregnancy. mg), 1 daily, were chosen as the control for iron-folate supplements	Hb	Worm prevalence Anemia Iron deficiency anemia Cure rate Egg reduction rate
5.	Urassa 2011	Randomised Controlled Trial	Rufiji district, Tanzania	3080 participants	Single dose Albendazole (400mg) (given at term and 4 months later) Daily iron folate supplements	Placebo	Parity Gestational age Distance of facility from residence Knowledge of anaemia	Hemoglobin Serum ferritin concentration during pregnancy Anaemia

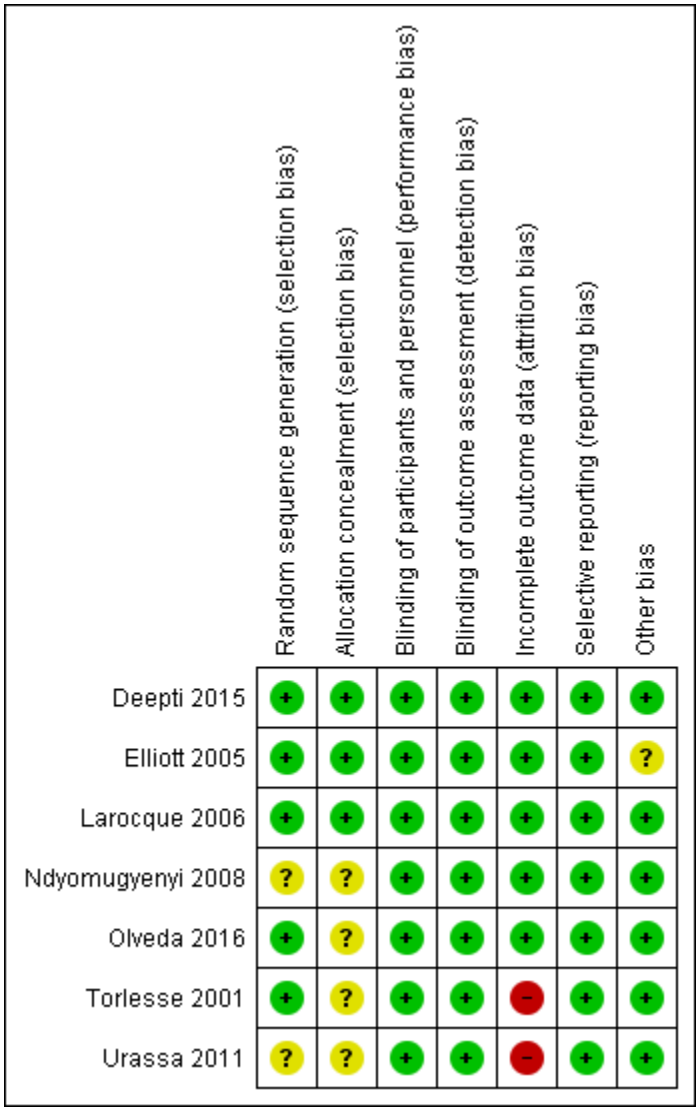
Serial no	Study ID	Study Design	Country/Setting	Sample Size	Intervention	Control Group	Baseline Characteristics Reported	Outcomes Reported
					(36mg iron; 5mg folate) Sulphadoxine pyramethamine		Knowledge of malaria Hb Anaemia	
6.	Deepti 2015	Randomised Controlled Trial	India	500 participants	-Albendazole -Mebendazole -Albendazole and mebendazole	Placebo	Education Socio-economic status Hb Baseline infestation	Maternal anemia Worm intensity Worm prevalence Birth weight Low birth weight
7.	Olveda 2016	Randomised Controlled Trial	Villages in northeastern Leyte, Philippines	370 pregnant women	over-encapsulated praziquantel (total dose 60 mg/kg given as two split doses)	Placebo	Socio-economic status Height Weight Baseline prevalence	Birth weight LBW SGA Maternal Hb Newborn Hb Maternal weight gain Treatment success Cure rate Maternal adverse events Congenital anomaly Fetal death Abortion

Quality of Studies

The quality of the studies was assessed using the Cochrane risk of bias assessment criteria. Overall, the included studies were judged to be of fairly good quality. For random sequence generation, five studies were judged to be at low risk of bias while two studies (Ndyomugyenyi, Kabatereine et al. 2008, Urassa, Nystrom et al. 2011) were rated as unclear since the method of sequence generation was not specified. Allocation concealment was judged to be adequately done in three studies (Elliott, Mpairwe et al. 2005, Larocque, Casapia et al. 2005, Deepti and Nandini 2015); four studies did not clearly specify the concealment of allocation and were judged to be at unclear risk (Torlesse and Hodges 2000, Ndyomugyenyi, Kabatereine et al. 2008, Urassa, Nystrom et al. 2011, Olveda, Acosta et al. 2016). All the included studies either adequately blinded the participants, personnel and outcome assessors or we felt that lack of blinding would be unlikely to affect the results and hence all the studies were rated to be at low risk for blinding. Four studies were rated at low risk of attrition bias while two studies were rated to be at high risk of attrition bias (Torlesse and Hodges 2000, Urassa, Nystrom et al. 2011). All the studies were judged to be at low risk of bias for selective reporting since the outcomes specified in the study protocol or methodology section of the study were reported in the outcome section. We judged one study as unclear risk of bias for 'other bias' since in the (Elliott, Mpairwe et al. 2005) study, enrolment was stopped after 104 women due to new guidelines by the WHO which recommended inclusion of treatment of women with schistosomiasis. Figure 4.2 depicts the risk of bias for the included studies.

Figure 4.2: Risk of Bias for the Included Trials

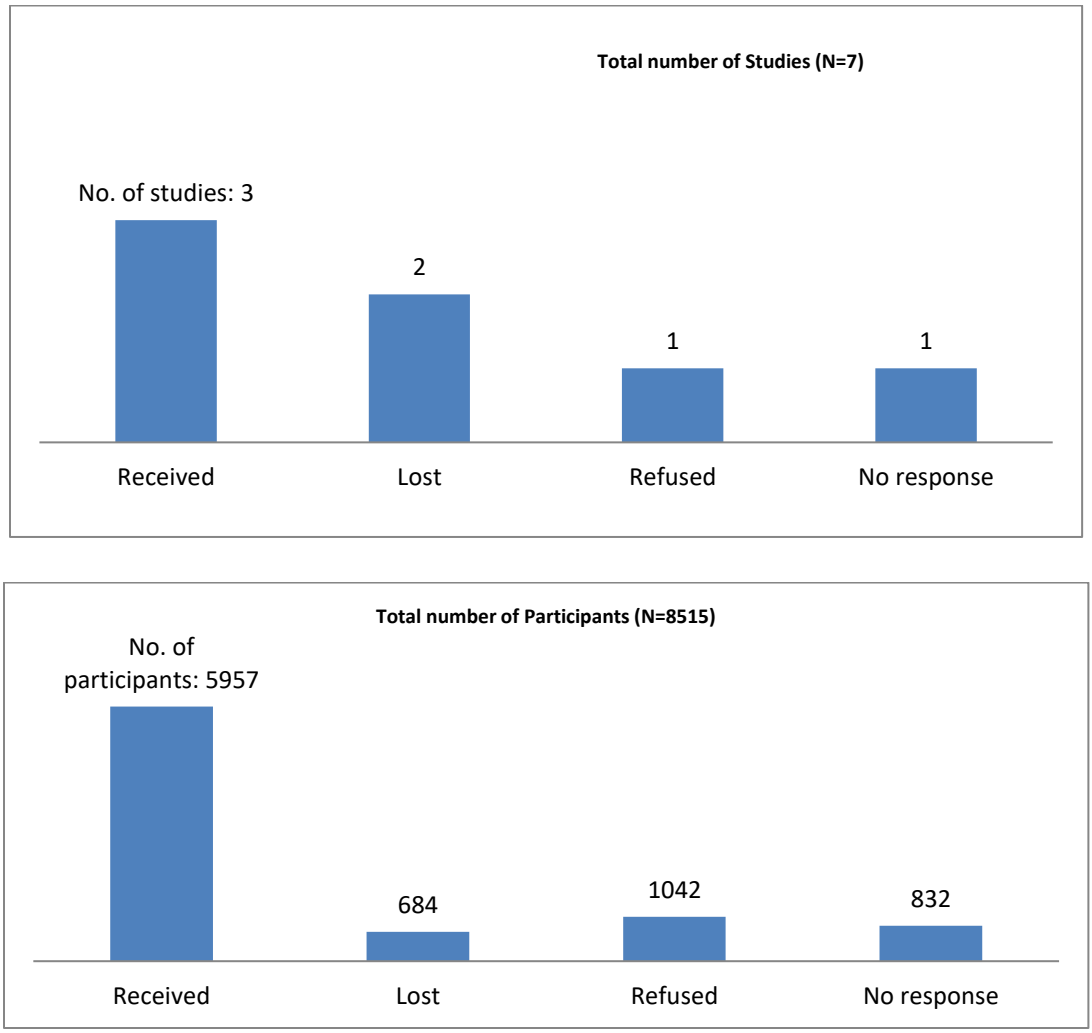




Contacting authors and yield of the studies

Trial authors were contacted for all seven trials deemed eligible for the IPD. Out of the seven trials, we received data from three trials (Elliott, Mpairwe, et al., 2005; Olveda et al., 2016; Urassa et al., 2011); data from two trials were lost (Deepti & Nandini, 2015; Torlesse & Hodges, 2000) (trialists were not able to retrieve the data); one trialist refused to share the data (Larocque et al., 2006) while one could not be contacted due to severe health conditions (Ndyomugyenyi et al., 2008). In terms of the number of participants; out of 8515 potential IPD participants; data were captured for 5957 participants (70%). Figure 4.3 depicts the number of studies and participants eligibility for IPD.

Figure 4.3: Number of Eligible Studies and Participants for IPD



Data Preparation: Missingness analysis

Table 4.3 and 4.4 provides an overview of the missing values for the baseline and endpoint variables in the data sets from each of the trial.

Table 4.3: Missing values for baseline variables

Baseline variables	Studies			Total
	Elliott 2005 (n=2505)	Olveda 2016 (n=362)	Urassa 2011 (n=3076)	N=5943
Education	0.15% (4)	0.55% (2)	NA	0.1% (6)
Parity	NA	0%	0%	0%
Gravidity	0%	NA	0%	0%
Weight	0.15% (5)	0%	NA	0.08% (5)
Height	1.12% (28)	0%	NA	0.5% (28)
Anaemia	0.5% (12)	0%	0%	0.2% (12)
S.Japonicum Intensity	NA	0%	NA	0%
S.Mansoni Intensity	0%	NA	NA	0%
A.Lumbricoides Intensity	NA	39% (141)	NA	2.4% (141)
T.Trichiura Intensity	0%	19% (69)	NA	1.15% (69)
Hookworm Intensity	0%	64% (231)	NA	3.88% (231)
Ascaris Intensity	0%	NA	NA	0%
Socioeconomic status	7.3% (183)	0%	NA	3.08% (183)

Table 4.4: Missing values for endpoint variables

Endline variables	Studies			Total
	Elliott 2005 (n=2505)	Olveda 2016 (n=362)	Urassa 2011 (n=3076)	N=5943
Maternal Weight	NA	0.82% (3)	NA	0.05% (3)
Anaemia	13.53% (339)	0.82% (3)	12.51% (385)	12.23% (727)
S.Japonicum Intensity	NA	63.5% (230)	NA	3.87% (230)
S.Mansoni Intensity	18% (451)	NA	NA	18% (451)
A.Lumbricoides Intensity	NA	0%	NA	0%
T.Trichiura Intensity	18% (451)	26% (94)	NA	9.17% (545)
Hookworm Intensity	18% (451)	0%	NA	18% (451)
Ascaris Intensity	18% (451)	0%	NA	18% (451)
Birth weight	23.91% (599)	0.27% (1)	NA	10.1% (600)
LBW	23.91% (599)	0.27% (1)	NA	10.1% (600)
Preterm Birth	6.38% (160)	0%	NA	2.7% (160)

Data Replications

Replication of the published study results was conducted for all three studies. The standardised differences between the published and replication results were all below 0.10 for all outcome measures and covariates. There were instances where the standardised difference could not be calculated because the published results did not report the outcome measure in question. Table 4.5 reports the standardised differences between the published and reproduced results for outcome measures.

Table 4.5: Standardised differences between published and reproduced results for outcome measures by eligible studies

Variables	Studies		
	Elliott 2005	**Olveda 2016**	**Urassa 2011**
Maternal weight	NA	0.00	NA
Maternal anaemia	0.02	NA	0.00
Maternal haemoglobin	0.74	0.005	NA
S. Japonicum intensity	NA	NA	NA
S. Mansoni intensity	0.00	NA	NA
Ascaris intensity	0.00	NA	NA
Trichuris intensity	0.04	NA	NA
Hookworm intensity	0.00	NA	NA
Birth weight	0.007	0.003	NA
LBW	0.05	0.05	NA
SGA	NA	0.00	NA
Preterm birth	NA	NA	NA
Perinatal mortality	0.00	NA	NA
Congenital anomaly	0.01	NA	NA
Infant survival	NA	NA	NA

IPD feasibility and changes to the analysis model

Based on the availability of data, we could only analyse one comparison of interest (mass deworming with any drug versus no mass deworming). The planned analysis and final model was also modified accordingly. Table 4.6 provides a comparison of the original analysis plan and the actual analysis model.

Table 4.6: Comparison of the original analysis plan and actual model employed

	Planned Analysis	Actual Analysis
Outcomes	Maternal anaemia at term Maternal infection intensity Maternal haemoglobin at term Maternal ferritin Maternal anthropometric measures Maternal BMI Birth weight Low birth weight Preterm birth Perinatal mortality Stillbirth Congenital anomalies Infant Mortality	Maternal anaemia at term *Trichiura* intensity Hookworm intensity LBW Preterm birth
Covariates	*Schistosoma* egg count *Ascaris* egg count Hookworm egg count *Trichuria* egg count Haemoglobin BMI Socio-economic status Deworming drug WASH practices Population level worm intensities	Hookworm egg count *Trichiura* egg count Haemoglobin
Effect Modifiers	BMI (<18.5 kg/m^2 , 18.5 to 25 kg/m^2) Anaemia status (none, mild, moderate, severe) *Schistosoma* intensity (light, moderate, heavy) *Ascaris* intensity (light, moderate, heavy) Hookworm intensity (light, moderate, heavy) *Trichuria* intensity (light, moderate, heavy) Any STH or *Schistosoma* infection (light, moderate, heavy) Concomitant interventions	BMI (<18.5 kg/m^2 , 18.5 to 25 kg/m^2) Anaemia *Trichiura* intensity

Main effects

This section provides the overall results for mass deworming compared to no mass deworming on the following outcomes: maternal anaemia; maternal infection intensity (*T.Trichiura* and hookworm); LBW and preterm birth. We report results for the evidence from study results pooled at the aggregate level (adjusted for covariates) and the evidence pooled using IPD (adjusted for covariates). However we advise caution in interpreting these findings due to small sample sizes. Following this section, we describe effect modifier analyses for each planned effect modifier for each outcome of interest.

-Maternal anaemia: The effect estimates from aggregate evidence were of similar size and direction as the IPD effect estimates. Three trials reported data on maternal anaemia. Mass deworming led to a 23% reduction in maternal anaemia (RR: 0.77, 95% CI: 0.73-0.81; three trials; 5216 participants; moderate quality evidence). Table 4.7 reports the aggregate and IPD adjusted estimates.

Table 4.7: Impact of mass deworming on maternal anaemia

Analysis	Effect estimates (RR and 95% CI)
Aggregate adjusted	0.94 (0.89-0.99)
IPD adjusted	0.77 (0.73-0.81)

-T.Trichiura intensity: Two trials reported *T.Trichiura* intensity showing no impact of mass deworming on any infection (RR: 0.69, 95% CI: 0.42-1.13; two trials; 2867 participants; moderate quality evidence). We attempted to categorize the participants according to the intensity of infection (none, light, moderate and heavy); however there were too few participants in each category to draw meaningful conclusions. The effect estimates from aggregate evidence were of similar size and direction as the IPD effect estimates. Table 4.8 reports the aggregate and IPD adjusted estimates for maternal *T.Trichiura* intensity.

Table 4.8: Mass deworming on *T.Trichiura* intensity (any infection)

Analysis	Effect estimates (RR and 95% CI)
Aggregate adjusted	1.06 (0.87- 1.30)
IPD adjusted	0.69 (0.42-1.13)

-Hookworm intensity: Two trials reported hookworm intensity. Overall there was no impact of mass deworming on any hookworm infection (RR: 0.52, 95% CI: 0.18, 1.47; two trials; 2867 participants; moderate quality evidence). We attempted to categorize the participants according to the intensity of infection (none, light, moderate and heavy); however there were too few participants in each category to draw meaningful conclusions. The effect estimates from aggregate evidence were of similar size and direction as the IPD effect estimates. Table 4.9 reports the aggregate and IPD adjusted estimates for maternal hookworm intensity.

Table 4.9: Mass deworming on hookworm intensity (any infection)

Analysis	Effect estimates (RR and 95% CI)
Aggregate direct adjusted	0.39 (0.04 - 3.93)
IPD direct adjusted	0.52 (0.18-1.47)

-Low Birth Weight: Two trials reported LBW suggesting no impact of mass deworming on LBW (RR: 0.89, 95% CI: 0.67-1.18; two trials; 2267 participants; moderate quality evidence). Table 4.10 reports the aggregate and IPD adjusted estimates for LBW.

Table 4.10: Mass deworming on LBW

Analysis	Effect estimates (RR and 95% CI)
Aggregate direct adjusted	1.04 (0.79, 1.38)
IPD direct adjusted	0.89 (0.67, 1.18)

-Preterm Birth: Two trials reported preterm birth suggesting no overall impact (RR: 0.69, 95% CI: 0.47-1.03; two trials; 2707 participants; moderate quality evidence). Table 4.11 reports the aggregate and IPD adjusted estimates for preterm birth.

Table 4.11: Mass deworming on preterm birth

Analysis	Effect estimates (RR and 95% CI)
Aggregate direct adjusted	0.84 (0.51, 1.39)
IPD direct adjusted	0.69 (0.47, 1.03)

Effect modifier analyses

Based on the availability of the data, we could only assess for effect modification by baseline *Trichiura* infection, maternal anemia at baseline and maternal BMI at baseline. The overall model suggested overall reduction in maternal anemia (RR: 0.77, 95% CI: 0.73-0.81) with no impact on *Trichiura* infection, hookworm infection, LBW and preterm birth. There was no evidence of effect modification by baseline *Trichiura* infection, maternal anaemia at baseline and maternal BMI at baseline. Table 4.12 depicts the estimates for full model and effect modification.

The outcomes were rated to be of moderate quality due to study limitations. Further studies accounting for maternal baseline worm intensities, concomitant iron/folic acid supplementation and antenatal care coverage could change our findings. These findings are summarized in the summary of findings table (Table 4.13).

Table 4.12: Potential effect modification of mass deworming during pregnancy by baseline infection intensity, anaemia status, and BMI

	Categories	Outcomes (RR with 95% CI)				
		Maternal Anaemia	***Trichiura* Infection**	**Hookworm Infection**	**LBW**	**Preterm Birth**
Mass deworming (overall)		**0.77 (0.73-0.81)**	**0.69 (0.42, 1.13)**	**0.52 (0.18, 1.47)**	**0.89 (0.67-1.18)**	**0.69 (0.47-1.03)**
***Trichiura* Intensity at baseline**	Not infected	0.93 (0.80-1.09)	-	-	0.67 (0.43-1.04)	0.82 (0.50-1.36)
	Infected	0.81 (0.65-1.02)	-	-	1.12 (0.68-1.86)	1.32 (0.68-2.55)
Maternal Anaemia at baseline	Normal	-	0.65 (0.53-0.81)	0.51(0.42-0.62)	0.80 (0.56-1.13)	0.57 (0.36-0.92)
	Anaemia (Hb <11 g/dl)	-	0.60 (0.46-0.78)	0.56 (0.45-0.70)	1.01 (0.68-1.49)	0.71 (0.41-1.22)
Maternal BMI at baseline	Normal	0.88 (0.77-1.01)	0.61 (0.51-0.73)	0.49 (0.42-0.57)	0.86 (0.65-1.15)	0.72 (0.48-1.09)
	Low (<18.5 kg/m2)	1.10 (0.74-1.63)	1.53 (1.01-2.32)	0.36 (0.17-0.78)	1.11 (0.47-2.64)	0.82 (0.20-3.34)

Table 4.13: Summary of findings table

Mass deworming for STH and Schistosomiasis during pregnancy compared to placebo					
Population: Pregnant women **Setting:** Low- middle- income countries of Uganda, Tanzania and Philippines **Intervention:** Mass deworming with any drug **Comparison:** Placebo					
Outcomes	**No of Participants (Studies)**	**Aggregate evidence**		**IPD evidence**	
		RR (95% CI)	**Quality of the evidence (GRADE)**	**RR (95% CI)**	**Quality of the evidence (GRADE)**
Maternal anaemia	5216 (3 studies)	0.94 (0.89-0.99)	⊕⊕⊕⊖ Moderate[1]	0.77 (0.73-0.81)	⊕⊕⊕⊖ Moderate[1]
Maternal *T.Trichiura* intensity	2867 (2 studies)	1.06 (0.87- 1.30)	⊕⊕⊕⊖ Moderate[1]	0.69 (0.42-1.13)	⊕⊕⊕⊖ Moderate[1]
Maternal hookworm intensity	2867 (2 studies)	0.39 (0.04 - 3.93)	⊕⊕⊕⊖ Moderate[1]	0.52 (0.18-1.47)	⊕⊕⊕⊖ Moderate[1]
LBW	2267 (2 studies)	1.04 (0.79 -, 1.38)	⊕⊕⊕⊖ Moderate[1]	0.89 (0.67, 1.18)	⊕⊕⊕⊖ Moderate[1]
Preterm birth	2707 (2 studies)	0.84 (0.51 - 1.39)	⊕⊕⊕⊖ Moderate[1]	0.69 (0.47, 1.03)	⊕⊕⊕⊖ Moderate[1]
STH: soil transmitted helminths; RR: risk ratio; CI: confidence interval; LBW: low birthweight					
GRADE Working Group grades of evidence High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.					
[1] Downgraded for study limitations - obtained only a selected sample of IPD					

Discussion and Conclusion

This IPD meta-analysis is based on the data from three trials with 5957 participants. The effect estimates from aggregate evidence were of similar size and direction as the IPD effect estimates. Findings from this IPD suggest reduction in anaemia among pregnant women with mass deworming. The reduction in anaemia could be attributable to the concomitant iron supplementation in one study since one of the three trials included in the IPD analysis provided daily iron folate supplements (36mg iron; 5mg folate) along with the deworming drugs. There was no effect on any of the other outcomes including *Trichiura* infection, hookworm infection or any of the pregnancy outcomes including LBW and preterm birth. Findings of no impact of mass deworming on infection intensity could be attributable to the fact that majority of the study population in the included studies were either not infected or lightly infected which could have diluted the impact. Based on the availability of the data, we could only assess for effect modification by baseline *Trichiura* infection, maternal anemia at baseline and maternal BMI at baseline. There was no evidence of effect modification by *Trichiura* intensity at baseline, maternal anaemia at baseline and maternal BMI at baseline; however we advise caution in interpreting these findings due to limited number of participants included in the analysis. Findings from this IPD analysis is based on 70% of the existing data deemed eligible for IPD (5957 participants of 8515 participants). The studies included in this review were conducted among pregnant women in LMIC settings. One of the three trials included in the IPD analysis provided daily iron folate supplements (36mg iron; 5mg folate) along with the deworming drugs. The trials included in the IPD were judged to be of fairly good quality except one study judged to be at high risk of attrition bias and one study lacked allocation concealment. The overall outcome quality was judged to 'moderate' based on the GRADE criteria. The outcome quality was downgraded since the estimates are based on 70% of the eligible IPD data.

Despite receiving the majority of the existing data (70%) to conduct the IPD, there were a few limitations. One limitation of this review is that we did not receive data from all eligible studies. Two major reasons for not receiving data were lost data and refusal. In the context of IPD, responsible data sharing is imperative to support efficient research and generate new knowledge. Another limitation is that we were unable to assess effect modification by pre-specified effect modifiers. The trials did not capture many of the variables of interest that restricted our analysis. Very few trials reported outcomes according to the baseline level of infection intensities and hence those conclusions could not be drawn. In terms of the infection intensities, the population studied were either not infected or lightly infected and hence it was difficult to categorize the sample according to the intensity of infection and have meaningful estimates. Trials did not report baseline data on the individual and environmental level effect modifiers and hence it was difficult to assess the effect

modification. Variables like socio-economic status were least studied and where reported, had different definitions and hence could not be accounted for. None of the included studies assessed any co-interventions including WASH practices and hence the impact of co-interventions could not be assessed. Future research accounting for baseline worm intensities, concomitant iron/folic acid supplementation and antenatal care coverage could change these findings. We could not assess for publication bias given the small number of included studies; however, considering the small universe of studies in the domain, the issues related to publication and small study sizes cannot be ignored.

The most recent Cochrane meta-analysis (Salam, Haider et al. 2015) on deworming for STH during pregnancy concluded that there was insufficient evidence to recommend deworming for STH. This review also highlighted the need for future well-designed, large scale RCTs to establish the benefit. These findings were based on four trials including 4265 participants. This review has some differences compared to our review. The inclusion criteria for this Cochrane review was limited to deworming for STH alone while our IPD meta-analysis also included trials with deworming for schistosomiasis. The Cochrane review reported no impact of mass deworming for STH on maternal anaemia while findings from our review suggests reduction in maternal anaemia associated with mass deworming,

There is a need to evaluate mass deworming for STH and schistosomiasis during pregnancy in large scale programmatic settings. Future impact evaluations should attempt to measure various individual and environmental factors that could potentially affect the impact of mass deworming. Future program evaluations should also assess the long term impact of mass deworming on birth and infant health outcomes along with the maternal health outcomes. There is an urgent need for open data from all research studies. The quality of evidence is rated as moderate for our findings.

Chapter 5: Mass Deworming during Pregnancy: From Policy to Implementation

Abstract

The World Health Organization (WHO) identifies three population groups at high risk for soil transmitted helminthiases (STH) and schistosomiasis including school-age children (SAC), pre-SAC, and girls and women of reproductive age (WRA). The case for schistosomiasis is relatively straightforward; however, more recently there has been some debate around the effectiveness of mass deworming for STH. Historically, much attention has been devoted to targeting SAC and pre-SAC through large-scale routine mass deworming programs for the prevention and management of STH. Children have been the main focus of mass deworming since schools provide a favourable delivery platform to target SAC and achieve high program coverage, making these programs more cost effective. In contrast, there has been little information on deworming programs specifically targeting WRA and hence there is a consequent gap in the evidence related to the health impacts, program coverage and potential cost-effectiveness related to mass deworming for WRA. However, this appears to be changing as new plans are being discussed by the WHO to include WRA in deworming activities. This chapter discusses the current guidelines on mass deworming for WRA, the challenges with the current recommendations, the economic perspective of mass deworming for WRA and the way forward.

Mass Deworming: WRA remains a neglected group

The World Health Organization (WHO) identifies three population groups at high risk for soil transmitted helminthiases (STH) and schistosomiasis including school-age children (SAC), pre-SAC, and girls and women of reproductive age (WRA) (WHO, 2006). A recent estimation suggests that approximately 688 million girls and WRA are at risk of STH infection; including 140 million pregnant and lactating women and another 108 million adolescent girls (Mupfasoni et al., 2018). Approximately 40 million WRA are infected with schistosomiasis (Friedman et al., 2007; Nour, 2010). Geographically, the regions of south-east Asia and Africa have the highest numbers of each WRA subgroup at risk of STH, accounting for 74.7% of all STH at-risk WRA (Mupfasoni et al., 2018).

Historically, much attention has been paid to target pre-SAC and SAC for the prevention and management of STH and schistosomiasis through mass deworming programs (periodic treatment of large groups of people with deworming drugs disregarding their status of infection). These mass deworming programs have been facilitated mainly through pharmaceutical drug donations, large-scale national deworming programs and global reporting systems (Mofid & Gyorkos, 2017). The initial focus of the large-scale deworming programs have been SAC owing to the fact that this age group was at high risk of morbidity from STH infections and the pharmaceutical companies provided the single-dose deworming medicines free of charge. Additionally, schools provide a favourable delivery platform to target pre-SAC and SAC and achieve high program coverage, making these programs more cost effective along with providing a convenient sampling frame for surveillance (Anderson, Turner, Truscott, Hollingsworth, & Brooker, 2015). The current WHO guidelines focus on SAC, both for monitoring infection and as a target for treatment, although treatment of pre-SAC and WRA is also recommended where sustainable delivery mechanisms exist, especially in areas of intense transmission (Anderson et al., 2015).

In contrast, there has been little information in either the published or unpublished literature on deworming programs specifically targeting WRA. A recent review evaluating the impact of mass deworming among non-pregnant adolescent girls and adult women identified sparse data from four trials with moderate to very low quality of evidence (Ghogomu et al., 2018). Moreover, in some settings it has proven difficult to achieve high coverage and good surveillance among adults for mass deworming. WRA were initially included as a part of the community-based mass deworming programs under the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000, whereby all individuals in a household except pregnant women were eligible for deworming. There have been other reports of deworming in WRA, but these have either been within particular

research projects or in limited geographical areas within specific countries. The WHO Preventive Chemotherapy Databank reports on deworming coverage for pre-SAC and SAC; however, no coverage estimates are available for deworming in WRA, and few countries include this risk group among deworming activities (WHO, 2018). In fact, the disease burden of STHs in WRA is largely unknown (Mofid & Gyorkos, 2017). It has been estimated that coverage rates for WRA within GPELF, on an annual basis, approximates 20% of all at-risk WRA (WHO, 2018). Although WRA may have indirectly benefited from mass deworming targeting children living in the same household, this group has been neglected and consequently they have not been able to get the direct benefits of treatment (Mofid & Gyorkos, 2017).

Current guidelines

Currently, mass deworming is recommended as an effective strategy to prevent and treat STH and schistosomiasis. The most recent recommendations by the WHO on deworming among pregnant women (WHO, 2017) recommends preventive chemotherapy (mass deworming), using single-dose albendazole (400 mg) or mebendazole (500 mg), as a public health intervention for pregnant women including pregnant adolescent girls after the first trimester (in the second or third trimester), living in areas where both:

(i) the baseline prevalence of hookworm and/or *T. trichiura* infection is ≥ 20% among pregnant women, and

(ii) where anaemia is a severe public health problem, with a prevalence of ≥ 40% among pregnant women.

For schistosomiasis, annual treatment with praziquantel in high risk communities (>50% prevalence) and once every two years in medium risk communities (>10% and <50% prevalence) is recommended. Women can be treated with praziquantel at any stage of pregnancy and lactation (WHO, 2006).

Challenges with the current recommendations

More recently, there has been a lot of discussion around routine mass deworming programs and their effectiveness has been questioned since the recent evidence synthesis suggested that these programs have very little or no benefit for children and pregnant women (Bundy et al., 2018; Salam et al., 2015; Turner et al., 2015; Welch et al., 2016). The key area for debate around mass deworming is not whether deworming medicine works but whether the benefits of deworming exceed the costs or whether it would be more prudent to invest in other interventions including education, sustainability of WASH programs, communication to encourage high treatment uptake and better integration of STH control with other relevant programs with existing wide-spread coverage (Anderson et al., 2015; Bundy, Kremer, Bleakley, Jukes, & Miguel, 2009).

Deworming drugs such as levamisole, mebendazole, albendazole, praziquantel and pyrantel have been reported to be efficacious with minimal side-effects (WHO, 1994, 2018) but a critical issue in evaluating current STH policies concerns who to treat, how frequently to treat, and how long to treat (Anderson et al., 2015). This section discusses the issues and gaps around the existing mass deworming guidelines with a closer look on issues specific to pregnant women and WRA.

Broadly, the field of neglected tropical diseases (NTDs) lags behind in terms of model development and parameter estimation and much of the existing treatment mechanisms are largely based on discussion and consensus, without detailed calculations (Anderson et al., 2015). The fact that the transmission cycle for STH is a dynamic process has hardly been considered in the existing research evidence and implementation programs. The fact that all intestinal worms are not the same; that not all intestinal worms respond to the same deworming medication; and that not all infested individuals exhibit the disease is hardly specified. Although existing studies have shown that treatment of some individuals lead to a reduction in transmission in the community as a whole; these studies do not adequately address the population dynamics of STH infection (Bundy et al., 2009). The majority of the studies on deworming have followed standard practice in clinical trials and considered untreated people as a control group. Since the current studies have been conducted in areas where most people have low to moderate intensity infection rather than high intensity infection, there is a potential for considerable and unknown variance in the intensity of individual infection. Consequently the intensity is unknown in any individual, as is the likelihood of morbidity and the potential scale of benefit from treatment. Such studies tends to average out the effectiveness when population as a whole is studied rather than studying population subgroups with varying intensity of infections (Bundy et al., 2018).

Another critical issue concerns the reach of these drugs to infected geographical pockets and the lack of focus on concomitant transmission control strategies like water, sanitation and hygiene (WASH) interventions. At present, many countries with endemic STH infections are not availing themselves of the freely donated drugs to treat children, partly due to the logistical challenges in getting the drugs to these populations. With this existing situation, the expansion of these programs to target WRA would also require an increase in drug donations as well as effective targeting platforms to achieve high program coverage for WRA. Even if the mass deworming coverage targets are reached, it might not be enough to eliminate transmission and the focus should be concomitant morbidity control, and ideally, the eventual elimination of transmission (Anderson et al., 2015). Consequently it is highly desirable to modify the existing guidelines with

a concomitant emphasis on education and sustainability of current WASH programs along with mass deworming to reduce transmission intensity and thereby enhance the impact of mass deworming programs (Anderson et al., 2015).

With regards to mass deworming during pregnancy, the data about the deworming drug use in pregnancy are scarce (WHO, 1994, 2018). Adverse events associated with deworming in girls and women themselves have rarely been published, and usually only within the context of specific research studies (Keiser & Utzinger, 2008; Ndyomugyenyi et al., 2008). Although mass deworming is regarded as the most effective means of controlling morbidity and mortality with STH; the long-term safety when administered during pregnancy, particularly in terms of birth outcomes has not been rigorously evaluated (WHO, 1994, 2018). However, serious adverse events have not been reported (Ndyomugyenyi et al., 2008a). A recent review investigating the scope of available evidence for benefits of deworming treatments in order to inform a decision about possible inclusion of deworming as an intervention in the Lives Saved Tool (LiST) found that deworming did not show consistent benefits for indicators of mortality, anaemia, or growth in children younger than five or WRA and hence did not recommend including deworming in the LiST model (Thayer, Clermont, & Walker, 2017). These concerns are further complicated by the lack of evidence supporting the health benefits of treating helminths during pregnancy on maternal and birth outcome (Salam et al., 2015). Consequently, there is the question of undue exposure to deworming drugs as a result of routine mass deworming and the potential adverse effects on the foetus. Another barrier to including WRA in mass deworming programs is likely the fear of inadvertently administering deworming drugs to women who may not be aware that they are in their first trimester of pregnancy (at which time deworming in contraindicated) since a comprehensive approach for targeting WRA is currently lacking (Mofid & Gyorkos, 2017).

More recently, issues related to limited efficacy profiles of albendazole, mebendazole, levamisole, and pyrantel pamoate have also been raised with some evidence supporting co-administration of some deworming drugs (Moser et al., 2017; Palmeirim et al., 2018). Furthermore, there are issues related to drug resistance associated with the scale-up of periodic mass deworming campaigns (Moser et al., 2017; Palmeirim et al., 2018).

Economic Perspective

From an economic policy perspective, the merits of mass deworming depend mainly on whether its long-term impact on earnings exceeds its cost. Deworming costs very little at about US$0.25 per child per year and a consequent high benefit to cost ratio. The cost effectiveness of targeting WRA with mass deworming

programs poses a different issue since there are no existing delivery platforms targeting WRA that might be as cost-effective and convenient as schools for targeting children (Anderson et al., 2015) and the cost of treating WRA might at times be higher when compared to SAC due to the ease of targeting children through school based platforms. Moreover, existing cost studies for deworming among WRA are scarce and mainly evaluate the cost of specific integrated delivery mechanism for deworming WRA. Cost studies for deworming among WRA suggest that implementation costs vary primarily by the type of delivery strategy used.

One study (Boselli et al., 2011) investigated the cost of the provision of anthelminthic drugs during existing immunization campaigns for Expanded Programme on Immunization (EPI) in Laos. The integrated delivery of mass deworming with the existing EPI reduced the individual cost of deworming by 10 times (from US$0.25 in the vertical deworming campaign to US$0.02 in the integrated campaign) compared to implementation of the vertical deworming campaign alone. Burden posed on health workers by the integration process was perceived as minimal and manageable. Besides, delivery of anthelminthic drugs during the immunization campaigns enabled campaign teams to directly observe drug intake, which assured safety. Such an integration was estimated to be cost-effective due to the shared use of resources (like campaign venues and the meeting opportunities as well as the simultaneous mobilization of communities, health workers and social mobilization teams) along with the non-remuneration of health workers for the additional time dedicated to deworming training and activities in the context of the integrated campaign. Furthermore, the deworming programs can potentially benefit from the existing high coverage of the EPI programs. According to the WHO and the United Nations International Children's Emergency Fund (UNICEF) immunization summary, EPI has already achieved at least 75% national coverage in over 90% of the STH-endemic countries in the world which could potentially increase the national coverage of deworming for WRA (Boselli et al., 2011).

Another study (Casey et al., 2011) estimated the cost and cost-effectiveness of a project administering deworming and weekly iron-folic acid supplementation to control anaemia among WRA in Yen Bai province, Vietnam. Cost effectiveness was evaluated using data on programmatic costs based on two surveys in 2006 and 2009 and impact on anaemia and iron status collected in 2006, 2007, and 2008. The cost per woman treated (defined as consuming at least 75% of the recommended intake) was USD 0.76 per annum. This estimate includes financial costs (for supplies, training), and costs of health care workers' time. The cost-effectiveness of the project was reported to be USD 4.24 per anemia case prevented per year. Based on estimated productivity gains for adult women, the benefit: cost ratio was 6.7:1. Cost of the supplements and deworming drugs was 47% of the total, while costs of training, monitoring, and health workers' time accounted

for 53%. This study demonstrated the effective uptake of weekly iron-folic acid supplementation by 70% of woman in Yen Bai province with an annual cost of USD 0.76/woman. This compares to estimates by the National Institute of Nutrition that only 20% of pregnant women are covered by the national antenatal program of daily iron supplementation for which there is no costing. This study concluded that weekly iron-folic acid supplementation and regular deworming is a low-cost and cost-effective intervention and would be appropriate for population-based introduction in settings with a high prevalence of anaemia and iron deficiency and low malaria infection rates (Casey et al., 2011).

One study (Lee, Bacon, Bailey, Wiringa, & Smith, 2011) assessed the effectiveness of hookworm vaccine and suggested that the vaccine would be strongly cost-effective (and in many situations economically dominant) especially when combined with a drug treatment program over a range of vaccine efficacies, vaccine costs, and hookworm rates. The model has demonstrated that incorporating vaccination into current hookworm drug treatment strategies targeting SAC and WRA may yield benefit at minimal cost. However, the findings suggest that while interventions were cost-effective for both SAC and WRA, the coverage and therefore economic return for targeting SAC may be greater and hence SAC may be an initial target for vaccination initiatives with subsequent expansion to WRA. The authors caution that this may vary with environmental conditions and infection risk among these groups. Less additional benefit may be seen with the initiation of vaccination in regions where infection prevalence is still able to be controlled through drug treatment. Low cost of anthelminthic drugs currently available make the cost-effectiveness of local vaccine distribution contingent upon the current drug efficacy present within the community. Findings warrant future studies that explore the implications of the introduction of a hookworm vaccine into other countries (Lee et al., 2011).

What's the way forward?

WRA have historically not been a focus of the deworming programs and hence there is a consequent gap in the evidence related to the health impacts, program coverage and potential cost-effectiveness related to mass deworming for WRA. However, this appears to be changing as new plans are being discussed by the WHO to include WRA in deworming activities (WHO, 2018). The recent report of the WHO Advisory Group on deworming in girls and WRA shows a renewed focus of deworming for WRA; although it does not answer some of the critical questions and highlight some issues as research priorities. Critical issues requiring more focus include: when to stop the deworming programs; ideal delivery strategies and platforms to target WRA;

cost-effectiveness of deworming programs with or without iron supplementation; and supplementary benefit of interventions other than deworming and its cost-effectiveness.

Although the existing deworming guidelines clearly specify the geographic prevalence cut-offs for mass deworming implementation; however, it does not take into account the infection intensities among various population groups and the existing deworming coverage. Along with mass deworming, various strategies to help identify pockets with high infection intensity, communities nearing elimination and those needing further interventions, should also be applied simultaneously. Geospatial and spatio-temporal analysis could help identify geographical areas where mass deworming still needs to be implemented and where these programs should now conclude. This will help the country level program implementers gauging the program success and coverage along with deciding on the future of the program.

There is a need to identify the most appropriate platforms, strategies, and target groups that need to be considered while planning for deworming for WRA. Antenatal clinics could be one of the potential delivery platforms to target pregnant and lactating women while existing community health programs could be potentially utilized to reach WRA in the community. Without much data to support deworming programs for WRA, it is imperative to assess the relative costs and cost-effectiveness of various potential strategies and platforms. With respect to deworming during pregnancy, it is of prime importance to treat pregnant women in the second and third trimester of pregnancy and hence measures to correctly and cost-effectively identify and exclude women in the first trimester of pregnancy also needs to be explored. There is a need to identify specific process and outcome indicators for mass deworming programs targeting WRA since these would largely vary from the existing SAC deworming programs. More specifically, the coverage goals and the morbidity reduction goals need to be specified for the specific subgroups of WRA including adolescent girls, pregnant and lactating women.

Further empirical evidence of impact of maternal infections with STH on health of infants and children need to be further explored. Moreover, the health benefits of treating pregnant women with deworming drugs for mother and infants needs exploration. Safety of mass deworming for the various subgroups of WRA, except pregnant women also need to be studied. Research on the benefits of maternal postpartum deworming is urgently needed to build on the deworming (Mofid & Gyorkos, 2017). There is a need to study the effectiveness of maternal postpartum deworming as a means to improve both maternal and child health.

Concomitantly, there is a need to broaden the scope of research to investigate the cost-effectiveness and feasibility of alternative treatment strategies in achieving the interruption of transmission across a range of settings. The debate on what is the best strategy to manage STH infection should shift from prevention and management to morbidity control and transmission interruption. It is highly desirable to shift the focus from deworming alone and include concomitant emphasis on education and sustainability of current WASH programs to reduce transmission intensity and thereby enhance the impact of existing mass deworming.

Possible future studies should assess the effectiveness of large scale implementation evaluations along with measuring and controlling for possible confounding variables including concomitant iron/folic acid supplementation, antenatal care coverage and WASH interventions. It is imperative to assess the outcomes that are programmatically relevant and contribute to the Global Burden of Diseases in a non-randomised setting. Due attention should be given to sustainability of the current WASH programs along with mass deworming to reduce transmission intensity and thereby enhance the impact of mass deworming programs.

Chapter 6: Overall Conclusions

Abstract

Mass deworming remains the recommended strategy to prevent and treat STH and schistosomiasis. Findings from the systematic review assessing mass deworming during pregnancy suggests that it does not have any impact on maternal anemia; however it significantly reduced the prevalence of hookworm, Trichuris, Ascaris, S.japonicum and S.mansoni. There was no impact of mass deworming during pregnancy haemoglobin, birth weight, low birth weight, preterm birth, perinatal mortality, stillbirths, neonatal mortality and congenital abnormalities. Findings from the systematic review on interventions other than mass deworming among pregnant women and WRA on maternal, birth and newborn health outcomes suggests that the data are too scarce and of low quality. The individual participant data meta-analysis (IPD) to explore whether the effect of mass deworming during pregnancy varies with individual characteristics, intensity of infection, infection status, socioeconomic status, sanitation environment and co-interventions analyzes majority of the existing data (70% of the total potential participant population). Findings from the IPD analysis suggest that mass deworming during pregnancy is associated with reducing anaemia with no apparent impact on infection intensity, low birth weight and preterm birth. These analyses were limited by the availability of data for the impact by subgroups and effect modification. Further studies accounting for maternal baseline worm intensities, concomitant iron/folic acid supplementation and antenatal care coverage could change our findings. There is a need to support and promote open data for future IPDs.

Summary of main results

Findings from the systematic review assessing mass deworming during pregnancy suggests that it does not have any impact on maternal anemia; however it significantly reduced the prevalence of hookworm, Trichuris, Ascaris, S.japonicum and S.mansoni. There was no impact of mass deworming during pregnancy haemoglobin, birth weight, low birth weight, preterm birth, perinatal mortality, stillbirths, neonatal mortality and congenital abnormalities. Findings from the systematic review on interventions other than mass deworming among pregnant women and WRA on maternal, birth and newborn health outcomes suggests that the data are too scarce and of low quality.

The IPD meta-analysis is based on the data from three trials with 5957 participants. Findings from this IPD suggest reduction in anaemia among pregnant women with mass deworming. There was no evidence of effect on any of the other outcomes including Trichiura infection, hookworm infection or any of the pregnancy outcomes including LBW and preterm birth. Findings of no impact of mass deworming on infection intensity could be attributable to the fact that majority of the study population in the included studies were either not infected or lightly infected which could have diluted the impact. Based on the availability of the data, we could only assess for effect modification by baseline Trichiura infection, maternal anemia at baseline and maternal BMI at baseline. There was no evidence of effect modification by Trichiura intensity at baseline, maternal anemia at baseline and maternal BMI at baseline; however we advise caution in interpreting these findings due to limited number of participants included in the analysis.

Overall completeness and applicability of evidence

Findings from this IPD analysis are based on 70% of the existing data deemed eligible for IPD (5957 participants of 8515 participants). The studies included in this review were conducted among pregnant women in LMIC settings. One of the three trials included in the IPD analysis provided daily iron folate supplements (36mg iron; 5mg folate) along with the deworming drugs. We conducted an extensive search of electronic databases. We screened 23,406 articles and updated this search to March 2018. We report the systematic review according to the reporting guidelines for IPD and systematic review and meta-analysis (PRISMA and PRISMA-IPD). We published and followed an a priori protocol (Salam, Middleton et al.). Our systematic review and IPD analysis was approved by the Research Ethics Boards at SickKids. We developed a data sharing agreement that was signed by all studies that contributed data. Study authors were invited to join the Investigator's Collaborative, participate in meetings and contribute to the final report. Our process and conduct of the IPD was driven by consultation with our expert Advisory board which included statistical, parasitology and nutrition expertise.

Quality of the evidence

The trials included in the systematic review and IPD were judged to be of fairly good quality. All of the included studies were judged to be at low risk of bias for blinding of participants, personnel and outcome assessor; and selective reporting. One of the included studies was judged to be at high risk of bias for allocation concealment while two studies were at high risk for attrition bias. The overall outcome quality was judged to 'moderate' based on the GRADE criteria. The outcome quality was downgraded due to study limitations since the estimates are based on selected sample eligible for IPD.

Limitations and potential biases in the review process

Despite of receiving majority of the existing data (70%) to conduct IPD, there were a few limitations. One limitation of this review is that we did not receive data from all eligible studies. Another limitation is that we were unable to assess effect modification by pre-identified effect modifiers. The trials did not capture many of the variables of interest that restricted our analysis. Very few trials reported outcomes according to the baseline level of infection intensities and hence those conclusions could not be drawn. In terms of the infection intensities, the population studied were either not infected or lightly infected and hence it was difficult to categorize the sample according to the intensity of infection and have meaningful estimates. Trials did not report baseline data on the individual and environmental level effect modifiers and hence it was difficult to assess the effect modification. Variables like socio-economic status were least studied and where reported, had different definitions and hence could not be accounted for. None of the included studies assessed any co-interventions including WASH practices and hence the impact of co-interventions could not be assessed. We could not assess for publication bias given the small number of included studies; however, considering the small universe of studies in the domain, the issues related to publication and small study sizes cannot be ignored.

Agreements and disagreements with other studies or reviews

The most recent Cochrane meta-analysis (Salam, Haider et al. 2015) on deworming for STH during pregnancy concluded that there was insufficient evidence to recommend deworming for STH. This review also highlighted the need for future well-designed, large scale RCTs to establish the benefit. These findings were based on four trials including 4265 participants. This review has some differences compared to our review. The inclusion criteria for this Cochrane review was limited to deworming for STH alone while our IPD meta-analysis also included trials with deworming for schistosomiasis. The Cochrane review reported no impact of mass deworming for STH on maternal anaemia while findings from our review suggests reduction in maternal anaemia associated with mass deworming.

Implications for policy

This systematic review and IPD suggest that mass deworming reduces maternal anemia with moderate quality evidence. The existing deworming guidelines clearly specify the geographic prevalence cut-offs for mass deworming implementation; however, it does not take into account the infection intensities among various population groups and the existing deworming coverage. There is a need to built-in these guidelines in existing deworming policies. Moreover, deworming alone is insufficient to achieve improvements in all maternal and newborn health outcomes. These findings reinforce that it is essential to focus on sustainable development to address the other factors such as poor sanitation, food insecurity and malnutrition. Mass deworming should be bundled as part of these packages to improve range of maternal and newborn health outcomes.

Implications for research

There is a need to evaluate mass deworming for STH and schistosomiasis during pregnancy in large scale programmatic settings. Future impact evaluations should attempt to measure various individual and environmental factors that could potentially affect the impact of mass deworming. Future program evaluations should also assess the long term impact of mass deworming on birth and infant health outcomes along with the maternal health outcomes. Safety of mass deworming for the various subgroups of WRA, except pregnant women also need to be studied. There is a need to broaden the scope of research to investigate the cost-effectiveness and feasibility of alternative treatment strategies in achieving the interruption of transmission across a range of settings. There is an urgent need for open data from all research studies. The quality of evidence is rated as moderate for our findings and further research on maternal baseline worm intensities and birth outcomes could change our findings.

Appendices

Appendix 1: Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1	flukes.tw.	33	Albendazole/	65	Oxamniquine.tw.
2	platyhelminth*.tw.	34	Mebendazole/	66	Praziquantel/
3	whipworm*.tw.	35	exp Piperazines/	67	Trichlorfon/
4	whip worm*.tw.	36	Levamisole/	68	metrifonate.tw.
5	hookworm*.tw.	37	exp Pyrantel/	69	Artemisinins/
6	hookworm*.tw.	38	Ivermectin/	70	(artesunate or artemether).tw.
7	hook worm*.tw.	39	exp Anthelmintics/	71	or/34-72
8	roundworm*.tw.	40	Ivermectin.tw.	72	(deworm* or de-worm*).tw.
9	round worm*.tw.	41	Albendazole.tw.	73	exp Anthelmintics/ or (anthelmint* or antihelmint*).tw.
10	geohelminth*.tw.	42	Mebendazole.tw.	74	72 or 73
11	ancylostoma*.tw.	43	Piperazine*.tw.	75	Pregnant Women/ or Pregnancy/ or Pregnancy Complications, Parasitic/ pregnant wom*n .tw.
12	Necator*.tw.	44	Levamisole.tw.	76	32 and 71
13	Ascaris.tw.	45	pyrantel.tw.	77	74 or 76
14	Ascaridida.tw.	46	tiabendazole.tw.	78	75 and 77
15	Ancylostoma.tw.	47	anthelmint*.tw.		
16	Necator americanus.tw.	48	Anticestodal.tw.		
17	Trichuris.tw.	49	Antiplatyhelmintic.tw.		
18	Trichuroidea.tw.	50	Anti-platyhelmintic.tw.		
19	Adenophorea.tw.	51	Albendazole.tw.		
20	Enoplida.tw.	52	Dichlorophen.tw.		
21	Ascaridida.tw.	53	Niclosamide.tw.		
22	Platyhelminth*.tw.	54	Bithionol.tw.		
23	Rotifera.tw.	55	Diamfenetide.tw.		
24	trichuriasis.tw.	56	Nitroxinil.tw.		
25	ascariasis.tw.	57	Oxyclozanide.tw.		
26	ancylostomiasis.tw.	58	Rafoxanide.tw.		
27	ascarid*.tw.	59	Schistosomicid*.tw.		
28	schistosom*.tw.	60	Antimony Potassium Tartrate.tw.		
29	bilharziosis.tw.	61	Antimony Sodium Gluconate.tw. =		
30	bilharzia*.tw.	62	Hycanthone.tw.		
31	exp Schistosoma/	63	Lucanthone.tw.		
32	or/1-31	64	Niridazole.tw.		

Database: Embase Classic+Embase

1 whipworm*.tw.	31 Secernentea.tw.	61 Piperazine*.tw.	91 (woman or women).tw.
2 whip worm*.tw.	32 Ascaridida.tw.	62 Levamisole.tw.	92 pregnan*.tw.
3 hookworm*.tw.	33 Rhabditida.tw.	63 pyrantel.tw.	93 or/90-92
4 hookworm*.tw.	34 Cestoda.tw.	64 tiabendazole.tw.	94 50 and 85
5 hook worm*.tw.	35 Trematod*.tw.	65 anthelmint*.tw.	95 94 or 89
6 roundworm*.tw.	36 Turbellaria.tw.	66 *Antiplatyhelmintic Agents/	96 95 and 93
7 round worm*.tw.	37 Platyhelminth*.tw.	67 Anticestodal.tw.	
8 pinworm*.tw.	38 Rotifera.tw.	68 Antiplatyhelmintic.tw.	
9 pin worm*.tw.	39 trichuriasis.tw.	69 Anti-platyhelmintic.tw.	
10 flukes.tw.	40 ascariasis.tw.	70 Albendazole.tw.	
11 geohelminth*.tw.	41 trichinellosis.tw.	71 Dichlorophen.tw.	
12 ancylostoma.tw.	42 Trichostrongyloidiasis.tw.	72 Niclosamide.tw.	
13 Necator*.tw.	43 ancylostomiasis.tw.	73 Bithionol.tw.	
14 Ascaris.tw.	44 enterobiasis.tw.	74 Diamfenetide.tw.	
15 Ascaridida.tw.	45 cestode*.tw.	75 Nitroxinil.tw.	
16 Ancylostoma.tw.	46 trematode*.tw.	76 Oxyclozanide.tw.	
17 Necator americanus.tw.	47 ascarid*.tw.	77 Rafoxanide.tw.	
18 Enterobius.tw.	48 schistosomiasis.tw.	78 Schistosomicide*.tw.	
19 Oxyuroidea.tw.	49 Schistosoma*.tw.	79 Antimony Potassium Tartrate.tw.	
20 Oxyurida.tw.	50 or/1-49	80 Antimony Sodium Gluconate.tw.	
21 Trichuris.tw.	51 Albendazole/	81 Hycanthone.tw.	
22 Trichuroidea.tw.	52 Mebendazole/	82 Lucanthone.tw.	
23 Capillaria.tw.	53 exp Piperazines/	83 Niridazole.tw.	
24 Trichinella.tw.	54 Levamisole/	84 Oxamniquine.tw.	
25 Strongyloid*.tw.	55 exp Pyrantel/	85 or/51-84	
26 Oesophagostomum.tw.	56 Ivermectin/	86 (deworm* or de-worm*).tw.	
27 Oesophagostomiasis.tw.	57 exp Anthelmintics/	87 anthelmint*.tw.	
28 Acanthocephala.tw.	58 Ivermectin.tw.	88 anthelmintic/	
29 Adenophorea.tw.	59 Albendazole.tw.	89 or/86-88	
30 Enoplida.tw.	60 Mebendazole.tw.	90 pregnant wom*n .tw.	

Cochrane Library – CDSR, DARE, CENTRAL, EED, HTA

ID Search	
#1 helmint*:ti,ab,kw (Word variations have been searched)	#17 piperazine
#2 Ancylostoma duodenale	#18 levamisole
#3 Necator americanus	#19 pyrantel
#4 Ascaris	#20 tiabendazole
#5 Enterobius vermicularis	#21 deworm*:ti,ab or de-worm*:ti,ab
#6 trichuris	#22 #15 or #16 or #17 or #18 or #19 or #20 or #21
#7 Strongyloid*	#23 #21 or #22
#8 hookworm*	#24 #23 and #14
#9 roundworm*	#25 deworm
#10 pinworm*	#26 de-worm
#11 whipworm*	#27 deworming
#12 schistosomiasis	#28 de-worming
#13 Schistosoma	#29 anthelmint*
#14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #13	#30 anthelmintic
#15 albendazole	#31 #25 or #26 or #27 or #28 or #29 or #30
#16 mebendazole	#32 #24 or #31

Appendix 2: Characteristics of the Excluded Studies

Studies	Reason for Exclusion
(Basra et al., 2012)	This study did not report any of the maternal, pregnancy or newborn health outcomes.
(Christian, Shahid, Rizvi, Klemm, & Bhutta, 2009)	This study compared different regimens of anti-helminthic treatment (single dose versus 3 days mebendazole) with appropriate control group.
(Nery et al., 2015)	This study assessed the anti-helminthic efficacy of a single dose of albendazole in communities and does not specifically targets pregnant women
(Insetta, Soriano, Totañes, Macatangay, & Belizario Jr, 2014)	This study qualitatively assessed the perceptions related to deworming during pregnancy.
(Boel et al., 2010)	This study assessed associations between STH and malaria infections among pregnant women.
(Casey et al., 2009)	This study assessed the effectiveness of deworming among women disregarding their pregnancy status.
(Ivan et al., 2014)	This study assessed deworming during pregnancy among HIV-infected women.
(Passerini et al., 2012)	This study assessed the effectiveness of pre-pregnancy deworming.
(Drevfuss et al., 1996)	This study assessed association between iron status and STH infection during pregnancy.
(Casey et al., 2011)	This study assessed the cost effectiveness of deworming for WRA
(Cowden & Hotez, 2000)	This study was a narrative review.

Appendix 3: Search Strategy

MEDLINE

1. ((exp water quality/ or exp water supply/ or exp water purification/ or exp filtration/ or (water adj2 stor*).tw.) and (consum* or drink*).mp.) or exp drinking water/ or potable water.mp. or ((household adj2 treatment).tw. and water.mp.)
2. ((exp groundwater/ or groundwater.tw.) and (suppl* or drink* or consum* or contamin*.mp.)).tw. or ((exp water pollutants/ or exp water pollution/) and ((consum* or suppl*).mp. or drink*.tw.))
3. (exp toilet facilities/ or exp sanitation/ or exp waste water/ or toilet*.tw. or latrine*.mp. or sanitation*.tw. or standpipe*.tw. or sewer*.tw. or excreta.tw. or open defecation.tw.) and health.tw.
4. (exp hygiene/ or hygien*.mp. or (health and sanitation and education).mp. or (wash adj1 (hand disinfection or hand hygiene or hand*)).mp. or hygiene behavio?r.tw.) and (child* or baby or newborn or infant or neonat* or infant).tw. and (interven* or compar* or control*).mp.
5. (wom*n or WRA or pegnan* or girl* or adolescen*)
6. 1 or 2 or 3 or 4
7. 6 and 5

Appendix 4: Characteristics of the Excluded Studies

Studies	Reasons for Exclusion
(Abebe, Kiros, Golasa, & Zeynudin, 2010)	This study did not report separate findings for WRA.
(Bella, de C. Marshall, Omer, & Vaughan, 1980)	This study did not report separate findings for WRA.
(Chandiwana, 1987)	This study did not report separate findings for WRA.
(Couto et al., 2014)	This study did not report separate findings for WRA.
(Gazzinelli et al., 2001)	This study did not report separate findings for WRA.
(Ghebreyesus et al., 2002)	This study did not report separate findings for WRA.
(Dalton & Pole, 1978)	This study did not report separate findings for WRA.
(Lima e Costa et al., 1991)	This study did not report separate findings for WRA.
(Firmo, Costa, Guerra, & Rocha, 1996)	This study did not report separate findings for WRA.
(Gazzinelli et al., 2006)	This study did not report separate findings for WRA.
(Kloos et al., 2006)	This study assessed the methods for assessing water contact.
(Kloos, Quites, Oliveira, LoVerde, & Gazzinelli, 2012)	This study assessed the methods for assessing water contact.
(Kvale, 1981)	This study did not report separate findings for WRA.
(Matthys et al., 2007)	This study did not report separate findings for WRA.
(de Moira, Kabatereine, Dunne, & Booth, 2011)	This study did not report separate findings for WRA.
(Mota & Sleigh, 1987)	This study did not report separate findings for WRA.
(Mwanga & Lwambo, 2013)	This study did not report separate findings for WRA.
(Ndassa, Mimpfoundi, Gake, Paul Martin, & Poste, 2007)	This study did not report separate findings for WRA.
(Ngui et al., 2015)	This study did not report separate findings for WRA.
(Ofoezie, Christensen, & Madsen, 1998)	This study only assessed various water contacts.
(Paredes et al., 2010)	This study did not report separate findings for WRA.
(Pham-Duc et al., 2013)	This study did not report separate findings for WRA.
(Phongluxa et al., 2013)	This study did not report separate findings for WRA.
(Schmidlin et al., 2013)	This study did not report separate findings for WRA.
(Schüle et al., 2014)	This study did not report separate findings for WRA.
(Taylor, Chandiwana, Govere, & Chombo, 1987)	This study did not report separate findings for WRA.
(Tefera & Mebrie, 2014)	This study did not report separate findings for WRA.
(Trang, Mølbak, Cam, & Dalsgaard, 2007)	This study did not report separate findings for WRA.
(Trönnberg, Hawksworth, Hansen, Archer, & Stenström, 2010)	This study did not report separate findings for WRA.
(Bethony et al., 2001)	This study did not report separate findings for WRA.
(Useh & Ejezie, 1999)	This study did not report separate findings for WRA.
(Wilkins, Blumenthal, Hagan, Hayes, & Tulloch, 1987)	This study did not report separate findings for WRA.
(Yajima et al., 2009)	This study did not report separate findings for WRA.
(Traub, Robertson, Irwin, Mencke, & Thompson, 2004)	This study did not report separate findings for WRA.
(Hidayah, Teoh, & Hillman, 1997)	This study did not report separate findings for WRA.
(Corrales, Izurieta, & Moe, 2006)	This study did not report separate findings for WRA.
(Knopp et al., 2013)	This study did not report separate findings for WRA.
(Mahmud et al., 2013)	This study did not report separate findings for WRA.
(Parajuli, Umezaki, & Watanabe, 2009)	This study did not report separate findings for WRA.
(Gunawardena, Karunaweera, & Ismail, 2004)	This study did not report separate findings for WRA.
(Balen et al., 2011)	This study did not report separate findings for WRA.
(Humphries et al., 2011)	This study did not report separate findings for WRA.
(Jiraanankul et al., 2011)	This study did not report separate findings for WRA.

Appendix 5: Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1	flukes.tw.	41	Albendazole.tw.
2	platyhelminth*.tw.	42	Mebendazole.tw.
3	whipworm*.tw.	43	Piperazine*.tw.
4	whip worm*.tw.	44	Levamisole.tw.
5	hookworm*.tw.	45	pyrantel.tw.
6	hookworm*.tw.	46	tiabendazole.tw.
7	hook worm*.tw.	47	anthelmint*.tw.
8	roundworm*.tw.	48	Anticestodal.tw.
9	round worm*.tw.	49	Antiplatyhelmintic.tw.
10	geohelminth*.tw.	50	Anti-platyhelmintic.tw.
11	ancylostoma*.tw.	51	Albendazole.tw.
12	Necator*.tw.	52	Dichlorophen.tw.
13	Ascaris.tw.	53	Niclosamide.tw.
14	Ascaridida.tw.	54	Bithionol.tw.
15	Ancylostoma.tw.	55	Diamfenetide.tw.
16	Necator americanus.tw.	56	Nitroxinil.tw.
17	Trichuris.tw.	57	Oxyclozanide.tw.
18	Trichuroidea.tw.	58	Rafoxanide.tw.
19	Adenophorea.tw.	59	Schistosomicid*.tw.
20	Enoplida.tw.	60	Antimony Potassium Tartrate.tw.
21	Ascaridida.tw.	61	Antimony Sodium Gluconate.tw. =
22	Platyhelminth*.tw.	62	Hycanthone.tw.
23	Rotifera.tw.	63	Lucanthone.tw.
24	trichuriasis.tw.	64	Niridazole.tw.
25	ascariasis.tw.	65	Oxamniquine.tw.
26	ancylostomiasis.tw.	66	Praziquantel/
27	ascarid*.tw.	67	Trichlorfon/
28	schistosom*.tw.	68	metrifonate.tw.
29	bilharziosis.tw.	69	Artemisinins/
30	bilharzia*.tw.	70	(artesunate or artemether).tw.
31	exp Schistosoma/	71	or/34-72
32	or/1-31	72	(deworm* or de-worm*).tw.
33	Albendazole/	73	exp Anthelmintics/ or (anthelmint* or antihelmint*).tw.
34	Mebendazole/	74	72 or 73
35	exp Piperazines/	75	Pregnant Women/ or Pregnancy/ or Pregnancy Complications, Parasitic/ pregnant wom*n .tw.
36	Levamisole/	76	32 and 71
37	exp Pyrantel/	77	74 or 76
38	Ivermectin/	78	75 and 77
39	exp Anthelmintics/		
40	Ivermectin.tw.		

Database: Embase Classic+Embase

1	whipworm*.tw.	51	Albendazole/
2	whip worm*.tw.	52	Mebendazole/
3	hookworm*.tw.	53	exp Piperazines/
4	hookworm*.tw.	54	Levamisole/
5	hook worm*.tw.	55	exp Pyrantel/
6	roundworm*.tw.	56	Ivermectin/
7	round worm*.tw.	57	exp Anthelmintics/
8	pinworm*.tw.	58	Ivermectin.tw.
9	pin worm*.tw.	59	Albendazole.tw.
10	flukes.tw.	60	Mebendazole.tw.
11	geohelminth*.tw.	61	Piperazine*.tw.
12	ancylostoma.tw.	62	Levamisole.tw.
13	Necator*.tw.	63	pyrantel.tw.
14	Ascaris.tw.	64	tiabendazole.tw.
15	Ascaridida.tw.	65	anthelmint*.tw.
16	Ancylostoma.tw.	66	*Antiplatyhelmintic Agents/
17	Necator americanus.tw.	67	Anticestodal.tw.
18	Enterobius.tw.	68	Antiplatyhelmintic.tw.
19	Oxyuroidea.tw.	69	Anti-platyhelmintic.tw.
20	Oxyurida.tw.	70	Albendazole.tw.
21	Trichuris.tw.	71	Dichlorophen.tw.
22	Trichuroidea.tw.	72	Niclosamide.tw.
23	Capillaria.tw.	73	Bithionol.tw.
24	Trichinella.tw.	74	Diamfenetide.tw.
25	Strongyloid*.tw.	75	Nitroxinil.tw.
26	Oesophagostomum.tw.	76	Oxyclozanide.tw.
27	Oesophagostomiasis.tw.	77	Rafoxanide.tw.
28	Acanthocephala.tw.	78	Schistosomicide*.tw.
29	Adenophorea.tw.	79	Antimony Potassium Tartrate.tw.
30	Enoplida.tw.	80	Antimony Sodium Gluconate.tw.
31	Secernentea.tw.	81	Hycanthone.tw.
32	Ascaridida.tw.	82	Lucanthone.tw.
33	Rhabditida.tw.	83	Niridazole.tw.
34	Cestoda.tw.	84	Oxamniquine.tw.
35	Trematod*.tw.	85	or/51-84
36	Turbellaria.tw.	86	(deworm* or de-worm*).tw.
37	Platyhelminth*.tw.	87	anthelmint*.tw.
38	Rotifera.tw.	88	anthelmintic/
39	trichuriasis.tw.	89	or/86-88
40	ascariasis.tw.	90	pregnant wom*n .tw.
41	trichinellosis.tw.	91	(woman or women).tw.
42	Trichostrongyloidiasis.tw.	92	pregnan*.tw.
43	ancylostomiasis.tw.	93	or/90-92
44	enterobiasis.tw.	94	50 and 85

45	cestode*.tw.	95	94 or 89
46	trematode*.tw.	96	95 and 93
47	ascarid*.tw.		
48	schistosomiasis.tw.		
49	Schistosoma*.tw.		
50	or/1-49		

Cochrane Library – CDSR, DARE, CENTRAL, EED, HTA

ID	Search
#1	helmint*:ti,ab,kw (Word variations have been searched)
#2	Ancylostoma duodenale
#3	Necator americanus
#4	Ascaris
#5	Enterobius vermicularis
#6	trichuris
#7	Strongyloid*
#8	hookworm*
#9	roundworm*
#10	pinworm*
#11	whipworm*
#12	schistosomiasis
#13	Schistosoma
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #13
#15	albendazole
#16	mebendazole
#17	piperazine
#18	levamisole
#19	pyrantel
#20	tiabendazole
#21	deworm*:ti,ab or de-worm*:ti,ab
#22	#15 or #16 or #17 or #18 or #19 or #20 or #21
#23	#21 or #22
#24	#23 and #14
#25	deworm
#26	de-worm
#27	deworming
#28	de-worming
#29	anthelmint*
#30	anthelmintic
#31	#25 or #26 or #27 or #28 or #29 or #30
#32	#24 or #31

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