Effect of administration of antihelminthics for soil transmitted helminths during pregnancy (Review)

Haider BA, Humayun Q, Bhutta ZA

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Effect of administration of antihelminthics for soil transmitted helminths during pregnancy

Batool A Haider[1], Quratulain Humayun[1], Zulfiqar A Bhutta[1]

[1]Division of Maternal and Child Health, The Aga Khan University, Karachi, Pakistan

Contact address: Zulfiqar A Bhutta, Division of Maternal and Child Health, The Aga Khan University, Stadium Road, PO Box 3500, Karachi, 74800, Pakistan. zulfiqar.bhutta@aku.edu. (Editorial group: Cochrane Pregnancy and Childbirth Group.)

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ABSTRACT

Background

Helminthiasis is infestation of the human body with parasitic worms and it is estimated to affect 44 million pregnancies, globally, each year. Intestinal helminthiasis is associated with blood loss and decreased supply of nutrients for erythropoiesis, resulting in iron deficiency anaemia. Over 50% of the pregnant women in low- and middle-income countries suffer from iron deficiency anaemia. Though iron deficiency anaemia is multifactorial, hook worm infestation is a major contributory cause in women of reproductive age in endemic areas. Antihelminthics are highly efficacious in treating hook worm but evidence of their beneficial effect and safety, when given during pregnancy, has not been established.

Objectives

To determine the effects of administration of antihelminthics for soil transmitted helminths during the second or third trimester of pregnancy on maternal anaemia and pregnancy outcomes.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (September 2008).

Selection criteria

All prospective randomised controlled trials evaluating the effect of administration of antihelminthics during the second or third trimester of pregnancy.

Data collection and analysis

Two review authors independently assessed trial quality and extracted the data.

Main results

Three studies (1329 women) were included in this review. Analysis showed that administration of a single dose of antihelminth in the second trimester of pregnancy is not associated with any impact on maternal anaemia in the third trimester (risk ratio (RR) 0.90; 95% confidence interval (CI) 0.68 to 1.19, random effects (2 studies, n = 1075)). Subgroup analysis on the basis of co-interventions other than antihelminthics which included iron supplementation given to both groups in the study by Larocque et al, and a subset

of the study by Torlesse et al, showed that a single dose of antihelminth along with iron supplementation throughout the second and third trimester of pregnancy was not associated with any impact on maternal anaemia in the third trimester as compared to iron supplementation alone (RR 0.76; 95% CI 0.39 to 1.45, random-effects (2 studies, n = 1017)). No impact was found for the outcomes of low birthweight (RR 0.94; 95% CI 0.61 to 1.42 (1study; n = 950)), perinatal mortality (RR 1.10; 95% CI 0.55 to 2.22 (2 studies, n = 1089)) and preterm birth (RR 0.85; 95% CI 0.38 to 1.87 (1 study, n = 984)). Impact on infant survival at six months of age could not be evaluated because no data were available.

Authors' conclusions

The evidence to date is insufficient to recommend use of antihelminthics for pregnant women after the first trimester of pregnancy. More well-designed, large scale randomised controlled trials are needed to establish the benefit of antihelminthic treatment during pregnancy.

PLAIN LANGUAGE SUMMARY

Effect of administration of antihelminthics for soil transmitted helminths during pregnancy

Intestinal worms (helminths) contribute to iron deficiency anaemia as they feed on blood and cause further bleeding by releasing anticoagulant compounds. They also affect the supply of nutrients and cause anorexia, vomiting and diarrhoea. Pregnancy complicated by maternal hookworm infection poses a serious threat to the health of mothers and their babies, especially in developing countries. Women who are anaemic during pregnancy are more likely to have ill health, give birth prematurely, and have low birthweight babies with low iron reserves. Antihelminthic drugs are highly effective and have minimal side-effects but information on their use during pregnancy is limited. The major concern is that the drugs may cause malformation of the fetus (teratogenic effects).

The review authors found only three randomised controlled trials evaluating the impact of giving a single antihelminth treatment in the second trimester of pregnancy. The studies were conducted in Sierra Leone, Peru and Entebbe Uganda. A total of 1329 women were randomly assigned to receive a single dose of albendazole or mebendazole, or a placebo. In one study, and a subset of another, the women were also given a daily iron or iron-folate supplement. Analysis of the impact of antihelminth intervention on maternal anaemia including all results showed that the intervention was not associated with any clear impact on maternal anaemia or on low birthweight, perinatal deaths or preterm births. Analysis of studies in which iron or iron-folate was also given to pregnant women along with antihelminths also failed to show any impact on maternal anaemia. The impact on infant survival at six months of age could not be evaluated because data were not available. Evidence provided so far from randomised controlled trials is, therefore, insufficient to recommend use of antihelminthics for pregnant women after the first trimester of pregnancy.

BACKGROUND

Helminthiasis is infestation of the human body with parasitic worms. There are about 20 major helminth infections of humans, and all have some public health significance, but among the commonest of all human infections are the geohelminthiasis (Warren 1993). Global estimates indicate that more than a quarter of the world's population are infected with one or more of the most common of these parasites: roundworms (*Ascaris lumbricoides)*; hookworms (*Necator americanus* and *Ancylostoma duodenale)*; and whipworm (*Trichuris trichura*) (Chan 1994). Infection with *Trichuris trichura* and *Ascaris lumbricoides* typically reaches maximum intensity at 5 to 10 years of age, after which it declines to a lower level that persists throughout adulthood. A different profile is apparent for hookworm infections, with maximum intensity not usually attained until 20 to 25 years (Stephenson 1987).

Intestinal helminths contribute to anaemia as they feed on blood and cause further haemorrhage by releasing anticoagulant compounds, thereby leading to iron deficiency anaemia. They also contribute by affecting the supply of nutrients necessary for erythropoiesis (Hotez 1983; Torlesse 2000). Although iron deficiency anaemia is multifactorial, hookworm infection is an important contributory factor in endemic areas, especially among women of reproductive age. It is the leading cause of pathological blood loss in tropical and subtropical regions (Pawlowski 1991). Globally, an estimated 44 million pregnancies a year are complicated by maternal hookworm infection alone, posing a serious threat to the health of mothers and fetuses (Bundy 1995). Women in low- and middle-income countries may be pregnant or lactating for as much

as half of their reproductive lives (WHO 1994) and estimates indicate that over 50% of the pregnant women have iron deficiency anaemia (ACC/SCN 2000; WHO 1997). *Trichuris trichura* also causes intestinal blood loss, although much less so than hookworms on a per-worm basis (Bundy 1989). *Ascaris lumbricoides* interferes with the utilisation of vitamin A, which is required for haematopoiesis. All three intestinal helminths may reduce the intake and absorption of iron and other haematopoietic nutrients by causing anorexia, vomiting and diarrhoea (WHO 2003). A study on pregnant women in Liberia found the intensity of hookworm infection, as estimated by faecal egg counts, to be negatively associated with haemoglobin concentration (Jackson 1987).

Anaemia during pregnancy is associated with premature delivery, low birthweight, maternal ill health, and maternal death (Seshadri 1997). Favourable pregnancy outcomes occur 30% to 45% less often in anaemic mothers, and their infants have less than one half of normal iron reserves. Iron deficiency also adversely affects cognitive performance and development as well as the physical growth of these infants (WHO 2001).

Antihelminthic treatment is regarded as the most effective means of controlling mortality and morbidity due to intestinal helminth infections (WHO 1994). Antihelminthics such as levamisole, mebendazole, albendazole and pyrantel are highly efficacious and have minimal side-effects but data about their use in pregnancy are extremely limited. Few endemic countries have incorporated control of hookworm infections into routine antenatal care. The major obstacles to routine antihelminthic treatment in pregnancy include concerns that the drugs may have teratogenic effects on the fetus, as well as the lack of evidence supporting the health benefits of treating during pregnancy on pregnancy outcome. In 1994, the World Health Organization convened an informal consultation on hookworm infection and anaemia in girls and women which promoted the use of antihelminthics in pregnancy after the first trimester in areas where these infections are endemic (prevalence > 20% to 30%) and where anaemia is prevalent, but it also recommended evaluation of the long-term safety, particularly in terms of birth outcomes (WHO 1994). A cross-sectional retrospective study in Sri Lanka in 1995, assessing the effect of mebendazole during pregnancy on birth outcome, found beneficial effects of the therapy on birth outcome, with significantly lower rates of stillbirths, perinatal deaths and very low birthweight babies in the mebendazole group than in the control group. A slightly higher rate of congenital defects was found in women who had taken the drug in the first trimester of pregnancy but the difference was non-significant (de Silva 1999). Another non-randomised effectiveness study also conducted in Si Lanka (Atukorala 1994) involved iron folate supplementation along with a single dose of mebendazole in the second trimester of pregnancy. Comparison of compliants versus non-compliants of the therapy showed an improvement in the iron status of pregnant women in the iron folate mebendazole group. An Indian community based pre-post experimental study (Abel 2000) demonstrated a significant decrease in the prevalence of anaemia and increased mean haemoglobin in both second and third trimester in the group receiving education focusing on anaemia, plus iron supplementation and 100 mg mebendazole taken twice daily for three days. Similar results were found in a non-randomised community based study in Nepal (Christian 2004) which showed an increase in haemoglobin levels and a lower proportion of anaemia in third trimester in women receiving albendazole in the second trimester. A systematic review of randomised controlled trials on the effect of administration of intestinal anthelmintic drugs showed a mean difference of 1.71 g/L (95% confidence interval 0.70 to 2.73) for change in haemoglobin level, however, this analysis included data from trials conducted in women, both pregnant and non-pregnant, and children (Gulani 2008). Hence the aim of this review is to identify the effects of administering antihelminthics during pregnancy and to evaluate the effect on maternal and pregnancy outcome.

OBJECTIVES

To determine the effects of administration of antihelminthics for soil transmitted helminths during the second or third trimester of pregnancy on maternal anaemia and pregnancy outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials assessing the effects of administration of antihelminthics during the second or third trimester of pregnancy, irrespective of language or publication status were included in the review. Both individual randomised and cluster-randomised trials were included. Quasi-randomised trials were excluded from the review.

Types of participants

Pregnant women in the second or third trimester.

Types of interventions

Antihelminthics versus placebo or no treatment. In case of co-interventions other than antihelminthics, both groups should receive the same co-intervention.

Types of outcome measures

Maternal outcome

1. Anaemia (haemoglobin less than 11 g/dl)

Pregnancy outcomes

1. Low birthweight (less than 2500 grams)
2. Preterm birth (birth before 37 weeks of gestation)
3. Perinatal mortality
4. Infant survival at six months

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (September 2008).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors, Batool Haider (BAH) and Quratulain Humayun (QH), independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion and, if required, we consulted the third review author, Zulfiqar Bhutta (ZAB).

Data extraction and management

We designed a form to extract data. For eligible studies, two review authors (BAH and QH) extracted the data using the agreed form. We resolved discrepancies through discussion and, if required, we consulted the third reviewer. Data were entered into Review Manager software (RevMan 2008) and checked for accuracy.

Assessment of methodological quality

Two review authors (BAH and QH) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Any disagreement was resolved by discussion.

(1) Sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- adequate (any truly random process, e.g. random number table; computer random number generator);
- inadequate (any non random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- adequate (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Studies were judged at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results.

We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We assessed methods as:

- adequate;
- inadequate;
- unclear.

(5) Selective reporting bias

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- inadequate (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear.

(6) Other sources of bias

We described for each included study any important concerns we have about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no;
- unclear.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

There are no continuous outcomes in this review.

Unit of analysis

All included studies were individual randomised trials so there were no unit of analysis issues involved.

Data analysis

We analysed the data using Review Manager (RevMan 2008) and generated RR with 95% CI for the dichotomous outcomes. We used fixed-effect meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar. Where we suspected clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we used random-effects meta-analysis.
If substantial heterogeneity was identified in a fixed-effect meta-analysis this was noted and the analysis repeated using a random-effects method.

Subgroup analysis and investigation of heterogeneity

Heterogeneity among the trials was measured by visually inspecting the forest plots and calculating the I^2 statistic. Values of I^2 statistic greater than 50% were considered to be substantial. We prespecified the following subgroup analysis to investigate heterogeneity:

1. differences in type, dosage, duration and frequency of antihelminthics;
2. differences in baseline infant mortality;
3. co-interventions other than antihelminthics;
4. prevalence of malaria.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Included studies

Three trials including 1329 participants were included in this review.

The trial conducted in Sierra Leone (Torlesse 2001) was a randomised controlled 2 x 2 factorial design. It included 184 pregnant women with haemoglobin (Hb) concentration > 80 g/L and gestational age < 14 weeks at baseline. Intervention began at the first antenatal visit in the second trimester and included one single dose of albendazole (2 x 200 mg) and daily iron-folate supplements (36 mg iron as ferrous gluconate and 5 mg folic acid) for entire duration of pregnancy. Women were assigned to one of four intervention groups; one group received daily iron-folate supplements and albendazole, the second group received daily iron-folate supplements and placebo albendazole, the third group received albendazole and placebo daily iron-folate supplements and the fourth group received placebos only. Both the groups were statistically similar at baseline in terms of demographic, social and reproductive characteristics. The frequency of intestinal helminths at baseline was: *Ascaris lumbricoides* 20%, *Necator americanus* 65.6%, and *Trichuris trichura* 74.4%, and anaemia was (Hb < 110 g/L) was found in 56% of the women and iron deficiency anaemia in 18.4% of women.

The study conducted in Peru (Larocque 2006) included 1042 pregnant women in second trimester (>= 18 weeks; <26 weeks) between 18 and 44 years of age, no anthelminth treatment in the past six months and resident of rural or periurban areas (defined as having no running water or flushing toilet facility at home). Any woman with severe anaemia (Hb < 70 g/L) or a medical condition requiring follow up were excluded. The women were randomised to receive either a single 500 mg dose of mebendazole plus a daily iron supplement (60 mg elemental iron) or a single dose placebo plus a daily iron supplement (60 mg elemental iron). Women in the two groups were similar at baseline in terms of socio-demographic characteristics and pregnancy-related variables. The frequency of intestinal helminths at baseline was: *Ascaris lumbricoides* 64.2%, hookworms 46.4%, and *Trichuris trichura* 82% and anaemia (Hb < 110 g/L) was found in 47% of the women.

The trial conducted by Elliott et al (Elliott 2005) in Entebbe, Uganda included 103 pregnant women in the second trimester of pregnancy. It was a randomised, double-blind, placebo controlled trial.The treatment group received albendazole 400 mg single dose and the control group received a placebo, regardless of whether they were infected with hookworm or not. Pregnant women with haemoglobin < 80 g/L, abnormal pregnancy and adverse reaction to anthelminthic drugs were excluded from the study. Women in the two groups were similar at baseline in age, HIV status, malaria and helminth prevalence, and baseline cytokine levels and responses. The baseline frequency of intestinal helminths was: *Ascaris lumbricoides* 15%, hookworms 38%, and *Trichuris trichura* 6%.

Please refer to the 'Characteristics of included studies' table for more details.

Excluded studies

Two studies (Bhutta 2007; Villar 1998) were excluded as they did not satisfy the inclusion criteria of the review. The study by Bhutta et al (Bhutta 2007) compared three days of mebendazole versus a single dose, whereas the study by Villar et al (Villar 1998) was published as an abstract and contained insufficient information.

Risk of bias in included studies

All three included studies had adequate sequence generation with allocation concealment done in two studies (Elliott 2005; Larocque 2006). Blinding of participants, study personnel and outcome assessors was achieved in two studies (Elliott 2005; Larocque 2006) whereas in Torlesse 2001, participants and outcome assessors were blinded to the assignment but we are unsure of the blinding of study personnel. Attrition and exclusions (incomplete outcome data) were 3.4% in Larocque 2006. This study gave reasons of attrition and exclusions at each level along with the various distribution in the two groups. However, incomplete outcome data were 30.8% and 29.8% in Elliott 2005 and Torlesse 2001, respectively.

Effects of interventions

Maternal outcome

Administration of a single dose of antihelminths in the second trimester of pregnancy failed to show a statistically significant impact on maternal anaemia in the third trimester (RR 0.90; 95% CI 0.68 to 1.19, random-effects (two studies, n = 1075)). This was associated with substantial heterogeneity observed both on the visual inspection and by the I^2 statistic. Subgroup analysis was conducted on the basis of co-interventions other than anthelminths which included iron supplementation given to both groups in the study by Larocque et al and a subset of the study by Torlesse et al. Analysis showed that a single dose of anthelminths along with iron supplementation throughout the second and third trimester of pregnany did not have any impact on maternal anaemia in the third trimester as compared to iron supplementation alone (RR 0.76; 95% CI 0.39 to 1.45, random effects (2 studies, n = 1017)).

Pregnancy outcomes

A single dose of anthelminth in the second trimester of pregnancy was not associated with any impact on low birthweight (RR 0.94; 95% CI 0.61 to 1.42 (1 study, n = 950), perinatal mortality (RR 1.10; 95% CI 0.55 to 2.22 (2, studies, n = 1089)) and preterm births (RR 0.85; 95% CI 0.38 to 1.87 (1 study, n = 984)). None of the included studies collected information on infant survival at six months of age.

Sensitivity analysis for the risk of bias introduced by incomplete outcome data was not conducted for the outcome of perinatal mortality due to the limited number of studies included in the analysis.

DISCUSSION

Intestinal helminthiasis, especially by hookworms, is a major contributor to anaemia in women of child bearing age, particularly in the developing countries (Bundy 1995). Anaemia during pregnancy due to chronic worm infestation may lead to poor pregnancy outcomes, evaluation of which was the aim of this review.

We found only three randomised controlled trials evaluating the impact of anthelminth treatment in the second trimester of pregnancy. All studies were conducted in developing countries in which a single dose of anthelminth in the second trimester of pregnancy was compared against the control group. Study by Larocque et al (Larocque 2006) also inlcuded iron supplementation which was given to both the groups. Torlesse 2001 had a 2 x 2 factorial design in which the researchers evaluated the impact of a single dose of albendazole not only with iron folate supplementation but also with their simultaneous controls, whereas, Elliott et al (Elliott 2005) only had an antihelminth as an intervention. The intestinal heminth infestation was found to be endemic in all three studies, with anaemia prevalent among the pregnant women. Analysis showed that a single dose of anthelminth given during the second trimester of pregnancy failed to produce an impact on maternal anaemia in the third trimester. Subgroup analysis on the basis of cointervention, which included iron supplementation to both the groups evaluated data from Larocque 2006 and a subset of Torlesse 2001. This also failed to show any impact on maternal anaemia in the third trimester. The subset of participants in Torlesse 2001, in which iron folate was given to both the group, shows an additive effect of the iron folate supplementation along with anthelminths, which is not seen in the other subset who did not receive iron folate supplements as a cointervention. This additive effect is not observed in Larocque 2006 in which iron was also supplemented to both groups. The differences observed could be explained by the fact that iron folate supplementation was semi-supervised in Torlesse 2001 whereas with Larocque 2006, being an effectiveness study, supplementation was unsupervised. Also, the dose of iron was 36 mg per day in Torlesse 2001 and 60 mg per day in Larocque 2006. According to the Institute of Medicine, the tolerable upper limit for iron during pregnancy, based on gastrointestinal side effects, is 45 mg per day (IOM 2001). So, a higher dose of iron in Larocque 2006 could have resulted in gastrointestinal side effects and hence non-compliance of the participants. Another supportive clause for the observation of a beneficial effect seen in the subset of Torlesse 2001 could be that in this study women were recruited in first trimester with the intervention initiated on the first antenatal visit in the second trimester of pregnancy, thus resulting in a longer period of iron folate supplementation (approximately 24 weeks). Whereas in Larocque 2006, the women were recruited throughout the second trimester of pregnancy resulting in a shorter time period of iron supplementation of around 13 to 20 weeks. Additionally, treatment with antihelminths earlier in the second trimester would improve food intake from the early half of the pregnancy by relieving the symptoms of anorexia caused by the soil transmitted infections, reduced blood loss and also increased absorption of nutrients by reducing vomitting and diarrhea associated with intestinal helminthiasis. Thus, improved food intake, nutrient absorption and reduced blood loss, along with iron folate supplementation over a longer period of time, would result in a better haematological response.

The review findings showed no impact of antihelminths on the outcomes of low birthweight, perinatal mortality and preterm births. The impact on infant survival at six months of age could not be evaluated due to the non-availability of data from the included studies. However, a randomised controlled trial (Christian 2004) in rural Nepal primarily designed to evaluate the impact of multiple micronutrient supplementation given to women during pregnancy also offered albendazole to these women. Since earlier studies in the same area had shown that intestinal helminthiasis was endemic in rural Nepal, Christian et al offered one 400 mg dose of albendazole in the second and third trimester of pregnancy for the treatment of possible geohelminth infection. Comparison of pregnancy outcomes for women who received two doses as compared to women who did not receive albendazole showed an increase in the birthweight of infants. Receiving two doses of albendazole also resulted in 41% lower infant mortality at six months of age as compared to the group who did not receive two doses of albendazole, adjusting for confounding factors. However, a single dose failed to show an impact on both of these outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence to date in this review is insufficient to recommed use of antihelminths for pregnant women after the first trimester of pregnacy. Although single dose anthelminth treatment early in the second trimester of pregnancy, along with iron folate, may have a beneficial effect on maternal anaemia, more studies are required to confirm this. Our review also provides insufficient evidence of the impact of antihelminths on the pregnancy outcomes of low birthweight, perinatal mortality and preterm birth.

Implications for research

More well-designed, large scale randomised controlled trials are needed to establish the benefit of anthelminth treatment during pregnancy.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

REFERENCES

References to studies included in this review

Elliott 2005 *{published data only}*

Elliott AM, Mpairwe H, Quigley MA, Nampijja M, Muhangi L, Oweka-Onyee J, et al.Helminth infection during pregnancy and development of infantile eczema. *JAMA* 2005;**294**(16):2032–4.

* Elliott AM, Namujju PB, Mawa PA, Quigley MA, Nampijja M, Nkurunziza PM, et al.A randomised controlled trial of the effects of albendazole in pregnancy on maternal responses to mycobacterial antigens and infant responses to bacille calmette-guerin (BCG) immunisation. *BMC Infectious Diseases* 2005;**5**:115.

Larocque 2006 *{published data only}*

Gyorkos TW, Larocque R, Casapia M, Gotuzzo E. Lack of risk of adverse birth outcomes after deworming in pregnant women. *Pediatric Infectious Disease Journal* 2006;**25**(9):791–4.

* Larocque R, Casapia M, Gotuzzo E, MacLean JD, Soto JC, Rahme E, et al.A double-blind randomized controlled trial of antenatal mebendazole to reduce low birthweight in a hookworm-endemic area of Peru. *Tropical Medicine and International Health* 2006;**11**(10): 1485-95.

Torlesse 2001 *{published data only}*

* Torlesse H, Hodges M. Albendazole therapy and reduced decline in Haemoglobin concentrations during pregnancy (Sierra Leone). *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2001; **95**:195–201.

Torlesse H, Hodges M. Antihelminthic treatment and haemoglobin concentrations during pregnancy. *Lancet* 2000;**356**:1083.

References to studies excluded from this review

Bhutta 2007 *{published data only}*

Bhutta ZA. Severe anaemia treatment trial, Pakistan. ClinicalTrials.gov (http://clinicaltrials.gov/) (accessed 2007).

Villar 1998 *{published data only}*

Villar MA, Dala FE, Cardona VA. Nematode infections in pregnancy: the pyrantel experience. American Journal of Obstetrics and Gynaecology 1998; Vol. 178, issue 1 Pt 2:S214.

References to ongoing studies

Elliott 2007 *{published data only}*

Elliott AM, Kizza M, Quigley MA, Ndibazza J, Nampijja M, Muhangi L, et al.The impact of helminths on the reponse to immunization and on the incidence of infection and disease in childhood in Uganda: design of a randomized, double-blind, placebo-controlled, factorial trial of deworming interventions delivered in pregnancy and early childhood. *Clinical Trials* 2007;**4**:42–57.

Additional references

Abel 2000

Abel R, Rajaratnam J, Kalaimani A, Kirubakaran S. Can iron status be improved in each of the three trimesters? A community-based study. *European Journal of Clinical Nutrition* 2000;**54**:490–3.

ACC/SCN 2000

United Nations Administrative Committee on Coordination, Subcommittee on Nutrition. *Fourth report on the world nutrition situation*. Geneva: WHO, 2000.

Atukorala 1994

Atukorala TMS, de Silva LDR, Dechering WH, Dassenaeike TS, Perera RS. Evaluation of effectiveness of iron-folate supplementation and anthelminthic therapy against anaemia in pregnancy- A study in the plantation sector of Sri Lanka. *American Journal of Clinical Nutrition* 1994;**60**:286–92.

Bundy 1989

Bundy DAP, Cooper ES. Trichuris and trichuriasis in humans. *Advances in Parasitology* 1989;**28**:108–73.

Bundy 1995

Bundy DAP, Chan MS, Savioli L. Hookworm infection in pregnancy. *Transactions of the Royal Society of Tropical Hygiene and Medicine* 1995; **89**:521–2.

Chan 1994

Chan MS, Medley GF, Jamison D, Bundy DAP. The evaluation of potential global morbidity due to intestinal nematode infections. *Parasitology* 1994;**109**:373–87.

Christian 2004

Christian P, Khatry SK, West KP Jr. Antenatal anthelmintic treatment, birthweight, and infant survival in rural Nepal. *Lancet* 2004; **364**:981–3.

de Silva 1999

de Silva NR, Sirisena JLGJ, Gunasekera DPS, Ismail MM, de Silva HJ. Effect of mebendazole therapy during pregnancy on the birth outcome. *Lancet* 1999;**353**:1145–9.

Gulani 2008

Gulani A, Nagpal J, Osmond C, Sachdev HP. Effect of administration of intestinal anthelmintic drugs on haemoglobin: systematic review of randomised controlled trials. *BMJ* 2007;**334**(7603):1095.

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Hotez 1983

Hotez PJ, Cerami A. Secretion of a proteolytic anticoagulant by ancylostoma duodenale hookworms. *Journal of Experimental Medicine* 1983;**157**:1594–603.

IOM 2001

Institute of Medicine. Iron. *Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc*. Washington DC: National Academy Press, 2001:290–393.

Jackson 1987

Jackson RT, Jackson LC. Biological and behavioural contributors to anaemia during pregnancy in Liberia, West Africa. *Human Biology* 1987;**59**:585–97.

Pawlowski 1991

Pawlowski ZS, Schad GA, Stott GJ. *Hookworm infection and anaemia: approaches to prevention and control*. Geneva: World Health Organization, 1991.

RevMan 2008

The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen, The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

Seshadri 1997

Seshadri S. Nutritional anaemia in South Asia. In: Gillespie S editor (s). *Malnutrition in South Asia*. Kathmandu: United Nations Children's Fund, 1997:75–124.

Stephenson 1987

Stephenson LS. *Impact of helminth infections on human nutrition: schistosomes and soil transmitted helminths*. London: Taylor and Francis, 1987.

Torlesse 2000

Torlesse H, Hodges M. Anthelminthic treatment and haemoglobin concentrations during pregnancy. *Lancet* 2000;**356**:1083.

Warren 1993

Warren KS, Bundy DAP, Anderson RM, Davis AR, Henderson DA, Jamison DT, et al.Helminth infection. In: Jamison DT, Mosley WH, Measham AR, Bobadilla JL editor(s). *Disease control priorities in developing countries*. Oxford: Oxford University Press, 1993:131–60.

WHO 1994

World Health Organization. *WHO Report of the informal consultation on hookworm infection and anaemia in girls and women. (WHO/CTD/SIP/96.1)*. Geneva: World Health Organization, 1994.

WHO 1997

World Health Organization. *The World Health Report 1997: conquering suffering, enriching humanity*. Geneva: World Health Organization, 1997:51.

WHO 2001

World Health Organization. *Iron deficiency anaemia assessment, prevention and control: a guide for program managers*. Geneva: World Health Organization, 2001:132.

WHO 2003

World Health Organization. *Controlling disease due to helminth infections*. Geneva: World Health Organization, 2003:135.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Elliott 2005

Methods	Randomised, double blind, placebo controlled trial. The randomisation sequence was generated by an independent statistician using blocks of 50. Albendazole and matching placebo tablets were packaged in identical envelopes, labelled with the randomisation code. Clinic staff gave participants the next number in the sequence, in order of enrolment.
Participants	Mothers in the second trimester of pregnancy, residing in the study area, planning to deliver in hospital and willing to know their HIV status were eligible for inclusion in the study. Mothers with haemoglobin < 80 g/L were excluded and treated for hookworm and anaemia. Other exclusion criteria were abnormal pregnancy or history of adverse reaction to antihelminthic drugs.
Interventions	All eligible mothers were randomised to treatment with single-dose albendazole (400 mg) or placebo, regardless of whether hookworm was detected or not. Number of women allocated to intervention was 53 and placebo was 50.
Outcomes	Primary outcomes were immune responses in mothers and infants.
Notes	Entebbe Hospital, Uganda between June-August, 2002. The study was designed to examine effects of albendazole treatment in pregnancy on immunological and disease outcomes in infants. Participants in the 2 groups were similar at baseline in age, HIV status, malaria and helminth prevalence, and baseline cytokine levels and responses. At baseline, the frequency of intestinal helminths was: *Ascaris lumbricoides* 15%, hookworms 38%, and *Trichuris trichura* 6%.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "the randomisation sequence was generated by an independent statistician using blocks of 50". Comment: probably done.
Allocation concealment?	Yes	Quote: "labelled with the randomisation code. Clinic staff gave participants the next number in the sequence, in order of enrolment". Comment: probably done.

Elliott 2005 (*Continued*)

Blinding? All outcomes	Yes	Quote: "double blind"; "Albendazole and matching placebo tablets were packaged in identical envelopes"; "Unblinded analyses was conducted by MQ. All other staff and participants remain blinded to treatment allocation as follow up continues". Comment: blinding of participants, study personnel and outcome assessors probably done.
Incomplete outcome data addressed? All outcomes	No	Exclusions and atttrition was 30.8%. Reasons for attrition not stated.
Free of selective reporting?	Unclear	Insufficient information to decide about selective reporting.
Free of other bias?	Unclear	Study enrolment was stopped after 104 women due to new guidelines by the World Health Organization which recommended inclusion of treatment of women with shistosomiasis.

Larocque 2006

Methods	Randomised, double blind, placebo controlled trial to compare the effectiveness of antenatal mebendazole plus iron supplements versus placebo plus iron supplements in a hookworm endemic area.
Participants	Pregnant women in second trimester (>= 18 weeks; < 26 weeks) between 18 and 44 years of age (gestastional age was assessed by using a combination of fundal height and the first day of last menstrual period); not having received anthelminth treatment for 6 months prior to recruitment; residing in rural or periurban areas (defined as having no running water or flushing toilet facility at home) and giving consent. Any subject having severe anaemia (Hb < 70 g/L) or a medical condition requiring follow up were excluded.
Interventions	Intervention group received a single dose of mebendazole (500 mg) plus a daily iron supplement (60 mg elemental iron, ferrous sulphate) and the control group received a single dose placebo plus a daily iron supplement (60 mg elemental iron, ferrous sulphate). Number of women allocated to intervention was 522 and control was 520.
Outcomes	Included mean infant birthweight (LBW and VLBW), maternal anaemia in third trimester measured by (1) mean Hb and (2) Hb < 110 g/L.
Notes	Pregnant women were recruited from 12 health centres in the Iquitos region of Peru from April 2003 to November 2003. Soil transmitted helminth infections, malaria and anaemia are endemic in the area. Women in the 2 groups were similar in terms of socio-demographic characteristics and pregnancy-related variables.

Larocque 2006 (*Continued*)

	At baseline, the frequency of intestinal helminths was: *Ascaris lumbricoides* 64.2%, hookworms 46.4%, and *Trichuris trichura* 82% and anaemia (Hb < 110 g/L) was found in 47% women

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Quote: "computer-generated randomly ordered blocks of 4, 6 and 8 were used to randomly allocate women to each intervention group". Comment: probably done.
Allocation concealment?	Yes	Quote: "2 researchers not otherwise involved in the trial prepared sealed envelopes containing the intervention assignment". Comment: probably done.
Blinding? All outcomes	Yes	Quote: "double-blind"; "the local project director, field workers, obstetrics, laboratory technologists and pregnant women were all blind to the group assignment"; and "placebo tablets were similar in appearance, smell and taste to the mebendazole tablets". Comment: blinding of participants, study personnel and outcome assessors probably done.
Incomplete outcome data addressed? All outcomes	Yes	Exclusions and atttrition was 3.4%. Reasons for attrition and exclusions; and numbers in each intervention group and for various outcomes are reported.
Free of selective reporting?	Unclear	Insufficient information to decide about selective reporting.
Free of other bias?	Yes	The study appears to be free of other sources of bias.

Torlesse 2001

Methods	A randomised controlled 2 x 2 factorial design was applied in order that 2 interventions, daily iron folate supplements (Fe) and single-dose albendazole (A), be simultaneously compared with each other and with the controls.
Participants	Women with a Hb >= 80 g/L and gestational age < 14 weeks at baseline were eligible for the study. Any women with Hb < 80 g/L at any stage of the study was treated immediately with appropriate therapy and withdrawn from the study in accordance with WHO ethical guidelines. A total of 184 women were included in this study.

Torlesse 2001 (*Continued*)

Interventions	Albendazole, 2 x 200 mg, single dose, at first antenatal visit in second trimester. Daily iron-folate supplements comprised 36 mg iron as ferrous gluconate and 5 mg folic acid started at first antenatal visit in second trimester for entire duration of pregnancy. Two tablets containing calcium with vitamin D were used as the control for albendazole. Calciferol tablets (1.25 mg), 1 daily, were chosen as the control for iron-folate supplements.
Outcomes	Included maternal anaemia, iron deficiency and anaemia, cure rate, egg reduction rate. Anaemia in pregnancy is defined as Hb < 110 g/L.
Notes	Pregnant women in their first trimester, attending 3 antenatal clinics in peri-urban and 6 in rural areas in Sierra Leone between December 1995 and June 1996 were recruited for the study. The groups were statistically similar at the time of recruitment with respect to demographics, social, reproductive and other baseline characteristics. The proportions of dropouts were statistically similar in each intervention groups. At baseline, the frequency of intestinal helminths was: *Ascaris lumbricoides* 20%, *Necator americanus* 65.6%, and *Trichuris trichura* 74.4% and anaemia (Hb < 110 g/L) was found in 56% and iron deficiency anaemia in 18.4% women.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Intervention groups were allocated using random number tables to generate the random-number sequence.
Allocation concealment?	No	Quote: "intervention groups were allocated using random number tables to generate the random-number sequence". Comment: probably not done.
Blinding? All outcomes	Yes	Quote: "Albendazole and control calcium with vitamin D tablets used were similar in colour, shape and size"; "calciferol tablets which were used as control for iron folate supplements were similar to the iron supplements in shape and size but were different in colour". Comment: blinding of participants and outcome assessors probably done. We are unsure about the blinding of study personnel.
Incomplete outcome data addressed? All outcomes	No	Attrition and exclusion was 29.8%. Reasons for attrition and numbers in each intervention group and for various outcomes are not reported. Reason for exclusion is given.
Free of selective reporting?	Unclear	Insufficient information to decide about selective reporting.

Torlesse 2001 (*Continued*)

Free of other bias?	Yes	

LBW: low birthweight
VLBW: very low birthweight

Characteristics of excluded studies *[ordered by study ID]*

Bhutta 2007	Different regimens of anthilminth treatment (single dose vs 3 days mebendazole) were compared.
Villar 1998	Published abstract with insufficient information was only available.

vs: versus

Characteristics of ongoing studies *[ordered by study ID]*

Elliott 2007

Trial name or title	The impact of helminths on the reponse to immunization and on the incidence of infection and disease in childhood in Uganda: design of a randomised, double-blind, placebo-controlled, factorial trial of deworming interventions delivered in pregnancy and early childhood.
Methods	3 randomised interventions at 2 times, twice in pregnant women, and once in their children.
Participants	Pregnant women in their second or third trimester of pregnancy and their children.
Interventions	Pregnant women are randomised to albendazole or placebo and praziquantel or placebo. At age 15 months their children are randomised to 3-monthly albendazole or placebo, to continue to age 5 years.
Outcomes	Main outomes include immunological responses to Bacille Calmette-Guérin (BCG) and tetanus immunization, incidence of malaria, tuberculosis, infectious and atopic disease events, anaemia, growth and development of children.
Starting date	April 2003.

Elliott 2007 (*Continued*)

Contact information	Dr AM Elliott, Uganda Virus Research Institute, Entebbe, Uganda. alison.tom@infocom.co.ug
Notes	

DATA AND ANALYSES

Comparison 1. Anthelminth versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal anaemia in third trimester (< 11 g/dL)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All study groups	2	1075	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.68, 1.19]
1.2 Received anthelminth with iron supplement	2	1017	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.39, 1.45]
1.3 Received anthelminth without iron supplement	1	58	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.94, 1.14]
2 Low birthweight	1	950	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.61, 1.42]
3 Perinatal mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 All studies	2	1089	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.55, 2.22]
3.2 Incomplete outcome data addressed (study with attritions and exclusions > 20% excluded from the analysis)	1	996	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.47, 2.55]
4 Preterm birth (birth before 37 weeks of gestation)	1	984	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.38, 1.87]

Analysis 1.1. Comparison 1 Anthelminth versus placebo, Outcome 1 Maternal anaemia in third trimester (< 11 g/dL).

Review: Effect of administration of antihelminthics for soil transmitted helminths during pregnancy

Comparison: 1 Anthelminth versus placebo

Outcome: 1 Maternal anaemia in third trimester (< 11 g/dL)

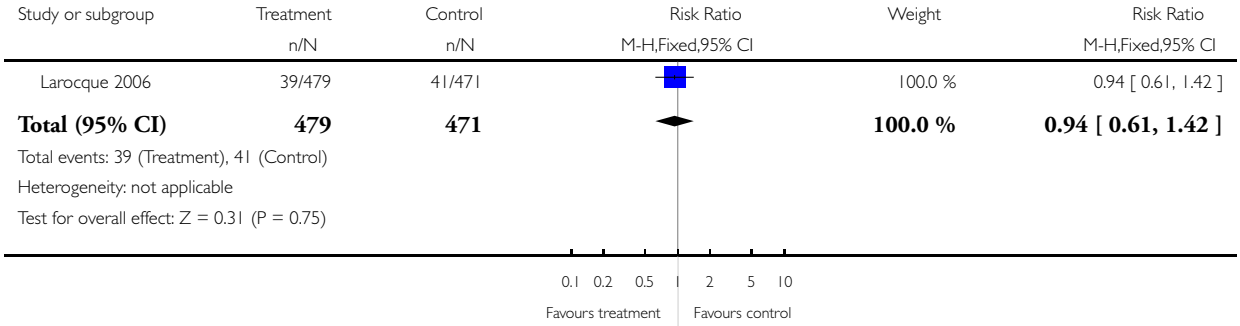
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 All study groups					
Torlesse 2001	43/61	57/64		49.9 %	0.79 [0.66, 0.95]
Larocque 2006	158/479	152/471		50.1 %	1.02 [0.85, 1.23]
Subtotal (95% CI)	**540**	**535**		**100.0 %**	**0.90 [0.68, 1.19]**
Total events: 201 (Treatment), 209 (Control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 4.72$, df = 1 (P = 0.03); $I^2 = 79\%$					
Test for overall effect: Z = 0.74 (P = 0.46)					
2 Received anthelminth with iron supplement					
Torlesse 2001	14/32	29/35		31.1 %	0.53 [0.35, 0.80]
Larocque 2006	158/479	152/471		68.9 %	1.02 [0.85, 1.23]
Subtotal (95% CI)	**511**	**506**		**100.0 %**	**0.76 [0.39, 1.45]**
Total events: 172 (Treatment), 181 (Control)					
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 8.07$, df = 1 (P = 0.005); $I^2 = 88\%$					
Test for overall effect: Z = 0.85 (P = 0.40)					
3 Received anthelminth without iron supplement					
Torlesse 2001	29/29	28/29		100.0 %	1.04 [0.94, 1.14]
Subtotal (95% CI)	**29**	**29**		**100.0 %**	**1.04 [0.94, 1.14]**
Total events: 29 (Treatment), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					

Analysis 1.2. Comparison 1 Anthelminth versus placebo, Outcome 2 Low birthweight.

Review: Effect of administration of antihelminthics for soil transmitted helminths during pregnancy

Comparison: 1 Anthelminth versus placebo

Outcome: 2 Low birthweight

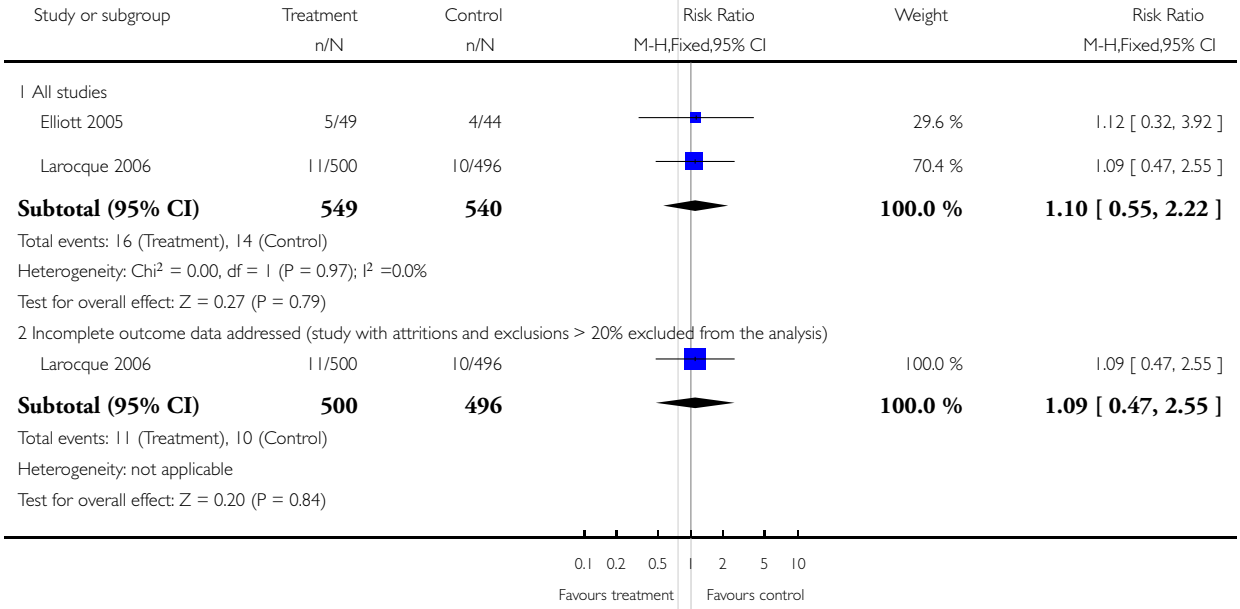


Analysis 1.3. Comparison 1 Anthelminth versus placebo, Outcome 3 Perinatal mortality.

Review: Effect of administration of antihelminthics for soil transmitted helminths during pregnancy

Comparison: 1 Anthelminth versus placebo

Outcome: 3 Perinatal mortality

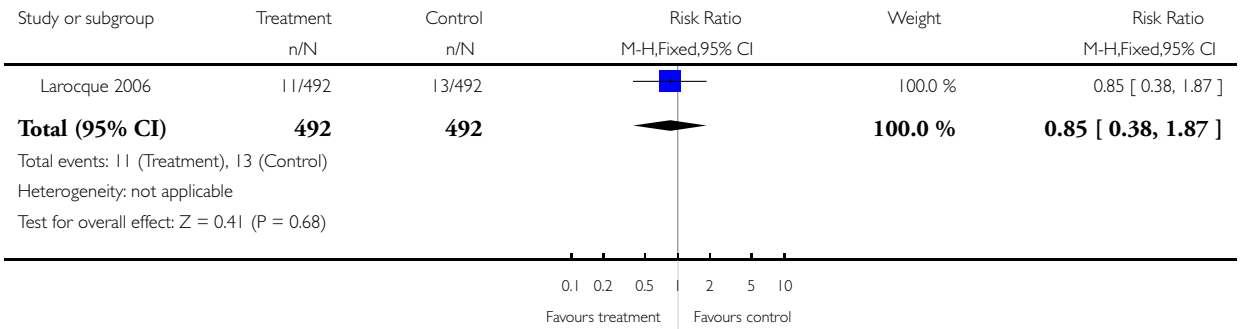


Analysis 1.4. Comparison 1 Anthelminth versus placebo, Outcome 4 Preterm birth (birth before 37 weeks of gestation).

Review: Effect of administration of antihelminthics for soil transmitted helminths during pregnancy

Comparison: 1 Anthelminth versus placebo

Outcome: 4 Preterm birth (birth before 37 weeks of gestation)



HISTORY

Protocol first published: Issue 4, 2005

Review first published: Issue 2, 2009

12 November 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

The protocol was written by Dr Batool Azra Haider (BAH) under the guidance of Dr Zulfiqar A Bhutta (ZAB).

Data extraction was done by BAH and Dr Quratulain Humayun. BAH entered the data, created the comparisons, carried out the analysis and wrote the text of the review. ZAB provided support and guidance for the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Aga Khan University, Pakistan.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Albendazole [administration & dosage]; Anemia, Iron-Deficiency [parasitology; *prevention & control]; Anthelmintics [*administration & dosage]; Helminthiasis [*drug therapy; transmission]; Iron Compounds [administration & dosage]; Pregnancy Complications, Hematologic [parasitology; *prevention & control]; Pregnancy Complications, Parasitic [*drug therapy; etiology]; Pregnancy Trimester, Second; Pregnancy Trimester, Third; Soil [*parasitology]

MeSH check words

Female; Humans; Pregnancy