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Systematic review of exposure to albendazole or mebendazole during pregnancy and effects on maternal and child outcomes, with particular reference to exposure in the first trimester

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ABSTRACT

Soil-transmitted helminth infections cause an important burden of morbidity worldwide, primarily from blood loss and malabsorption of nutrients. Where STH endemicity ≥20%, the World Health Organization (WHO) recommends preventive chemotherapy with single dose anthelminthic drugs: albendazole or mebendazole. Although WHO recommends that women of reproductive age, including pregnant women after the first trimester, be included in large-scale deworming programs, there are concerns related to the use of anthelminthic drugs during pregnancy, especially inadvertent use in the first few weeks when the pregnancy may not yet be confirmed. We therefore conducted a systematic review using the MEDLINE database with the aim of appraising all peer-reviewed evidence, published up to July 1, 2018, on the association between exposure to albendazole or mebendazole and outcomes in pregnant women, including those in the first trimester of pregnancy, and their children. From a yield of 205 papers based on titles alone, 58 papers, reporting results from 46 originator studies conducted in pregnant populations, constituted the initial evidence base. Among the nine originator observational studies which had included women in the first trimester of pregnancy within their study population, five compared birth outcomes between women exposed in the first trimester with women who were not exposed, and none reported higher rates of adverse birth outcomes in the exposed group. Due to heterogeneity in terms of study design, sample size, deworming drug, dosage and outcomes measured, data from these studies could not be pooled. Based on this cumulative evidence, it is unlikely that inadvertent exposure to albendazole or mebendazole in the first trimester carries an additional risk of adverse birth outcomes. To optimize relevance for policy making, future research in pregnant populations should aim to provide data disaggregated by trimester and to report on maternal and child adverse events, whenever possible.

1. Introduction

Soil-transmitted helminth (STH) infections, caused by the parasitic worms *Ascaris lumbricoides* (the roundworm), *Trichuris trichiura* (the whipworm) and certain hookworms (*Necator americanus* and *Ancylostoma duodenale*), infect over 1.45 billion people worldwide (Pullan et al., 2014). Of these, an estimated 688 million women of reproductive age, who live in 102 STH-endemic countries, are affected (Mupfasoni et al., 2018). STH infections cause a significant burden of morbidity including blood loss, anaemia, malabsorption of nutrients and nutrient loss (Stephenson et al., 2000; Crompton and Nesheim, 2002; Bethony et al., 2006; Hotez et al., 2006; Montresor et al., 2017).

Due to important STH-attributable morbidity, the World Health Organization (WHO) has identified three population groups at highest risk which would benefit from preventive chemotherapy where endemicity levels equal, or exceed, 20% (WHO, 2017). These include school-age children, preschool children and women of reproductive age (WRA), including lactating and pregnant women (after the first trimester). The large-scale preventive chemotherapy programs which usually only include the single dose benzimidazoles, albendazole or mebendazole, have largely targeted school-age children because school-based deworming programs are highly cost-effective (Bundy et al., 2018).

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Large-scale deworming programs specifically targetting WRA have not been widely established. Implementation platforms have yet to be effectively identified to reach all four WRA sub-groups (adolescent girls, pregnant women, lactating women and non-pregnant, non-lactating women) (WHO, 2018) and concerns about inadvertent exposure to benzimidazoles in the first trimester of pregnancy have been raised (Gyapong et al., 2003; Insetta et al., 2014). A recent Cochrane Review which reported on the effect of albendazole and mebendazole during pregnancy was limited to results from four trials (Salam et al., 2015). Here, we expand on this review by adding evidence from other trials, from observational studies, and from case reports, and specifically highlight evidence pertaining to outcomes experienced in the first trimester of pregnancy.

2. Materials and methods

2.1. Search strategy and selection criteria

The MEDLINE database of publications presenting primary research outcomes and involving human subjects published between 1950 and July 1, 2018 was electronically searched via PubMed (www.pubmed.com), using the search terms "albendazole" or "mebendazole" in combination with "pregnant", "pregnancy" or "trimester". The query sequence was entered in the following sequence, with individual search concepts nested in parentheses: (albendazole OR mebendazole) AND (pregnant OR pregnancy OR trimester). No additional time or language restrictions were applied.

Publications identified with this search strategy were subjected to a preliminary screening, in which titles and/or abstracts were examined to assess eligibility. A brief full text examination was then carried out to identify publications in which original research was conducted, following which a complete comprehensive review was performed. Lastly, the bibliography of each full text study was examined to identify any additional eligible study that might have been missed during the computerised search process.

2.2. Data analysis

Publications using the same study populations were considered separately when examining factors surrounding the publication process itself (e.g., year of publication, language of publication); however, these were later considered together, according to the originator pregnant study population (the first study to have presented primary pregnancy outcomes for each grouping) so as to ensure that every exposure event was accounted for only once.

Variables for which data were extracted included study setting, study design, language of publication, type of exposure (albendazole or mebendazole), dosage, timing of exposure during pregnancy, and adverse maternal and child outcomes (if any). No standard definition of trimester was applied across studies, so the individual definition of trimester in each study was used, when reported. Where no definition for trimester was reported, that of the WHO was used. According to the WHO, the first trimester of pregnancy corresponds to the weeks preceding the 16th week of pregnancy; the second trimester of pregnancy corresponds to weeks 16–28 inclusive, and the third trimester corresponds to weeks 29–40 and onwards (WHO, 2015).

The risk of bias in originator studies employing an analytic research design was assessed as per the PRISMA 2009 Guidelines for transparent reporting of systematic reviews and meta-analyses (Liberati, 2009). Among the studies employing an analytical design, a bias assessment was conducted by two independent reviewers by consulting the CONSORT checklist and the Cochrane Collaboration tool for randomised controlled trials, and the ROBINS-I tool and STROBE statements for cross-sectional, cohort and case-control studies (Vandenbroucke et al., 2007; Higgins et al., 2011; Moher et al., 2012; Sterne et al., 2016). Disagreements between reviewers were resolved through discussion.

Due to the considerable differences among the studies in terms of research design, sample size, deworming drug, dosage and outcomes measured, pooled estimates of results were not calculated. The basis for the assessment of heterogeneity is presented in the Tables 1–4 and an overall interpretation is provided according to the PRISMA framework (Liberati, 2009).

3. Results

3.1. Results of the search

The search strategy yielded 205 records (Fig. 1). Of these, 56 presented research on non-human subjects and one was a duplicate. A total of 41 records (consisting of article types not presenting primary research data) were further excluded based on the full text examination. Of the 107 potentially relevant articles which met the inclusion criteria, a comprehensive full text analysis led to 50 additional articles being excluded. Notably, the majority of these articles had reported excluding pregnant women from treatment cohorts ($n = 17$), or had administered the deworming treatment outside the period of gestation (either before the pregnancy or following delivery) ($n = 16$). Other exclusion factors included a lack of assessment of pregnancy status or outcomes by pregnancy status among women of reproductive age ($n = 7$) and an absence of information regarding definitive benzimidazole exposure during pregnancy ($n = 11$).

Overall, 58 studies were thus judged to be eligible for inclusion in this review (Table 1). Three publications presented results from a single originator pregnant population from Peru (Trial ISRCTN08446014) (Gyorkos et al., 2006, 2011; Larocque et al., 2006). Similarly, eight publications presented results from a single originator pregnant population from Uganda (Trial ISRCTN32849447) (Ndibazza et al., 2010, 2012; Webb et al., 2011, 2012; Mpairwe et al., 2011, 2014; Nash et al., 2017; Namara et al., 2017). Two publications presented results from a single dataset extracted from the Danish Fertility Database (Torp-Pedersen et al., 2012, 2016). Finally, two publications shared the same study population from an observational study nested in the 'Malaria in Pregnancy Preventive Alternative Drugs' clinical trial conducted in Benin (Mireku et al., 2015; Moya-Alvarez et al., 2018). Therefore, the 58 studies included in this review were based on 46 originator pregnant study populations.

The earliest publication included in this review, in 1989, reports on a non-randomised trial of different dosages of mebendazole-fortified salt in China (Tang et al., 1989), and the most recent, a randomised controlled trial of mebendazole in 2018, in Nigeria (Akpan et al., 2018). There has been a steady increase in the frequency of publications on this topic over time.

A summary of study characteristics, with exposure and outcome data, is presented in Table 2. Of the 46 originator studies, nine were trials, 17 were observational studies (10 cohort; 6 cross-sectional; 1 case-control) and 20 consisted of case reports ($n = 19$) and case series ($n = 1$).

In total, 27 originator studies provided reports of albendazole exposure during pregnancy and 18, of mebendazole exposure. One study reported on both types of benzimidazoles (Shiferaw et al., 2017). Various dosages and treatment regimens have been studied, with case reports and case series having multiple dose regimens of either benzimidazole. Only five of the 17 observational studies used the single 400 mg dose of albendazole or the

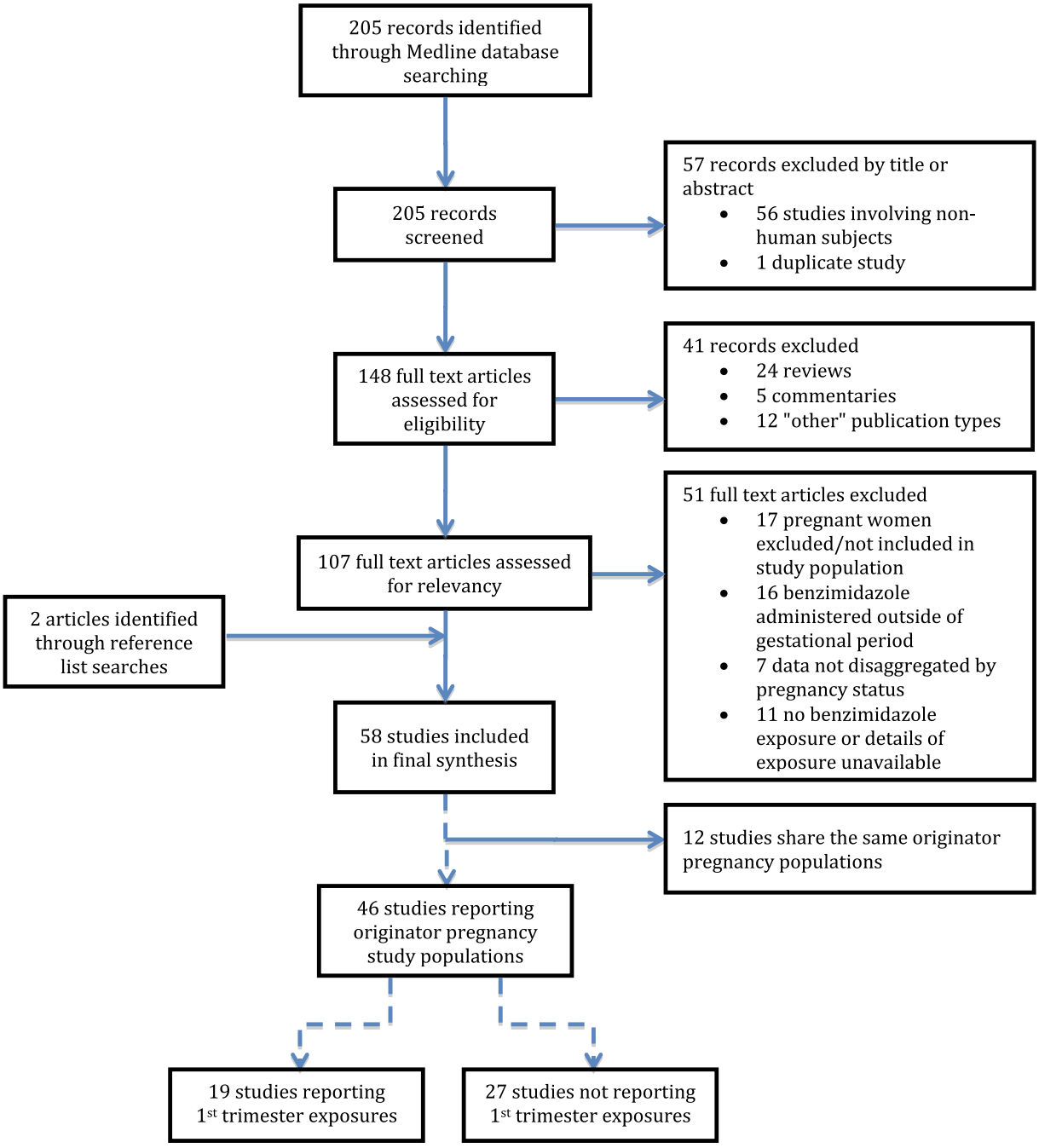

Fig. 1. Diagram illustrating the stepwise search of the literature for published studies investigating albendazole or mebendazole treatment during pregnancy.

500 mg dose of mebendazole, singly or in combination with another drug or supplement, while all but one of the nine trials used the single dose formulations (Table 1). Many of the case reports and case series were reported in high-income settings, most often among women who had recently travelled to low and middle income (LMIC) settings or in patients with hydatid disease (echinococcosis). In contrast, most of the observational studies, and all of the nine trials, were conducted in LMIC settings endemic for STH infections.

3.2. Case reports and case series

The case studies document the use of albendazole or mebendazole as curative therapy in cases of echinococcosis, trichinellosis, gnathostomiasis and, rarely, for other parasitic diseases (Table 1). Despite a likely strong publication bias, these case studies demonstrate a trend towards administering albendazole or mebendazole later in pregnancy, and that treatment, even at high doses, can result in a healthy birth. Of the 19 case reports, nine reported benzimidazole exposure in the first trimester, with outcomes including healthy births ($n = 3$), either fetal or neonatal death ($n = 2$), some impairment at birth ($n = 1$), voluntary termination of pregnancy (VTOP) ($n = 2$) and one report did not include any follow-up, either maternal or infant. Of the other 10 case reports, where benzimidazole exposure occurred in the second or third trimester, outcomes included healthy births ($n = 9$) and one VTOP. The only published case series reported outcomes from 49 women who had been exposed to albendazole in the first trimester (Bradley

Table 1
Characteristics of studies, published between 1989 and July 1, 2018, reporting on maternal and child outcomes of women exposed to albendazole or mebendazole during pregnancy, by study type ($n = 58$): case reports and case series ($n = 20$); observational studies (cohort, cross-sectional and case-control studies) ($n = 21$; 17 originator studies); and trials (RCTs) ($n = 17$; 9 originator studies).

First author (Year of publication)	Study year(s)	Study setting	Study design[a]	Original sample size[b]	Trimester of exposure[c]	Drug and dosage[d]	Primary birth outcomes and effect sizes (if available)[e]
Case reports and series (n = 20 originator studies)							
Ghosh (2014)	2013	India	Case report	*n* = 1 Echinococcosis	3	ALB: 400 mg 2×/d for 3 wk	Healthy birth
Bhattacharyya (2013)	Not specified	India	Case report	*n* = 1 Echinococcosis	2	ALB: 400 mg 2×/d (duration unknown)	Healthy birth
Tyagi (2012)	Not specified	India	Case report	*n* = 1 Echinococcosis	2	ALB: 400 mg 1×/d for 10 wk (4 wk on, 2 wk off, 6 wk on)	Healthy birth
Erol (2011)	2007	Turkey	Case report	*n* = 1 Echinococcosis	2, 3	ALB: Not specified	Healthy birth
Nuñez (2008)	2005	Argentina	Case series	*n* = 1 Trichinellosis	1	MEB: 400 mg/d for 9 d	Healthy birth
Djakovic (2006)	Not specified	Germany	Case report	*n* = 1 Pinworm	3	MEB: 100 mg/d for 3 d	Healthy birth
Yilmaz (2006)	Not specified	Turkey	Case report	*n* = 1 Echinococcosis	3	ALB: 400 mg 2×/d for 3 d	Healthy birth
Yang (2005)	1994	China	Case report	*n* = 1 Echinococcosis	1, 2	MEB: 40 mg/kg/d for >1 yr	Birth with cognitive impairment
Can (2003)	Not specified	Turkey	Case report	*n* = 1 Echinococcosis	2, 3	ALB: Not specified	Healthy birth
Schellenberg (2003)	2000	Canada	Case report	*n* = 1 Trichinellosis	1	ALB: 400 mg 2×/d for 14 d	Healthy birth
Montes (2002)	Not specified	United States	Case report	*n* = 1 Echinococcosis	2, 3	ALB: 400 mg 2×/d for 28 d	Healthy birth
Bradley (2001)	Not specified	Various	Case series	*n* = 49 → All 49 E+ Various helminth infections	1	ALB: Various dosages from 200 mg to 54 g	• 1 miscarriage in E+ • 1 neonatal death in E+ • 3 minor CA, 0 major CA in E+ • 6 VTOP in E+
Dubinský (2001)	1998	Slovakia	Case report	*n* = 1 Trichinellosis	2	MEB: 1.5 g/d for 10 d	VTOP
Joki-Erkkilä (2001)	Not specified	Finland	Case report	*n* = 1 Ascariasis	1, 2	MEB: Not specified	Fetal death at 24 weeks
Srour (2001)	Not specified	Israel	Case report	*n* = 1 Echinococcosis	1	ALB: Not specified	VTOP
Christensen (2000)	Not specified	Denmark	Case report	*n* = 1 Pinworms	1	MEB: Not specified	No maternal or birth outcomes reported
Potasman (1998)	1997	Israel	Case report	*n* = 1 Gnathostomiasis	1	ALB: 400 mg/d for 3 wk	VTOP
Golaszewski (1995)	Not specified	Austria	Case report	*n* = 1 Echinococcosis	1, 2, 3	ALB: 400 mg 2×/d for ~4 mo	Premature birth; early neonatal death
van Vliet (1995)	Not specified	Netherlands	Case report	*n* = 1 Echinococcosis	3	ALB: 10 mg/kg/d for 30 d	Healthy birth
Auer (1994)	Not specified	Austria	Case report	*n* = 1 Echinococcosis	1	ALB: 400 mg 2×/d for 2 wk	Healthy birth
Observational studies (cohort, cross-sectional and case-control studies) (n = 21; 17 originator studies)							
Moya-Alvarez (2018) *(Ouedraogo 2013 is the originator study)*	2010–2012	Benin	Cohort	*n* = 318 → All 318 presumed E+	2	ALB: 600 mg for 3 d + 2-dose IPTp-SP + 200 mg/d ferrous sulphate + 5 mg/d folic acid	No ALB-related maternal or birth outcomes reported
Choi (2017)	Not specified	South Korea	Cohort	*n* = 506 → 124 E+ 1st; 382 E−	1	ALB: single dose 200 mg or 400 mg	• Loss-to-follow-up: E+ 1st: 45%; E−: 50% • 4 miscarriages in 68 E+ vs. 9 miscarriages in 192 E− (OR = 1.27 [0.4, 4.3]) • 2 VTOP in E+ vs. 2 VTOP in E− • 3/64 (4.7%) CA in E+ vs. 4/183 (2.2%) CA in E− (OR = 2.2 [0.5, 10.1])

Shiferaw (2017)	2015	Ethiopia	Cross-sectional	n = 180 → 46 E+; 134 E−	Not specified	ALB: 400 mg single dose or MEB: 500 mg single dose	Women not treated with ALB or MEB had a higher STH infection rate than treated women (aOR = 3.57 [1.19, 10.69]). No birth outcomes reported
Raut (2016)	2011	Nepal	Cross-sectional	n = 192 → 67 E+; 125 E−	Not specified	ALB: Not specified	Unclear correlation between ALB and maternal anaemia reported. No ALB-related birth outcomes reported
Torp-Pedersen (2016) *(Torp-Pedersen 2012 is the originator study)*	1997–2007	Denmark	Cohort	n = 713,667 → 2567 E+ (1022 1st trimester); 708,982 E−	1, 2, 3	MEB: various dosage schemes	• 2.3% major CA in E+ (1st trimester) vs. 3.2% major CA in E− (OR = 0.7 [0.4, 1.1], aOR = 0.7 [0.4, 1.1]) • 1.2% minor CA in E+ (1st trimester) vs. 1.9% minor CA in E− (OR = 0.6 [0.3, 1.1], aOR = 0.8 [0.5, 1.4]) • 0.3% stillbirths in E+ vs. 0.4% stillbirths in E− (OR = 0.8 [0.4, 1.6], aOR = 0.9 [0.4, 2.1]) • 0.2% neonatal deaths in E+ vs. 0.3% neonatal deaths in E− (OR = 0.7 [0.3, 1.6], aOR = 0.8 [0.3, 2.2] • 7.7% SGA in E+ vs. 9.9% SGA in E− (OR = 0.8 [0.7, 0.9], aOR = 1.0 [0.8, 1.1])
Mireku (2015) *(Ouedraogo 2013 is the originator study)*	2010–2012	Benin	Cohort	n = 863 of 1005 HIV-negative pregnant women → All 863 E+ (35 infant deaths excluded)	2	MEB: 100 mg 2×/d for 3 d, repeated in case of reinfection (n = 62) + 2-dose IPTp-SP + 200 mg/d ferrous sulphate	• 84 (0.11%) LBW in 797 E+ • 60 (0.07%) preterm births in 828 E+ • 40 stillbirths in E+ • 8 VTOP in E+
Mpairwe (2014) *(Ndibazza 2010 is the originator study)*	2003–2011	Uganda	Cohort	n = 2345 livebirths of 2507 pregnant women → 1253 E+; 1254 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	• 277/1170 (23.7%) eczema events in E+ children up to 5 years of age vs. 175/1175 (14.9%) eczema events in E− children up to 5 years of age (HR = 1.58 [1.15, 2.17], P = 0.005)
McClure (2014)	2006–2009	Kenya	Cohort	n = 544 of 813 women provided stool specimens (number treated unknown)	2, 3	ALB: dosage not specified + IPTp-SP + iron 60/mg/d + multi-vitamins	No ALB-related maternal or birth outcomes reported
Ouédraogo (2013)	2010–2011	Benin	Cohort	n = All 941 of 1005 women provided stool specimens E+	1, 2	ALB: 600 mg (100 mg 2×/d for 3 d)	Prevalence of any STH decreased from 11.1% at recruitment to 2.4% at delivery. No birth outcomes reported
Torp-Pedersen (2012)	1997–2007	Denmark	Cohort	Danish Fertility Database study population: n = 718,900 → 3109 E+; 710,558 E−	1, 2, 3	MEB: 1 or 2 doses, dosage not specified	MEB more frequently consumed by women prior to and after pregnancy. Birth outcomes reported elsewhere (see Torp-Pedersen et al., 2016)
Sanjel (2011)	2011	Nepal	Cross-sectional	n = 194 (153 respondents) → 96 E+; 57 E−	1, 2, 3	ALB: Not specified	No ALB-related adverse outcomes reported
Liabsuetrakul (2009)	2006	Thailand	Cohort	n = 1063 → 174 E+; 889 assumed E−	2, 3	ALB: 400 mg single dose; ALB: 400 mg/d for 3 d for rE−treatment in n = 8	13 (7.5%) of 174 not cured following treatment
Acs (2005)	1980–1996	Hungary	CasE−control	n = 22,843 CA case mothers + 38,151 control (non-CA) mothers	1, 2, 3	MEB: 100 mg single dose or 100 mg 2×/d for 3 d	• 14/22,843 (0.06%) E+ among CA case mothers vs. 14/38,151 (0.04%) E+ among control (non-CA) mothers (crude POR = 1.8 [0.7, 4.2])
Luoba (2005)	1998–2001	Kenya	Cohort	n = 824 → 824 presumed E+	3	MEB: 500 mg single dose	Reinfection rates among 700 cured or uninfected increased between delivery and 6 mo post-partum, especially for *Ascaris*-infected women who were geophagous
Christian (2004)	Not specified	Nepal	Cohort	n = 4998 → 3269 E+; 58 E− (for BW analysis) → 3847 E+; 261 E− (for 6-month mortality analysis)	2, 3	ALB: 400 mg single dose ×1 (n = 866) or ×2 (n = 2981)	• Higher mean BW in E+ vs. E− (1-dose diff. in mean: +31 [−94, 157], 2-dose diff. in mean: +59 [19, 98]) • 88/866 (101.6 per 1000) (1 dose) + 116/2981 (38.9 per 1000) (2 doses) 6-month mortality in E+ vs. 25/261 (95.8 per 1000) deaths in E− (1-dose RR = 0.86 [0.49, 1.54], 2-dose RR = 0.59 [0.43, 0.82]) • Hb in the third trimester was higher (P = 0.21), and anaemia lower (aOR = 0.23 [0.05, 0.99], in ALB-treated women
Diav-Citrin (2003)	1988–1999	Israel	Cohort	n = 382 → 192 E+; 192 E−	1, 2, 3	MEB: 100 mg single dose (28.6%) or 100 mg single dose repeated once (36.3%) or 100 mg/day × 3 days (35.2%)	• 22 (11.5%) miscarriages in E+ vs. 18 (9.4%) miscarriages in E− (P = 0.504) • 22 (11.5%) VTOP in E+ vs. 3 (1.6%) VTOP in E− (P < 0.001)

(*continued on next page*)

Table 1 (*continued*)

First author (Year of publication)	Study year(s)	Study setting	Study design[a]	Original sample size[b]	Trimester of exposure[c]	Drug and dosage[d]	Primary birth outcomes and effect sizes (if available)[e]
							• 0 (0%) ectopic pregnancies in E+ vs. 1 (0.5%) ectopic pregnancy in E− ($P = 1.000$) • 5/150 (3.3%) CA in E+ vs. 3/175 (1.7%) CA in E− (RR = 1.94 [0.47, 8.00], $P = 0.478$) • Among 1st trimester E+: 4/92 (4.3%) CA in E+ (1st trimester) vs. 3/175 (1.7%) CA in E− (RR = 2.54 [0.58, 11.09], $P = 0.238$)
Gyapong (2003)	Not specified	Ghana	Cross-sectional	$n = 343$ → 50 E+; 293 E−	1, 2, 3	ALB: Not specified	• 2 miscarriages in E+ vs. 7 miscarriages in E− (RR = 1.67 [0.36, 7.83]) • 1/40 CA in E+ vs. 5/210 CA in E− (RR = 1.05 [0.13, 8.75])
de Silva (1999)	1996–1997	Sri Lanka	Cross-sectional	$n = 7087$ 75 excluded → 5275 E+; 1737 E−	1, 2, 3	MEB: 100 mg 2×/d for 3 d (92.7%)	• 99/5275 (1.9%) stillbirths and perinatal deaths in E+ vs. 58/1737 (3.3%) stillbirths and perinatal deaths in E− (OR = 0.55 [0.40, 0.77], $P < 0.001$) • 59/5271 (1.1%) LBW in E+ vs. 40/1737 (2.3%) LBW in E− (OR = 0.47 [0.32, 0.71], $P < 0.001$) • 97/5275 (1.8%) CA in E+ vs. 26/1737 (1.5%) CA in E− (OR = 1.24 [0.80, 1.91], $P = 0.39$) • Among 1st trimester E+: 10/407 (2.5%) CA in E+ (1st trimester) vs. 26/1737 (1.5%) CA in E− (OR = 1.66 [0.81, 3.56], $P = 0.23$)
de Silva (1999)	1995	Sri Lanka	Cross-sectional	$n = 309$ → 92 E+; 217 E−	1, 2, 3	MEB: Not specified	Maternal STH infection status determined in 59% of participants finding no difference in E+ versus E−
Atukorala (1994)	Not specified	Sri Lanka	Cohort	$n = 115$ of 195 women who took iron folate supplements → 51 E+; 64 E−	2	MEB: Not specified	MEB and iron-folate supplements increased haemoglobin concentrations and iron status in the 3rd trimester
Tang (1989)	1984–1987	China	Cohort	$n = 40$ → All 40 E+	not specified; most early stage	MEB: 100 mg/d for 30 d medicated salt	All healthy births
Trials (RCTs and non-randomised trials) (n = 17; 9 originator studies)							
Akpan (2018)	2015	Nigeria	RCT	$n = 560$ → 300 E+; 260 E−	2	MEB: 500 mg single dose	• 9 (3.1%) LBW, 0 VLBW, 6 (2.1%) ELBW and 23 (8.0%) macrosomia in E+ vs. 11 (4.5%) LBW, 0 (0%) VLBW, 9 (3.7%) ELBW and 17 (7.0%) macrosomia in E− • 2.9% perinatal deaths[f] in E+ vs. 3.3% perinatal deaths in E− • 1 CA in E+ vs. 1 CA in E− • 5.6% asphyxia in E+ vs. 7.1% asphyxia in E− ($P = 0.706$) • Positive difference in packed cell volume higher in MEB group ($P < 0.001$); all other maternal outcomes similar
Namara (2017) *(Ndibazza 2010 is the originator study)*	2003–2005	Uganda	RCT	$n = 2515$ (628 ALB + PZQ, 629 ALB, 628 PZQ, 630 control) →1257 E+; 1258 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	At nine years of age: • No diff. in reported wheeze, skin prick test positivity to common allergens or allergen-specific IgE to dust mite or cockroach
Ivan (2015)	Not specified	Rwanda	RCT	$n = 979$ of 1100 HIV + ART + women randomised → unclear n in each group	2	ALB: 400 mg 1×/visit (up to 4 visits) + NVP + combination ART	Unclear comparisons. Only maternal outcomes reported
Nash (2017) *(Ndibazza 2010 is the originator study)*	2003–2007	Uganda	RCT	$n = 2515$ (628 ALB + PZQ, 629 ALB, 628 PZQ, 630 control) →1257 E+; 1258 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	• No effect on infant vaccine responses (BCG, polio, DT, pertussis toxin, TT, Hep B, HiB)
Webb (2012) *(Ndibazza 2010 is the originator study)*	2003–2007	Uganda	RCT	$n = 264$ HIV-infected women of 2515 randomised (79 of 628 ALB + PZQ, 71 of 629 ALB, 61 of 628 PZQ, 88 of 630 control) →150 E+; 149 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	No diff. in viral load at six weeks post treatment or at delivery

Ndibazza (2012) *(Ndibazza 2010 is the originator study)*	2003–2005	Uganda	RCT	*n* = 2515 (628 ALB + PZQ, 629 ALB, 628 PZQ, 630 control)→1257 E+; 1258 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	At five years of age: • No diff. in clinic visits of children of mothers in either group • No diff. in incidence of malaria, diarrhoea, pneumonia between groups • Eczema higher in ALB group • Hb or growth no diff. between groups • No diff. in mortality rates between groups
Gyorkos (2011) *(Larocque 2006 is the originator study)*	2003	Peru	RCT	*n* = 935 of 1042 →474 E+; 461 E−	2	MEB: 500 mg single dose E+ 60 mg elemental iron	Lower STH prevalence and intensity in 3rd trimester in E+
Mpairwe (2011) *(Ndibazza 2010 is the originator study)*	2003–2007	Uganda	RCT	*n* = 2515 (628 ALB + PZQ, 629 ALB, 628 PZQ, 630 control) →1257 E+; 1258 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	In infants at one year of age: • 148 doctor-diagnosed eczema events/1109 PY (13.35/100 PY) in E+ infants vs. 82/1092 PY (7.33/100 PY) in E− infants (HR = 1.82 [1.26, 2.64] • Reported eczema events in E+ infants vs. E− infants (OR = 1.29 [0.96, 1.72], *P* = 0.09) • Reported recurrent wheeze in E+ infants vs. E− infants (OR = 1.58 [1.13, 2.22], *P* = 0.008) • No diff. in reported urticaria
Urassa (2011)	2001–2003	Tanzania	RCT	*n* = 3080 → 1475 E+; 1605 E−	2	ALB: 400 mg single dose + 36 mg iron + 5 mg folate + SP	• No diff. in mean haemoglobin or prevalence of moderate or severe anaemia at delivery • Reduction in moderate anaemia between baseline and delivery larger in ALB group (*P* < 0.001) • At 4 mo postpartum, mean Hb higher, anaemia lower in ALB group, no difference in hookworm prevalence
Webb (2011) *(Ndibazza 2010 is the originator study)*	2003–2007	Uganda	RCT	*n* = 2515 (628 ALB + PZQ, 629 ALB, 628 PZQ, 630 control) →1257 E+; 1258 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	• No effect on infant vaccine responses (BCG, tetanus, measles) • No effect on infectious disease incidence in infants (malaria, diarrhoea, pneumonia)
Ndibazza (2010)	2003–2005	Uganda	RCT	*n* = 2515 (628 ALB + PZQ, 629 ALB, 628 PZQ, 630 control) →1257 E+; 1258 E−	2, 3	ALB: 400 mg single dose ± 40 mg/kg PZQ	• 43 (8.5%) LBW and 2 (0.4%) VLBW (ALB only) + 35 (7.0%) LBW and 4 (0.8%) VLBW (ALB + PZQ) in E+ vs. 45 (9.5%) and 1 (0.2%) VLBW (PZQ only) + 42 (8.6%) LBW and 4 (0.8%) VLBW (control) in E− (no diff.) • Lower mean BW in ALB only vs. control when given in 2nd trimester (diff.: −0.08 kg [−0.14, −0.01]), but higher mean BW when given in 3rd trimester (diff.: +0.07 kg [0.01, 0.14]) • 6/629 (ALB only) + 4/628 (ALB + PZQ) miscarriages in E+ vs. 4/628 (PZQ only) + 4/630 (control) miscarriages in E− • 11 (1.9%) (ALB only) + 12 (2.0%) (ALB + PZQ) stillbirths in E+ vs. 13 (2.2%) (PZQ only) + 8 (1.3%) (control) in E− • 10 (1.7%) (ALB only) + 8 (1.4%) (ALB + PZQ) early neonatal deaths in E+ vs. 11 (1.9%) (PZQ only) + 12 (2.0%) (control) in E− • 45 (7.7%) (ALB only) + 50 (8.4%) (ALB + PZQ) CA in E+ vs. 43 (7.5%) (PZQ only) + 42 (7.1%) (control) in E− • No diff. in maternal Hb or anaemia between groups
Christian (2009)	2004–2007	Pakistan	RCT	*n* = 547 severely anaemic women (275 standard MEB regimen, 272 enhanced MEB regimen) → All 547 E+	2, 3	MEB: 500 mg single dose (*n* = 275) or MEB: 100 mg 2×/d for 3 d (*n* = 272)	• 2–3% fetal loss in both treatment groups • Hb increase higher in enhanced MEB group (*P* < 0.05) • No change in DBS retinol between groups • Reduction in vitamin A deficiency not different between groups
Ndyomugyenyi (2008)	2003–2006	Uganda	RCT	*n* = 832 of 834 included (199 ALB + IVM, 194 ALB, 198 IVM, 241 control) → 393 E+; 439 E−	2	ALB: 400 mg single dose ± IVM (dose not specified)	• 18 (11.3%) (ALB only) + 21 (12.3%) (ALB + IVM) LBW in E+ vs. 16 (7.7%) (control) in E− (*P* = 0.25 for ALB only vs. control, *P* = 0.14 for ALB + IVM vs. control) • 1 VTOP in E+ (ALB only)

(*continued on next page*)

Table 1 (*continued*)

First author (Year of publication)	Study year(s)	Study setting	Study design[a]	Original sample size[b]	Trimester of exposure[c]	Drug and dosage[d]	Primary birth outcomes and effect sizes (if available)[e]
							• 2 (1.3%) (ALB only) + 3 (1.8%) (ALB + IVM) premature deliveries in E+ vs. 5 (2.4%) (control) in E− ($P = 0.67$ for ALB only vs. control, $P = 0.94$ for ALB + IVM vs. control) • 5 (3.1%) (ALB only) + 3 (1.8%) (ALB + IVM) stillbirths in E+ vs. 1 (0.5%) (control) in E− ($P = 0.12$ for ALB only vs. control, $P = 0.49$ for ALB + IVM vs. control) • 0 CA in E+ vs. 1 (control) CA in E− • 6 (3.8%) (ALB only) + 6 (3.5%) (ALB + IVM) anaemia at birth in E+ vs. 9 (4.6%) (control) in E− ($P = 0.72$ for ALB only vs. control, $P = 0.61$ for ALB + IVM vs. control) • 1 (0.7%) (ALB only) + 2 (1.4%) (ALB + IVM) neonatal deaths in E+ vs. 5 (2.5%) (control) neonatal deaths in E− ($P = 0.42$ for ALB only vs. control, $P = 0.74$ for ALB + IVM vs. control) • At 1 mo post-delivery, no differences in child morbidity among groups • 1 maternal death in ALB group and 1 in ALB + IVM group, unrelated to ALB or IVM • Less mild and transient side effects in E+ compared to IVM group
Gyorkos (2006) *(Larocque 2006 is the originator study)*	2003–2004	Peru	RCT	$n = 1042$ → 522 E+; 520 E−	2	MEB: 500 mg single dose + 60 mg elemental iron	• 2 miscarriages in E+ vs. 3 in E− ($P = 0.647$) • 8 stillbirths in E+ vs. 4 in E− • 3 early neonatal deaths in E+ vs. 6 in E− • 7 (1.40%) CA in E+ vs. 8 (1.61%) E− ($P = 0.783$) • 11 premature deliveries in E+ vs. 13 in E− • Overall: 28 (5.6%) adverse birth outcomes in E+ vs. 31 (6.3%) in E− ($P = 0.664$)
Larocque (2006)	2003–2004	Peru	RCT	$n = 1042$ → 522 E+; 520 E−	2	MEB: 500 mg single dose + 60 mg elemental iron	• No diff. in mean BW ($P = 0.629$) • 39 (8.1%) LBW in E+ vs. 41 (8.7%) in E− ($P = 0.755$) • 0 (0%) VLBW in E+ vs. 7 in E− ($P = 0.007$) • 33.0% maternal anaemia in 3rd trimester vs. 32.3% ($P = 0.815$)
Elliott (2005)	2002	Uganda	RCT	$n = 103$ of 104 randomised → 53 E+; 50 E−	2	ALB: 400 mg single dose	• 5/53 perinatal deaths in E+ vs. 4/50 in E− • No evidence of effect on infant vaccine responses to BCG • Cord blood IL-10 lower in ALB group • Hookworm prevalence and IFN-γ response to CFP significantly reduced in ALB group
Torlesse (2001)	1995–1996	Sierra Leone	RCT	$n = 125$ completed of 184 recruited; 32 ALB + iron-folate, 35 iron-folate, 29 ALB, 29 control → 61 E+; 64 E−	2	ALB: 2 × 200 mg single dose ± 36 mg iron-5 mg folate	• 4 miscarriages in E+ vs. 4 in E− • 1 CA in E+ vs. 0 in E− • Increase in maternal haemoglobin and decrease in maternal anaemia, iron-deficiency anaemia and serum ferritin concentration in ALB + iron-folate group between 1st and 3rd trimester

[a] RCT = Randomised controlled trial.

[b] E+, population exposed; E+ 1st, population exposed in the first trimester of pregnancy; E−, population unexposed; for case reports, disease treated is noted; APEC study, Anaemia in Pregnancy: Etiology and Consequences study.

[c] Trimester as reported in the publication.

[d] MEB, mebendazole; ALB, albendazole; PZQ, praziquantel; SP, sulfadoxine-pyrimethamine; IPTp-SP, intermittent preventive treatment in pregnancy with sulfadoxine-pyrimethamine; ART, antiretroviral treatment; NVP, nevirapine. Other treatments may also have been received by the women over the course of the study (e.g. iron, multivitamins, etc); d, day; wk, week; mo, month; yr, year.

[e] BW, birth weight; LBW, low birth weight (<2500 g); VLBW, very low birth weight (<1500 g); ELBW, extremely low birth weight (<1000 g); CA, congenital anomaly; VTOP, voluntary termination of pregnancy; SGA, small for gestational age; BCG, bacillus Calmette-Guérin; CFP, culture filtrate proteins; hb, haemoglobin; diff., difference; PY, person years; OR [,], odds ratio [95% confidence internal (CI)]; aOR [,], adjusted OR [95%CI]; RR, rate ratio; POR, prevalence OR; HR, hazard ratio; IVM, ivermectin.

[f] 2.9% mentioned in text; 2.4% in Fig. 2 of the publication.

Table 2
Characteristics of the 46 originator studies.

Overall	
n (number of studies)	46[a]
Study characteristics	
Study design, n (%)	
Randomised controlled trial	9 (20%)
Cohort study	10 (22%)
Cross-sectional study	6 (13%)
Case-control study	1 (2%)
Case report/case series	20 (43%)
Language of publication, n (%)	
English	42 (91%)
Danish	1 (2%)
Finnish	1 (2%)
German	1 (2%)
Mandarin	1 (2%)
Study site by World Health Organization region, n[b] (%)	
Europe	15 (33%)
Africa	12 (26%)
Southeastern Asia	10 (22%)
Americas	4 (9%)
Western Pacific	3 (7%)
Eastern Mediterranean	1 (2%)
Study site by World Bank country income classifications,[b] n[c] (%)	
Low income country	11 (24%)
Lower middle income country	11 (24%)
Upper middle income country	8 (17%)
High income country	15 (33%)
Benzimidazole, n[d] (%)	
Albendazole	27 (59%)
Mebendazole	18 (39%)
Exposure timing, n (%)	
1st trimester only	8 (17%)
1st trimester + 2nd and/or 3rd trimesters	11 (24%)
2nd and/or 3rd trimesters only	25 (54%)
Unspecified	2 (4%)

[a] Numbers may not sum to 100% due to rounding.
[b] Country classification is according to World Bank income designations in 2018.
[c] One study (Bradley and Horton, 2001) is a case series which includes multiple study sites in different countries and is not included in the number reported here.
[d] One study (Shiferaw et al., 2017) reported on both types of exposure and is not included in the number reported here.

and Horton, 2001). Adverse outcomes included six VTOPs, two deaths and three minor congenital anomalies, with the remaining 38 determined, or presumed, not to have had any adverse maternal or birth outcomes.

3.3. Observational studies

Results from a total of 17 originator studies have been published in 21 publications (Table 1). Most study populations included women in all trimesters of pregnancy. The second trimester was the most frequently investigated, either alone or concurrently with first and/or third trimester exposures. Three publications did not report on any benzimidazole-related child or maternal outcomes. Outcomes from the administration of albendazole are reported in eight publications, and in 11 for mebendazole. First trimester exposures were reported in 10 publications. Only one observational study was a case-control study (Acs et al., 2005). It analysed 17 years of data from the Hungarian Congenital Abnormality Registry and found no difference in exposure to mebendazole between cases of congenital anomalies ($n = 22,843$) and controls from the National Birth Registry, matched on sex, birth week and parent's residence ($n = 38,151$) (Acs et al., 2005). Results below are presented separately for albendazole and mebendazole (because their efficacy and effectiveness differ) and for maternal and child outcomes, overall and in the first trimester.

3.3.1. Albendazole

Among the eight studies where albendazole was administered during pregnancy and where albendazole-related outcomes were reported, adverse child outcomes were reported in four studies (in terms of congenital anomalies, miscarriages, asphyxia, mean birth weight and 6-month mortality) with rates similar between exposed (with single dose albendazole) and unexposed intervention groups (Gyapong et al., 2003; Christian et al., 2004; Mpairwe et al., 2014; Choi et al., 2017). Differences were found in two instances: (i) a higher frequency of eczema was found among children 5 years following their mothers' exposure to albendazole during pregnancy (23.7% compared with 14.9%) (Mpairwe et al., 2014) and (ii) a lower 6-month mortality rate was found in children of mothers who had received two doses of albendazole during pregnancy (38.9 deaths per 1000 children compared with 95.8 deaths per 1000 children) (Christian et al., 2004).

Among the six studies reporting maternal outcomes (Christian et al., 2004; Liabsuetrakul et al., 2009; Ouédraogo et al., 2013; Raut et al., 2016; Shiferaw et al., 2017; Choi et al., 2017), the following outcomes were assessed: anaemia, haemoglobin levels, STH infection and VTOPs. One study reported on VTOPs (Choi et al., 2017). No other adverse events were noted while benefits of treatment included increased haemoglobin and reduced anaemia in the third trimester (Christian et al., 2004) and a lower STH infection rate (Ouédraogo et al., 2013; Shiferaw et al., 2017).

3.3.1.1. Albendazole: first trimester child outcomes. A total of two studies reported on birth outcomes following albendazole use during the first trimester (Gyapong et al., 2003; Choi et al., 2017). One study did not publish disaggregated results by trimester (Gyapong et al., 2003). The other study investigated first trimester exposures exclusively (Choi et al., 2017). Among a study population of pregnant women who had sought risk counseling at a hospital clinic, no difference in birth outcomes (e.g. frequency of miscarriages or congenital anomalies) was found between women exposed to albendazole versus women not exposed to albendazole. Unfortunately, the loss-to-follow-up rate among both groups was over 45% and no multivariate analyses were performed.

3.3.1.2. Albendazole: first trimester maternal outcomes. Only one study specifically reported on maternal outcomes following albendazole use during the first trimester. It reported two VTOPs in each of the exposed and unexposed groups (Choi et al., 2017).

3.3.2. Mebendazole

Among the 11 studies where mebendazole was administered during pregnancy, adverse birth outcomes were reported in five studies (de Silva et al., 1999; Diav-Citrin et al., 2003; Acs et al., 2005; Mireku et al., 2015; Torp-Pedersen et al., 2016). Outcomes included miscarriages, ectopic pregnancies, stillbirths, preterm births, congenital anomalies, perinatal deaths, and low birth weights. No statistically or clinically significant differences were found between exposed and unexposed groups, with one exception. This study found significantly fewer stillbirths and perinatal deaths in the mebendazole-exposed group, as well as a lower proportion of low birth weight babies in the exposed group compared with the unexposed group (de Silva et al., 1999).

Seven studies reported maternal outcomes (Atukorala and de Silva, 1994; de Silva et al., 1996; Diav-Citrin et al., 2003; Luoba et al., 2005; Torp-Pedersen et al., 2012; Mireku et al., 2015; Shiferaw et al., 2017). One study reported improvement in terms of haemoglobin and anaemia during the pregnancy (Atukorala and de Silva, 1994). STH infection was found to be reduced in one study (Shiferaw et al., 2017) but not in another (de Silva et al., 1996). Two studies reported on VTOPs. One found a significantly higher number of VTOPs in the exposed group ($P < 0.001$)

(Diav-Citrin et al., 2003) while the other study included only exposed pregnant women with no unexposed comparator group (Mireku et al., 2015).

3.3.2.1. Mebendazole: first trimester child outcomes. Four studies included study populations of pregnant women receiving mebendazole in the first trimester and child outcomes (de Silva et al., 1999; Diav-Citrin et al., 2003; Acs et al., 2005; Torp-Pedersen et al., 2016). Three studies reported disaggregated data on birth outcomes (notably only on congenital abnormalities) in the first trimester (de Silva et al., 1999; Diav-Citrin et al., 2003; Torp-Pedersen et al., 2016). None found any statistically significant difference in the frequency of congenital anomalies between the exposed and unexposed groups.

3.3.2.2. Mebendazole: first trimester maternal outcomes. No study specifically investigated maternal outcomes following mebendazole use exclusively in the first trimester.

3.4. Trials

No trial included pregnant women in their first trimester (Table 1). A total of 17 publications report outcomes from nine originator studies administering albendazole (n = 12) or mebendazole (n = 5) in the second or third trimester.

3.4.1. Albendazole

Of the 12 publications reporting trial results in terms of birth, child and maternal outcomes following exposure to albendazole during pregnancy, only one reported a difference in a birth outcome (i.e. cord blood IL-10 was lower in the albendazole group compared with the unexposed group) (Elliott et al., 2005). Differences were also found in terms of child outcomes (i.e. higher rates of eczema in one and 5-year-old children of mothers in the exposed group) (Mpairwe et al., 2011; Ndibazza et al., 2012) and maternal outcomes (reduction in moderate anaemia, reductions in hookworm prevalence and interferon-gamma response to culture filtrate proteins (Elliott et al., 2005)).

3.4.2. Mebendazole

A total of five publications reported results from trials where mebendazole was administered. Neither the Akpan et al. (2018) trial nor the Larocque et al. (2006) trial showed any difference in terms of birth outcomes between the exposed or unexposed groups. However, in a secondary analysis, Larocque et al. (2006) reported fewer newborns of very low birth weight in the mebendazole-exposed group compared with the unexposed group. Follow-up studies from this Peru trial showed no difference in additional birth outcomes and a lower STH prevalence and intensity among women who had received mebendazole compared with the unexposed group (Gyorkos et al., 2006; Gyorkos et al., 2011). The Christian et al. (2009) trial reported improvement in haemoglobin in the intervention group that received an enhanced mebendazole regimen (100 mg twice a day for 3 days) compared with the standard mebendazole regimen (500 mg single dose once).

3.5. Risk of bias

According to the PRISMA 2009 Guidelines (Liberati, 2009) for transparent reporting of systematic reviews and meta-analyses, the overall risk of bias within the analytical studies was judged to be low to moderate (data not shown). Selection bias and missing data were the most frequently noted limitations of observational studies while attrition bias resulting in incomplete outcome data was most frequently noted in the trials.

3.6. Maternal side effects

Only two analytical studies, both observational, (Tang et al., 1989; Ndyomugyenyi et al., 2008) reported on the occurrence of adverse side effects in the pregnant women themselves. These included abdominal pain, fever, headaches, mild short-term dizziness, watery stools, and occasional mild diarrhoea, and were all deemed to be minor. The mebendazole used in the study by Tang et al. (1989) was in the form of a medicated salt, a format which is not recommended in current preventive chemotherapy programs (WHO, 2018).

3.7. Summary of adverse events in the first trimester

Table 3 summarises the adverse events reported following exposure to albendazole and mebendazole in the first trimester of pregnancy. Of a total of nine studies, five are case reports, one is a case series and three are observational studies. No difference in the frequency of adverse events was documented in any of the observational studies.

Table 3
Summary of adverse events known to have occurred from exposure to albendazole or mebendazole in the first trimester.

First author (Year)	Study setting	Study design[a]	Adverse outcomes reported[b]	Results of comparisons of adverse events between exposed and unexposed groups[c]
Albendazole				
Choi (2017)	South Korea	Case-control	Miscarriages Congenital anomalies VTOPs	No difference
Bradley (2001)	Various	Case series (various helminth infections)	Miscarriage Neonatal death Congenital anomalies VTOPs	NA
Golaszewski (1995)	Austria	Case report (Echinococcosis)	Fatal premature birth	NA
Srour (2001)	Israel	Case report (Echinococcosis)	VTOP	NA
Potasman (1998)	Israel	Case report (Gnathostomiasis)	VTOP	NA
Mebendazole				
Torp-Pedersen (2016)	Denmark	Cohort	Congenital anomalies	No difference
Yang (2005)	China	Case report (Alveolar echinococcosis)	Congenital anomaly	NA
Diav-Citrin (2003)	Israel	Cohort	Congenital anomalies	No difference
Joki-Erkkilä (2001)	Finland	Case report (Ascariasis)	Fetal death	NA

[a] For case reports, indication for benzimidazole treatment is provided.
[b] VTOP, voluntary termination of pregnancy.
[c] NA, not applicable.

Table 4
Studies with the potential for including pregnant women in their first trimester within their study population, using the World Health Organization (WHO) definition for first trimester (up to and including 16 weeks of gestation).

First author (Year)	Study design[a]	Sample size	Number exposed to ALB or MEB	Trimester at documented exposure	Source of trimester definition	Length of 1st trimester as reported in paper
Akpan (2018)	RCT	560	300	2nd	Inferred from text, no source	Weeks 1–13
Mireku (2015)	Cohort	863	863	2nd	Benin Ministry of Health	Weeks 1–15
Ivan (2015)	RCT	1100	606	2nd	Not stated in text	Not stated in text
Urassa (2011)	RCT	3080	1475	2nd	Not stated in text	Not stated in text
Ndibazza (2010)	RCT	2507	1253	2nd, 3rd	Not stated in text	Not stated in text
Liabsuetrakul (2009)	Cohort	1063	174	2nd, 3rd	Inferred from text, no source	Weeks 1–14
Elliott (2005)	RCT	103	53	2nd	Not stated in text	Not stated in text
Christian (2004)	Cohort	4998	≥3847	2nd, 3rd	Stated in text, no source	Weeks 1–12
Torlesse (2001)	RCT	184	161	2nd	Stated in text, no source	Weeks 1–14

[a] RCT, randomised controlled trial.

3.8. Definition of trimester

WHO standard definitions for trimesters were applied to classify the trimester of exposure in studies which provided the number of weeks at exposure but did not specify the corresponding trimester, and from which an interpretation of the length of the trimester could not be inferred. In addition, however, several studies specified the trimester of exposure as either the second or third trimester but did so under differing interpretations of the length of each trimester (as either explicitly defined or inferred from the

Case reports	***20 reports in total*** **Locations:** Argentina, Austria, Canada, China, Denmark, Finland, Germany, India, Israel, Netherlands, Slovakia, Turkey, United States **Clinical indication:** mostly echinococcosis **Treatment:** mostly albendazole **Outcome:** mostly healthy births
Observational studies	***21 reports in total from 17 originator studies*** **Locations:** Benin, China, Denmark, Ethiopia, Ghana, Hungary, Israel, Kenya, Nepal, South Korea, Sri Lanka, Thailand, Uganda **Treatment:** mostly *not* single dose (both albendazole and mebendazole) **Outcome:** no difference in adverse birth outcomes between exposed and unexposed groups in the first trimester; *still to confirm*: lower mortality, stillbirth and low birth weight rates in exposed groups; higher voluntary termination of pregnancy rate in exposed groups; higher eczema rate in children of exposed groups; lower rate of STH in exposed groups
Trials	***17 reports in total from 9 originator trials*** **Locations:** Nigeria, Pakistan, Peru, Rwanda, Sierra Leone, Tanzania, Uganda **Treatment:** all single dose (both albendazole and mebendazole); no first trimester pregnancies; mostly co-administered with iron, folic acid, and/or praziquantel **Outcome:** between intervention groups, mostly no difference in birth outcomes; some reduction in maternal STH prevalence and intensity, and anemia in exposed groups

Fig. 2. Overall summary of published evidence (1989–2018) investigating maternal and child outcomes following exposure to albendazole or mebendazole during pregnancy, by study design.

text) (Table 4). Relative to the WHO standard, which provides a very conservative definition of the first trimester, it is likely that some of these studies misclassified their study population as having been exposed after the 1st trimester, when they would have been considered as exposed during the first trimester according to the WHO standard. This potential for misclassification casts uncertainty over what should be considered an exposure event.

4. Discussion

This systematic review presents the cumulative evidence documenting outcomes following exposure to albendazole or mebendazole during pregnancy (see Fig. 2 for results highlights by study design). It should be noted that none of the studies reporting on adverse birth outcomes found a statistically or clinically significant difference in the frequency of adverse events between the group exposed to albendazole or mebendazole and the unexposed group, with the exception of the study by de Silva et al. (1999) which found the rate of stillbirths and perinatal deaths to be significantly lower in the exposed group (odds ratio (OR) = 0.55 (95% confidence interval (CI) 0.4–0.77)). Moreover, in case studies detailing treatment provided to individual patients, adverse events could not be directly attributed to the use of benzimidazoles in pregnancy due to the presence of pre-existing medical conditions.

Published empirical evidence on the effects of benzimidazoles in the first trimester of pregnancy is limited. Much of the evidence to date still includes individual case reports in highly specialised clinical settings in high income countries. Large population studies conducted in pregnant populations living in LMIC countries which report data by trimester are rare. This paucity of research is likely due, in part, to ethical concerns related to studying pregnant populations. Nonetheless, what the evidence from the 46 originator studies in this review does provide is an appreciation that there has been no observed increased risk of adverse birth outcomes among pregnant women who were exposed to albendazole or mebendazole in the first trimester. The capacity to detect increased risk in what are relatively rare outcomes would require a level of statistical power which can only be achieved with extremely large sample sizes which may only now be able to be considered with national deworming programs that will include women of reproductive age. Such opportunities for relevant data would arise if these programs have a comprehensive monitoring component. In addition, future research should consider the following: using the WHO definition of trimester (or providing trimester data in weeks); reporting data disaggregated by trimester; specifying the source and dosage of the deworming drug administered; reporting the full spectrum of adverse events from both woman and child (i.e. not only focusing on congenital anomalies); detailing the epidemiological methods used, especially regarding the assembly and follow-up of the study population; and minimising missing data.

The quality of the individually reviewed studies represents an important limitation of this systematic review. None of the identified randomised controlled trials assessed exposure to albendazole and mebendazole in the first trimester of pregnancy. The limited number of observational studies, and their heterogeneity in terms of both exposure and outcome, hinders our ability to provide a coherent summary of the evidence linking exposure to albendazole and mebendazole with adverse birth outcomes. The diversity of study types and other substantive differences among studies included in this review further prevent us from presenting a pooled estimate of the risk of adverse birth outcomes. Therefore, these results should be interpreted with appropriate care.

To our knowledge, this is the first systematic review to investigate exposure to benzimidazoles, namely albendazole and mebendazole, during the first trimester of pregnancy. These results demonstrate that, despite a continual increase in publications investigating deworming during pregnancy over the years, there is an important shortage of analytical and experimental research on this topic. Future research evaluating the effectiveness of deworming programs targeting women of reproductive age and, in particular, pregnant women, will contribute much-needed empirical evidence to inform optimal program implementation.

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