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On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections

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The WHO recommends the administration of sulfadoxine-pyrimethamine (SP) to all pregnant women living in areas of moderate (stable) to high malaria transmission during scheduled antenatal visits, beginning in the second trimester and continuing to delivery. Malaria parasites have lost sensitivity to SP in many endemic areas, prompting the investigation of alternatives that include azithromycin-based combination (ABC) therapies. Use of ABC therapies may also confer protection against curable sexually transmitted infections and reproductive tract infections (STIs/RTIs). The magnitude of protection at the population level would depend on the efficacy of the azithromycin-based regimen used and the underlying prevalence of curable STIs/RTIs among pregnant women who receive preventive treatment. This systematic review summarizes the efficacy data of azithromycin against curable STIs/RTIs.

Keywords: azithromycin • bacterial vaginosis • Chlamydia • gonorrhea • malaria • pregnancy • reproductive tract infections • sexually transmitted infections • sub-Saharan Africa • syphilis • trichomoniasis

The WHO recommends the administration of sulfadoxine-pyrimethamine (SP) to all pregnant women who live in areas of moderate (stable) to high malaria transmission during scheduled antenatal care (ANC) visits, beginning in the second trimester and continuing to delivery [1]. This intervention, known as intermittent preventive treatment of malaria in pregnancy (IPTp), is national policy in 36 countries worldwide, 35 of which are in sub-Saharan Africa [2]. The objective of IPTp-SP is to reduce the incidence of low birthweight and maternal anemia attributable to malaria. In recent years, however, malaria parasites have developed resistance to SP such that IPTp no longer reduces the incidence of low birthweight in some epidemiological settings, particularly in East Africa [3]. Evidence suggests that in areas where parasites express the 581G *dhps* mutation that is associated with SP resistance, the administration of IPTp-SP may even harm fetal growth [4–6]. Thus, the urgency to replace SP has never been greater and azithromycin-based combination (ABC) therapies are among leading candidates to do so.

Azithromycin is a slow-acting analog of erythromycin in the macrolide (azalide) class of drugs, which targets the ribosomal subunit of susceptible microorganisms and causes cellular death by inhibiting protein synthesis [7]. It has *in vitro* and *in vivo* antimalarial properties [8] and can be safely administered during pregnancy [9]. Two human challenge studies have published results of azithromycin monotherapy treatment against *Plasmodium falciparum* infection. The first study reported a protective effect of 40% (n = 10; 95% CI: 12–74%) among immunologically naïve patients who received 250 mg azithromycin daily for 2 weeks prior to inoculation and for 1 week more following exposure [10]. When the same regimen was used for one additional week post-inoculation, treatment efficacy was 100% (n = 10) [11]. Despite this finding, comparable results have not been replicated in endemic settings where patients often have

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mixed and multiple infections. However, *in vitro* evidence suggests that azithromycin may be combined with antimalarial partner drugs to prevent or to cure *P. falciparum* infection [12], the malaria species most prevalent in sub-Saharan Africa and which uniquely adhere to the placenta of pregnant women. In addition to reducing the burden of malaria infection, ABC therapies may also protect against adverse birth outcomes attributable to curable sexually transmitted and reproductive tract infections (STIs/RTIs). This could offer considerable public health impact. A recent meta-analysis suggests that curable STIs/RTIs are as prevalent as malaria parasitemia, if not more so, among pregnant women who attend ANC facilities in sub-Saharan Africa [13]. Five curable STIs/RTIs – *Treponema pallidum*, *Neisseria gonorrheae*, *Chlamydia trachomatis*, *Trichomonas vaginalis* and bacterial vaginosis – are associated with adverse birth outcomes that include spontaneous abortion [14–18], stillbirth [19–21], intrauterine growth retardation [20,22,23], premature rupture of membranes [24–26], preterm birth [17,22,23,26–33] and low birthweight (Table 1) [20,23,24,28,29,33–35]. This paper summarizes azithromycin efficacy and sensitivity against these curable STIs/RTIs and highlights important issues for policymakers to consider while determining the potential use of ABC therapies in IPTp.

Methodology

Between April and May 2013, PubMed, MEDLINE and EMBASE were searched using Medical Subject Headings and free-text terms for publications specific to the curable STIs/RTIs noted above. With each query, the infection and causal organism were used together, for example, 'Syphilis' AND '*Treponema pallidum*', and then combined with search terms 'azithromycin' OR 'macrolide'. Because the evidence base is limited with respect to azithromycin and some curable STIs/RTIs, both 'azithromycin' and 'macrolide' were used as filters. We had particular interest in randomized clinical trials (RCTs) that compared azithromycin against the current first-line treatments for curable STIs/RTIs in pregnancy, noting that azithromycin is the WHO-recommended treatment for pregnant women infected with *C. trachomatis*. Searches were limited to the English language and strict inclusion and exclusion criteria were applied so as to narrow the number of papers retained. Reference lists were also reviewed for additional documents. Excluded records and full-text articles were in seven categories:

- **'Unrelated outcomes'** were studies that reported nonclinical aspects of azithromycin use such as cost-effective analysis, noncommunicable diseases such as heart disease or pharmacological outcomes involving a route of administration that is not applicable to this review (e.g., intravenous);
- **'Unrelated organisms'** were papers dedicated to microbes that are not the focus of this review;
- **'Not specific to STI/RTI'** were articles on the subject of same genus of interest, for example, *Chlamydia*, but were not specific to the genital tract, for example, *Chlamydia pneumoniae*;
- **'Not related to azithromycin or close macrolide family'** were papers that did not contain macrolides in their analysis or outcomes, but focused on different antimicrobials against the organisms in question;
- **'Sequential observations from same source'** involved surveillance reports from which most recent data set was used;
- **'General discussion papers'** contained information pertinent to the search, but failed to provide specific data for STIs/RTIs.
- **'Contraindicated in pregnancy'** were papers that reported outcomes of azithromycin combined with antimicrobial compounds that are considered unsafe in pregnancy.

A total of 122 articles met our primary inclusion criteria (Figure 1).

Results

Treponema pallidum

In vivo evidence

The WHO recommends treating pregnant women with syphilis infection using 2.4 million units of benzanthine penicillin G (BPG) administered by intramuscular injection [36]. Thus, we summarize the results of the six clinical trials that reported outcomes among nonpregnant adults following treatment with BPG, azithromycin or a combination of BPG and azithromycin (Table 2). The oldest data are from a trial in the USA (1993–1997) in which individuals who discovered they had been exposed to infectious stage syphilis through sexual intercourse in the preceding 30 days were given either 1 g azithromycin (n = 40) or BPG (n = 23). Three months post-treatment, rapid plasma reagin (RPR) and fluorescent treponemal antibody absorption tests (FTA-ABS) were negative for all participants in both treatment groups [37]. Another trial in the USA during the same time period was designed to measure treatment outcomes in a population at high risk of contracting STIs/RTIs. Although diagnostic methods were not reported, the trial was suspended after two of the first 12 patients were provided 1 g azithromycin failed their test of cure while all 13 participants were cured using BPG (p = 0.18) [38]. A three-arm trial of early syphilis in the USA then compared treatment outcomes among patients given BPG, or 2 g azithromycin once or 2 g azithromycin two-times with 1 week in between doses. RPR and FTA-ABS testing showed that cure was achieved in 85.7% (n = 14; 95% CI: 60.0–95.7%) of patients given BPG, 94.1% (n = 17; 95% CI: 72.7–98.6%) among recipients of 2 g azithromycin once and 82.8% (n = 29; 95% CI: 65.3–92.3%) in participants who twice received 2 g azithromycin [39].

In sub-Saharan Africa, three trials have investigated BPG versus azithromycin, the first being a community-randomized trial in Uganda (1994–1998) among nonpregnant adults with serological syphilis. Diagnosis and test of cure were based on toluidine red unheated serum tests (TRUSTs) and *Treponema pallidum* hemagglutination assays. Treatment efficacy varied across regimens depending on TRUST titers at enrolment. Among patients with initial titers <1:2, BPG cured 71.0% (n = 93; 95% CI: 61.0–79.2%) of cases compared with 58.5%

Table 1. Efect of curable STIs/RTIs on pregnancy outcomes.

Study (year)	Country	Year(s)	Spontaneous abortion	Stillbirth	IUGR	PROM	Preterm	Low birthweight	Ref.
Treponema pallidum									
Watson-Jones *et al.* (2002)	Tanzania	1998–2000	NR	18 (5.5–59.6) RR	2.1 (1.0–4.2) RR	NR	6.1 (2.5–15.3) RR	3.3 (2.0–5.4)[†]	[21]
Temmerman *et al.* (1995)	Kenya	1991	NR	3.34 RR	NR	NR	NR	4.01[†]	[120]
McDermott *et al.* (1993)	Malawi	1987–1990	NR	10.98	NR	NR	NR	NR	[19]
Donders *et al.* (1993)	South Africa	1988	NR	NR	NR	NR	33%; 5 of 15 cases	NR	[34]
Elliott *et al.* (1990)	Kenya	1985	NR	NR	NR	NR	1.4 (0.5–4.1)	NR	[121]
Ratnam *et al.* (1982)	Zambia	NR	42% of cases	NR	NR	NR	NR	NR	[15]
Williams *et al.* (1923)	USA	1923	40% of cases	NR	NR	NR	NR	NR	[14]
Neisseria gonorrhoeae									
Johnson *et al.* (2011)	USA	1996–2002	NR	NR	NR	NR	2.0 (1.0–4.0)	0.8 (0.3–2.3)	[122]
Donders *et al.* (1993)	South Africa	1988	NR	NR	NR	NR	56%; 5 of 9 cases	$p < 0.005$	[34]
Elliott *et al.* (1990)	Kenya	1985	NR	NR	NR	NR	3.2 (1.3 to 8.4)	NR	[121]
Chlamydia trachomatis									
Rours *et al.* (2011)	Netherlands	2003–2005	NR	NR	NR	NR	4.4 (1.3–15.2)[†]; 2.7 (1.1–6.5)[‡]; 1.17 (0.6–2.4)[§]	1.0 (0.4–2.2)	[32]
Silveira *et al.* (2009)	USA	2005–2008	NR	NR	NR	NR	0.7 (0.4–1.4)	NR	[123]
Wilkowska-Trojniel *et al.* (2009)	Poland	2003–2006	12 versus 2% $p = 0.029$	NR	NR	NR	NR	NR	[18]
Blas *et al.* (2007)	USA	2003	NR	NR	NR	1.5 (1.0–2.2) RR	1.5 (1.1–2.0) RR	1.1 (0.7–1.7)	[124]
Odendaal *et al.* (2006)	South Africa	2002–2003	NR	NR	NR	NR	22.2%; 8 of 36 cases versus 10.4%; 32 of 307 cases; $p = 0.037$	NR	[30]

Results reported as odds ratios unless otherwise noted and 95% confidence intervals in parentheses.
[†]Preterm delivery before 32 weeks.
[‡]Preterm delivery before 35 week.
[§]Preterm delivery before 37 weeks.
[¶]Bacterial vaginosis at 16–20 weeks.
[††]Bacterial vaginosis at 28–32 weeks.
[‡‡]Intermediate flora (Nugent scores 4–7) and bacterial vaginosis (Nugent scores 7–10).
IUGR: Intrauterine growth retardation; NR: Not reported; PROM: Premature rupture of membranes; RR: Risk ratio.

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Table 1. Efect of curable STIs/RTIs on pregnancy outcomes (cont.).

Study (year)	Country	Year(s)	Spontaneous abortion	Stillbirth	IUGR	PROM	Preterm	Low birthweight	Ref.
Chlamydia trachomatis (cont.)									
Johnson *et al.* (2011)	USA	1996–2002	NR	NR	NR	NR	1.0 (0.6–2.0)	2.1 (1.0–4.2)	[122]
Kovacs *et al.* (1998)	Hungary	1994–1995	NR	NR	7.3 versus 5.8% p > 0.05	20 versus 21% p > 0.05	NR	15.5 versus 13.2% p > 0.05	[125]
Donders *et al.* (1993)	South Africa	1988	NR	NR	NR	NR	27%; 6 of 22 cases	NR	[34]
Elliott *et al.* (1990)	Kenya	1985	NR	NR	NR	NR	0.7 (0.4–1.4)	NR	[121]
Johns Hopkins *et al.* (1989)	USA	1983–1985	NR	NR	2.4 (1.3– 4.2)	NR	1.6 (1.0–4.2)	NR	[126]
Gravett *et al.* (1986)	USA	1983	NR	NR	NR	2.4 (1.7–5.4)	NR	2.7 (1.3–5.7)	[24]
Trichomonas vaginalis									
Johnson *et al.* (2011)	USA	1996–2002	NR	NR	NR	NR	1.4 (0.7–2.8)	1.5 (0.9–2.6)	[122]
Meis *et al.* (1995)	USA	1992–1994	NR	NR	NR	NR	1.5 (0.1–8.1) week 24; 0.9 (0.2–3.6) week 28	NR	[127]
Sutton *et al.* (1999)	DR Congo	1989–1990	NR	NR	NR	NR	NR	2.1 (1.0–4.7)	[35]
Minkoff *et al.* (1984)	USA	NR	NR	NR	NR	p < 0.03	NR	NR	[128]
Cotch *et al.* (1997)	USA	1984–1989	NR	NR	NR	NR	1.3 (1.1–1.4)	1.3 (1.1–1.5)	[28]
Bacterial vaginosis									
Johnson *et al.* (2011)	USA	1996–2002	NR	NR	NR	NR	1.3 (0.9–2.1)	1.1 (0.6–1.8)	[122]
Svare *et al.* (2006)	Denmark	1998–2002	NR	NR	NR	NR	2.5 (1.6–3.9)	2.0 (1.3–2.9)	[29]
Watson-Jones *et al.* (2007)	Tanzania	1997–2000	NR	NR	NR	NR	3.0 (1.3–6.6)	NR	[31]
Leitich *et al.* (2003)	Multiple	Multiple	9.9 (2.0–49.3)	NR	NR	NR	2.2 (1.5–3.1)	NR	[17]
Meis *et al.* (1995)	USA	1992–1994	NR	NR	NR	NR	1.4 (0.9–2.05) week 24; 1.8 (1.2–3.0) week 28	NR	[127]

Results reported as odds ratios unless otherwise noted and 95% confidence intervals in parentheses.
†Preterm delivery before 32 weeks.
‡Preterm delivery before 35 week.
§Preterm delivery before 37 weeks.
¶Bacterial vaginosis at 16–20 weeks.
††Bacterial vaginosis at 28–32 weeks.
‡‡Intermediate flora (Nugent scores 4–7) and bacterial vaginosis (Nugent scores 7–10).
IUGR: Intrauterine growth retardation; NR: Not reported; PROM: Premature rupture of membranes; RR: Risk ratio.

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Table 1. Efect of curable STIs/RTIs on pregnancy outcomes (cont.).

Study (year)	Country	Year(s)	Spontaneous abortion	Stillbirth	IUGR	PROM	Preterm	Low birthweight	Ref.
Bacterial vaginosis (cont.)									
McGregor *et al.* (1995)	USA	1991–1992	NR	NR	NR	3.5 (1.4–8.9) RR	1.9 (1.2–3.0); 1.5 (0.7–3.0)¶ RR	NR	[25]
Hillier *et al.* (1995)	USA	1984–1989	NR	NR	NR	1.1 (0.8–1.6)	1.4 (1.1–1.8)	1.5 (1.2–1.7)	[129]
Hay *et al.* (1994)	UK	NR	5.5 (2.3–13.3)††	NR	NR	NR	13.1 (4.0–42.6)‡‡	NR	[16]
Elliott *et al.* (1990)	Kenya	1985	NR	NR	NR	NR	1.0 (0.6–1.8)	NR	[121]
Gravett *et al.* (1986)	USA	1983	NR	NR	NR	2.0 (1.1–3.7)	NR	1.5 (0.8–2.0)	[24]

Results reported as odds ratios unless otherwise noted and 95% confidence intervals in parentheses.
†Preterm delivery before 32 weeks.
‡Preterm delivery before 35 week.
§Preterm delivery before 37 weeks.
¶Bacterial vaginosis at 16–20 weeks.
††Bacterial vaginosis at 28–32 weeks.
‡‡Intermediate flora (Nugent scores 4–7) and bacterial vaginosis (Nugent scores 7–10).
IUGR: Intrauterine growth retardation; NR: Not reported; PROM: Premature rupture of membranes; RR: Risk ratio.

(n = 94; 95% CI: 48.4–68.0%) among recipients of 1 g azithromycin and 70.6% (n = 313; 95% CI: 65.3–75.4%) of participants given 1 g azithromycin plus BPG. If titers at enrolment were >1:4, the efficacy of BPG was reduced to 41.3% (n = 75; 95% CI: 30.9–52.7%). Treatment efficacy was also lower among groups given azithromycin but higher than BPG alone. Recipients of 1 g azithromycin alone had a cure rate of 53.3% (n = 71; 95% CI: 42.0–64.7%), whereas 1 g azithromycin plus BPG cured 54.7% of cases (n = 309; 95% CI: 49.1–60.2%) [40].

These results were followed by a trial carried out in Tanzania (2000–2003) among patients who were recruited by screening high-risk populations. All 328 subjects had a titer of at least 1:8 on RPR test; 106 had baseline titers of >1:64, levels indicative of active syphilitic lesions. Confirmed by RPR test and *T. pallidum* particle agglutination assay, serological cure was observed in 97.5% (n = 163; 95% CI: 93.9–99.0%) of participants given 2 g azithromycin versus 95.2% (n = 165; 95% CI: 90.7–97.5%) in the BPG group [41].

The most recent study comparing the efficacy of azithromycin versus BPG is a multicenter trial (2000–2007) in Madagascar (n = 421) and North America (n = 94) among HIV-negative patients with early syphilis. Based on RPR testing, serological cure was reported in 77.6% of subjects given 2 g azithromycin (n = 232; 95% CI: 71.8–82.5%) and 78.5% (n = 237; 95% CI: 72.8–83.3%) in the BPG group. Nonserious adverse events were reported by 61.5% (n = 174; 95% CI: 55.7–67.0%) of individuals treated with 2 g azithromycin, most of whom had self-limiting gastrointestinal discomfort, whereas 46.1% (95% CI: 40.6–52.1%) of BPG recipients reported nonserious adverse events [42].

In vitro evidence

Fourteen *in vitro* studies met our inclusion criteria, seven with isolates from low-risk populations (Table 3) and seven from high-risk or mixed-risk groups (Table 4). A report from San Francisco in 2001 was the first to associate azithromycin treatment failure with A→G mutations at the 2,058 position of the 23S rRNA gene of *T. pallidum* [43]. Retrospective analysis of samples revealed that 4.0% (n = 25; 95% CI: 0.9–19.6%) of isolates had A→G mutations between 1999 and 2002. In 2003, the proportion of isolates with A→G mutations increased to 36.7% (n = 30; 95% CI: 21.9–54.6%) [44]; by 2004, 56.1% (n = 66; 95% CI: 44.0–67.3%) had selected for resistance [43]. However, in Dublin, 88.2% (n = 17; 95% CI: 65.3–96.4%) of isolates already had A→G mutations by 2002 [44].

Macrolide resistance is strongly associated with use by an individual in the previous year. Isolates from Seattle (2001–2005) were two-times more likely to be resistant if patients had been treated with macrolides in the past 12 months (RR: 2.2; 95% CI: 1.1–4.4; p = 0.02) [45]. This relationship persisted over the decade. A2058G and A2059G mutations, which are associated with clinical failures of azithromycin, were found in 88.9% (n = 36; 95% CI: 74.6–95.5%) of isolates from 2001 to 2010 among patients exposed to macrolides in the preceding

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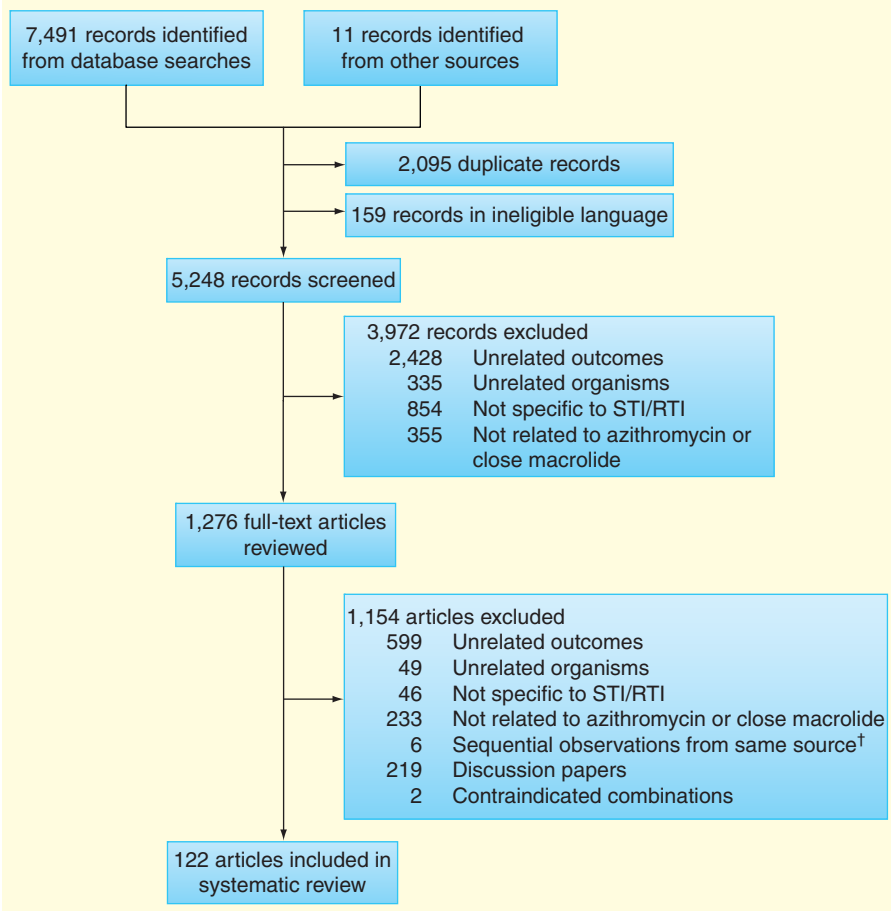

Figure 1. Identification, screening and eligibility of studies included in systematic review.
†Surveillance reports from which the most recent data set was used.
STI/RTI: Sexually transmitted infection and reproductive tract infection.

12 months, whereas 61.2% (n = 98; 95% CI: 51.3–70.4%) of isolates from patients who had not received prior macrolide treatment contained the same mutations [46]. Similar mutations were found among strains of *T. pallidum* in eight cities across China (2008–2011). A2058G was present in 97.0% individuals who had taken macrolides in the previous 12 months versus 62.5% of patients who had not (n = 211; OR: 19.65; 95% CI: 5.8–66.9) [47]. The opposite was found in Taiwan (2009–2011) where no single A2058G or A2059G mutation was seen among 211 isolates tested from a population where only one person had been given macrolide therapy in the previous year [48]. Similarly, there was no evidence of resistance among 141 amplified samples from HIV-negative heterosexual patients in Madagascar [49]. Although use of macrolides in the previous year was not reported, the Essential Drugs List of the Malagasy Ministry of Health does not include macrolides [301].

Neisseria gonorrhoeae

In vivo evidence

The WHO recommends treating pregnant women with *Neisseria gonorrhoeae* infection using 400 mg cefixime as a single dose or 125 mg ceftriaxone by intramuscular injection [50]. However, azithromycin has been used for the treatment of gonorrhea among nonpregnant adults during the past two decades. Eleven trials were identified through our review (Table 5). Nine trials conducted between the late 1980s and 1999 investigated the use of 1 g azithromycin among individuals attending sexually transmitted infection (STI) clinics. Of these, three were open label without comparators [51–53] and six were two-arm trials that compared azithromycin to ciprofloxacin and/or doxycycline [54–59]. The pooled efficacy of azithromycin against *N. gonorrhoea*, estimated using random effects models [60], was 97.0% (n = 539; 95% CI: 95.5–98.5%). This is slightly higher than 96.5% (n = 539; 95% CI: 94.3%–97.6%) reported in a 2010 review [61] that added numerators and divided the sum of denominators among the same nine trials. Such an approach does not account for heterogeneity across study populations and gives equal weight to all trials regardless of their precision. Regardless of pooling methods, it is unlikely that the same efficacy would be observed today using 1 g azithromycin in high-income countries following 25 years of cumulative drug pressure. However, the epidemiological context in sub-Saharan Africa is likely different where azithromycin use has been almost exclusively limited to trachoma eradication campaigns [62].

We identified two RCTs that investigated the use of 2 g azithromycin among patients at STI clinics. The first was a multicenter trial in the USA (1991–1992) in which 98.9% (n = 374; 95% CI: 97.3–99.6%) of patients were cured [63]. A similar RCT in New Delhi (2005–2006) involved 42 participants; loss to follow-up was high, 52.4%, but all 22 subjects who returned for a test of cure had their *N. gonorrhoeae* infections cured [64].

In vitro evidence

Over the past decade, *in vitro* studies have documented the loss of *N. gonorrhoeae* sensitivity to azithromycin. There are no standard breakpoints of minimum inhibitory concentrations (MICs) used to categorize *N. gonorrhoeae* resistance to azithromycin, but >1 µg/ml [65] and >2 µg/ml [66] have both been used. In this section, we summarize the key regional observations from 36 *in vitro* studies (Tables 6 & 7).

The Public Health Agency of Canada reported that 0.17% (n = 40,875; 95% CI: 0.001–0.002%) of *N. gonorrhoeae*

Table 2. Randomized clinical trials of azithromycin versus benzathine penicillin G for the treatment of *Treponema pallidum*

Study (year)	Country	Year(s)	Regimen	Number cured of treated	Percent cured	95% CI	Diagnostic methods used	Follow up	Stage of infection	Ref.
Specified low-risk populations										
Hook *et al.* (2010)	Madagascar, USA	2000–2007	2 gazithromycin 2.4 mu BPG	180/232 186/237	77.6% 78.5%	71.8–82.5% 72.8–83.2%	RPR and FTA-ABS	6 months	Primary, secondary, early latent syphilis	[42]
Kiddugavu *et al.* (2005)	Uganda	1994–1998	1 g azithromycin 2.4 mu BPG 1 g azithromycin plus 2.4 mu BPG	55/94 66/93 221/313	58.5% 71.0% 70.6%	48.4–68.0% 61.0–79.2% 65.3–75.4%	TRUST and TPHA (initial TRUST titers ≤ 1:2)	10 months	Serologic syphilis	[130]
			1 g azithromycin 2.4 mu BPG 1 g azithromycin plus 2.4 mu BPG	38/71 31/75 169/309	53.3% 41.3% 54.7%	42.0–64.7% 30.9–52.7% 49.1–60.2%	TRUST and TPHA (initial TRUST titers ≥ 1:4)	10 months	Serologic syphilis	
Unspecified low-risk populations										
Klausner *et al.*(2006)	USA	2004	1 g azithromycin 2.4 mu BPG	10/12 13/13	83.3% 100%	54.6–95.0% NA	NR	NR	Exposed to infectious syphilis	[38]
Hook *et al.* (2002)	USA	1995–1997	2 g azithromycin 2 g azithromycin (two-times) week apart 2.4 mu BPG	14/14 19/22	100% 86.4%	NA 66.4–95.0%	RPR and MHA-TP or FTA-ABS	12 months	Primary, secondary, early latent syphilis	[39]
Hook *et al.* (1999)	USA	1995–1997	1 g azithromycin 2.4 mu BPG	40/40 23/23	100% 100%	NA NA	RPR and FTA-ABS	3 months	Exposed to infectious syphilis	[131]
High-risk population										
Riedner *et al.* (2005)	Tanzania	2000–2003	2 g azithromycin 2.4 mu BPG	159/163 157/165	97.5% 95.2%	93.9–99.0% 90.7–97.5%	RPR and PCR	9 months	Primary, secondary, higher titer latent syphilis	[132]

2.4 mu BPG: 2.4 million units benzathine penicillin G; FTA-ABS: Fluorescent treponemal antibody absorption; MHA-TP: Microhemagglutination assay-*Treponema pallidum*; NA: Not applicable; NR: Not reported; RPR: Rapid plasma regain; TPHA: *Treponema pallidum* hemagglutination; TRUST: Toluidine red unheated serum test.

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Table 3. Sensitivity testing of *T. pallidum* isolates to azithromycin and other macrolides.

Study (year)	Country	Year(s)	Specimen source	Sample size	Resistant mutation	Number resistant	Percent resistant	95% CI	Additional details	Ref.
Low-risk populations										
Chen *et al.* (2013)	USA	2007-2009	Surveillance	129	2058A 2058G 2059G	83 67 17	64.3% 51.9% 13.2%	55.8–72.1% 43.4–60.4% 8.4–20.1%	From patients with primary of secondary syphilis attending STI clinics	[133]
Van Damme *et al.* (2009)	Madagascar	NR	Randomized clinical trial	186	23S rRNA	0	0.0%	NA	DNA of *T. pallidum* was detected in 141 samples; 61% of patients were male; 98% were heterosexual	[49]
Unspecified low-risk populations										
Mller *et al.* (2012)	South Africa Lesotho	2005–2010	Surveillance	100	A2058G A2059G	1 0	1.0% 0.0%	0.0–5.4%	117 ulcer specimens collected of which 100 were positive for *T. pallidum*	[134]
A2058G Prevalence Workgroup (2012)	USA	2007–2009	Surveillance	141	A2058G	75	53.1%	45.0–61.2%	From patients with primary of secondary syphilis attending STI clinics; MSM were nearly 6 times more likely to have resistant syphilis compared with heterosexual women and men	[135]
Matejková *et al.* (2009)	Czech Republic	2005–2008	Passive case detection	22	23S rRNA A2058G A2059G	8 4 4	36.4% 18.2% 18.2%	19.7–57.3% 7.5–38.8% 7.5–38.8%		[136]
Martin *et al.* (2009)	China	2007–2008	Passive case detection	38	A2058G	38	100%	NA	Patients presenting to STI clinic with symptoms compatible with primary syphilis	[137]
Lukehart *et al.* (2004)	USA								PCR to detect 23S rRNA gene mutations; confirmation of azithromycin resistance was conducted through intradermal rabbit inoculation	[44]
	San Francisco	1999–2002	Surveillance	25	23S rRNA	1	4.0%	1.0–19.6%		
	San Francisco	2003		30		11	36.7%	21.9–54.6%		
	Seattle	2001–2003		23		3	13.0%	4.7–32.3%		
	Baltimore	1998–2000		19		2	10.5%	3.2–31.7%		
	Ireland									
	Dublin	2002	Surveillance	17	23S rRNA	15	88.2%	65.3–96.4%		
	Multiple locations	1912–1987	Historical	18	23S rRNA	1	5.6%	1.3–2.6%		

DNA: Deoxyribonucleic acid; MSM: Men who has sex with men; NA: Not applicable; NR: Not reported; STI: Sexually transmitted infection.

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Table 4. Sensitivity testing of *T. pallidum* isolates to azithromycin and other macrolides.

Study (year)	Country	Year(s)	Specimen source	Sample size	Resistant mutation	Number resistant	Percent resistant	95% CI	Additional details	Ref.
High-risk populations										
Tipple *et al.* (2011)	UK	2006–2008	Cross-sectional survey	18	23S rRNA A2058G	12 11	66.6% 61.1%	43.4–83.7% 38.4–79.7%	Specimens from men, 94.1% were MSM	[138]
Rekart *et al.* (2003)	Canada	2000	Mass drug administration	25	23S rRNA	0	0.0%	NA	1.8 g azithromycin given to sex workers and clients (n = 4,384)	[139]
Mixed-risk populations										
Chen *et al.* (2012)	China	2008–2011	Cross-sectional survey	211	A2058G	194	91.9%	87.2–95.1%	391 samples collected; 6.1% from FSW, 71.8% reported sex with FSW and 1.4% were MSM	[47]
Muldoon *et al.* (2012)	Ireland	2009–2010	Cross-sectional survey	29	A2058G	27	93.1%	77.9–97.9%	34.6% (36/104) of samples were positive for *T. pallidum* by PCR; 29 sequenced	[140]
Martin *et al.* (2010)	Canada	2007–2009	Cross-sectional survey	43	A2058G	7	16.3%	8.2–30.1%	449 samples collected from 374 patients; 43 were positive for *T. pallidum* and sequenced	[141]
Mitchell *et al.* (2006)	USA	2000–2002	Retrospective study	25	23S rRNA	1	4.0%	1.0–19.6%	Patients (n = 1,308) diagnosed primary or secondary syphilis; all treatment failure and resistance in MSM/ bisexual patients	[43]
		2003		32		13	40.6%	25.5–57.9%		
		2004		66		37	56.1%	44.0–67.4%		
Morshed *et al.* (2006)	Canada	2000–2003	Retrospective study	47	23S rRNA	1	2.1%	0.5–11.1%	MSM patients presenting to STI clinic with primary or secondary syphilis	[142]
		2004		9		4	44.4%	18.7–73.8%		

FSW: Female sex worker; MSM: Men who have sex with men; NA: Not applicable; STI: sexually transmitted infection.

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Table 5. Randomized clinical trials of azithromycin for the treatment of *Neisseria gonorrhoeae*

Study (year)	Country	Year(s)	Azithromycin dose	Number cured of evaluated	Percent cured	95% CI	Diagnostic methods	Additional details	Ref.
Dose of 2 g azithromycin									
Khaki *et al.* (2007)	India	2005–2006	2 g	22/22	100%	NA	>Gram stain TOC days 5–7		[143]
Handsfield *et al.* (1994)	USA	1991–1992	2 g	370/374	98.9%	97.3–99.6%			[63]
Dose of 1 g azithromycin									
Rustomjee *et al.* (2002)	South Africa	1999	1 g	30/31	96.8%	83.8–99.2%	LCR for NG/CT TOC day 14	100% (n = 21) NG infections cured 100% (n = 14) CT infections cured 90.0% (n = 10; 95% CI: 58.7–97.8%) co-infections cured	[60]
Swanston *et al.* (2001)	Trinidad and Tobago	1996	1 gram	125/127	98.4%	94.5–99.5%	ELISA for NG culture for CT; TOC days 7–10	100% (n = 115) NG infections cured 95.7% (n = 23; 95% CI: 78.9–99.0%) CT infections cured 88.3% (n = 12; 95% CI: 54.6–95.0%) co-infections cured	[53]
Gruber *et al.* (1997)	Croatia	1994–1995	1 g	48/50	96.0%	86.5–98.8%	Culture and gram stain for NG; TOC day 14		[58]
Gruber *et al.* (1995)	Croatia	1991–1993	1 g	24/24	96.0%	80.4–99.1%	Culture and gram stain for NG; TOC day 14		[57]
Steingrimsson *et al.* (1994)	Iceland	NR	1 g	27/28	96.4%	82.4–99.2%	Culture for NG w/ DFA; Culture for CT; TOC day 28	92.4% (n = 79; 84.4–96.4%) CT infections cured	[56]

CT: *Chlamydia trachomatis*; DFA: Direct fluorescent antibody; ELISA: Enzyme-linked immunosorbent assay; LCR: Ligase chain reaction; mg: milligrams; NA: Not applicable NG: *Neisseria gonorrhoeae*; NR: Not reported; TOC: Test of cure.

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Table 5. Randomized clinical trials of azithromycin for the treatment of *Neisseria gonorrhoeae*

Study (year)	Country	Year(s)	Azithromycin dose	Number cured of evaluated	Percent cured	95% CI	Diagnostic methods	Additional details	Ref.
Dose of 1 g azithromycin (cont.)									
Waugh *et al.* (1993)	UK	1990–1991	1 g	85/89	95.5%	89.0–98.2%	Culture and gram stain for NG; culture for CT; TOC day 10	100% (n = 22) NG/CT co-infections cured	[52]
Odugbemi *et al.* (1993)	Nigeria	1989–1990	1 g	114/120	95.0%	89.5–97.6%	Culture for NG; TOC day 14		[51]
Steingrimsson *et al.* (1990)	Iceland	NR	1 g (day 0)	11/12	91.7%	64.0–98.1%	Culture for NG/CT; TOC day 28	97.7% (n = 44; 88.2–99.5%) CT infections cured	[55]
			500 mg (day 0 x 2)	7/8	87.5%	51.8–97.2%		96.3% (n = 27; 81.7–99.1%) CT infections cured	
			500 mg (day 0) 250 mg (days 1 and 2)	7/7	100%	NA		88.0% (n = 25; 69.8–95.6%) CT infections cured	
Lassus *et al.* (1990)	Finland	NR	1 g (day 0)	15/15	100%	NA	Culture and gram stain for NG/CT w/ DFA; TOC day 14	100% (n = 12) CT infections cured 100% (n = 5) co-infections cured	[54]
			500 mg (day 0) 250 mg (days 1 and 2)	14/14	100%	NA		100% (n = 9) CT infections cured 83.3% (n = 6; 95% CI: 42.1–96.3%) co-infections cured	

CT: *Chlamydia trachomatis*; DFA: Direct fluorescent antibody; ELISA: Enzyme-linked immunosorbent assay; LCR: Ligase chain reaction; mg: milligrams; NA: Not applicable NG: *Neisseria gonorrhoeae*; NR: Not reported; TOC: Test of cure.

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Table 6. Sensitivity testing of *Neisseria gonorrhoeae* isolates to azithromycin.

Study (year)	Country	Year(s)	Sample size	MIC range (μg/ml)	Percent strains susceptible	Additional details	Ref.
Olsen *et al.* (2013)	Vietnam	2011	108	NR	62%	11% isolates fully resistant, 29% intermediate susceptibility	[144]
Lahra *et al.* (2012)	Australia	2011	3,293	≤4	98.1%	Isolates from all states in Australia	[145]
Sethi *et al.* (2013)	India/Pakistan/ Bhutan	2007–2011	65	0.016–4.0	76.9%	7.7% isolates fully resistant, 15.4% intermediate susceptibility	[72]
Lo *et al.* (2012)	Hong Kong	2010	485	<0.25 to >256	69.7%		[146]
Lefebvre *et al.* (2011)	Canada	2010	831	≤16	98.7%		[147]
Hottes *et al.* (2013)	Canada	2006–2011	1,837	0.064–16	99%	Elevated MIC showed increasing trend over time	[148]
CDC (2011)	USA	2002–2009	87,566		99.9%	39 (0.04%) had MICs ≥8 μg/ml (25 with 8 μg/mL; 14 with 16 μg/mL)	[69]
Yuan *et al.* (2011)	China	2008–2009	318	NR	94.7%		[149]
Takahashi *et al.* (2013)	Japan	2007–2009	52	0.016–1	100%	100% of isolates from men[†]	[150]
Herchline *et al.* (2010)	USA	2006–2008	286	0.032–1.0	99.0%	Median MIC 0.125 μg/ml	[151]
Cole *et al.* (2010)	Europe (17 countries)	2006–2008	3,528	≤256	2.0–7.0%	High resistance (>256 μg/ml) in 4 isolates from Scotland and 1 in Ireland	[68]
Olsen *et al.* (2012)	Guinea-Bissau	2006–2008	31	NR	100%	Of resistant strains, two had MIC >64 μg/ mL	[152]
Tanaka *et al.* (2011)	Japan	2001–2009	242	0.004–1.0	99.9%	Modal shift of MIC was 0.25–0.5 μg/mL	[153]
Martin *et al.* (2011)	Canada	2000–2009	40,875	≤64	99.8%	100% isolates susceptible also to sefixime, ceftriaxone and spectinomycin.	[66]
Bala *et al.* (2011)	India	2000–2009	274	NR	99.7%	One isolate was resistant to azithromycin, quinolones and penicillin	[154]
Chisholm *et al.* (2008)	UK	2001–2007	108	<0.03 to >256	94.0%	6/108 isolates had MIC >256 μg/mL; shift to high level resistance	[155]
Khaki *et al.* (2007)	India	2004–2005	60	0.016–0.25	100%		[156]
Enders *et al.* (2006)	Southern Germany	2004–2005	65	0.016–5.0	100%	100% of isolates susceptible to azithromycin	[157]

Unspecified low-risk populations.
[†]Sexual practices were not reported; isolates are assumed not to be from men who have sex with men;
[‡]Dislocated males workers are among high-risk populations.
NR: Not reported.

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Table 6. Sensitivity testing of *Neisseria gonorrhoeae* isolates to azithromycin (cont.).

Study (year)	Country	Year(s)	Sample size	MIC range (μg/ml)	Percent strains susceptible	Additional details	Ref.
Vorobieva *et al.* (2007)	Russia	2004	76	NR	100%	Although all susceptible, reduced susceptibility seen in 14%	[158]
Sutrisna *et al.* (2006)	Indonesia	2004	163	NR	100%	53% resistant to ciprofloxacin	[159]
Martin *et al.* (2004)	Western Europe	2004	965	NR	91.8%	Variation from 31.2% (Austria 30/96) to 0% (France 0/101, Greece 0/79, Portugal 0/17)	[160]
Chaudhary *et al.* (2005)	Nepal	2003	16	0.008–0.5	100%	No isolates resistant, but 3/16 (19%) had reduced susceptibility	[161]
Chen *et al.* (2009)	Taiwan	1999–2004	65	NR	100%		[162]
Hsueh *et al.* (2005)	Taiwan	1999–2003	55	0.03–9.0	72.7%		[163]
Aydin *et al.* (2005)	Turkey	1998–2002	78	0.004–0.25	100%	100% of isolates from men†	[164]
Moodley *et al.* (2001)	South Africa	1995–2000	58	0.015–1.0	100%	37% (37/100) strains resistant to penicillin; tetracyclines had reduced susceptibility.	[165]
Kobayashi *et al.* (2003)	Japan	1995–1999	699	0.015–1	100%	100% of isolates from men†	[166]
Llanes *et al.* (2003)	Cuba	1995–1999	52	0.064–0.5	76.9%	23.1% intermediate susceptibility: MIC= 0.125 (10 isolates) MIC= 0.5 (2 isolates)	[167]
Sosa *et al.* (2003)	Cuba	1995–1999	91	0.063–4.0	90.1%	Isolates with reduced susceptibility also resistant to penicillin and tetracycline	[168]
Dillon *et al.* (2001)	Brazil	1998	81	0.032–0.5	100%	28% reduced susceptibility	[169]
Zarantonelli *et al.* (1999)	Uruguay	1996–1997	51	0.032–0.5	100%	Decreased susceptibility (MIC 0.025 to 0.5) in 72%; isolates from men†	[170]
Young *et al.* (1997)	Scotland	1996	67	0.023–0.75	100%	Isolates randomly selected from with penicillin MIC≥1	[171]
Mehaffey *et al.* (1996)	USA	NR	105	0.06–2.0	100%	Two tests compared. Data from agar dilution method not Etest.	[172]
Dillon *et al.* (2001)	Guyana & St Vincent	1992–1996	136	0.032–8.0	85.5 and 97.0%	Two isolates had MIC = 8 μg/l. 49% (67/137) reduced susceptibility (combined)	[173]
Van Rijsoort-Vos *et al.* (1995)	Netherlands	1991–1993	114	0.03–1.0	100%	One isolate reduced susceptibility	[174]
Ison *et al.* (1993)	South Africa	1989–1990	192	0.03–1.0	100%	Study in migrant mine workers (men only)‡	[175]

Unspecified low-risk populations.
†Sexual practices were not reported; isolates are assumed not to be from men who have sex with men;
‡Dislocated males workers are among high-risk populations.
NR: Not reported.

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Table 7. Sensitivity testing of *N. gonorrhoeae* isolates to azithromycin.

Study (year)	Country	Year(s)	Sample size	MIC range (μg/ml)	Percent of strains susceptible	Additional details	Ref.
High-risk populations							
CDC (2011)	USA	2009	55	NR	90.9%	9.1% resistant (95% CI: 4.0 to 19.6%); of 5 resistant (all from MSM), 3 had MIC = 8 μg/ml and two had MIC = 16ug/ml	[69]
Starnino *et al.* (2009)	Italy	2007–2008	219	1.0–256.0	90.0%	72.7% (95% CI: 51.6–86.8%) of resistant isolates from MSM	[176]
Donegan *et al.* (2004)	Bali	2004	147	0.013–0.512	100%	Study in FSWs; prevalence of NG estimated to be 35-60%	[177]
Morris *et al.* (2009)	USA	2000–2002	79	0.03–0.5	100%	Increased MIC values seen in MSM subject isolates	[178]
Leven *et al.* (2003)	Indonesia	1996	267	0.032–0.5	100%	Study in FSWs; prevalence of NG estimated to be 18–44%	[179]
CDC (2000)	USA	1999	12	1.0–4.0	NR	Median MIC was 2.0 μg/ml. 6 of 12 samples were from men who had sex with a CSW; 2 of 12 were from HIV positive men	[180]
Mixed-risk populations							
Bruck *et al.* (2012)	UK	2005–2006	147	NR	99.3%	Mixed male heterosexual, MSM and female heterosexual isolates	[181]
Dan *et al.* (2010)	Israel	2002–2007	406	0.023–8.0	91.8%	Mixed male heterosexual, MSM and female heterosexual; resistance to azithromycin did not appear to rise over 5 year period	[182]
McLean *et al.* (2004)	USA	1999–2001	1,248	≤4	97.4%	Mixed high- and low-risk population. Median MIC was 2.0ug.mL	[183]
Arreaza *et al.* (2003)	Spain	1992–2001	63	0.03–4.0	96.8%	58.7% of strains had reduced susceptibility (0.25–1.0 μg/ml). 50% of resistant isolates were from FSW	[184]

BV: Bacterial vaginosis; CSW: Commercial sex worker (gender not specified); FSWs: Female sex workers; GI: Gastrointestinal; MIC: Minimum inhibitory concentration; MSM: Men who have sex with men; NG: *Neisseria gonorrhoeae*; NR: Not reported; PROM: Preterm premature rupture of the membranes; SD: Standard deviation; TOC: Test of cure.

samples were resistant to azithromycin between 2000 and 2009, although the modal value of the MIC shifted from 0.25 μg/ml in 2001 to 0.5 μg/ml between 2007 and 2009 [67]. During the same 10-year period, the Centers for Disease Control and Prevention in the USA reported that 0.04% (n = 87.566; 95% CI: 0.03–0.06%) of *N. gonorrhoeae* isolates tested had MICs ≥8 μg/ml (including 25 with 8 μg/ml and 14 with 16 μg/ml) [68]. This did not include five cases of azithromycin-resistant *N. gonorrhoeae* found between August and October 2009 among men who have sex with men; three had MICs of 8 μg/ml and two had 16 μg/ml [69]. Resistance may have appeared in Europe slightly before North America. Analysis of isolates from 17 European countries found that 3.2% (n = 836; 95% CI: 0.02–0.05%) of gonococcal isolates were resistant to azithromycin in 2006. By 2007, 6.8% (n = 973; 95% CI: 0.05–0.09) of samples were resistant. The overall proportion of resistant isolates declined in 2008 to 1.8% (n = 940; 95% CI: 0.01–0.03%), although only 5.2% (95% CI: 4.1–6.8%) of strains tested in the same year were fully susceptible to azithromycin and ciprofloxacin. Four isolates from Scotland and one from Ireland exhibited MICs >256 mg/l [68].

Gonococcal isolates examined from South America and Cuba exhibited high but stable levels of resistance between 2000 and 2009 in most settings [70]. Collectively, azithromycin resistance was 13.0% (n = 8,373; 95% CI: 12.3–13.7%) based on data from six countries including Chile, an outlier.

Averaged over the decade, 26.7% (n = 3,116; 95% CI 25.2–28.3%) of samples from Chile were resistant, rising to 45.6% (n = 463; 95% CI: 41.1–50.1%) according to the most recent data from 2009. Removing Chile from the regional summary, 4.4% (n = 5,257; 95% CI: 3.9–5.1%) of isolates were resistant over the decade.

All 60 gonococcal isolates from India between 2004 and 2005 were susceptible to azithromycin [71]. Pooled analysis of samples collected from India, Pakistan and Bhutan between 2007 and 2011 found that 76.9% (n = 65; 95% CI: 65.3–85.5%) were susceptible. Results were not stratified by country and, therefore, it is not known whether the sensitivity of isolates from India had changed [72]. Applying the more conservative breakpoint of >1 μg/ml to the *in vitro* studies identified in this review, 35% (7 of 20) of the *in vitro* studies reported upper range MICs that included gonococcal isolates resistant to azithromycin. This percentage does not include 16 studies we identified and included in Tables 6 & 7 that did not report MICs.

Chlamydia trachomatis

In vivo evidence

The WHO recommends treating pregnant women with *Chlamydia trachomatis* infection using 1 g azithromycin as a single oral dose [50]. We found eight RCTs in the literature that reported the treatment efficacy of 1 g azithromycin among pregnant women (Table 8) [73–80]. Using random effect models, we estimate the pooled treatment efficacy to be 92.1% (n = 268; 95% CI: 88.4–95.7%). The estimated efficacy would be higher if we excluded two trials that were conducted in the USA. The first trial (1995–1997) reported a 3-week test of cure rate to be 88.1% (n = 42; 95% CI: 74.9–94.7%) [76], whereas the second trial (1998–2000) was terminated early due to poor efficacy, 63.3% (n = 55; 95% CI: 50.4–75.1%), based on test of cure ≥4 weeks post-treatment [74]. These results need to be interpreted with caution because no distinction was made between treatment failures and new infections, sex partners were not treated by trial staff, but were referred to a treatment center, and only 35% of women were seen within 7 days of the scheduled test of cure.

Studies investigating sexual activity following treatment offer some perspectives on post-treatment infections and the extent to which they may be failures or *de novo* infections. A trial in Seattle (1998–2003) found that persistent or recurrent chlamydial or gonorrheal infection occurred in 7.6% (n = 289; 95% CI: 5.1–4.9%) of female patients who reported no sexual intercourse after treatment [81]. Another study reported that 19.0% (n = 79; 95% CI 11.9–29.0%) of women were positive for *C. trachomatis* 3 months after treatment using 1 g azithromycin. Of these women, 13.3% (n = 15; 95% CI: 4.0–38.3%) reported being sexually inactive during the post-treatment period [82]. These findings may be attributable to false reporting of sexual contact, or treatment failure or may lend credence to the hypothesis that *C. trachomatis* enters a latent asymptomatic state that is undetectable by culture or, possibly, Nucleic Acid Amplification Tests, but can later reactivate [83].

In vitro evidence

Thresholds for antimicrobial susceptibility and resistance of *C. trachomatis* are not universally standardized, although MICs >4 μg/ml are often used to characterize therapeutic failure [84–87]. The lowest concentration of antimicrobial compound needed to inhibit chlamydial formation is between 0.03 and 0.125 μg/ml, whereas the minimum bactericidal concentration (MBC; also referred to as the minimum chlamydicidal concentration, or MCC) is between 0.06 and 0.5 μg/ml [88,89]. The published *in vitro* studies of azithromycin collectively suggest the persistence of high and widespread treatment efficacy (Table 9). One noted exception is the study of six isolates from three patients who experienced treatment failure in Russia (2000–2002); four isolates were resistant to azithromycin, doxycycline and ofloxacin at MICs and MBCs >5.12 μg/ml [90]. Not surprisingly, *in vitro* resistance appears to be more common in individuals with greater severity of disease or recurrent disease. A study in the USA during the early 1990s described decreased susceptibility and emerging resistance to azithromycin and doxycycline in isolates from women with mucopurulent cervicitis but not in isolates from women with asymptomatic infections [91]. Similar observations were reported in 2010 from India; six of eight isolates with modified susceptibility had been obtained from recurrently infected individuals, whereas the remaining two were from nonrecurrently infected patients. MICs and MBCs for azithromycin were 8 μg/ml for two of the patients from which the modified susceptibility isolates were taken. One individual had chronic cervicitis and the other had pelvic inflammatory disease [92].

Trichomonas vaginalis

In vivo evidence

Trichomonas vaginalis is a protozoal infection which causes cervicitis and nongonococcal urethritis. The WHO recommends treating pregnant women with *T. vaginalis* infection after the first trimester using 2 g metronidazole orally as a single dose, or 400–500 mg twice daily for 7 days or 300 mg clindamycin orally twice a day for 7 days [36]. If treatment is imperative during the first trimester of pregnancy, the single-dose regimen of 2 g metronidazole orally is recommended [36]. Azithromycin has not been used directly for prevention or treatment purposes because *T. vaginalis* is anaerobic. Nevertheless, azithromycin has demonstrated protection against *T. vaginalis* in studies of mass STI/RTI treatment (Tables 10 & 11).

In Kenya (1998–2002), 1 g azithromycin or placebo was given once per month to 466 HIV-negative female sex workers [93]. At the end of the trial, HIV incidence was the same across treatment groups, the primary endpoint, but the incidence of *T. vaginalis* was reduced significantly among those given azithromycin versus placebo (RR: 0.56; 96% CI: 0.40–0.78; $p < 0.001$). A similar observation was made in a three-arm IPTp trial in Malawi (2003–2006) [94]. Pregnant women received standard IPTp-SP, or monthly IPTp-SP or monthly IPTp-SP plus 1 g azithromycin during two antenatal visits; the prevalence of *T. vaginalis* at delivery was 16.7% (n = 411;

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Table 8. Treatment efficacy studies of 1 g azithromycin for the treatment of *Chlamydia trachomatis* in pregnant women.

Study (year)	Country	Year(s)	Number cured of evaluated	Percent cured	95% CI	Diagnostic method	Birth outcomes	Additional details	Ref.
Kacmar *et al.* (2001)	USA	1998–2000	18/19	94.7%	84.4–105.1%	Ligase chain reaction; TOC 28–42 days	NR	52.6% (n = 19; 95% CI: 31.5–72.8%) had side effects; passive or active solicitation not reported; 13.6 weeks (±8.0 SD) mean gestational age at enrolment	[73]
Jacobson *et al.* (2001)	USA	1998–2000	35/55	63.6%	47.7–79.6%	DNA LCx STD assay; TOC 28 days	13.3% (6/45) preterm	10.1% (n = 55; 95% CI: 5.2–21.9%) had side effects; passive or active solicitation not reported; 20.6 weeks (±8.8 SD) mean gestational age at enrolment	[74]
Wehbeh *et al.* (1998)	USA	NR	26/27	96.3%	89.0–103.6%	Culture	NR	100% (n = 27) of partners treated	[75]
Adair *et al.* (1998)	USA	1995–1997	37/42	88.1%	77.7–98.5%	DNA assay; TOC 28 days	NR	11.9% (n = 5; 95% CI: 5.3–25.1%) had side effects; passive or active solicitation not reported; 21.6 weeks (±9.5 SD) mean gestational age at enrolment; 54.8% (n = 23) of partners treated	[76]
Edwards *et al.* (1996)	USA	1993–1994	61/65	93.8%	87.8–99.9%	DNA assay; TOC 14 days	9.2% (6/65) preterm, 3 due to PROM; mean birth age 38.8 weeks ±1.6	20.4 weeks mean gestational age at enrolment	[78]
Rosenn *et al.* (1995)	USA	1994–1995	21/23	91.3%	79.3–103.4%	PCR (Amplicor); TOC 21 days	NR	19.3 weeks (±3.5 SD) mean gestational age at enrolment	[79]
Gunter *et al.* (1996)	USA	NR	22/22	100%	NA	DNA assay; TOC 14 days	NR	13.6% (n = 3; 95% CI: 5.0–33.6%) had gastrointestinal side effects; passive or active solicitation not reported	[77]
	USA	NR	15/15	100%	NA		NR		[80]

NR: Not reported; TOC: Test of cure.

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Table 8. Treatment efficacy studies of 1 g azithromycin for the treatment of *Chlamydia trachomatis* in pregnant women (cont.).

Study (year)	Country	Year(s)	Number cured of evaluated	Percent cured	95% CI	Diagnostic method	Birth outcomes	Additional details	Ref.
Bush & Rosa (1994)						DNA assay; TOC 14 days		0% of women experienced side effects; 100% (n = 15) of partners treated	
Rahangdale *et al.* (2006)	USA	1999–2000	137/141	97.2%	94.4–99.9%	DNA assay; TOC days 7–20; 21–34; 35–55; >56	7.5% (16/221 'any' preterm azithromycin)	13.1% (n = 191; 95% CI: 9.0–18.6%) also had BV 14.1 weeks (±6.3 SD) mean gestational age at enrolment	[185]
Miller *et al.* (1995)	USA	1993–1994	132/138	95.6%	92.2– 99.1%	DNA assay; TOC 10–14 days	15.2% (19/125) preterm	5.5% (n = 146; 95% CI: 2.8–10.4%) had side effects; 23.9% (n = 138; 17.6–31.7%) women also had NG; 17.4% (4/17) reported side effects (all GI); mean gestational age at enrolment not reported	[186]

NR: Not reported; TOC: Test of cure.

95% CI: 13.5–20.7%), 15.1% (n = 411; 95% CI: 12.0–18.9%) and 11.0% (n = 419; 95% CI: 8.3–14.3%), respectively. Thus, women who received azithromycin had 35% (RR: 0.65; 95% CI: 0.46–0.93; p = 0.02) fewer *T. vaginalis* infections at delivery compared with monthly recipients of IPTp-SP.

A cluster randomized trial in Uganda (1994–1998) compared the incidence of HIV infections among nonpregnant adults who received 1 g azithromycin, 250 mg ciprofloxacin and 2 g metronidazole versus multivitamins plus antihelminthics [95]. Although the trial was terminated early for lack of protection against the primary endpoint, the incidence of several curable STIs/RTIs was lower in the control group, most notably *T. vaginalis*. The cumulative incidence of newly diagnosed *T. vaginalis* infection was 4.8/100 person-years (116/2,397 person-years) in the intervention group compared with 9.1/100 person-years (182/1,993 person-years) in the control group (RR: 0.52; 95% CI: 0.35–0.79).

The same combination of antimicrobials was provided to female sex workers in rural Zimbabwe as a one-time treatment followed by 3 monthly check-ups [96]. The prevalence of *T. vaginalis* was just under 20% at baseline, decreased to approximately 5% at visit 2, rose to nearly 13% at visit 3 and lowered again to just over 10%, that is, one-half of the pretreatment levels.

Bacterial vaginosis

The WHO recommends treating bacterial vaginosis in pregnant women, preferably after the first trimester, with 200 or 250 mg metronidazole three-times per day for 7 days, or 5 g metronidazole gel (0.75%) applied intravaginally twice a day for 5 days or 300 mg clindamycin 300 mg orally twice a day for 7 days [36]. As with *T. vaginalis*, if treatment is imperative during the first trimester of pregnancy, 2 g metronidazole orally is recommended [36]. Bacterial vaginosis has no single causative agent, but is thought to result from destabilization of *Lactobacillus* species (spp.) with secondary colonization of anaerobic organisms that include *Gardnerella vaginalis, Bacteroides* spp, *Mobiluncus* spp. and *Mycoplasma hominis* alongside an increase in vaginal pH [97,98].

In vivo evidence

Our review identified no trials that have attempted to measure the treatment efficacy of azithromycin alone against bacterial vaginosis. Only one study in the USA (2002–2005) investigated the use of azithromycin as a partner drug with metronidazole for the treatment of symptomatic bacterial vaginosis. Nonpregnant women received one of four treatments: 750 mg metronidazole once per day for 7 days, or metronidazole once per day for 7 days plus 1 g azithromycin on days 1 and 3, or metronidazole for 14 days or metronidazole for 14 days plus azithromycin on days 1 and 3 [99]. No additional benefit of cure was observed among women who received metronidazole plus azithromycin compared with metronidazole alone.

Antibiotic treatment for bacterial vaginosis is challenging, in part, because it is a syndrome that involves multiple

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Table 9. Sensitivity testing of *Chlamydia trachomatis* isolates to azithromycin.

Study (year)	Country	Year(s)	Azithromycin		Other macrolides		Additional details	Ref.
			MIC (μg/ml)	MBC/MCC (μg/ml)	MIC (μg/ml)	MBC (μg/ml)		
No resistance observed								
Ljubin-Sternak *et al.* (2012)	Croatia	2010	0.064 to 0.125	0.064–2.0	Doxycycline: 0.016–0.064	0.032–1.0	24 urogenital strains assessed	[187]
Donati *et al.* (2010)	Italy	2005–2006	0.25–0.5	0.5–1.0	Doxycycline: 0.03–0.06 Erythromycin: 0.5–1.0	0.06–0.125 1.0–2.0	All serovars had comparable susceptibilities. Azithromycin and doxycycline bactericidal with MBC at one to two-times the MIC. (50 strains)	[188]
Hong *et al.* (2009)	Ethiopia	2006	0.25–0.5	0.25–1.0	Doxycycline: 0.015–0.03	0.03–0.06	Azithromycin unchanged between pre- and post-mass biannual treatment of trachoma (10 strains)	[189]
Samra *et al.* (2001)	Israel	1997–1999	0.06–0.125	0.06–0.25	Doxycycline: 0.125–0.25 Tetracyclines: 0.25–0.5	0.125–4.0 0.25–4.0	Smallest MBC and MIC difference in azithromycin versus doxycycline (4 dilutions differences; 50 isolates)	[84]
Lefèvre *et al.* (1993)	France	NR	0.06–0.125	0.25–0.5	Clarithromycin: 0.008 Erythromycin : 0.06–0.125 Tetracyclines: 0.125–0.25	0.03–0.125 0.25–2.0 1.0–4.0	15 clinical isolates tested	[190]
Agacfidan *et al.* (1993)	United States	1993	≤0.06–1	0.12–2.0	Doxycycline: 0.015–0.06 Tetracyclines: 0.03–0.12	0.015–0.06 0.06–0.12	Azithromycin highly active against CT in isolates from urethral and cervical samples (azithromycin 10 strains, doxycycline 22 strains, tetracycline 22 strains)	[191]
Scieux *et al.* (1990)	UK	1990	0.064–0.25	2.0–8.0	Doxycycline: 0.016–0.064 Erythromycin: 0.064–0.128	0.5–8.0 0–64.0	10 strains used from the USA	[192]
Resistance observed								
Bhengraj *et al.* (2010)	India	2006–2007	0.12–8	≤8.0	Doxycycline: 0.025–8.0	≤8.0	Decreased antimicrobial susceptibility in recurrently infected female patients (21 isolates)	[92]
Misyurina *et al.* (2004)	Russia	2000–2002	>5.12	>5.12	Erythromycin: >5.12	>5.12	Isolates from salpingitis, endocervicitis, and urethritis showed resistance (6 isolates)	[90]
Somani *et al.* (2000)	USA	1995–1998	0.5 to >4.0	>4.0	Doxycycline: 0.125–>4.0	>4.0	Resistance of strains causing relapsing or persistent infection in 3 patients (3 isolates)	[193]
Rice *et al.* (1995)	USA	1995	0.125–2.0	0.5 to >4.0	Doxycycline: 0.008–0.06	0.015–4.0	Isolates susceptible to azithromycin and doxycycline in asymptotic infection	[91]

Unspecified low-risk populations.
CT: *Chlamydia trachomatis*; MBC: Minimum bactericidal concentration; MCC: Minimum chlamydicidal concentrations; MIC: Minimum inhibitory concentrations; NR: Not reported; PID: Pelvic inflammatory disease.

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Table 10. Trials using azithromycin alone and in combination with other drugs reporting protection curable STIs/RTIs among pregnant women.

Study (year)	Country	Year(s)	Regimen	Number of cases post-treatment (%)					Additional details	Ref.
				Treponema pallidum[†]	Neisseria gonorrhoeae	Chlamydia trachomatis	Trichomonas vaginalis	Bacterial vaginosis		
Luntamo *et al.* (2010)	Malawi	2003–2006	**Intervention** 1 g AZ two-times + SP monthly	NR	0.5% (2/391)	0.3% (1/391)	11.0% (46/419)	NR	Significant protection against *T. vaginalis* p = 0.05	[94]
			Intervention SP monthly	NR	2.1% (8/384)	0.3% (1/384)	15.1% (62/411)	NR		
			Control SP two-times	NR	0.7% (3/391)	0.3% (1/391)	16.7% (69/411)	NR		
van den Broek *et al.* (2009)	Malawi	2004–2005	**Intervention** 1 g AZ two-times + SP two-times	NR	NR	NR	NR	NR	No difference in preterm birth (16.8% versus 17.4%); potential explanatory factors include use of sub-optimal syphilis treatment [196,197]	[194]
			Control SP two-times	NR	NR	NR	NR	NR		
Gray *et al.* (2001)	Uganda	1994–1998	**Intervention** 1 g AZ + 250 mg CIPX + 2 g MTZ	3.4% (57/1,677)	0.9% (14/1,503)	1.1% (16/1,503)	4.7% (4/1,779)	36.3% (645/1,779)	Neonatal death RR: 0.83; 95% CI: 0.71–0.97; Low birth weight RR: 0.68; 95% CI: 0.53–0.86; Preterm delivery RR: 0.77; 95% CI: 0.56 to 1.05. Vertical transmission of HIV was no different between intervention and control groups	[104]
			Control Iron-folate + 100 mg MBZ two-times	3.3% (46/1,376)	1.7% (24/1,394)	2.7% (38/1,394)	15.9% (248/1,569)	48.5% (764/1,576)		
Wawer *et al.* (1999)	Uganda	1994–1998	**Intervention** 1 g AZ + 250 mg CIPX + 2 g MTZ	6.0% (80/1,323)	1.0% (8/770)	1.2% (9/770)	5.3% (72/1,350)	39.1% (533/1,364)	Vertical transmission of HIV was no different between intervention and control groups	[95]
			Control Iron-folate + 100 mg MBZ two-times	7.1% (75/1,056)	2.1% (15/714)	3.5% (25/714)	17.4% (198/1,137)	52.8% (609/1,154)		

Low-risk populations
[†]2.4 mu benzathine Penicillin G was administered to pregnant women in all treatment groups per national guidelines (exception being [194].
AZ: Azithromycin; CIPX: Ciprofloxacin; NR: Not reported; RR: Risk ratio; SP: Sulfadoxine-pyrimethamine.

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Table 11. Trials using azithromycin alone and in combination with other antimicrobial therapies not contraindicated in pregnancy and reporting protection curable STIs/RTIs among commercial sex workers.

Study (year)	Country	Year(s)	Regimen		Proportion of cases cured (cases pre-treatment/cases post-treatment)					Additional details	Ref.
					Treponema pallidum[†]	Neisseria gonorrhoeae	Chlamydia trachomatis	Trichomonas vaginalis	Bacterial vaginosis		
Kaul *et al.* (2004)	Kenya	1998–2002	**Intervention** 1 g AZ monthly (multi-yr pd)		3.9%	2.6%	1.1%	11.3%	53.0%	Incidence reported per 100 women-years	[93]
			Control Placebo		3.8%	5.7%	6.5%	20.4%	57.4%		
Labbe *et al.* (2012)	Benin Ghana	2001	**Intervention** 1 g AZ or 500 g CIPX monthly for 9 months alternating AZ & CIPX		NR	5.6% (7/126)	1.6% (2/126)	NR	NR	Significant protection against *N. gonorrhoeae* p = 0.05	[197]
			Control Placebo		NR	12.5% (14/112)	2.7% (3/112)	NR	NR		
Cowan *et al.* (2005)	Zimbabwe	NR	**Intervention** 1 g AZ+2 g MTZ+500 mg CIPX		Base: 5.0% (2.8–8.7%); *V2, V3, V4:* NR in any form	Base: 1.9% (0.5–3.4%) *V2, V3, V4*: visible inaccuracies in graphs; cannot estimate	Base: 1.7% (0.3–3.0%) *V2, V3, V4*: visible inaccuracies in graphs; cannot estimate	Base: 19.3% (15.2–23.4%) *V2: 4.3% (7.7–2.2%) V3: 12.6% (17.7–8.8%) V4: 11.5% (15.7–7.8%)*			[96]
			Intervention 1 g AZ+2 g MTZ								
Wi *et al.* (2006)	Philippines	2001	**Intervention** 1 g AZ one time	Prior to intervention 1 month post-intervention	NR	18.3% (207/1,130) 11.9% (82/687)	28.6% (323/1,130) 15.1% (104/687)	NR	NR		[198]
Williams *et al.* (2003)	South Africa	1998–2000	**Intervention** 1 g AZ nine-times in 9 months	Prior to intervention 9-month post-intervention	9.8% (68/691) 18.7% (166/893)	6.9% (48/691) 8.6% (77/893)	7.9% (55/691) 13.8% (123/893)	NR	NR	HIV prevalence among CSW in the mining community was 68.6%	[199]
Steen *et al.* (2000)	South Africa	1996–1997	**Intervention** 1 g AZ every month for 9 months	Prior to intervention 9-month post-intervention	NR	17.3% (70/407) 4.7% (5/108)	14.3% (58/407) 0.9% (1/108)	NR	NR	Pre-intervention NG and/or CT = 24.9% (101/407); Post-intervention NG and/or CT = 5.7% (6/108)	[200]

Italicized values are approximate based on enlarged graphs published in Cowan *et al.* and percentages in parentheses reflect the 95% confidence intervals [96].
[†]2.4 mμ benzathine Penicillin G was administered to commercial sex workers who tested positive for syphilis in all treatment groups per national guidelines.
AZ: Azithromycin; NR: Not reported; CIPX: Ciprofloxacin; CT: *C. trachomatis*; CSW: Commercial sex worker; MTZ: Metronidazole; NG: *Neisseria gonorrhoeae*.

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Table 12. Sensitivity of macrolides and structurally related agents against key causative organisms in bacterial vaginosis

Study (year)	Country	Year(s)	Minimum inhibitory concentrations of specific macrolides (μg/ml)						Ref.
			Azithromycin	Erythromycin	Clarithromycin	Roxithromycin	Clindamycin†	Telithromycin†	
Gardnerella vaginalis									
Jones *et al.* (1998)	UK	NR	<0.03–0.125	<0.03–0.06	NR	NR	NR	NR	[201]
Shanker *et al.* (1982)	Australia	NR	NR	0.007–0.06	NR	NR	0.007–0.06	NR	[202]
King† *et al.* (1987)		NR	NR	0.008–0.016	NR	0.016	NR	NR	[203]
Bacteroides species									
Jones *et al.* (1998)	UK	NR	0.06 –16	<0.03–32	NR	NR	NR	NR	[201]
Dubreuil *et al.* (1987)	England, France, Germany, Japan	NR	NR	0.003–>64	NR	0.003–>64	NR	NR	[204]
Maskell *et al.* (1990)	UK	NR	0.5–>16	<0.25–16	NR	NR	NR	NR	[205]
Chang *et al.* (1995)	Taiwan	1989–1992	1–>256	0.25–>256	≤0.03–>256	0.25–>256	NR	NR	[206]
Ednie *et al.* (1997)	USA	NR	1–>64	0.5–>64	0.5–>64	2–>64	≤0.06–>64	NR	[207]
Mikamo *et al.* (2003)	Japan	2000	0.125– 32	0.125–32	0.063 to16	NR	NR	0.032–16	[208]
Marina *et al.* (2009)	Bulgaria	1983–2007	NR	0.5–>64	NR	NR	0.125–32	NR	[209]
Chen *et al.* (1992)	Australia	1986–1991	0.5 to128	0.25–128	NR	NR	NR	NR	[210]
Wexler *et al.* (2001)	USA	NR	NR		NR	NR	NR	0.25–>64	[211]
Mycoplasma hominis									
Ridgway *et al.* (1987)	UK	NR	NR	>32	NR	8 to16	NR	NR	[203]
Mobinculus species									
Spiegel *et al.* (1987)	USA	NR	NR	≤0.2–>200	NR	NR	≤0.015–4	NR	[212]

Unspecified low-risk population.
†Not a macrolide but has similar mechanism of action and included for comparability.
NR: Not reported.

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microorganisms rather than a single etiological agent. Comparable data from other macrolides suggest potential therapeutic value for azithromycin against bacterial vaginosis (Table 12). Analysis of azithromycin against the anaerobic and carboxyphilic bacteria that replace the normal vaginal flora may provide a better understanding as to the potential role of azithromycin against bacterial vaginosis.

Discussion

Azithromycin has been used against curable STIs/RTIs for 25 years. It has been an attractive option for preventive and curative treatment because it is efficacious as a single dose and offers reasonable tolerability against *T. pallidum, N. gonorrhoeae* and *C. trachomatis*. During the 1990s, and prior to the advent of antiretroviral therapies for HIV, the management of curable STIs/RTIs received renewed importance, particularly as trials showed that treatment of *N. gonorrhoeae, C. trachomatis* and *T. vaginalis* reduced the genital viral load of HIV among men and women [100–103]. Groups at high risk for transmitting HIV have since been targeted by treatment campaigns using 1 g azithromycin. Thus, it is not a surprise that changes in azithromycin sensitivity within high-income settings have often been observed first among members of high-risk groups. Pregnant women attending ANC facilities in sub-Saharan Africa do not have the same risk profile. Thus, on this basis alone, it is less likely that the use of ABC therapies in IPTp would be a catalyst for the rapid emergence of azithromycin resistance, although its emergence cannot be ruled out. The potential benefits of ABC therapies may be best viewed through prior experience with mass drug administration among pregnant women. In the context of the AIDS epidemic and before the age of antiretroviral therapies, researchers attempted to prevent maternal-to-child transmission (MTCT) of HIV by providing pregnant women in Uganda 1 g azithromycin, in combination with 250 mg ciprofloxacin and 2 g metronidazole [104]. The data safety monitoring board suspended the trial early for reasons of futility, despite having cut neonatal deaths by 17% (RR: 0.83; 95% CI: 0.71–0.97), decreased the incidence of low birthweight by 32% (RR: 0.68; 95% CI: 0.53–0.86), and reduced the incidence of preterm delivery by 23% (RR: 0.77; 95% CI: 0.56–1.05). These impressive results were achieved at a time when neither IPTp-SP nor insecticide treated bed nets for the control of malaria in pregnancy had been deployed.

If ABC therapies are used in IPTp, then there are several key factors to consider that are pathogen specific. Regarding syphilis, 1 g azithromycin should be used alongside 2.4 mu BPG for three reasons: combination therapy has been shown to achieve higher rates of cure than either therapy alone [105]; use of ABC therapy with BPG would likely reduce selection of the A→G mutation associated with azithromycin and preserve *T. pallidum* sensitivity; and only BPG can be expected to cure congenital infection if the placenta has been invaded by spirochetes [106]. As for *N. gonorrhoeae*, 1 g azithromycin may be just above the MIC of fully susceptible strains. Thus, ABC therapies containing >1 g azithromycin may be preferable from the standpoint of reducing selection pressure. However, a single 2 g dose may not be well tolerated as 6 in 10 patients reported self-limiting gastrointestinal discomfort when treated for syphilis infection with such a regimen [42]. The dose could be split over 2 days to improve tolerability. ABC therapies that contain 2 g azithromycin, either a single- or split-dose, would be protective against *C. trachomatis.* Although the data are limited and the mechanism of action is not understood, ABC therapies that have 1 g azithromycin may protect against *T. vaginalis* based on reports from Malawi among pregnant women [107] and commercial sex workers in Kenya [93]. It is curious, however, that *T. vaginalis* infection during pregnancy is associated with adverse birth outcomes, but the first-line treatment of 2 g metronidazole does not always improve birth outcomes. A trial in Uganda reported that pregnant women treated for *T. vaginalis* infection were 2.5-times more likely to deliver a low birthweight infant than untreated women (RR: 2.49; 95% CI: 1.12–5.50) [108]. The authors suggest that this may be attributable to metronidazole exposure. Another trial in the USA reported an increase in the risk of preterm delivery among pregnant women exposed to metronidazole for the treatment of asymptomatic trichomoniasis compared with those who were not treated (RR: 1.8; 95% CI: 1.2–2.7) [109]. In contrast to these findings from high-income settings, data from a multicenter trial in sub-Saharan Africa indicate that treatment of *T. vaginalis* infection using metronidazole does not increase the chances of preterm birth [110]. Apart from bacterial vaginosis, which is not transmitted through sexual contact, re-infection will remain a risk for pregnant women and, therefore, providers should continue to offer education and screening as appropriate.

None of the studies identified in this review indicate that azithromycin offers preventive or curative effect against bacterial vaginosis, the most prevalent of curable STIs/RTIs. Antibiotic therapy has only been shown to reduce the risk of preterm delivery by one-half (RR: 0.53; 95% CI: 0.34–0.84) among pregnant women with bacterial vaginosis (Nugent scores 7–10) or intermediate flora (Nugent scores 4–6) [111]. A Nugent score of 0–3 is considered normal [112] for which no protection against adverse birth outcomes has been observed.

Conclusions

ABC therapies are among leading candidates to replace SP for use in IPTp and may offer important public health benefits by also reducing the burden of curable STIs/RTIs in pregnancy. Evidence from nonpregnant adults suggests that ABC therapies containing 1 g azithromycin may cure maternal *T. pallidum* infection. BPG should still be administered with azithromycin because the combination has been shown to be more efficacious in nonpregnant adults than either treatment alone. Moreover, evidence from pregnant women indicates that eradication of congenital syphilis may require BPG treatment. *Neisseria gonorrhoea*e infection among pregnant women in sub-Saharan Africa, where strains are likely to be fully sensitive to azithromycin, is likely to be cured by ABC therapies containing 1 g azithromycin. However, 2 g may be needed to reduce persistent and/or

recurrent infection, and opportunities for the emergence of drug resistance. ABC therapy containing 1 g azithromycin would be curative of *C. trachomatis* infection, whereas some protection against *T. vaginalis* infection could be expected with the same dose. It remains unknown whether ABC therapies could offer protection against bacterial vaginosis if administered during the first half of pregnancy. ABC therapies merit investigation for the use in IPTp given their potential to reduce the dual burden of malaria and curable STIs/RTIs in pregnancy and improve maternal, fetal and neonatal health.

Expert commentary

Current strategies for addressing the dual-burden of malaria and curable STIs/RTIs in pregnancy are suboptimal. In West Africa, IPTp-SP continues to provide protection against the effects of malaria infection but, as previously noted, malaria parasites in East Africa have developed resistance so that IPTp-SP no longer protects against the malaria attributable fraction of low birthweight [3]. Some evidence suggests that IPTp-SP may even be harmful in areas where parasites express the 581G *dhps* mutation [4–6]. ABC therapies are likely to be more efficacious against malaria parasites in these settings. However, there is an urgent need for trials of ABC therapies to be conducted by independent researchers for policymakers to review alongside the results of trials produced and reported by industry.

In the case of curable STIs/RTIs, the focused ANC package recommended by the WHO includes screening for syphilis and the provision of BPG to women who test positive [50]. Screening would need to continue even if ABC therapies were used in IPTp. The WHO currently recommends the use of rapid point of care tests for syphilis in the ANC setting [113]. Using such tests will expedite case finding and treatment with BPG because results are available during the same consultation. As for the four other curable STIs/RTIs of this review, health care providers are limited to the use of a syndrome-based management algorithm to diagnose and to treat suspected infections. However, 80% of gonococcal and 70–75% chlamydial infections in women are asymptomatic [114] and, therefore, rarely recognized using the syndromic approach. As a result, the diagnostic algorithm has a low sensitivity (30–80%) and specificity (40–80%) for *N. gonorrhoeae* and *C. trachomatis* among pregnant women [115–117]. The sensitivity for *T. vaginalis* (54–83%) and bacterial vaginosis (51–69%) is slightly higher, with moderate specificity for *T. vaginalis* (40–54%) and bacterial vaginosis (40–58%) [118]. Given the evidence of this review, ABC therapies used in IPTp could be expected to mitigate a considerable proportion of this unattended burden of curable STIs/RTIs.

Much is debated about the utility of a syndrome-based approach to diagnosing and treating many STIs/RTIs. Its shortcomings, as described above, illuminate a much-needed area for research. Specifically, more refined definitions of diagnosis need to be used when characterizing adverse birth outcomes. This is particularly so with *T. vaginalis* for which successful treatment does not necessarily reduce the risk of adverse birth outcomes. Similarly with bacterial vaginosis, treatment of women who have Nugent scores of 1–3 has not reduced the incidence of preterm birth. With both of these infections, is the recommended regimen of metronidazole inadequate for radical cure? Is it administered too late in pregnancy to alter the course of events? Or are asymptomatic infections simply much less virulent and, therefore, treatment has a marginal effect on selected downstream measures of the adverse birth outcome? Studies of descriptive epidemiology are needed to understand better the extent to which symptomatic versus asymptomatic curable STIs/RTIs contribute to adverse birth outcomes. Such descriptive epidemiology, however, would be incomplete if the prevalence of co-infections were not also considered. The apparent failure to reduce the incidence of adverse birth outcomes following treatment for one infection may be masked by the presence of co-infection(s) that will only be mitigated with the use of combination therapies and consideration of downstream outcomes. The trial in Uganda that failed to reduce the incidence of MTCT of HIV is illustrative. HIV transmission was not interrupted for providing combination treatment against curable STIs/RTIs, but significant reductions were observed in the incidence of neonatal deaths by 17% (RR: 0.83; 95% CI: 0.71–0.97) and low birthweight by 32% (RR: 0.68; 95% CI: 0.53–0.86) [104].

Five-year view

Discussion of the future of IPTp needs to be placed in the context of broader malaria elimination efforts. IPTp-SP has long been considered a malaria control intervention that can be expected to protect less against the fraction of low birthweight attributable to malaria infection as malaria transmission decreases. Recent evidence suggests that IPTp-SP continues to protect against low birthweight among multigravidae in areas where the prevalence of malaria parasitemia measured in children is between 7 and 8%, whereas protection is conferred by IPTp-SP among paucigravidae until very low levels of transmission [119]. Unpublished results from a recently completed multicenter trial in West Africa, where there remain malaria parasites sensitive to SP, indicate that an approach of intermittent screening and treatment (IST) of malaria in pregnancy is noninferior to IPTp-SP (Manuscript under review/personal communication with D. Chandramohan). Thus, there is an urgent need for clinical trials in an area of high SP resistance in East Africa, designed to compare ABC therapies versus IST versus IPTp-SP. ABC therapies, given their action against malaria and curable STIs/RTIs, would be superior to IST and IST would be superior to IPTp-SP, potentially paving the way for adoption of an integrated malaria and curable STI/RTI control package that employs the use of combination treatment.

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Key issues

- Use of azithromycin-based combination (ABC) therapies may have a transformative effect on maternal, fetal and newborn heath by mitigating the dual-burden of malaria and curable sexually transmitted infections and reproductive tract infections sexually transmitted infections and reproductive tract infections (STIs/RTIs) in pregnancy.
- ABC therapies containing two or more grams of azithromycin may be less likely to select for resistance when exposed to *Treponema pallidum, Neisseria gonorrhoeae* and potentially, *Chlamydia trachomatis*.
- In the absence of evidence that azithromycin is curative of congenital syphilis, not simply maternal infection, benzanthine penicillin G (BPG) will still need to be administered to pregnant women who have a syphilis infection; however, the combination of azithromycin plus BPG is more efficacious that BPG alone.
- ABC therapies may be preventive of *Treponema vaginalis* infection during pregnancy, although its impact on birth outcomes needs to be investigated.
- The most prevalent of all STIs/RTIs, bacterial vaginosis, may or may not be mitigated by the use of ABC therapies.
- Studies of descriptive epidemiology are needed to understand better the extent to which symptomatic versus asymptomatic curable STIs/RTIs contribute to adverse birth outcomes. There is an urgent need for clinical trials in an area of high sulfadoxine-pyrimethamine resistance in East Africa, designed to compare ABC therapies versus IPTp-SP versus providing IST for malaria in pregnancy during ANC visits.

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