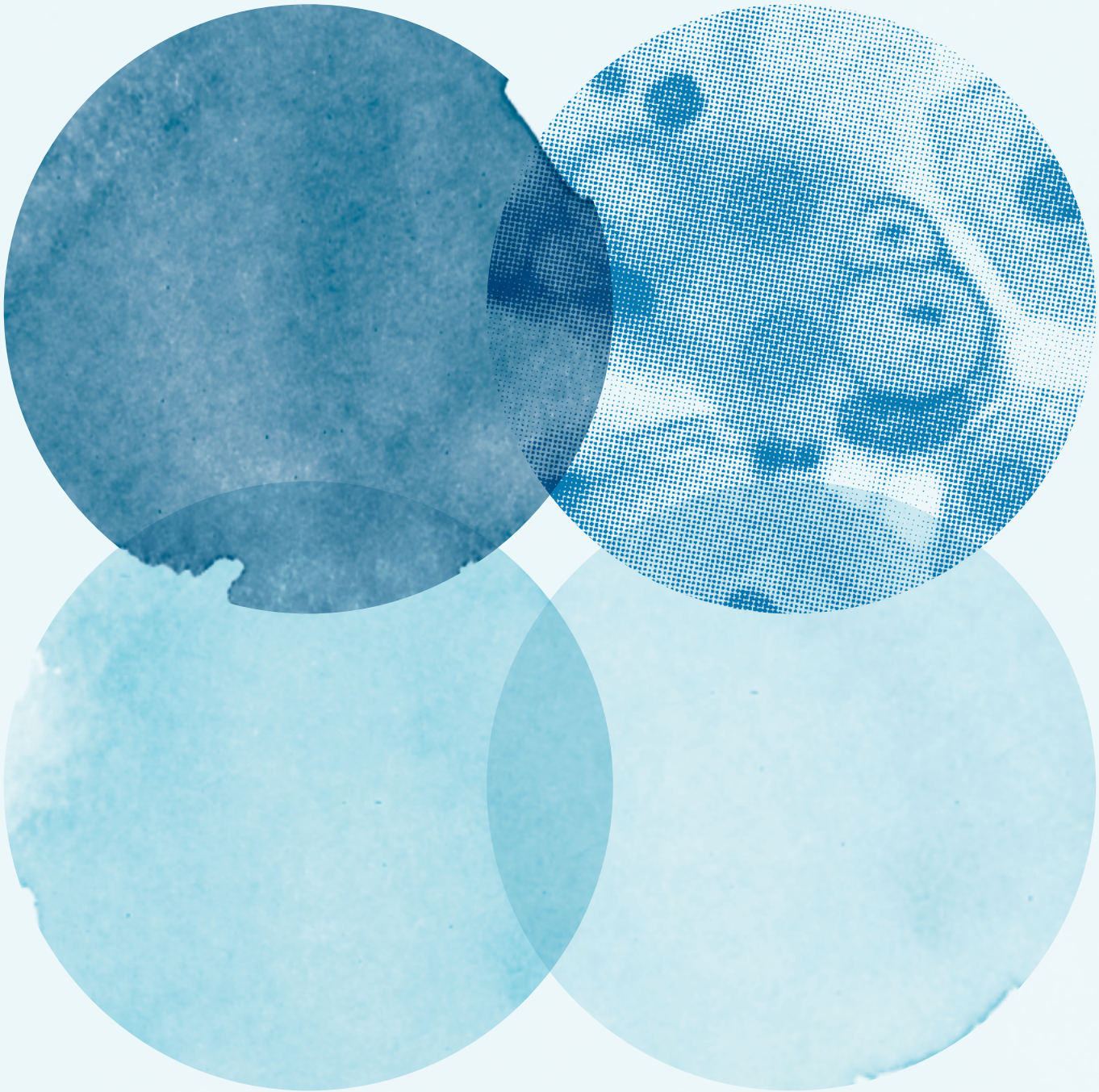
World Health Organization

WHO GUIDELINES FOR THE

Treatment of *Chlamydia trachomatis*

Web annex D: Evidence profiles and evidence-to-decision frameworks



The full guidelines are available at:
www.who.int/reproductivehealth/publications/rtis/chlamydia-treatment-guidelines/en/

WHO GUIDELINES FOR THE

Treatment of *Chlamydia trachomatis*

Web annex D: Evidence profiles and evidence-to-decision frameworks

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WHO guidelines for the treatment of Chlamydia trachomatis.

Contents: Web annex D: Evidence profiles and evidence-to-decision framework -- Web annex E: Systematic reviews -- Web annex F: Summary of conflicts of interest

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CONTENTS

RECOMMENDATION 1

Treatments for adults and adolescents with uncomplicated genital (cervix, urethra) chlamydial infections?	
Population:	Adults and adolescents with uncomplicated genital (cervix, urethra) chlamydial infections
Intervention:	Azithromycin or doxycycline
Comparison:	Other antibiotics
Main outcomes:	**Critical:** Clinical cure, microbiological cure, sexually transmitted infections (STIs), complications, side-effects (including allergy, toxicity, gastro), compliance **Important:** Quality of life, HIV transmission and acquisition, partner transmission
Setting:	Outpatient
Perspective:	Population
Background:	The global prevalence and incidence of chlamydia in adult women and men, like other STIs, remain high, with nearly one million new curable infections each day. This infection causes acute conditions such as cervicitis, urethritis and genital ulceration. The 2003 WHO guidelines recommend treatment of uncomplicated anogenital infections with either doxycycline 100 mg orally twice daily for 7 days, or azithromycin 1 g orally in a single dose. Alternatively, amoxicillin 500 mg orally thrice daily for 7 days; erythromycin 500 mg orally four times daily for 7 days; ofloxacin 300 mg orally twice daily for 7 days; or tetracycline 500 mg orally four times daily for 7 days. The Guideline Development Group (GDG) identified azithromycin and doxycycline for comparison to other treatments for review.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** An estimated 131 million new cases of chlamydia (100–166 million) were reported (Newman, 2012) globally in 2012. According to 2013 Global Burden of Disease estimates, chlamydia was the 10th most common incident condition. Chlamydial infection can also lead to severe complications and long-term sequelae, including pelvic inflammatory disease, ectopic pregnancy, infertility, chronic pelvic pain, neurological and cardiovascular disease in adults, neonatal death, premature delivery and severe disability in infants (Holmes, 2008). Furthermore, STIs such as chlamydia frequently result in stigma, stereotyping, vulnerability and shame and have been associated with gender-based violence (Amin, 2013). There is also an associated risk of HIV transmission. **Additional considerations:** The GDG agreed that the global estimates of chlamydia are generally underestimated due to under-diagnosis. However, the global estimates made by Newman took this factor into consideration. It was also noted that considerations for sex workers and other key populations should be of importance.
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • Large • **Varies** • Don't know	**Research evidence:** Evidence from a not yet published Cochrane systematic review was used (see Páez-Canro et al., 2013 – protocol for the review). This review included 25 randomized studies comparing tetracycline, quinolones and macrolides. We compared azithromycin to doxycycline, doxycycline to ofloxacin, high-dose azithromycin to low-dose azithromycin, high-dose tetracycline to low-dose tetracycline, extended release to standard-dose doxycycline, tetracyclines to quinolones, and erythromycin to other quinolones. There were no data for amoxicillin. See the evidence profiles for each of the comparisons. **Additional considerations:** • There were trivial differences in cure rates between azithromycin 1 g and doxycycline 100 mg twice daily for 7 days (8 or 10 fewer per 1000). • There may be more clinical cures with 3 g azithromycin (high dose) versus 1 g azithromycin (low dose) (94 more per 1000).
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • Trivial • **Varies** • Don't know	• Doxycycline hyclate delayed-release probably leads to slightly fewer cures than using the standard dose. • Doxycycline compared to ofloxacin may yield fewer cures. • High dose any tetracycline compared to lower dose may lead to more clinical cures. • Tetracyclines compared to quinolones may lead to fewer cures. • Erythromycin compared to other quinolones may lead to fewer cures. • There were trivial differences in adverse events between azithromycin 1 g and doxycycline 100 mg twice daily for 7 days (3 more per 1000). This data did not include women. • Doxycycline hyclate delayed-release probably leads to fewer adverse events than standard dose. • Doxycycline compared to ofloxacin may have lead to slightly fewer adverse events. • Any high-dose tetracycline compared to lower dose probably leads to fewer adverse events. • Tetracyclines compared to quinolones may lead to slightly fewer adverse events. • Erythromycin compared to other quinolones may lead to more adverse events.

Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • Low • **Moderate** • High • No included studies	**Additional considerations:** Moderate certainty for comparisons between azithromycin and doxycycline, but low certainty for some comparisons of other drugs. Lower certainty is primarily due to the studies including few events, and using confidence intervals that included the potential for benefit and harm.
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • Possibly important uncertainty or variability • Probably no important uncertainty or variability • **No important uncertainty or variability** • No known undesirable outcomes	**Research evidence:** Qualitative studies suggest that in making the decision to seek help, women act on a range of specific prompts, including lay ideas about the significance of symptoms, their own behaviour, their partner's symptoms or behaviour, contact tracing and health promotion. Psychosocial factors, such as embarrassment, are also important. **Additional considerations:** The GDG indicated that much of the research is about cure (clinical or microbiological) and about long-term consequences of the infection. However, the GDG agreed that it is unlikely people would vary in the importance placed on these outcomes.
Balance of effects	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • **Varies** • Don't know	**Research evidence:** None **Additional considerations:** Due to trivial differences, neither azithromycin nor doxycycline was favoured over the other. Due to little evidence, neither high dose nor low dose was favoured over the other. Doxycycline hyclate delayed-release is probably favoured over the standard dose. Neither doxycycline nor ofloxacin were favoured over the other. Other quinolones may be favoured over erythromycin.

Resources required

How large are the resource requirements (costs)?

- Large costs
- Moderate costs
- Negligible costs and savings
- Moderate savings
- Large savings
- **Varies**
- Don't know

A	B	C	D*	E	F
Azithromycin 1 g po	1	1	$0.38 (500 mg)	$0.76	$0.95
Doxycycline 100 mg po	2	7	$0.0191	$0.2674	$0.3342
Doxycycline (ER) 200 mg po	1	7	n.a.	n.a.	n.a.
Erythromycin ES 800 mg po	4	7	n.a.	n.a.	n.a.
Erythromycin 500 mg po	2	10-14	$0.0738	$1.476 – $2.06	$1.88 – $2.57
Amoxicillin 500 mg po	3	7	$0.032	$0.672	$0.84
Quinolones po			n.a.	n.a.	n.a.

Additional considerations:
The GDG agreed that azithromycin is more expensive than doxycycline but less expensive than erythromycin. Globally, most STI drugs come from out-of-pocket payments, and this should be the primary consideration rather than how much governments or donors are willing to pay.

For many of these drugs, costs may be different across countries, and in places with high incidence of chlamydia, the cost differences may be larger with a greater number of people treated.

The GDG also indicated that co-treatment for gonorrhoea infection must be considered in determining cost of treatments.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

- **Very low**
- Low
- Moderate
- High
- No included studies

No studies exploring resource costs were found.

Cost–effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

- Favours the comparison
- Probably favours the comparison
- Does not favour either the intervention or the comparison
- Probably favours the intervention
- Favours the intervention
- **Varies**
- No included studies

Research evidence:
Sahin-Hodoglugil et al. (2003) found that the "gold standard" protocol with diagnosis and treatment, using azithromycin for chlamydial infections, was found to be more cost-effective than using doxycycline. For both the gold standard and syndrome management protocols, the total cost of the program was most sensitive to the percentage of women seeking STI treatment and the prevalence of non-STI vaginal discharge. In contrast, the cost of mass treatment was almost exclusively determined by coverage rates.

Additional considerations:
The GDG agreed that azithromycin is more expensive than doxycycline but less expensive than erythromycin. Globally, most STI drugs come from out-of-pocket payments, and this should be the primary consideration rather than how much governments or donors are willing to pay.

For many of these drugs costs may be different across countries, and in places with high incidence of chlamydia the cost differences may be larger with a greater number of people treated.

The GDG also indicated that co-treatment for gonorrhoea infection must be considered in determining cost of treatments.

Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • **Varies** • Don't know	**Research evidence:** No research evidence **Additional considerations:** It was suggested that multi-dose regimens (like doxycycline) may reduce equity because of a stigma surrounding taking treatments, but this may vary across different populations, including men who have sex with men (MSM), transgender patients and young women at increased risk of anorectal infections. More research is needed. Therefore, azithromycin probably increases equity.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** A systematic review (in India) of the literature for treatment utilization in STI reported that utilization ranged from 16% to 55% in community-based studies and was higher (approximately 70%) in research trials. Treatment may not be acceptable to patients due to the resources and availability of services, social factors and/or distance from a clinic. Non-utilization was also due to ignorance, illiteracy and lack of awareness. Women reported a lack of female doctors, being afraid of results, judgement from doctors, stigma, shyness and embarrassment. Cost of care and lack of faith in clinical care were also factors. A review of the literature for single versus multi-dosing found 2 studies specifically for treatment of chlamydia (Kingston, 2002) reporting 70% of men preferred the single dose regimen. Furthermore, overview of reviews of medication adherence (Ryan, 2014) reported that adherence may be improved with simpler drug regimens. **Additional considerations:** The GDG agreed that one dose of azithromycin would be more acceptable than a course of doxycycline twice daily for 7 days. The GDG also discussed the need for sexual abstinence during treatment. It was noted that for azithromycin therapy, sexual abstinence may be more important than with doxycycline treatment in avoiding reinfection, as the prolonged doxycycline concentration could maintain some protection throughout the course of the treatment. However, there is no clear evidence for these effects.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • **Probably yes** • Yes • Varies • Don't know	**Research evidence:** No research evidence **Additional considerations:** The GDG noted that important social considerations were needed for adolescent girls (and other populations), due to difficulties in bringing therapy home. The treatments were considered feasible, with distribution and compliance concerns taken into account.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for uncomplicated genital (cervix, urethra) chlamydial infections

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	For people with uncomplicated genital chlamydia, the WHO STI guideline suggests one of the following options: • Azithromycin 1 g as a single oral dose • Doxycycline 100 mg twice a day for 7 days *Alternative options* • Tetracycline 500 mg four times a day for 7 days • Erythromycin 500 mg twice a day for 7 days • Ofloxacin 200–400 mg twice a day for 7 days *Conditional recommendation, moderate quality evidence* **Remarks:** While good practice, resulting from large net benefit, dictates that patients should be treated for chlamydial infection, the choice of treatment may depend on the convenience of dosage, the cost and quality of the medicines in different resource settings and equity considerations. When high value is placed on reducing costs, doxycycline in a standard dose may be the best choice; however, when high value is placed on convenience, azithromycin in a single dose may be the best choice. Doxycycline extended release (ER) may be an alternative to twice daily dosing of doxycycline, but the high cost of the delayed release formulation may prohibit its use. Note that doxycycline, tetracycline and ofloxacin are contraindicated in pregnant women (see Recommendation 3).				
Justification	Evidence from a not yet published Cochrane systematic review was used (Páez-Canro et al., 2013 – protocol for the review). This review included 25 randomized studies comparing tetracycline, quinolones and macrolides. There is no data for amoxicillin. Overall there is moderate to low quality evidence for most comparisons of treatments. Moderate quality evidence shows trivial differences between azithromycin 1 g and doxycycline 100 mg twice daily for 7 days in the number of people microbiologically cured and experiencing adverse events. There were 10 fewer per 1000 people cured with azithromycin versus doxycycline, ranging from 38 fewer to 10 more (risk ratio [RR] 0.99, 95% confidence interval [CI] 0.96 to 1.10). In addition, there were 3 more per 1000 adverse events with azithromycin versus doxycycline, ranging from 42 fewer to 64 more (RR 1.02, 95% CI 0.72 to 1.43). Similar results are shown in a recently published randomized study. Doxycycline hyclate delayed release probably leads to little to no difference in number of people microbiologically cured, but probably has fewer side-effects than the standard dose. Ofloxacin may have fewer cures, but slightly fewer adverse events compared to doxycycline. When comparing high doses of azithromycin (1 g weekly for 3 weeks) to a single dose, there may be more people cured, but there is no data for adverse events related to very high doses. Higher doses of any tetracycline compared with lower doses may lead to more cures and probably lead to more adverse events. Tetracyclines compared with quinolones may lead to fewer cures but slightly fewer adverse events. Erythromycin compared with quinolones may lead to fewer cures and more adverse events.				

	There is no evidence for patient values and preferences, however, the GDG agreed that there are no known reasons to suspect values would vary between different people. Research in other conditions indicates that adherence may be improved with simpler drug regimens. The GDG, therefore, agreed that azithromycin may be perceived to be more acceptable since it is a single dose and a majority of the GDG members consider single-dose regimens as preferable for patient compliance over multi-dose regimens. There is little-to-no evidence for equity issues and feasibility. Resistance in other infections (e.g. gonorrhoea and *Mycoplasma genitalium*) that co-occur with chlamydia may restrict the use of some medicines, such as ofloxacin. For many of these drugs, costs may differ between countries; for example, in places with high incidence of chlamydia, the minimal cost differences between azithromycin and doxycycline may be large due to greater numbers of people requiring treatment. In summary, there was moderate quality evidence for trivial differences in benefits and harms between azithromycin and doxycycline; and although the cost of azithromycin is higher, the single dose may be more convenient than doxycycline. While the differences are also trivial with the other drugs, the evidence is low quality and is therefore provided as alternatives, with the exception of doxycycline-delayed release, which is currently expensive.
Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research priorities	The potential for resistance to azithromycin, doxycycline and other treatment options should be investigated. Future research could compare these treatments and recommended dosages in randomized controlled trials measuring important outcomes such as clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastro-intestinal), compliance, quality of life, HIV transmission and acquisition, and partner transmission of chlamydia. Studies are also needed that evaluate amoxicillin (500 mg thrice a day for 7 days).

EVIDENCE PROFILES

Azithromycin 1 g compared to doxycycline 100 mg for uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With doxycycline 100 mg	**With azithromycin 1 g**		**Risk with doxycycline 100 mg**	**Risk difference with azithromycin 1 g**
Microbiological cure[1]											
605 (8 RCTs)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	263/277 (94.9%)	310/328 (94.5%)	**RR 0.99** (0.96–1.01)	950 per 1000	**10 fewer per 1000** (38 fewer to 10 more)
Clinical cure – Men											
587 (4 RCTs)	not serious[2]	not serious	not serious	serious[2]	none	⨁⨁⨁◯ MODERATE	188/226 (83.2%)	308/361 (85.3%)	**RR 0.99** (0.88–1.12)	820 per 1000	**8 fewer per 1000** (98 fewer to 98 more)
Adverse events											
1026 (5 RCTs)	not serious[2]	not serious	not serious	serious[2]	none	⨁⨁⨁◯ MODERATE	72/454 (15.9%)	98/572 (17.1%)	**RR 1.02** (0.72–1.43)	150 per 1000	**3 more per 1000** (42 fewer to 64 more)
STI complications – not measured											
Compliance – not measured											
Quality of life – not measured											
HIV transmission and acquisition – not measured											
Partner transmission – not measured											

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. The results were similar across men and women.
2. Some concern with no or unclear method of randomization, and results considered imprecise since 95% CI includes potential for more or fewer cures and adverse events.

Any dose doxycycline compared to ofloxacin for uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With ofloxacin	**With doxycycline**		**Risk with ofloxacin**	**Risk difference with any dose doxycycline**
Microbiological cure											
116 (2 RCTs)	not serious	not serious	not serious	serious[1,3]	none	⨁⨁⨁◯ MODERATE	57/57 (100.0%)	55/59 (93.2%)	**RR 0.94** (0.83 to 1.08)	990 per 1000	**59 fewer per 1000** (168 fewer to 79 more)
Clinical cure											
96 (2 RCTs)	serious	not serious	not serious	serious[1,3]	none	⨁⨁◯◯ LOW	41/53 (77.4%)	32/43 (74.4%)	**RR 0.91** (0.73 to 1.13)	780 per 1000	**70 fewer per 1000** (211 fewer to 101 more)
Adverse events											
297 (2 RCTs)	serious[2]	not serious	not serious	serious[4]	none	⨁⨁◯◯ LOW	19/150 (12.7%)	11/147 (7.5%)	**RR 0.62** (0.31 to 1.24)	70 per 1000	**27 fewer per 1000** (48 fewer to 17 more)
STI complications – not measured											
Compliance – not measured											
Quality of life – not measured											
HIV transmission and acquisition – not measured											
Partner transmission – not measured											

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. 95% CI includes potential for more or fewer cures
2. Some concern with no or unclear method of randomization
3. Few events across studies
4. 95% CI includes potential for more or fewer adverse events.

High dose azithromycin compared to lower dose of azithromycin for uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With lower dose of azithromycin	**With high dose azithromycin**		**Risk with lower dose of azithromycin**	**Risk difference with high dose azithromycin**
Microbiological cure											
100 (1 RCT)	serious[1]	not serious	not serious	serious[2,3]	none	⨁⨁◯◯ LOW	36/46 (78.3%)	48/54 (88.9%)	**RR 1.12** (0.90–1.39)	780 per 1000	**94 more per 1000** (78 fewer to 304 more)
Clinical cure – not measured											
Adverse events – not measured											
STI complications – not measured											
Compliance – not measured											
Quality of life – not measured											
HIV transmission and acquisition – not measured											
Partner transmission – not measured											

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. Some concern with no or unclear method of randomization.
2. 95% CI includes potential for more or fewer cures.
3. Few events across studies.

High dose any tetracycline compared to lower dose any tetracycline for uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With lower dose any tetracycline	**With high dose any tetracycline**		**Risk with lower dose any tetracycline**	**Risk difference with high dose any tetracycline**
Microbiological cure											
438 (3 RCTs)	not serious	not serious	not serious	serious[1]	none	⨁⨁⨁◯ MODERATE	204/221 (92.3%)	202/217 (93.1%)	**RR 1.00** (0.95–1.05)	950 per 1000	**0 fewer per 1000** (48 fewer to 48 more)
Clinical cure – Men											
290 (2 RCTs)	serious[3]	not serious	not serious	serious[2]	none	⨁⨁◯◯ LOW	97/147 (66.0%)	119/143 (83.2%)	**RR 1.25** (1.10–1.42)	660 per 1000	**165 more per 1000** (66 more to 277 more)
Adverse events – Men											
494 (1 RCT)	not serious	not serious	not serious	serious[2]	none	⨁⨁⨁◯ MODERATE	132/248 (53.2%)	99/246 (40.2%)	**RR 0.76** (0.62–0.92)	530 per 1000	**127 fewer per 1000** (201 fewer to 42 fewer)
STI complications – not measured											
Compliance – not measured											
Quality of life – not measured											
HIV transmission and acquisition – not measured											
Partner transmission – not measured											

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. 95% CI includes potential for more or fewer cures
2. Few events across studies.
3. Some concern with no or unclear method of randomization.

High dose any tetracycline compared to lower dose any tetracycline for uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With vibramycin doxycycline	**With doxycycline hyclate**		**Risk with vibramycin doxycycline**	**Risk difference with doxycycline hyclate**
Microbiological cure											
323 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	159/167 (95.2%)	146/156 (93.6%)	**RR 0.98** (0.93–1.04)	950 per 1000	**19 fewer per 1000** (66 fewer to 38 more)
Clinical cure – not measured											
Adverse events											
494 (1 RCT)	not serious	not serious	not serious	serious[1]	none	⨁⨁⨁◯ MODERATE	132/248 (53.2%)	99/246 (40.2%)	**RR 0.76** (0.62–0.92)	530 per 1000	**127 fewer per 1000** (201 fewer to 42 fewer)
STI complications – not measured											
Compliance – not measured											
Quality of life – not measured											
HIV transmission and acquisition – not measured											
Partner transmission – not measured											

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. Few events across studies.

Tetracyclines compared to quinolones for uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With quinolones	**With tetracyclines**		**Risk with quinolones**	**Risk difference with tetracyclines**
Microbiological cure											
898 (6 RCTs)	serious[1]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	405/418 (96.9%)	447/480 (93.1%)	**RR 0.97** (0.93–1.02)	980 per 1000	**29 fewer per 1000** (69 fewer to 20 more)
Clinical cure – Men											
442 (3 RCTs)	serious[1]	not serious	not serious	serious[2,3]	none	⨁⨁◯◯ LOW	122/183 (66.7%)	139/259 (53.7%)	**RR 0.79** (0.50–1.23)	660 per 1000	**139 fewer per 1000** (330 fewer to 152 more)
Adverse events											
1071 (6 RCTs)	serious[1]	not serious	not serious	serious[4]	none	⨁⨁◯◯ LOW	159/474 (33.5%)	166/597 (27.8%)	**RR 0.88** (0.50–1.56)	160 per 1000	**19 fewer per 1000** (80 fewer to 90 more)
STI complications – not measured											
Compliance – not measured											
Quality of life – not measured											
HIV transmission and acquisition – not measured											
Partner transmission – not measured											

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. Some concern with no or unclear method of randomization.
2. 95% CI includes potential for more or fewer cures.
3. Few events across studies.
4. 95% CI includes potential for more or fewer adverse events.

Erythromycin compared to other quinolones for uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With other quinolones	**With erythromycin**		**Risk with other quinolones**	**Risk difference with erythromycin**
Microbiological cure											
193 (3 RCTs)	serious[1]	not serious	not serious	serious[2,3]	none	⨁⨁◯◯ LOW	88/97 (90.7%)	63/96 (65.6%)	**RR 0.80** (0.44 to 1.43)	900 per 1000	**180 fewer per 1000** (504 fewer to 387 more)
Clinical cure											
195 (2 RCTs)	serious[1]	not serious	not serious	serious[2,3]	none	⨁⨁◯◯ LOW	87/102 (85.3%)	56/93 (60.2%)	**RR 0.73** (0.35 to 1.52)	850 per 1000	**230 fewer per 1000** (553 fewer to 442 more)
Adverse events											
386 (4 RCTs)	serious[1]	not serious	not serious	serious[3,4]	none	⨁⨁◯◯ LOW	32/191 (16.8%)	71/195 (36.4%)	**RR 2.11** (1.19 to 3.75)	180 per 1000	**200 more per 1000** (34 more to 495 more)
STI complications – not measured											
Compliance – not measured											
Quality of life – not measured											
HIV transmission and acquisition – not measured											
Partner transmission – not measured											

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio

1. Some concern with no or unclear method of randomization.
2. 95% CI includes potential for more or fewer cures.
3. Few events across studies.
4. 95% CI includes potential for more or fewer adverse events.

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RECOMMENDATION 2

Treatments in adults and adolescents with uncomplicated anorectal chlamydial infections (excluding lymphogranuloma venereum	
Population:	Adults and adolescents with uncomplicated anorectal chlamydial infections
Intervention:	Azithromycin or doxycycline
Comparison:	Other antibiotics
Main outcomes:	**Critical:** Clinical cure, microbiological cure, STI complications, side-effects (including allergy, toxicity, gastro), compliance **Important:** Quality of life, HIV transmission and acquisition, partner transmission
Setting:	Outpatient
Perspective:	Population
Background:	The global prevalence and incidence of chlamydia in adult women and men remain high, like other STIs, with nearly one million new curable infections each day. This infection causes acute conditions such as cervicitis, urethritis and genital ulceration. The 2003 WHO guidelines recommend treatment of uncomplicated anogenital infections with either doxycycline 100 mg orally twice daily for 7 days, or azithromycin 1 g orally, in a single dose. Alternatively, amoxicillin 500 mg orally thrice daily for 7 days; erythromycin 500 mg orally four times daily for 7 days; ofloxacin 300 mg orally twice daily for 7 days; or tetracycline 500 mg orally four times daily for 7 days. The Guideline Development Group (GDG) identified azithromycin and doxycycline for comparison to other treatments for review.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** There is no global prevalence data for anorectal chlamydial infections. Rectal infections are rarely tested for chlamydia and usually occur concurrently with genital infections. An estimated 131 million new cases of chlamydia (100–166 million) were reported (Newman, 2012) globally in 2012, and at any point in 2012, there were about 128 million cases of chlamydia among adults aged 15–49 years. Infection can lead to severe complications and long-term sequelae, including pelvic inflammatory disease, ectopic pregnancy, infertility, chronic pelvic pain, neurological and cardiovascular disease in adults, neonatal death, premature delivery and severe disability in infants (Holmes, 2008). Furthermore, STIs, including chlamydia, frequently result in stigma, stereotyping, vulnerability and shame and have been associated with gender-based violence (Amin, 2013). **Additional considerations:** The GDG agreed that treatment of anorectal infections will be related to treatment of genital infections as rectal infection may be unknown and usually occurs concurrently with genital infection. While the consequences of vaginal infection are worse, anorectal infection is still a priority due to the risk of vaginal reinfection (creating a pool of infection). Antimicrobial resistance data should be considered given the risks. However, there is little research in this area. Of particular interest to some in the group is the sensitivity of chlamydia to azithromycin. The GDG also noted that this infection preferentially affects certain populations and may consequently have effects on equity, feasibility and acceptability.
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • **Moderate** • Large • Varies • Don't know	**Research evidence:** We included 8 non-randomized studies (5 direct comparisons and 3 single arms studies). These studies evaluated doxycycline and azithromycin. Doses included were azithromycin 1 g orally x 1, and doxycycline 100 mg twice daily x 7 days. The studies included primarily men, but some data (from two studies) were available from women. **Additional considerations:** Evidence showed that there may be 200/1000 fewer cures with azithromycin compared to doxycycline, and little-to-no difference in side-effects. Although there were fewer women in the studies, the evidence suggested little difference in the effects between men and women. However, the GDG agreed that emphasis should be placed on treating women, since they might be tested for genital but not anal infection, despite the serious potential long-term consequences. The GDG also questioned the timing of testing, which may have been short as reinfection is common. Only one patient in one trial was noted to have diarrhoea with azithromycin. However, studies in people with genital infections using doxycycline or azithromycin found few and similar numbers of side-effects (approximately 15%). Therefore this difference was considered trivial.
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • **Low** • Moderate • High • No included studies	**Additional considerations:** Data for clinical cure was not available, and therefore microbiological cure was used to inform clinical cure.

<table>
<tr>
<td>Values</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?

• Important uncertainty or variability
• Possibly important uncertainty or variability
• Probably no important uncertainty or variability
• No important uncertainty or variability
• No known undesirable outcomes</td>
<td>Research evidence:
Qualitative studies suggest that in making the decision to seek help, women act on a range of specific prompts, including lay ideas about the significance of symptoms, their own behaviour, their partner's symptoms or behaviour, contact tracing and health promotion. Psychosocial factors, such as embarrassment, are also important.

Additional considerations:
The GDG agreed that women who are tested positive for rectal chlamydia would want to be treated. There were no known reasons to believe that the values of outcomes would vary, and the group placed emphasis on the need to remove the infection from the community in general.

The panel considered noting screening for anorectal infections in men who have sex with men (MSM), transgender women and other at-risk populations, but this was decided against due to the sensitivity required in many settings concerning these populations.</td>
</tr>
<tr>
<td>Balance of effects</td>
<td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?

• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention

• Varies
• Don't know</td>
<td>Additional considerations:
The GDG agreed that the greater benefits and little-to-no difference in side-effects with doxycycline, favoured doxycycline over azithromycin.</td>
</tr>
<tr>
<td>Resources required</td>
<td>How large are the resource requirements (costs)?

• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings

• Varies
• Don't know</td>
<td>
<table>
<tr><th>A</th><th>B</th><th>C</th><th>D*</th><th>E</th><th>F</th></tr>
<tr><td>Azithromycin 1 g po</td><td>1</td><td>1</td><td>$0.38 (500 mg)</td><td>$0.76</td><td>$0.95</td></tr>
<tr><td>Doxycycline 100 mg po</td><td>2</td><td>7</td><td>$0.0191</td><td>$0.2674</td><td>$0.3342</td></tr>
<tr><td>Doxycycline (ER) 200 mg po</td><td>1</td><td>7</td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
<tr><td>Erythromycin ES 800 mg po</td><td>4</td><td>7</td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
<tr><td>Erythromycin 500 mg po</td><td>2</td><td>10-14</td><td>$0.0738</td><td>$1.476 – $2.06</td><td>$1.88 – $2.57</td></tr>
<tr><td>Amoxicillin 500 mg po</td><td>3</td><td>7</td><td>$0.032</td><td>$0.672</td><td>$0.84</td></tr>
<tr><td>Quinolones po</td><td></td><td></td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
</table>
*Sources: International drug price indicator guide (MSH, 2015) and www.drugs.com
A: treatment; B: dose per day; C: treatment duration; D: drug cost, per dose;
E: drug per full-course treatment; F: 25% procurement

Additional considerations:
The GDG agreed that azithromycin is more expensive than doxycycline, and since globally, most STI drugs come from out-of-pocket payments, this should be the primary consideration, rather than what governments or donors are willing to pay.</td>
</tr>
</table>

Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** • **Very low** • Low • Moderate • High • No included studies	**Research evidence:** No studies of resource requirements were found. **Additional considerations:** None
Cost–effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • **Probably favours the intervention** • Favours the intervention • Varies • No included studies	**Research evidence:** No cost-effectiveness studies were found. **Additional considerations:** Similar to issues related to genital chlamydial infections, the GDG stated that cost was the main factor driving effectiveness, as it dictated how many patients could access treatment, and if a patient could afford a full course of treatment. In addition, there may be a greater number of cures with doxycycline, resulting in higher cost-effectiveness compared to azithromycin.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • **Varies** • Don't know	**Research evidence:** No studies assessed equity issues. **Additional considerations:** The GDG noted that azithromycin is not on the essential medicines list for rectal infections and is only regarded as essential for genital infections. However, it was mentioned that currently this is being reviewed. One barrier is that the essential medicines list requires evidence for particular uses, and as such, research was required for rectal infections. An opinion emerged that, by being unavailable for anorectal infections, azithromycin may be more expensive than it would otherwise be. It was suggested that multi-dose regimens (like doxycycline) may reduce equity because of a stigma surrounding taking treatments, but this may vary across different populations including MSM, transgender patients and young women at increased risk of anorectal infections. More research is needed.

Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** A systematic review (in India) of the literature for treatment utilization in STIs reported that utilization ranged from 16% to 55% in community-based studies, and was higher (approximately 70%) in research trials. Treatment may not be acceptable to patients due to the resources and availability of services, social factors, and distance from a clinic. Non-utilization was also due to ignorance, illiteracy and lack of awareness. Women reported a lack of female doctors, being afraid of results, judgement from doctors, stigma, shyness and embarrassment. Cost of care and lack of faith in clinical care were also factors. An overview of reviews of medication adherence (Ryan, 2014) reported that adherence may be improved with simpler drug regimens. **Additional considerations:** The GDG agreed that one dose of azithromycin would be more acceptable than a course of doxycycline twice daily for 7 days. The GDG also discussed the need for sexual abstinence during treatment. It was noted that for azithromycin therapy, sexual abstinence may be more important than with doxycycline treatment in avoiding reinfection, as the prolonged doxycycline concentration could maintain some protection throughout the course of the treatment. However, there is no clear evidence for these effects.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** We found no studies assessing feasibility issues. **Additional considerations:** The GDG noted that important social considerations were needed for adolescent girls (and other populations), due to difficulties in bringing therapy home. The importance of including the existing prevalence data for subpopulations in these considerations was indicated by the GDG, as it is rare to know if a person has anorectal as well as genital chlamydia. It was asserted that the recommendations should explicitly mention that treatment varies between settings where only presumptive treatment of anorectal infection is possible, and settings where anorectal infections can be tested.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for uncomplicated anorectal chlamydial infections (excluding lymphogranuloma venereum)?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	In people with anorectal chlamydial infection, the WHO STI guideline suggests using doxycycline 100 mg twice daily for 7 days over azithromycin 1 g single dose. *Conditional recommendation, very low quality evidence.* Remarks: This recommendation applies to people with known anorectal infection and to people with suspected anorectal infections with genital co-infection. Clinicians should ask men, women and key populations, such as MSM, transgender persons and female sex workers about anal sex and treat accordingly. Doxycycline should not be used in pregnant women because of adverse effects. (see Recommendation 3).				
Justification	There is low quality evidence from 8 non-randomized studies (5 direct comparisons and 3 single arms studies) that evaluated doxycycline and azithromycin. There is no data for amoxicillin, erythromycin, or quinolones. Evidence showed that there may be 200/1000 fewer people with microbiological cure with azithromycin compared with doxycycline (RR 0.80, 95% CI: 0.71 to 0.91). Evidence in studies of genital infections shows little to no difference in side-effects with these treatments (RR 1.02, 95% CI: 0.72 to 1.43). Although there are fewer women in the studies, the evidence suggested little difference in effects between men and women. There is no evidence for patient values and preferences, but the GDG agreed that there are no known reasons to suspect values would vary between different people. There is little-to-no evidence for acceptability, but research into other conditions indicates that adherence may be improved with simpler drug regimens. There is little-to-no evidence for equity issues and feasibility, but azithromycin is more expensive and typically the cost is paid by the consumers. The GDG agreed that equity may vary between the medicines depending on the population; in some populations, azithromycin may be more acceptable since it is a single-dose treatment, and some people may experience stigma related to visibility of a multi-dose regimen with doxycycline. Therefore, suggesting doxycycline over azithromycin could create inequity for people sensitive to stigma related to multi-doses. Azithromycin is currently not listed as an essential drug for anorectal chlamydial infection. In summary, doxycycline may result in more cures, and although less expensive than azithromycin, azithromycin may be better accepted due to single dose treatment.				

CONCLUSIONS

Treatments for uncomplicated anorectal chlamydial infections (excluding lymphogranuloma venereum)?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	The global incidence of chlamydial anorectal infections should be determined. More research is necessary on the effects of treatments used for anorectal infections, in particular azithromycin, as it is currently not on the WHO Essential Medicines list for anorectal chlamydial infections. Effects should be assessed in both men and women and in key populations (including MSM, transgender persons and female sex workers).				

EVIDENCE PROFILE

Should azithromycin or doxycycline vs other antibiotics be used for anorectal chlamydial infections in adults and adolescents?								
Outcomes	Azithromycin 1 g po x 1 dose	Doxycycline 100 mg bid x 7 days	Erythromycin 500 mg po bid x 10–14 days	Erythromycin ES 800 mg po qd x 7 days	Erythromycin 500 mg po qd x 7 days	Doxycycline (ER) 200 mg qd x 7 days	Quinolones	Amoxicillin 500 mg po tid x 7 days
Microbiological cure	RR 0.80 (95% CI: 0.71–0.91) **198 fewer cures** (from 287 fewer to 89 fewer) ⨁⨁◯◯[1] LOW		No study found	No study found	No study found	No study found	No study found	No study found
Quality of evidence	275/347	298/303						
	840 per 1000 (810–880) 372/461 (7 non-RCTs) ⨁⨁◯◯ VERY LOW[2, 3]	**990 per 1000**[4] (980–1010) 395/401 (5 non-RCTs) ⨁⨁◯◯ VERY LOW[2, 3]						
Side-effects (including allergy, toxicity, gastrointestinal)	1 study reported one patient in the azithromycin cohort had diarrhoea	Not reported	No study found	No study found	No study found	No study found	No study found	No study found
Quality of evidence	⨁⨁◯◯ LOW[3, 4] Risk of bias							

Should azithromycin or doxycycline vs other antibiotics be used for anorectal chlamydial infections in adults and adolescents?								
Outcomes	Azithromycin 1 g po x 1 dose	Doxycycline 100 mg bid x 7 days	Erythromycin 500 mg po bid x 10–14 days	Erythromycin ES 800 mg po qd x 7 days	Erythromycin 500 mg po qd x 7 days	Doxycycline (ER) 200 mg qd x 7 days	Quinolones	Amoxicillin 500 mg po tid x 7 days
Clinical cure – Not measured								
STI complications – Not measured								
Transmission to partners – Not measured								
Compliance – Not measured								
HIV transmission and acquisition – Not measured								
Quality of life – Not measured								

bid: twice daily; ER: extended release; ES: ethylsuccinate; po: by mouth (orally); qd: daily; RCT: randomized controlled trial; tid: thrice daily

1. Most studies with unclear risk of bias criteria due to poor reporting.
2. 1 arm of the study was considered, and authors did not mention any information related to the use of an appropriate analysis method that adjusted for all the critically important confounding domain.
3. Few participants.
4. Selectively reported outcome.

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Patient values and preferences, acceptability and cost: specific to chlamydial infections

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RECOMMENDATION 3

Treatments in pregnant women with chlamydial infections	
Population:	Chlamydial infections in pregnant women
Intervention:	Azithromycin or erythromycin
Comparison:	Other antibiotics
Main outcomes:	**Critical:** Fetal outcomes (e.g. teratogenicity, toxicity), fetal loss,prematurity/low birth weight (LBW), chorioamnionitis, infant pneumonitis/ neonatal ophthalmia, postpartum endometritis, microbiological cure, side-effects (including allergy, toxicity, gastro), clinical cure (symptoms), compliance **Important:** HIV acquisition, quality of life, transmission to partner
Setting:	Out- or inpatient
Perspective:	Population
Background:	Chlamydia is a STI that can cause eye or lung infections in the newborn infant if the mother is infected during pregnancy or labour. Postpartum endometritis has also been associated with chlamydial infection. The 2003 WHO Guidelines recommend treatment of chlamydial infections during pregnancy with erythromycin 500 mg orally four times daily or 7 days or amoxicillin 500 mg orally thrice daily for 7 days. The Guideline Development Group (GDG) identified azithromycin and erythromycin for comparison to other treatments for review.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** According to 2013 Global Burden of Disease estimates, chlamydia was the 10th most common incident condition. Mother-to-child transmission can occur at the time of delivery and may result in ophthalmia neonatorum or pneumonitis in the neonate. Estimates of the risk of transmission at the time of delivery vary. The risk of mother-to- child transmission resulting in moderate to severe conjunctivitis appears to be approximately 15% to 25% and for pneumonitis or infection of the lungs the risk is 5% to 15%. Mothers may also be at increased risk of infection of the uterus (Brocklehurst, 2013). Furthermore, STIs, including chlamydia, frequently result in stigma, stereotyping, vulnerability and shame, and have been associated with gender-based violence (Amin, 2013). **Additional considerations:** None
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • **Small** • Moderate • Large • Varies • Don't know	**Research evidence:** We included a systematic review of 11 randomized controlled trials published up to January 1998 and found an additional 3 trials. There were two additional non-randomized studies with over 100 pregnant women included. See the evidence profile below for the summary of the results. **Additional considerations:** The differences in benefits between the different treatments were small and confidence intervals used included the possibility of more benefit and less benefit. There are probably 95/1000 more microbiological cures with azithromycin versus erythromycin; and may be 72/1000 more microbiological cures with azithromycin versus amoxicillin. There are probably 40 fewer cures with erythromycin versus amoxicillin.
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • **Small** • Trivial • Varies • Don't know	There may be slightly fewer side-effects with azithromycin compared to erythromycin or amoxicillin (approximately 50/1000), but there may be more side-effects with erythromycin versus amoxicillin. Much of the evidence was uncertain for fetal outcomes, as it came from indirect comparisons in large cohort studies. There were few events, and confidence intervals around the small differences included the potential for fewer or more events between comparisons. The GDG noted that adverse events may depend on the stage of pregnancy, but this was not investigated in studies.
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • **Low** • Moderate • High • No included studies	**Additional considerations:** There was moderate-to-low quality evidence for the desirable effects, but low-to-very-low quality evidence for the side-effects and fetal outcomes. However, the fetal outcomes with very low quality evidence did not change the direction of the recommendation and so the evidence was assessed as low quality.

<table>
<tr>
<td>Values</td>
<td>Is there important uncertainty about or variability in how much people value the main outcomes?
• Important uncertainty or variability
• Possibly important uncertainty or variability
• Probably no important uncertainty or variability
• No important uncertainty or variability
• No known undesirable outcomes</td>
<td>Research evidence:
According to economic evaluation studies, the disutilities of different health states related to chlamydia (utility loss due to the health states), are as following:
Pelvic inflammatory disease (outpatient): –0.37
Pelvic inflammatory disease (inpatient): –0.43
Ectopic pregnancy: –0.42
Chronic pelvic pain: –0.4
Neonatal conjunctivitis: –0.03
Neonatal pneumonia: –0.21

Qualitative studies suggest that in making the decision to seek help, women act on a range of specific prompts, including lay ideas about the significance of symptoms, their own behaviour, their partner's symptoms or behaviour, contact tracing and health promotion. Psychosocial factors, such as embarrassment, are also important.

Additional considerations:
The GDG was confident that pregnant women values would not vary.</td>
</tr>
<tr>
<td>Balance of effects</td>
<td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention
• Varies
• Don't know</td>
<td>Additional considerations:
Azithromycin vs erythromycin: Favours azithromycin
Azithromycin vs amoxicillin: Probably favours azithromycin
Erythromycin vs amoxicillin: Probably favours amoxicillin</td>
</tr>
<tr>
<td>Resources required</td>
<td>How large are the resource requirements (costs)?
• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings
• Varies
• Don't know</td>
<td>
<table>
<tr><th>A</th><th>B</th><th>C</th><th>D*</th><th>E</th><th>F</th></tr>
<tr><td>Azithromycin 1 g po (orally)</td><td>1</td><td>1</td><td>$0.38 (500 mg)</td><td>$0.76</td><td>$0.95</td></tr>
<tr><td>Erythromycin 500 mg po</td><td>4</td><td>7</td><td>$0.0738</td><td>$2.06</td><td>$2.57</td></tr>
<tr><td>Amoxicillin 500 mg po</td><td>3</td><td>7</td><td>$0.032</td><td>$0.672</td><td>$0.84</td></tr>
<tr><td>Erythromycin 500 mg po</td><td>2</td><td>14</td><td>$0.0738</td><td>$2.06</td><td>$2.57</td></tr>
<tr><td>Erythromycin 250 mg po</td><td>4</td><td>14</td><td>$0.0428</td><td>$2.39</td><td>$2.98</td></tr>
<tr><td>Erythromycin ES 800 mg po</td><td>4</td><td>7</td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
<tr><td>Erythromycin ES 400 mg po</td><td>4</td><td>14</td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
</table>

* Sources: International drug price indicator guide (MSH, 2015) and www.drugs.com
A: treatment; B: dose per day; C: treatment duration; D: drug cost, per dose; E: drug per full-course treatment; F: 25% procurement

In a systematic review (Pitsouni, 2007) of treatments for chlamydia in pregnant women, 3/7 studies measured costs. All three reported greater total costs of therapy with azithromycin versus amoxicillin or erythromycin.

Additional considerations:

Azithromycin vs erythromycin: Being cheaper than erythromycin, it was thought that azithromycin would have savings.

Azithromycin vs amoxicillin: There is no large cost differential between azithromycin and amoxicillin. The GDG indicated that amoxicillin is slightly cheaper than azithromycin, easier to source, and could therefore have a smaller impact on resources.</td>
</tr>
</table>

Certainty of evidence of required resources	**What is the certainty of the evidence of resource requirements (costs)?** • **Very low** • Low • Moderate • High • No included studies	We found no studies assessing the resource use with these treatments
Cost-effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	**Research evidence:** Although, there were many studies assessing costs of screening for chlamydia, there were no recent studies focused on cost of treatment. Resource factors in other models included index patient interview, record search, field visit, STD evaluation, treatment with dose of drug, expected late detection costs, investigation of the partner's sexual partners, infection cost, disease intervention and specialist time/cost. Patient variability to consider: probability of care being sought, probability of consent to treatment, probability of adherence to referral, and probability of partner seeking care. **Additional considerations:** The GDG agreed that cost-effectiveness probably favours azithromycin over erythromycin, because it is more effective and it is cheaper. Cost-effectiveness also probably favours azithromycin over amoxicillin due to effectiveness. Amoxicillin may be more cost-effective than erythromycin because it costs less, is more effective and leads to fewer side-effects.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • **Varies** • Don't know	**Research evidence:** We found no research evidence for equity issues. **Additional considerations:** The GDG identified that azithromycin may not be accessible in many settings and suggested that equity would decrease in these settings. In areas where azithromycin is unavailable, penicillin allergies pose equity problems, and erythromycin would therefore be the next best treatment.

Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** A systematic review of treatments for chlamydia in pregnant women analysed compliance across studies. Patients treated with azithromycin compared with erythromycin showed better compliance (374 patients, 6 RCTs): odds ratio (OR) 23.7 (95% CI: 9.34–60.14). Patients treated with azithromycin compared with erythromycin or amoxicillin showed better compliance (413 patients, 7 RCTs): OR = 21.96, 95% CI 9.05–53.3). An overview of reviews of medication adherence (Ryan, 2014) reported that adherence may be improved with simpler drug regimens. A systematic review (in India) of the literature for treatment utilization in STIs reported that utilization ranged from 16% to 55% in community-based studies and was higher (approximately 70%) in research trials. Treatment may not be acceptable to patients due to the resources and availability of services, social factors and distance from a clinic. Non-utilization was also due to ignorance, illiteracy and lack of awareness. Women reported a lack of female doctors, being afraid of results, judgement from doctors, stigma, shyness and embarrassment. Cost of care and lack of faith in clinical care were also factors. **Additional considerations:** The GDG noted that azithromycin may have better adherence, resulting in better effect in studies. The side-effects for erythromycin may make it a less acceptable treatment than amoxicillin, provided no allergies.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** We found no studies assessing feasibility. **Additional considerations:** The GDG believed that in countries where azithromycin is not being procured, it is generally due to a belief that it is more expensive, which is not true.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable Effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost–effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for adults and adolescents, and pregnant women with late syphilis

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	•	●
Recommendation	**Recommendation 3a** In pregnant women with genital chlamydial infection, the WHO STI guideline recommends using azithromycin over erythromycin. *Strong recommendation, moderate quality evidence* **Recommendation 3b** In pregnant women with genital chlamydial infection, the WHO STI guideline suggests using azithromycin over amoxicillin. *Conditional recommendation, low quality evidence* **Recommendation 3c** In pregnant women with genital chlamydial infection, the WHO STI guideline suggests using amoxicillin over erythromycin. *Conditional recommendation, low quality evidence* **Dosages:** • Azithromycin 1 g as a single dose • Amoxicillin 500 mg 3 × a day × 7 days • Erythromycin 500 mg twice a day × 7 days **Remarks:** Azithromycin is the first choice of treatment, but it may not be available in some settings. However, it is less expensive than erythromycin and since it is provided as a single dose this may result in better adherence and by extension better outcomes.				

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	•	●
Justification	Overall, there is moderate-to-low quality evidence from 14 RCTs, 2 non-randomized comparative studies and 2 large cohort studies assessing the effects of azithromycin, erythromycin and amoxicillin in pregnant women with chlamydial infections. The difference in benefits between these different treatments is small and wide confidence intervals included the possibility of greater or less benefit with azithromycin compared to other drugs. Moderate quality evidence found that there are probably 94/1000 more people microbiologically cured with azithromycin versus erythromycin (RR 1.11; 95% CI: 0.94–1.30), and low-quality evidence found that there may be 72/1000 more people cured with azithromycin versus amoxicillin (RR 1.09, 95%CI: 0.93–1.28). There are probably 40 fewer people microbiologically cured with erythromycin versus amoxicillin (RR 0.95; 95% CI: 0.88–1.02). There may be slightly fewer side-effects with azithromycin compared with erythromycin or amoxicillin (approximately 50/1000 fewer), but there may be more side-effects with erythromycin versus amoxicillin (approximately 400/1000 more). Much of the evidence was uncertain for fetal outcomes as it came from indirect comparisons in large cohort studies. There were few events and confidence intervals around the small differences and included the potential for fewer or more events between comparisons. In summary, the GDG agreed azithromycin would be preferred over erythromycin because of greater effectiveness and lower cost, and preferred over amoxicillin due to greater effectiveness. Azithromycin may also be more acceptable due to single dosage; however, it may not be available in all settings due to misconceptions that it is costly. Amoxicillin is preferred over erythromycin as it is less costly and may result in greater benefits and fewer side-effects. The GDG judged the benefits of treatment with benzathine penicillin G versus no treatment as large, based on the historically successful treatment of syphilis over the past 70 years. It was also judged that the differences in benefits between medicines used for treatment are likely to be trivial. The differences in the undesirable anticipated effects (side-effects) were judged to be small. Because the benefits probably outweigh the harms, and because of the potential for resistance to azithromycin, greater cost and lack of historical data for azithromycin, benzathine penicillin G and procaine penicillin were suggested. The penicillins were suggested over doxycycline due to the lack of historical data in late syphilis and unknown side-effects and benefits of doxycycline. For pregnant women, the penicillins were also suggested over erythromycin since erythromycin does not cross the placental barrier. The GDG also judged administration of benzathine and procaine penicillins by injection as being acceptable to most people.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	Research in pregnant women comparing these treatments and the recommended dosages should be conducted. Although these drugs are relatively safe in pregnancy, maternal and fetal complications (e.g. adverse pregnancy outcome, fetal defects) with the use of these treatments for STIs and other infections should be monitored, collected and analysed to inform these recommendations in the future. When conducting these studies, costs and acceptability of the treatments could be measured.				

EVIDENCE PROFILE

Chlamydia in pregnant women

Azithromycin versus erythromycin											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**
Microbiological cure											
290 (4 RCTs)	not serious	not serious	not serious	serious[1, 2]	none	⨁⨁⨁◯ MODERATE	118/145 (81.4%)	134/145 (92.4%)	**RR 1.11** (0.94–1.30)	850 per 1000	**94 more per 1000** (51 fewer to 255 more)
169 (1 non-RCT)	serious[3]	not serious	not serious	serious[1]	none	⨁◯◯◯ VERY LOW	18/28 (64.3%)	137/141 (97.2%)	**RR 1.51** (1.15–1.99)	850 per 1000	**434 more per 1000** (127 more to 842 more)
Side-effects sufficient to stop treatment											
160 (3 RCTs)	not serious	not serious	not serious	serious[1,]	none	⨁⨁⨁◯ MODERATE	13/80 (16.3%)	1/80 (1.3%)	**RR 0.11 (0.02–0.59)**	**Low**	
										50 per 1000	**45 fewer per 1000** (49 fewer to 21 fewer)
										High	
										100 per 1000	**89 fewer per 1000** (98 fewer to 41 fewer)

Azithromycin versus erythromycin (continued)											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**
Side-effects not sufficient to stop treatment											
289 (4 RCTs)	not serious	not serious	not serious	serious[1]	none	⨁⨁⨁◯ MODERATE	92/144 (63.9%)	21/145 (14.5%)	**RR 0.26** (0.16–0.42)	400 per 1000	**296 fewer per 1000** (336 fewer to 232 fewer)
Fetal anomalies											
130 (1 RCT)	serious[4]	not serious	not serious	very serious[1,5,6]	none	⨁◯◯◯ VERY LOW	1/65 (1.5%)	1/65 (1.5%)	**RR 1.00** (0.06–15.65)	15 per 1000	**0 fewer per 1000** (14 fewer to 186 more)
Delivery < 37 weeks											
130 (1 RCT)	serious[4]	not serious	not serious	very serious[1,5,6]	none	⨁◯◯◯ VERY LOW	8/65 (12.3%)	6/65 (9.2%)	**RR 0.75** (0.28–2.04)	110 per 1000	**28 fewer per 1000** (79 fewer to 114 more)
138 792 (2 observational studies)	serious[3]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	530/6825 (7.8%)	8332/131967 (6.3%)	**RR 1.03** (0.94–1.13)	60 per 1000	**2 more per 1000** (4 fewer to 8 more)

Azithromycin versus erythromycin (continued)											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**
Neonatal mortality/fetal loss											
130 (1 RCT)	serious[4]	not serious	not serious	very serious[1,5]	none	⨁◯◯◯ VERY LOW	0/65 (1.5%)	0/65 (1.5%)	0 events , Not estimable		
138 695 (2 observational studies)	serious[3]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	86/6780 (1.3%)	1186/131915 (0.9%)	**RR 1.19** (0.93–1.52)	7 per 1000	**1 more per 1000** (0 fewer to 4 more)
Maternal postpartum endometritis and chorioamnionitis (non-RCT)											
210 (1 observational study)	serious[3]	not serious	not serious	serious[1,6]	none	⨁◯◯◯ VERY LOW	1/32 (3.1%)	3/178 (1.7%)	**RR 0.54** (0.06–5.02)	31 per 1000	**14 fewer per 1000** (29 fewer to 126 more)
Clinical cure – not measured											
Compliance – not measured											
HIV acquisition – not measured											
Quality of life – not measured											
Transmission to partner – not measured											

CI: confidence interval; OR: odds ratio; RR: risk ratio

Azithromycin versus amoxicillin											
Microbiological cure							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**
Neonatal mortality/fetal loss											
168 (2 RCTs)	not serious	not serious	not serious	very serious[1,2]	none	⨁⨁◯◯ LOW	59/85 (69.4%)	62/83 (74.7%)	**RR 1.09** (0.93–1.28)	800 per 1000	**72 more per 1000** (56 fewer to 224 more)
162 (1 non-RCT)	serious[3]	not serious	not serious	serious[2]	none	⨁◯◯◯ VERY LOW	20/21 (95.2%)	137/141 (97.2%)	**RR 1.02** (0.92–1.13)	800 per 1000	**16 more per 1000** (64 fewer to 104 more)
Side-effects sufficient to stop treatment											
129 (1 RCT)	not serious	not serious	not serious	very serious[1,5,6]	none	⨁⨁◯◯ LOW	6/63 (9.5%)	3/66 (4.5%)	**RR 0.48** (0.12–1.83)	100 per 1000	**52 fewer per 1000** (88 fewer to 83 more)
Side-effects not sufficient to stop treatment											
39 (1 RCT)	not serious	not serious	not serious	very serious[1,5,6]	none	⨁⨁◯◯ LOW	10/20 (50.0%)	5/19 (26.3%)	**RR 0.53** (0.22–1.26)	500 per 1000	**235 fewer per 1000** (390 fewer to 130 more)
Delivery < 37 weeks											
138,792 (2 observational studies)	serious[3]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	634/6780 (6.3%)	8332/131,967 (6.3%)	**RR 0.96** (0.89–1.04)	64 per 1000	**3 fewer per 1000** (7 fewer to 3 more)

Azithromycin versus amoxicillin (continued)											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**
Neonatal mortality/fetal loss											
138,695 (2 observational studies)	serious[3]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	86/6780 (1.3%)	1186/131,915 (0.9%)	**RR 1.19** (0.93–1.52)	9 per 1000	**2 more per 1000** (1 fewer to 5 more)
Maternal postpartum endometritis and chorioamnionitis (non-RCT)											
210 (1 observational study)	serious[3]	not serious	not serious	serious[1,6]	none	⨁◯◯◯ VERY LOW	0/22 (0.0%)	3/178 (1.7%)	**RR 0.90** (0.05–16.86)		
Clinical cure – not measured											
Compliance – not measured											
HIV acquisition – not measured											
Quality of life – not measured											
Transmission to partner – not measured											

CI: confidence interval; OR: odds ratio; RR: risk ratio

Erythromycin versus amoxicillin											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**
Microbiological cure											
390 (3 RCTs)	not serious	not serious	not serious	serious[2]	none	⨁⨁⨁◯ MODERATE	182/199 (91.5%)	163/191 (85.3%)	**RR 0.95** (0.88 to 1.02)	800 per 1000	**40 fewer per 1000** (96 fewer to 16 more)
Microbiological cure											
171 (2 non-RCTs)	serious[3]	not serious	not serious	serious[1,2]	none	⨁◯◯◯ VERY LOW	83/85 (97.6%)	73/86 (84.9%)	**RR 0.82** (0.52 to 1.30)	800 per 1000	**144 fewer per 1000** (384 fewer to 240 more)
Side-effects sufficient to stop treatment											
565 (5 RCTs)	not serious	not serious	not serious	very serious[1,6]	none	⨁⨁◯◯ LOW	10/285 (3.5%)	50/280 (17.9%)	**RR 5.11** (1.67 to 15.63)	100 per 1000	**411 more per 1000** (67 more to 1463 more)
122 (1 non-RCT)	serious[4]	not serious	not serious	serious[1,6]	none	⨁◯◯◯ VERY LOW	2/64 (3.1%)	13/58 (22.4%)	**RR 7.17** (1.69 to 30.44)	100 per 1000	**617 more per 1000** (69 more to 2944 more)

Erythromycin versus amoxicillin (continued)											
Quality assessment							**Summary of findings**				
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**
Side-effects not sufficient to stop treatment											
304 (3 RCTs)	not serious	not serious	not serious	very serious[1,5,6]	none	⨁⨁◯◯ LOW	10/154 (6.5%)	35/150 (23.3%)	**RR 3.35** (1.74 to 6.46)	500 per 1000	**1175 more per 1000** (370 more to 2730 more)
122 (1 non-RCT)	serious[4]	not serious	not serious	serious[1,6]	none	⨁◯◯◯ VERY LOW	6/64 (12.5%)	2/58 (3.4%)	**RR 0.37** (0.08 to 1.75)	500 per 1000	**315 fewer per 1000** (460 fewer to 375 more)
Preterm delivery/ Delivery < 37 weeks											
13872 (1 observational study)	serious[3]	not serious	not serious	serious[1]	none	⨁◯◯◯ VERY LOW	450/8143 (5.5%)	346/5729 (6.0%)	**RR 1.09** (0.95 to 1.25)	55 per 1000	**5 more per 1000** (3 fewer to 14 more)
Fetal death											
12553 (1 observational study)	serious[3]	not serious	not serious	serious[1,6]	none	⨁◯◯◯ VERY LOW	62/6824 (0.9%)	41/5729 (0.7%)	**RR 0.79** (0.53 to 1.17)	9 per 1000	**2 fewer per 1000** (4 fewer to 2 more)

Erythromycin versus amoxicillin (continued)												
Quality assessment							**Summary of findings**					
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**		
							With erythromycin	**With azithromycin**		**Risk with other erythromycin**	**Risk difference with azithromycin**	
Major malformations												
3385 (1 observational study)	serious[3]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	36/1599 (2.3%)	51/1786 (2.9%)	**RR 1.27** (0.83 to 1.93)	23 per 1000	**6 more per 1000** (4 fewer to 21 more)	
Maternal postpartum endometritis and chorioamnionitis												
54 (1 non-RCT)	serious[3]	not serious	not serious	serious[1, 6]	none	⨁◯◯◯ VERY LOW	0/22 (0.0%)	1/32 (3.1%)	**RR 2.09** (0.09 to 49.09)			
Clinical cure – not measured												
Compliance – not measured												
HIV acquisition – not measured												
Quality of life – not measured												
Transmission to partner – not measured												

CI: confidence interval; OR: odds ratio; RR: risk ratio

1. Few events or participants.
2. 95% CI includes potential for more or fewer cures.
3. It was a non-RCT, and authors did not mention any information related to the use of an appropriate analysis method that adjusted for all the critically important confounding domains.
4. Selective reporting likely since few trials reported on this outcome.
5. Number of participants based on total pregnant women in study.
6. 95% CI includes potential for more or fewer adverse events.

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RECOMMENDATION 4

Treatments for adults and adolescents with lymphogranuloma venereum	
Population:	Adults and adolescents with lymphogranuloma venereum (LGV)
Intervention:	Doxycycline or azithromycin
Comparison:	Other antibiotics
Main outcomes:	**Critical:** Clinical cure, microbiological cure Important: STI complications, side-effects (including allergy, toxicity, gastro), quality of life, HIV transmission and acquisition, compliance, LGV transmission to partner
Setting:	Out- or inpatient
Perspective:	Population
Background:	Lymphogranuloma venereum (LGV) is a bacterial infection caused by variations of *Chlamydia trachomatis*. Diagnosis of LGV may be missed due to the lack of tests/tools to distinguish LGV from chlamydial infections. LGV has been reported in men who have sex with men (MSM) and is associated with HIV infection. LGV infection is curable using antibiotics. The 2003 WHO guidelines recommend treatment with doxycycline 100 mg orally twice daily for 14 days or erythromycin 500 mg orally four times daily for 14 days. An alternative regimen is also recommended: tetracycline 500 mg orally four times daily for 14 days. The Guideline Development Group (GDG) requested a review of evidence for doxycycline and erythromycin for a longer duration (21 days), as well as for azithromycin 1 g orally once a week x 1–3 weeks.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Epidemiological research reports that LGV is endemic in parts of Africa, Asia, South America and the Caribbean. A report from 2008 found that of 162 men attending a STI clinic, 14% had LGV (O'Farrell, 2008). LGV is a more invasive form of chlamydia, lacks clinically convenient diagnostic tests for strains, and has historically required longer treatment than genital chlamydia. People infected with LGV can experience discharge, pain, bleeding, ulcers, tenesmus and cramping. Long-term consequences without treatment can include tissue damage, abscesses, chronic fissures or strictures. **Additional considerations:** The GDG also indicated the concern that the potential for HIV and hepatitis C transmission could be increased with LGV infection.
Desireable effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** We found no randomized controlled trials (RCTs) or comparative studies comparing doxycycline or azithromycin to other treatments. We found 12 non-randomized studies with no comparisons. None of these studies assessed the effects of the doses previously recommended in the 2003 WHO STI guidelines (i.e. 14-day regimens). See the evidence profile below for the summary of the results. **Additional considerations:** Low quality data show that doxycycline twice daily for 21 days may have high cure rates. The effects of azithromycin and erythromycin were uncertain with only 14 people receiving azithromycin and 31 people receiving erythromycin in studies. However, indirect evidence for azithromycin use in other chlamydial infections suggests it may have large effects. More research into the use of erythromycin and azithromycin in these infections is needed, specifically an RCT comparing doxycycline and azithromycin. There was no evidence in clinical studies to determine whether the type of LGV could impact the effectiveness of treatments.
Undesireable effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	There was very low quality evidence for trivial side-effects of doxycycline. However, there is moderate quality evidence for trivial side-effects of these treatments for other chlamydial infections.
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • **Very low** • Low • Moderate • High • No included studies	

<table>
<tr><td>Values</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?
• Important uncertainty or variability
• Possibly important uncertainty or variability
• Probably no important uncertainty or variability
• No important uncertainty or variability
• No known undesirable outcomes</td><td>Research evidence:
No research evidence

Additional considerations:
The GDG agreed that there were no reasons to believe that values would vary between different people; however, it was noted that LGV proctitis is a more significant problem for HIV- and hepatitis C-infected patients and especially for MSM.</td></tr>
<tr><td>Balance of effects</td><td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention
• Varies
• Don't know</td><td>Research evidence:
None

Additional considerations:
The GDG agreed that the balance of effects favoured doxycycline, probably favoured azithromycin, and was unsure of erythromycin.</td></tr>
<tr><td>Resources required</td><td>How large are the resource requirements (costs)?
• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings
• Varies
• Don't know</td><td>
<table>
<tr><th>A</th><th>B</th><th>C</th><th>D*</th><th>E</th><th>F</th></tr>
<tr><td>Azithromycin 1 g po × 3</td><td>1</td><td>1</td><td>$0.38 (500 mg)</td><td>$ 0.76</td><td>$0.95</td></tr>
<tr><td>Doxycycline 100 mg po</td><td>2</td><td>7</td><td>$0.0191</td><td>$0.2674</td><td>$0.3342</td></tr>
<tr><td>Doxycycline (ER) 200 mg po</td><td>1</td><td>7</td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
<tr><td>Erythromycin ES 800 mg po</td><td>4</td><td>7</td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
<tr><td>Erythromycin 500 mg po x 21 days</td><td>2</td><td>10–14</td><td>$0.0738</td><td>1.476–2.06</td><td>$1.88–$2.57</td></tr>
<tr><td>Amoxicillin 500 mg po</td><td>3</td><td>7</td><td>$0,032</td><td>$0.672</td><td>$0.84</td></tr>
<tr><td>Quinolones po</td><td></td><td></td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
</table>
Sources: International drug price indicator guide (MSH, 2015) and www.drugs.com
A: treatment; B: dose per day; C: treatment duration; drug cost, per dose; E: drug per full-course treatment; F: 25% procurement

Additional considerations:
The GDG agreed that doxycycline was less expensive than the alternative antibiotics, but that these too were also inexpensive.</td></tr>
<tr><td>Certainty of evidence</td><td>What is the certainty of the evidence of resource requirements (costs)?
• Very low
• Low
• Moderate
• High
• No included studies</td><td>Research evidence:
No studies were found with details of resource use.

Additional considerations:
none</td></tr>
</table>

Cost-effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • Probably favours the comparison • Does not favour either the intervention or the comparison • **Probably favours the intervention** • Favours the intervention • Varies • No included studies	**Research evidence:** Sahin-Hodoglugil (2003) found that the "gold standard" protocol with diagnosis and treatment, using azithromycin for chlamydial infections, was found to be more cost-effective than using doxycycline. For both the gold standard and syndrome management protocols, the total cost of the program was most sensitive to the percentage of women seeking STI treatment and the prevalence of non-STI vaginal discharge. Although, there were many studies assessing costs of screening for chlamydia, there were no recent studies focused on cost of treatment. Resource factors in other models included index patient interview, record search, field visit, STD evaluation, treatment with dose of drug, expected late detection costs, investigation of the partner's sex partners, infection cost, disease intervention and specialist time/cost. Patient variability to consider: probability of care being sought, probability of consent to treatment, probability of adherence to referral, and probability of partner seeking care. **Additional considerations:** Given the benefits and low cost, cost-effectiveness probably favours doxycycline or azithromycin, however cost-effectiveness is unknown for erythromycin due to its unknown effectiveness.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • Probably no impact • Probably increased • Increased • Varies • **Don't know**	**Research evidence:** No research evidence was found. **Additional considerations:** The GDG noted that LGV was a significant infection in MSM, and that there was evidence of its association with proctitis and hepatitis C infection. It was emphasized that this was not a trivial condition. If treatment is associated with a reduction in HIV transmission, it may help increase equity.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** A systematic review (in India) of the literature for treatment utilization in STIs reported that utilization ranged from 16% to 55% in the community-based studies, and was higher (approximately 70%) in research trials. Treatment may not be acceptable to patients due to the resources and availability of services, social factors, and distance from a clinic. Non-utilization was also due to ignorance, illiteracy and lack of awareness. Women reported a lack of female doctors, being afraid of results, judgement from doctors, stigma, shyness and embarrassment. Cost of care and lack of faith in clinical care were also factors. **Additional considerations:** The GDG agreed that the length of treatment may be an issue for compliance. However, if a patient does not take the course perfectly over 21 days, the course of treatment still appears to work.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** None **Additional considerations:** The GDG considered the treatments as feasible, but distribution and compliance concerns should be taken into account.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidenceof required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatments for lymphogranuloma venereum (LGV)

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	●	•
Recommendation	In adults and adolescents with LGV, the WHO STI guideline suggests using doxycycline 100 mg twice daily for 21 days over azithromycin 1 gram weekly for 21 days. *Conditional recommendation, very low quality evidence* Remarks: Good practice dictates treatment of LGV, in particular for MSM and for people living with HIV. When doxycycline is contraindicated, azithromycin should be provided. When neither treatment is available, erythromycin 500 mg orally four times daily for 21 days is an alternative. Doxycycline should not be used in pregnant women because of adverse effects (see Recommendation 3).				
Justification	There is very low quality evidence from 12 non-randomized studies with no comparisons between treatments. These studies assessed azithromycin and doxycycline for 21 days, and erythromycin for 14 days. Evidence for doxycycline showed that there may be large benefits (number of people clinically and microbiologically cured was greater than 90%) and trivial side-effects (such as persistent mucous membrane abnormalities, perirectal abscess and allergy). The effects of azithromycin and erythromycin were uncertain, with only 14 people receiving azithromycin and 31 people receiving erythromycin in studies. Side-effects are likely trivial and similar to the side-effects of these treatments in people with other chlamydial infections. There is no evidence for variation of patient values and preferences, but the GDG agreed that there are no known reasons to suspect values would vary between different people. There is little to no evidence for acceptability, but research in other conditions indicates that adherence may be improved with simpler drug regimens. There is little evidence for equity issues and feasibility, but the GDG agreed that these may be dependent on individuals and countries. Data for drug prices and procurement indicate that doxycycline is cheaper than azithromycin and erythromycin, although the latter drugs are still inexpensive. In summary, there is very low quality evidence for all drugs for treatment of LGV. The evidence suggests large benefits with doxycycline over azithromycin, and the effects of erythromycin are unknown. In addition, doxycycline is also the least expensive. In summary, there is very low quality evidence for all drugs for treatment of LGV. The evidence suggests large benefits with doxycycline over azithromycin, and the effects of erythromycin are unknown. In addition, doxycycline is also the least expensive.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	Additional research for each of the treatments and the dosages recommended is needed, in particular for erythromycin and azithromycin. Randomized controlled trials should be conducted and measure critical and important outcomes, such as clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastrointestinal effects), quality of life, HIV transmission and acquisition, compliance and LGV transmission to partners. The effects of shorter courses of treatment should also be investigated.				

EVIDENCE PROFILE

Outcomes	Quality of evidence	Doxycycline 100 mg bid x 21 days[a]	Azithromycin 1 g single dose	Azithromycin 1 g single dose x 12 days	Azithromycin 1 g single dose x 3 weeks	Azithromycin 500 mg x 3–5 days[b]	Erythromycin 500 mg bid x 21 days
Clinical cure	⊕⊖⊖⊖ Very low[c]	0.92 (0.75–1.09) 11/12		0.00 (–0.40 – 0.40) 0/1		1.00 (0.60–1.40) 1/1	1.00 (0.94–1.06) 30/30
Microbiological cure	⊕⊖⊖⊖ Very low[c]	0.98 (0.95–1.00) 181/186	1.00 (0.80–1.20) 6/6		1.00 (0.76–1.24) 4/4	0.00 (–0.33 – 0.33) 0/2	1.00 (0.60–1.40) 1/1
Persistent mucous membrane abnormalities	⊕⊖⊖⊖ Very low[c]	0.38 (0.16–0.59) 6/16					
Perirectal abscess	⊕⊖⊖⊖ Very low	0.17 (–0.10 – 0.43) 1/6					
Side-effects (doxycycline allergy)	⊕⊖⊖⊖ Very low[c]	0.02 (–0.03 – 0.06) 1/60					
STI complications	Not measured						
Quality of life	Not measured						
HIV transmission and acquisition	Not measured						
Compliance	Not measured						
LGV transmission to partner	Not measured						

bid: twice daily
Note: Data are presented as pooled proportions (95% CI) and study event rates n/N (%) (n=number of events, N = total number of patients followed-up).

a Two studies (Krishnamurthy, 1982; Hevia, 1971) not included: one study provided doxycycline 200 mg once daily × 10 days (6/8 patients had complete ulcer healing after treatment; 2 were resistant and retreated with spectinomycin; authors reported no side-effects); the other study provided 100 mg twice daily × 3 days, then 100 mg once daily × 12 days (10/10 had microbiological and clinical cure within 15 days; authors reported 4/36 had vomiting or nausea early in treatment).

b Clinical cure data is based on patient treated for 5 days (Sethi, 2009) where as microbiological cure data is based on a study reported after 3 days of treatment (Kamarashev, 2010).

c Quality of evidence very low due to high risk of bias in studies and imprecision.

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RECOMMENDATION 5

Treatment of chlamydial ophthalmia neonatorum	
Population:	Neonatal conjunctivitis
Intervention:	Erythromycin
Comparison:	Erythromycin, azithromycin, or trimethoprim
Main outcomes:	**Critical:** Clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastro), antimicrobial resistance, compliance
Setting:	Out- or inpatient
Perspective:	Population
Background:	*Chlamydia trachomatis* can be transmitted from the mother to the newborn infant during labour, causing neonatal conjunctivitis (ophthalmia neonatorum). Today, *Chlamydia trachomatis* appears to be the most common cause, but other pathogens include *Neisseria gonorrhoeae*, *Staphylococcus spp., Streptococcus sp., Haemophilus influenza* and *Enterobacteriaceae* can also cause neonatal conjunctivitis. Different strategies are available for prophylaxis, although many high-income countries do not utilize them. The 2003 WHO Guidelines recommend treatment of neonatal chlamydial conjunctivitis with erythromycin syrup 50 mg/kg daily orally given in 4 divided doses for 14 days. An alternative regimen of trimethoprim 40 mg with sulfamethoxazole 200 mg orally twice daily for 14 days is also recommended. The Guideline Development Group (GDG) identified erythromycin, azithromycin and trimethoprim for review.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Recent research reports the risk of developing neonatal chlamydial conjunctivitis from mothers with *Chlamydia trachomatis* is 18–50% (Kakar, 2010). In addition, a review of the literature showed similar incidence in mothers exposed, and 1–10% in mothers not exposed or with unknown exposure (Darling, 2010). Long-term consequences of ophthalmia neonatorum may include blindness, and this is particularly prevalent in areas with poor access to health care. **Additional considerations:** The reviewers stated that there were no RCTs making direct comparisons of these treatments. There was one direct NRS comparison, and the remaining data were extracted from single arms of RCTs or non-randomized studies, hence the recommendation was made largely on indirect data. No data for trimethoprim was included. This was put down to the rarity of neonatal conjunctivitis in developed countries, where the panel said azithromycin was probably being used. Trimethoprim was included in the question because it forms part of the erstwhile WHO recommendation for this infection and while it is cheaper, one panel member emphasized that it is not used and should not be considered in this recommendation. Another issue raised was that diagnosis of specifically chlamydial conjunctivitis is rare. Most treatment of neonatal conjunctivitis would therefore be syndromic, and some panel members expressed concern that the recommendation should reflect this need to treat other infectious agents. WHO: A subgroup of the GDG discussed this question and others some weeks later, bringing in ophthalmic expertise. The outcomes of this teleconference are included where appropriate. WHO: The GDG automatically treated the problem as a priority, In the teleconference that followed, the team decided to look at whether treatment was recommended over no treatment and it was decided that treatment was recommended given the minimal adverse effects and large benefit of treatment. This is fully delineated in the question concerning gonococcal neonatal conjunctivitis.

<table>
<tr><td>Desireable effects</td><td>How substantial are the desirable anticipated effects?
• Trivial
• Small
• Moderate
• Large
• Varies
• Don't know</td><td rowspan="2">Research evidence:
We found no randomized controlled trials (RCTs) comparing erythromycin, azithromycin, or trimethoprim.

We found 9 studies (1 comparative, 6 non-randomized studies with a single arm, 2 randomized trials of which a single arm was used). We also found a review including 2 comparative studies for risk of pyloric stenosis with erythromycin for ophthalmia neonatorum, and a non-randomized study for risk of pyloric stenosis with erythromycin or other oral antibiotics for any indication.

See the evidence profile below for the summary of the results.

Additional considerations:
The GDG agreed that the effects were uncertain given the small number of neonates in the studies: 12 provided data for cure rates with azithromycin.

Additionally, it was noted that trimethoprim was included in the old guidelines, but more research is needed for its efficacy after some concern that there may not be in vitro data supporting its use.

The GDG regarded pyloric stenosis as a widely known adverse effect of erythromycin use in children, to the extent that many paediatricians routinely opt for alternative antibiotics as standard practice. However, there is no data suggesting that azithromycin does not cause pyloric stenosis.

The GDG also noted that a number of the negative outcomes (such as pneumonia, coughing, conjunctivitis, etc.) were complications of chlamydia and not side-effects of the intervention itself.</td></tr>
<tr><td>Undsireable effects</td><td>How substantial are the undesirable anticipated effects?
• Large
• Moderate
• Small
• Trivial
• Varies
• Don't know</td></tr>
<tr><td>Certainty of evidence</td><td>What is the overall certainty of the evidence of effects?
• Very low
• Low
• Moderate
• High
• No included studies</td><td>Research evidence:
None

Additional considerations:
None</td></tr>
<tr><td>Values</td><td>Is there important uncertainty about or variability in how much people value the main outcomes?
• Important uncertainty or variability
• Possibly important uncertainty or variability
• Probably no important uncertainty or variability
• No important uncertainty or variability
• No known undesirable outcomes</td><td>Research evidence:
The GDG identified the following outcomes as critical: Clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastro), antimicrobial resistance, compliance.

Economic evaluation studies found the disutilities of different health states related to chlamydia (utility loss due to the health states as: Neonatal conjunctivitis: –0.03; Neonatal pneumonia: –0.21

Additional considerations:
None</td></tr>
</table>

<table>
<tr>
<td>Balance of effects</td>
<td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?

• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention

• Varies
• Don't know</td>
<td>Additional considerations:
The GDG agreed that, on the basis of negligible favourability for efficacy of erythromycin in addition with concern for its correlation with pyloric stenosis in children, azithromycin was favoured over erythromycin.</td>
</tr>
<tr>
<td>Resources required</td>
<td>How large are the resource requirements (costs)?

• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings

• Varies
• Don't know</td>
<td>
<table>
<tr><th>A</th><th>B</th><th>C</th><th>D</th><th>E</th><th>F</th></tr>
<tr><td>Azithromycin 500 mg po</td><td>n.a.</td><td>n.a.</td><td>$0.38</td><td>n.a</td><td>n.a</td></tr>
<tr><td>Erythromycin base 500 mg po</td><td>n.a.</td><td>n.a.</td><td>$0.0738</td><td>n.a.</td><td>n.a</td></tr>
<tr><td>Trimethoprim</td><td>n.a.</td><td>n.a.</td><td>n.a.</td><td>n.a.</td><td>n.a.</td></tr>
</table>
*Sources: International drug price indicator guide (MSH, 2015) and www.drugs.com
A: treatment; B: dose per day; C: treatment duration; D: drug cost, per dose; E: drug per full-course treatment; F: 25% procurement

Additional considerations:
The GDG agreed that the treatments are relatively inexpensive.
</td>
</tr>
<tr>
<td>Certainty of evidence of required resources</td>
<td>What is the certainty of the evidence of resource requirements (costs)?

• Very low
• Low
• Moderate
• High

• No included studies</td>
<td>Research evidence:
No studies were found that measured resource use.

Additional considerations:
None</td>
</tr>
</table>

Cost-effectiveness	**Does the cost- effectiveness of the intervention favour the intervention or the comparison?** • Favours the comparison • **Probably favours the comparison** • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	**Research evidence** We found no studies assessing cost-effectiveness. **Additional considerations:** None
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence:** We found no studies assessing equity. **Additional considerations:** The GDG noted that many countries were already using erythromycin; however, it was agreed that this would not affect equity.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Non-compliance was reported in 2 studies (31 babies/mothers) at 11% and 23%. **Additional considerations:** Treatment options are already being used.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** We found no studies assessing feasibility. **Additional considerations:** The GDG indicated that erythromycin is already used to treat a variety of paediatric infections, and a recommendation to shift towards azithromycin use might result in a procurement gap: a time during which there might not be suitable drugs available to treat infections. Therefore, certain drugs should be used according to availability.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Treatment of neonatal ophthalmia neonatorum

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	•	●
Recommendation	In neonates with chlamydial conjunctivitis, the WHO STI guideline recommends using oral azithromycin 20 mg/kg for 3 days over erythromycin 50 mg/kg/day for 14 days. *Strong recommendation, very low quality evidence* Remarks: This is a strong recommendation given the potential risk of pyloric stenosis with the use of erythromycin in neonates. In some settings, azithromycin suspension is not available and therefore erythromycin may be used. Side-effects should be monitored with the use of either medication.				
Justification	There is low-quality evidence for a cure rate of 98% with erythromycin 50 mg/kg/day for 14 days and uncertain effects on cures given the small number of neonates receiving azithromycin in the study. There was very low-quality evidence for 7 more instances of pyloric stenosis per 1000 with erythromycin. The GDG regarded the risk of pyloric stenosis as a serious adverse effect of erythromycin use in children. There is no data evaluating pyloric stenosis due to azithromycin. There is also no data assessing the effects of trimethoprim. There is no evidence for variation in patient values and preferences, but compliance with treatments ranged from 77% to 89%. The costs for treatments are relatively low and similar, and most treatments are currently being used. In summary, azithromycin is preferred over erythromycin because of the risk of serious adverse events with erythromycin, and a lack of data for trimethoprim. In summary, azithromycin is preferred over erythromycin because of the potential risk of serious adverse events with erythromycin, and there is no data for trimethoprim.				
Subgroup considerations					
Implementation considerations	Azithromycin suspension should be made widely available.				
Monitoring and evaluation					
Research priorities	Additional research should be conducted to determine the effects of these drugs to treat ophthalmia neonatorum. The effects of other medications, such as trimethoprim, should also be investigated. Pyloric stenosis should be monitored or research conducted to evaluate this risk with the drugs suggested.				

EVIDENCE PROFILE

Data are presented as pooled proportions (95% CI) and study event rates n/N (n=number of events, N = total number of patients followed-up). Superscript numbers link to the alphabetized list of references on the next page.

Outcomes	Overall quality of evidence	Erythromycin 200 mg/day × 10 days	Erythromycin 50 mg/kg/day × 10 days	Erythromycin 50 mg/kg/day × 14 days	Erythromycin < 50 mg/kg/day × 21 days	Azithromycin 20 mg/kg single dose	Azithromycin 20 mg/kg/day x 3 days
Clinical and microbiological cure	⨁⨁⊖⊖ Low[a,b,c]	0.93 [0.78–1.08] 10/14[d, 11]	0.78 [0.60–0.96] 14/18[2]	0.98 [0.96–1.01] 126/130[3,4,5,8,9,10]	1.00 [0.93–1.07] 22/22[6]	0.60 [0.27–0.93] 3/5[5]	0.86 [0.61–1.10] 6/7[5]
Treatment relapses	Not assessed		0.07 [–0.08–0.22] 1/14[2]	0.12 [0.01–0.23] 4/33[9]	0.14 [–0.01 – 0.28] 3/22 6		
Pneumonia	⨁⊖⊖⊖ Very low[a,b]			1.04 [0.98–1.09] 3/58[4,10]			
Nasopharyngeal co-infection	⨁⊖⊖⊖ Very low[a,b]	0.31 [0.16–0.48] 9/28[11]	0.23 [0.06–0.39] 5/22[2]	0.57 [0.51–0.63] 98/170[3,4,5,8,9,10]	0.27 [0.10–0.45] 6/22[6]	0.50 [0.25–0.75] 6/12[5]	0.50 0.25–0.75] 6/12[5]
Upper respiratory tract infections	⨁⊖⊖⊖ Very low[a,b]			0.53 [0.31–0.76] 8/15[4]			
Otitis media	⨁⊖⊖⊖ Very low[a,b]			0.06 [–0.01 – 0.13] 5/48[4,9]			
Vaginal infection	⨁⊖⊖⊖ Very low[a,b]			0.03 [–0.04 – 0.10] 1/33[9]			
Conjunctival scarring	⨁⊖⊖⊖ Very low[a,b]			0.06 [–0.00 – 0.13] 4/62[9,10]			
Coughing	⨁⊖⊖⊖ Very low[a,b]		0.04 [–0.06 – 0.15] 1/22 2				
Side-effects: gastrointestinale	⨁⊖⊖⊖ Very low[a,b]	0.43 [0.20–0.66] 6/14[9]	0.07 [0.01–0.13] 6/85[2]	0.12 [0.05–0.20] 10/71[7,10]	0.18 [0.03–0.34] 4/22[6]		

Outcomes	Overall quality of evidence	Erythromycin 200 mg/day × 10 days	Erythromycin 50 mg/kg/day × 10 days	Erythromycin 50 mg/kg/day × 14 days	Erythromycin < 50 mg/kg/day × 21 days	Azithromycin 20 mg/kg single dose	Azithromycin 20 mg/kg/day x 3 days
Pyloric stenosis	⨁⊖⊖⊖ Very low[f]	See additional table					
Non-compliance	NA			0.11 [−0.10 – 0.32] 1/9[3]	0.23 [0.06–0.39] 5/22[6]		
Antimicrobial resistance- not measured							

Note: Nasopharyngeal co-infections also included oropharyngeal co-infections from one study (Fransen, 1986).

a Non-randomized studies were at risk of bias due to unclear losses of follow-up, assessment of cure using inaccurate cultures, short-term follow-up for complications, outcome assessment and attrition bias.

b Imprecision due to small sample sizes and few events.

c Upgraded due to large effect, dose response and no plausible confounding.

d This event rate represents microbiological cure only. The clinical cure at that follow-up time was 13/14 (92.9%).

e All gastrointestinal-related issues were grouped under this outcome including diarrhoea, watery stools, nausea, vomiting and abdominal pain.

f Few events and confidence intervals around absolute event rates include little to no effect and important harm.

RISK OF PYLORIC STENOSIS WITH ERYTHROMYCIN VERSUS OTHER ORAL ANTIBIOTIC (ESTIMATES PER 1000)

Age	Risk ratio of erythromycin vs other	Risk with other oral antibiotics (per 1000)	Risk with erythromycin (per 1000)	Risk difference (per 1000)	Quality of evidence
All ages (1 to 90 days)	1.75 (0.85–3.60)	8.9	15.6	6.7 more (1 fewer to 23 more)	⨁⊖⊖⊖ Very low[1]
3–13 days	12.75 (1.23–132.61)	9.8	17.2	115 more (2 more to ∞)	⨁⊖⊖⊖ Very low[1]
14–27 days	0.83 (0.11–6.42)	17.3	30.3	3 fewer (15 fewer to 94 more)	⨁⊖⊖⊖ Very low[1]
28–90 days	1.60 (0.66–3.84)	7.6	13.3	5 more (3 fewer to 22 more)	⨁⊖⊖⊖ Very low[1]

1 Very few events and confidence intervals around absolute event rates typically include little to no effect and important harm

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RECOMMENDATIONS 6 AND 7

Prevention of gonococcal and chlamydial ophthalmia neonatorum	
Population:	Neonates
Intervention:	One treatment
Comparison:	Another treatment
Main outcomes:	Absence of conjunctivitis, keratitis, complications, blindness, corneal scarring, antimicrobial resistance
Setting:	Out- and in-patient care
Perspective:	Population
Background:	Ophthalmia neonatorum is a form of conjunctivitis occurring within the neonatal period. It is the most common cause of acute ophthalmic disease in newborns and is generally acquired during vaginal delivery from an infected mother. There are numerous causes of conjunctivitis, which can be either infectious or chemical in origin. The most frequent infectious agents involved in ophthalmia neonatorum are *Chlamydia trachomatis* and *Neisseria gonorrhoeae*; other agents include *Escherichia coli, Haemophilus and Enterococcus*. There is no guidance in the 2003 WHO Guidelines specific to prevention of ophthalmia neonatorum. The Guideline Development Group (GDG) identified preventative medications for ophthalmia neonatorum due to *N. gonorrhoeae* (i.e. gonorrhoea) (ophthalmic ointment including erythromycin 0.5%; silver nitrate 1%; chloramphenicol; tetracycline 1%; povidone iodine 2.5%).

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Recent research reports that the risk of developing neonatal chlamydial conjunctivitis from mothers with *Chlamydia trachomatis* is 18–50% (Kakar, 2010). In addition, a review of the literature showed similar incidence in mothers exposed, and 1–10% in mothers not exposed or with unknown exposure (Darling, 2010). Infection can lead to serious conjunctivitis and severe swelling of the eyelids. Long-term consequences of ophthalmia neonatorum (from any cause) may include blindness, and this is particularly prevalent in areas with poor access to health care. **Additional considerations:** The GDG panel noted that these numbers may be underestimating incidence, as the mothers' status may be unknown and screening may not be done.
Desirable Effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** We included 16 studies: 15 randomized studies and 1 non-randomized study with 2 comparison groups. See summary of the evidence in the evidence tables. **Additional considerations:** There were large benefits of prophylaxis when compared to no prophylaxis, particularly in babies born to women with known infection (approximately 70% reduction in conjunctivitis with various treatments). There were smaller differences in benefits between treatments.
Undesirable Effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	Side-effects were often not reported. Non-infectious conjunctivitis was measured when comparing prophylaxis to no prophylaxis, but there were few infants and few events included in the studies. It is uncertain, and data showed reductions or little difference. When comparing prophylaxis, low-quality evidence showed differences between 4 and 50 per 1000 infants of - infectious conjunctivitis. The GDG noted that there have been incidences of using alcohol povidone iodine instead of water based, which have resulted in serious consequences. Therefore, warning should be included in this recommendation.
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • Very low • **Low** • Moderate • High • No included studies	**Research evidence:** None **Additional considerations:** Overall, evidence is typically low quality between comparisons.
Values	**Is there important uncertainty about or variability in how much people value the main outcomes?** • Important uncertainty or variability • Possibly important uncertainty or variability • **Probably no important uncertainty or variability** • No important uncertainty or variability • No known undesirable outcomes	**Research evidence:** The GDG identified the following outcomes as critical: Clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastro), antimicrobial resistance, compliance. Economic evaluation studies found the disutilities of different health states related to chlamydia (utility loss due to the health states) as: Neonatal conjunctivitis: –0.03 Neonatal pneumonia: –0.21 **Additional considerations:** The GDG felt that there would likely be little difference in value placed on avoiding long-term consequences.

<table>
<tr>
<td>Balance of effects</td>
<td>Does the balance between desirable and undesirable effects favour the intervention or the comparison?
• Favours the comparison
• Probably favours the comparison
• Does not favour either the intervention or the comparison
• Probably favours the intervention
• Favours the intervention
• Varies
• Don't know</td>
<td>Research evidence:
None
Additional considerations:
None</td>
</tr>
<tr>
<td>Resources required</td>
<td>How large are the resource requirements (costs)?
• Large costs
• Moderate costs
• Negligible costs and savings
• Moderate savings
• Large savings
• Varies
• Don't know</td>
<td>
<table>
<tr><th>Ophthalmic ointment</th><th>Drug cost*</th></tr>
<tr><td>Erythromycin 0.5%</td><td>$0.74</td></tr>
<tr><td>Silver nitrate 1%</td><td>$7.30</td></tr>
<tr><td>Chloramphenicol</td><td>$0.2956</td></tr>
<tr><td>Tetracycline</td><td>$0.069</td></tr>
<tr><td>Povidone iodine</td><td>$0.01</td></tr>
</table>
*Based on the International drug price indicator guide (MSH, 2015)
Additional considerations:
The GDG agreed that silver nitrate was most expensive and a high cost relative to other prophylaxis.
</td>
</tr>
<tr>
<td>Certainty of evidence of required resources</td>
<td>What is the certainty of the evidence of resource requirements (costs)?
• Very low
• Low
• Moderate
• High
• No included studies</td>
<td>Research evidence:
No research studies assessing other resource issues were found.
Additional considerations:
None</td>
</tr>
</table>

Cost-effectiveness	**Does the cost-effectiveness of the intervention favour the intervention or the comparison?** • **Favours the comparison** • Probably favours the comparison • Does not favour either the intervention or the comparison • Probably favours the intervention • Favours the intervention • Varies • No included studies	**Research evidence:** A cost analysis published in 2010 estimated costs of prophylaxis with povidone iodine, 2.5%, erythromycin 0.5%, or azithromycin 1% in the United States of America (USA). Costs were considered in the USA and included preparation of the medications, but outcomes of prophylaxis were not calculated. The analysis was based on 354 000 births per month. The average monthly estimated cost of universal prophylaxis was $2.8 million for povidone iodine (assuming costs of $7.77 per infant), $0.7 million for erythromycin (assuming $1.94 per infant), and $25.5 million for topical azithromycin (assuming $72.12 per infant). Authors reported that there was initial concern that the detergent formulation of povidone iodine could mistakenly be applied to infants' eyes, but that preparation and delivery would be distinguishable. **Additional considerations:** Cost-effectiveness may not consider the long-term consequences of prophylaxis. Costs favour the use of prophylaxis to prevent long-term consequences.
Equity	**What would be the impact on health equity?** • Reduced • Probably reduced • **Probably no impact** • Probably increased • Increased • Varies • Don't know	**Research evidence:** No studies assessed equity issues. **Additional considerations:** Tetracycline is more available and more procured than erythromycin. Prophylaxis is currently provided in most settings; therefore, there is probably no impact on equity.
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** No studies assessed acceptability. **Additional considerations:** Prophylaxis is currently being provided in most settings and acceptable to a majority of stakeholders.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** No studies assessed feasibility. **Additional considerations:** Prophylaxis is currently being provided in most settings.

SUMMARY OF JUDGEMENTS

	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

CONCLUSIONS

Prevention of gonococcal and chlamydial ophthalmia neonatorum in neonates?

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	•	●
Recommendation	For all neonates, the WHO STI guideline recommends topical ocular prophylaxis for the prevention of gonococcal and chlamydial ophthalmia neonatorum. *Strong recommendation, low quality evidence* For ocular prophylaxis, the WHO STI guideline suggests one of the following options for topical application to both eyes immediately after birth: • Tetracycline hydrochloride 1% eye ointment • Erythromycin 0.5% eye ointment • Povidone iodine 2.5% solution (water-based) • Silver nitrate 1% solution • Chloramphenicol 1% eye ointment *Conditional recommendation, low quality evidence* Remarks: This recommendation applies to the prevention of both chlamydial and gonococcal ophthalmia neonatorum. Cost and local resistance to erythromycin, tetracycline and chloramphenicol in gonococcal infection may determine the choice of drug. Caution should be taken to avoid touching eye tissue when applying the topical treatment and to provide a water-based solution of povidone iodine. **DO NOT USE ALCOHOL-BASED POVIDONE IODINE SOLUTION.**				
Justification	Overall, the quality evidence from 16 studies is low to very low: 15 randomized and 1 non-randomized study with 2 comparison groups. There is little data for the effects of chloramphenicol. There were large benefits of prophylaxis compared with no prophylaxis, particularly in babies born to women with known infection (approximate 70% reduction in conjunctivitis with prophylaxis using different drugs). The benefits with different drugs are similar, however, the low- to very-low-quality evidence shows that benefits of tetracycline hydrochloride, erythromycin, or povidone iodine may be slightly greater than silver nitrate. Little data is available for the incidence of non-infectious conjunctivitis after prophylaxis or no prophylaxis. Low-quality evidence shows a reduction or little difference. Low-quality evidence shows between 4 and 50 per 1000 infants have non-infectious conjunctivitis after application of different prophylaxis. There is little evidence for patient values and preferences, but the GDG agreed that there would likely be little difference in the high value placed on avoiding long-term consequences of both gonococcal or chlamydial conjunctivitis. The GDG also agreed that there would be little effect on acceptability, equity and feasibility, as prophylaxis is currently used in many countries. The GDG reported that alcohol-based povidone iodine has erroneously been used as prophylaxis resulting in serious harm to babies. Silver nitrate is the most expensive prophylaxis option. In summary, there are large benefits for prophylaxis to prevent ophthalmia neonatorum, which are greater than the risk of non-infectious conjunctivitis due to prophylaxis with any of the topical drugs. Some topical drugs may provide greater protection (tetracycline hydrochloride, erythromycin, or povidone iodine), but all are feasible to provide.				

Type of recommendation	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	•	•	•	•	●
Justification	In summary, there are large benefits for prophylaxis to prevent ophthalmia neonatorum, which are greater than the risk of non-infectious conjunctivitis due to prophylaxis with any of the topical drugs. Some topical drugs may provide greater protection (tetracycline hydrochloride, erythromycin, or povidone-iodine), but all are feasible to provide.				
Subgroup considerations					
Implementation considerations					
Monitoring and evaluation					
Research priorities	The prevalence of gonococcal ophthalmia should be determined, given the high prevalence of maternal gonorrhoea in some settings. The state of resistance to the medications should be explored, and it should be established whether these organisms would be killed by ocular prophylaxis despite resistant strains being established in the organisms. More research comparing the benefits and harms of the different drugs is needed, in particular comparisons with chloramphenicol.				

EVIDENCE PROFILES

For prevention of gonococcal and chlamydial ophthalmia neonatorum in neonates, what are the effects of different interventions?

Treatments versus erythromycin

Silver nitrate 1% vs erythromycin 0.5%					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with erythromycin 0.5%	Risk difference with silver nitrate
Incidence of conjunctivitis among Infants exposed to chlamydia during delivery					
	228 (2 RCTs)	⨁⨀⨀⨀ VERY LOW[1,3]	**RR 3.59** (0.25 to 50.99)	70 per 1000	**181 more per 1000** (53 fewer to 3499 more)
Incidence of gonococcal conjunctivitis					
	12808 (4 RCTs)	⨁⨁⨀⨀ LOW[1,3]	**RR 0.39** (0.14 to 1.08)	3 per 1000	**2 fewer per 1000** (3 fewer to 0 fewer)
	47424 (1 Non-RCTs)	⨁⨀⨀⨀ VERY LOW[3,4]	**RR 3.27** (0.18 to 60.82)	3 per 1000	**7 more per 1000** (2 fewer to 179 more)
Incidence of chlamydial conjunctivitis					
	5324 (3 RCTs)	⨁⨁⨀⨀ LOW[1,3]	**RR 1.38** (0.99 to 1.92)	28 per 1000	**11 more per 1000** (0 fewer to 26 more)
	47424 (1 Non-RCT)	⨁⨀⨀⨀ VERY LOW[4]	**RR 0.24** (0.07 to 0.86)	28 per 1000	**21 fewer per 1000** (26 fewer to 4 fewer)
Incidence of infectious conjunctivitis					
	2041 (1 RCT)	⨁⨁⨀⨀ LOW[1,3]	**RR 1.15** (0.95 to 1.41)	78 per 1000	**12 more per 1000** (4 fewer to 32 more)
	47424 (1 Non-RCT)	⨁⨁⨀⨀ LOW[4]	**RR 0.39** (0.24 to 0.63)	78 per 1000	**47 fewer per 1000** (59 fewer to 29 fewer)

Silver nitrate 1% vs erythromycin 0.5%					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with erythromycin 0.5%	Risk difference with silver nitrate
Incidence of conjunctivitis among Infants exposed to chlamydia during delivery					
Incidence of non-infectious conjunctivitis					
	2041 (1 RCT)	⨁⨁⨀⨀ LOW[1,3]	**RR 1.04** (0.84 to 1.30)	70 per 1000	**3 more per 1000** (11 fewer to 21 more)
	47424 (1 Non-RCT)	⨁⨀⨀⨀ VERY LOW[3,4]	**RR 0.53** (0.25 to 1.14)	70 per 1000	**33 fewer per 1000** (53 fewer to 10 more)
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Tetracycline 1% vs erythromycin 0.5%					
Outcomes	**No. of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with erythromycin 0.5%	**Risk difference with tetracycline 1%**
Incidence of conjunctivitis among Infants exposed to chlamydia during delivery					
	154 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,3]	**RR 0.80** (0.34 to 1.89)	70 per 1000	**14 fewer per 1000** (46 fewer to 62 more)
Incidence of gonococcal conjunctivitis					
	10,946 (2 RCTs)	⨁⊖⊖⊖ VERY LOW[1,3]	**RR 0.70** (0.16 to 3.12)	3 per 1000	**1 fewer per 1000** (3 fewer to 6 more)
Incidence of chlamydial conjunctivitis					
	2744 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,3]	**RR 0.90** (0.52 to 1.57)	28 per 1000	**3 fewer per 1000** (13 fewer to 16 more)
Incidence of infectious conjunctivitis – not measured					
Incidence of non-infectious conjunctivitis – not measured					
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Povidone iodine 2.5% vs erythromycin 0.5%					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with erythromycin 0.5%	Risk difference with povidone iodine 2.5%
Incidence of gonococcal conjunctivitis					
	2391 (2 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 0.85** (0.35 to 2.03)	3 per 1000	**0 fewer per 1000** (2 fewer to 3 more)
Incidence of chlamydial conjunctivitis					
	2391 (2 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 0.76** (0.55 to 1.05)	28 per 1000	**7 fewer per 1000** (13 fewer to 1 more)
Incidence of infectious conjunctivitis					
	2391 (2 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 0.87** (0.71 to 1.07)	78 per 1000	**10 fewer per 1000** (22 fewer to 5 more)
Incidence of non-infectious conjunctivitis					
	2391 (2 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 0.52** (0.21 to 1.28)	70 per 1000	**34 fewer per 1000** (55 fewer to 20 more)
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Treatments versus tetracycline 1%

Silver nitrate 1% vs tetracycline 1%					
Outcomes	**No. of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with tetracycline 1%	**Risk difference with silver nitrate 1%**
Conjunctivitis among Infants exposed to gonorrhoea during delivery					
	137 (1 RCT)	⨁◯◯◯ VERY LOW[1,2,3]	**RR 2.32** 0.47 to 11.57)	30 per 1000	**40 more per 1000** (16 fewer to 317 more)
Incidence of conjunctivitis among infants exposed to chlamydia during delivery					
	348 (2 RCTs)	⨁◯◯◯ VERY LOW[1,2,3]	**RR 1.58** (0.86 to 2.90)	90 per 1000	**52 more per 1000** (13 fewer to 171 more)
Incidence of gonococcal conjunctivitis					
	14501 (5 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 1.39** (0.16 to 12.13)	1 per 1000	**0 fewer per 1000** (0 fewer to 6 more)
Incidence of chlamydial conjunctivitis					
	5870 (3 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 1.31** (0.76 to 2.25)	7 per 1000	**2 more per 1000** (2 fewer to 9 more)
Incidence of infectious conjunctivitis					
	3991 (3 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 1.40** (1.09 to 1.79)	52 per 1000	**21 more per 1000** (5 more to 41 more)
Incidence of non-infectious conjunctivitis					
	1259 (2 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 1.25** (0.80 to 1.97)	18 per 1000	**4 more per 1000** (3 fewer to 17 more)
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					

Povidone iodine 2.5% vs tetracycline 1%					
Outcomes	**No. of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with tetracycline 1%	**Risk difference with povidone iodine 2.5%**
Incidence of gonococcal conjunctivitis					
	394 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	not estimable – no events occurred		
Incidence of chlamydial conjunctivitis					
	394 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	not estimable – no events occurred		
Incidence of infectious conjunctivitis					
	394 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2,3]	**RR 2.02** (0.97 to 4.17)	52 per 1000	**53 more per 1000** (2 fewer to 164 more)
Incidence of non-infectious conjunctivitis					
	394 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	**RR 20.17** (1.19 to 341.82)	18 per 1000	**345 more per 1000** (from 3 more to 1000 more)
Side-effects and complications					
	394 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	not estimable – no events occurred		
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Povidone iodine versus other treatments

Povidone iodine 2.5% vs silver nitrate 1%					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with silver nitrate	Risk difference with povidone iodine 2.5%
Incidence of gonococcal conjunctivitis					
	2005 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2,3]	**RR 1.94** (0.60 to 6.29)	4 per 1000	**4 more per 1000** (2 fewer to 23 more)
Incidence of chlamydial conjunctivitis					
	2005 (1 RCT)	⨁⊖⊖⊖ LOW[1]	**RR 0.52** (0.38 to 0.71)	110 per 1000	**53 fewer per 1000** (68 fewer to 32 fewer)
Incidence of infectious conjunctivitis					
	2005 (1 RCT)	⨁⊖⊖⊖ LOW[1]	**RR 0.75** (0.61 to 0.92)	176 per 1000	**44 fewer per 1000** (68 fewer to 14 fewer)
Incidence of non-infectious conjunctivitis					
	2005 (1 RCT)	⨁⊖⊖⊖ LOW[1]	**RR 0.70** (0.55 to 0.89)	139 per 1000	**42 fewer per 1000** (63 fewer to 15 fewer)
Side-effects - not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Povidone iodine 2.5% vs chloramphenicol eye drops					
Outcomes	**No. of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with chloramphenicol eye drops	**Risk difference with povidone iodine 2.5%**
Incidence of gonococcal conjunctivitis					
	2004 (1 RCT)	⨁⊖⊖⊖ LOW[1]	not estimable – no events occurred		
Incidence of chlamydial conjunctivitis					
	2004 (1 RCT)	⨁⊖⊖⊖ LOW[3]	**RR 1.77** (0.97 to 3.22)	20 per 1000	**15 more per 1000** (1 fewer to 44 more)
Incidence of infectious conjunctivitis					
	2004 (1 RCT)	⨁⊖⊖⊖ LOW[1,3]	**RR 1.36** (1.03 to 1.79)	79 per 1000	**29 more per 1000** (2 more to 63 more)
Incidence of non-infectious conjunctivitis					
	2004 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,3]	**RR 0.10** (0.01 to 1.94)	4 per 1000	**4 fewer per 1000** (4 fewer to 4 more)
Side-effects					
	2004 (1 non-RCT)	⨁⊖⊖⊖ VERY LOW[1,4]	Author reports, ocular side-effects were rare and self-limiting in both groups ($P = 0.223$).		
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Povidone iodine 2 drops and povidone iodine 1 drop					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with povidone iodine 1 drop	Risk difference with povidone iodine 2 drops
Incidence of gonococcal conjunctivitis					
	719 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	not estimable – no events occurred		

Povidone iodine 2 drops and povidone iodine 1 drop					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with povidone iodine 1 drop	Risk difference with povidone iodine 2 drops
Incidence of chlamydial conjunctivitis					
	719 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	**RR 1.27** (0.26 to 6.24)	8 per 1000	**2 more per 1000** (6 fewer to 39 more)
Incidence of infectious conjunctivitis					
	719 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	**RR 1.55** (0.65 to 3.69)	22 per 1000	**12 more per 1000** (8 fewer to 60 more)
Incidence of non-infectious conjunctivitis					
	719 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	**RR 1.29** (0.95 to 1.74)	169 per 1000	**49 more per 1000** (8 fewer to 125 more)
Side-effects – not measured					
Inflammation (conjunctival redness, swelling and discharge)					
	719 (1 RCT)	⨁⊖⊖⊖ VERY LOW[1,2]	Authors report no differences between the two groups. However, eyelid oedema was significantly greater in the double-dose group than the single (scores 1.4 [67] vs 1.2 [73], *P*=0.0002).		
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

One treatment versus no treatment

Silver nitrate 1% vs no treatment					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with silver nitrate 1%
Conjunctivitis among Infants exposed to gonorrhoea during delivery					
	138 (1 RCT)	⨁⨁◯◯ LOW[1,2]	**RR 0.17** (0.07 to 0.41)	418 per 1000	**347 fewer per 1000** (389 fewer to 247 fewer)
Incidence of conjunctivitis among Infants exposed to chlamydia during delivery					
	300 (1 RCT)	⨁⨁◯◯ LOW[1,2]	**RR 0.32** (0.17 to 0.60)	313 per 1000	**213 fewer per 1000** (260 fewer to 125 fewer)
Incidence of gonococcal conjunctivitis					
	4804 (3 RCTs)	⨁⨁◯◯ LOW[1,2]	**RR 0.14** (0.06 to 0.31)	20 per 1000	**17 fewer per 1000** (19 fewer to 14 fewer)
Incidence of chlamydial conjunctivitis					
	4477 (2 RCTs)	⨁◯◯◯ VERY LOW[1,3]	**RR 0.36** (0.04 to 3.12)	37 per 1000	**24 fewer per 1000** (36 fewer to 78 more)
Incidence of infectious conjunctivitis					
	2579 (2 RCTs)	⨁⨁⨁◯ MODERATE[3]	**RR 0.27** (0.05 to 1.37)	75 per 1000	**54 fewer per 1000** (71 fewer to 28 more)
Incidence of non-infectious conjunctivitis – not measured					
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Tetracycline 1% vs no treatment					
Outcomes	No. of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no treatment	Risk difference with tetracycline 1%
Incidence of conjunctivitis among Infants exposed to gonorrhoea during delivery					
	133 (1 RCT)	⨁◯◯◯ VERY LOW[1,2]	**RR 0.07** (0.02 to 0.29)	420 per 1000	**391 fewer per 1000** (412 fewer to 298 fewer)
Incidence of conjunctivitis among infants exposed to chlamydia during delivery					
	312 (1 RCT)	⨁◯◯◯ VERY LOW[1,2]	**RR 0.23** (0.11 to 0.46)	310 per 1000	**239 fewer per 1000** (from 167 fewer to 276 fewer)
Incidence of gonococcal conjunctivitis					
	5031 (3 RCTs)	⨁⨁◯◯ LOW[1]	**RR 0.05** (0.01 to 0.17)	20 per 1000	**19 fewer per 1000** (20 fewer to 17 fewer)
Incidence of chlamydial conjunctivitis					
	4817 (2 RCTs)	⨁⨁◯◯ LOW[3]	**RR 0.26** (0.02 to 2.69)	37 per 1000	**27 fewer per 1000** (36 fewer to 63 more)
Incidence of infectious conjunctivitis					
	2732 (2 RCTs)	⨁⨁⨁◯ MODERATE[1]	**RR 0.29** (0.22 to 0.37)	75 per 1000	**53 fewer per 100**0 (58 fewer to 47 fewer)
Incidence of non-infectious conjunctivitis – not measured					
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Erythromycin 0.5% vs no treatment					
Outcomes	**No. of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with no treatment	**Risk difference with erythromycin 0.5%**
Incidence of gonococcal conjunctivitis					
	3170 (3 RCTs)	⨁⨁◯◯ LOW[1]	not estimable – no events occurred		
Incidence of chlamydial conjunctivitis					
	4048 (2 RCTs)	⨁⨁◯◯ LOW[1,3]	**RR 0.92** (0.55 to 1.56)	37 per 1000	**3 fewer per 1000** (17 fewer to 21 more)
Incidence of infectious conjunctivitis					
	210 (1 RCT)	⨁◯◯◯ VERY LOW[1,2,3]	**RR 0.83** (0.23 to 3.01)	75 per 1000	**13 fewer per 1000** (57 fewer to 150 more)
Incidence of non-infectious conjunctivitis					
	210 (1 RCT)	⨁◯◯◯ VERY LOW[1,2,3]	**RR 0.82** (0.44 to 1.53)	153 per 1000	**28 fewer per 1000** (86 fewer to 81 more)
Incidence of non-infectious conjunctivitis					
	210 (1 RCT)	⨁◯◯◯ VERY LOW[1,2]	Author reports no significant differences between groups - clinical or culture were observed. In drug-free group, 53 (38.4%) cases were observed, and in normal saline group, 44 cases (31.9%). Cultures were performed for 111 newborns (11.1%), 91 cases (9.1%) were positive and 20 newborns (2%) were negative. Greatest number of negative cultures were in the normal saline group and erythromycin group stood second.		
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

Povidone iodine 2.5% vs no treatment					
Outcomes	**No. of participants (studies) Follow-up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with no treatment	**Risk difference with povidone iodine 2.5%**
Incidence of gonococcal conjunctivitis					
	706 (2 RCTs)	⨁⊖⊖⊖ VERY LOW[1,2]	not estimable – no events occurred		
Incidence of chlamydial conjunctivitis					
	706 (2 RCTs)	⨁⊖⊖⊖ VERY LOW[1,2,3]	**RR 2.14** (0.20 to 23.24)	37 per 1000	**42 more per 1000** (30 fewer to 823 more)
Incidence of infectious conjunctivitis					
	706 (2 RCTs)	⨁⊖⊖⊖ VERY LOW[1,2,3]	**RR 1.04** (0.52 to 2.08)	75 per 1000	**3 more per 1000** (36 fewer to 80 more)
Incidence of non-infectious conjunctivitis					
	706 (2 RCTs)	⨁⊖⊖⊖ VERY LOW[1,2,3]	**RR 0.52** (0.11 to 2.49)	153 per 1000	**73 fewer per 1000** (136 fewer to 228 more)
Side-effects – not measured					
Keratitis – not measured					
Complications – not measured					
Blindness – not measured					
Corneal scarring – not measured					

1. Few events across studies.
2. Sample size does not meet optimum minimum sample size criteria.
3. 95% CI includes potential for more or fewer events.
4. Non-RCT, and authors did not mention any information related to the use of an appropriate analysis method that adjusted for all the critically important confounding domains.

Resistance to prophylaxis

Tetracycline may prove inconvenient as it may select resistant strains (Ison, 1988). Erythromycin 0.5% also selects resistant bacterial strains (Schwarcz, 1990; Hedberg, 1990). Povidone iodine 2.5% does not select resistant strains (Isenberg, 1995). Moreover Knapp et al. (1987) reported tetracycline resistant *N. gonorrhoeae* (TRNG) in the USA. Isolates of TRNG have been confirmed from 17 states. In addition, unconfirmed reports based on disk-diffusion testing in local laboratories have been reported from Alabama and the District of Columbia.

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