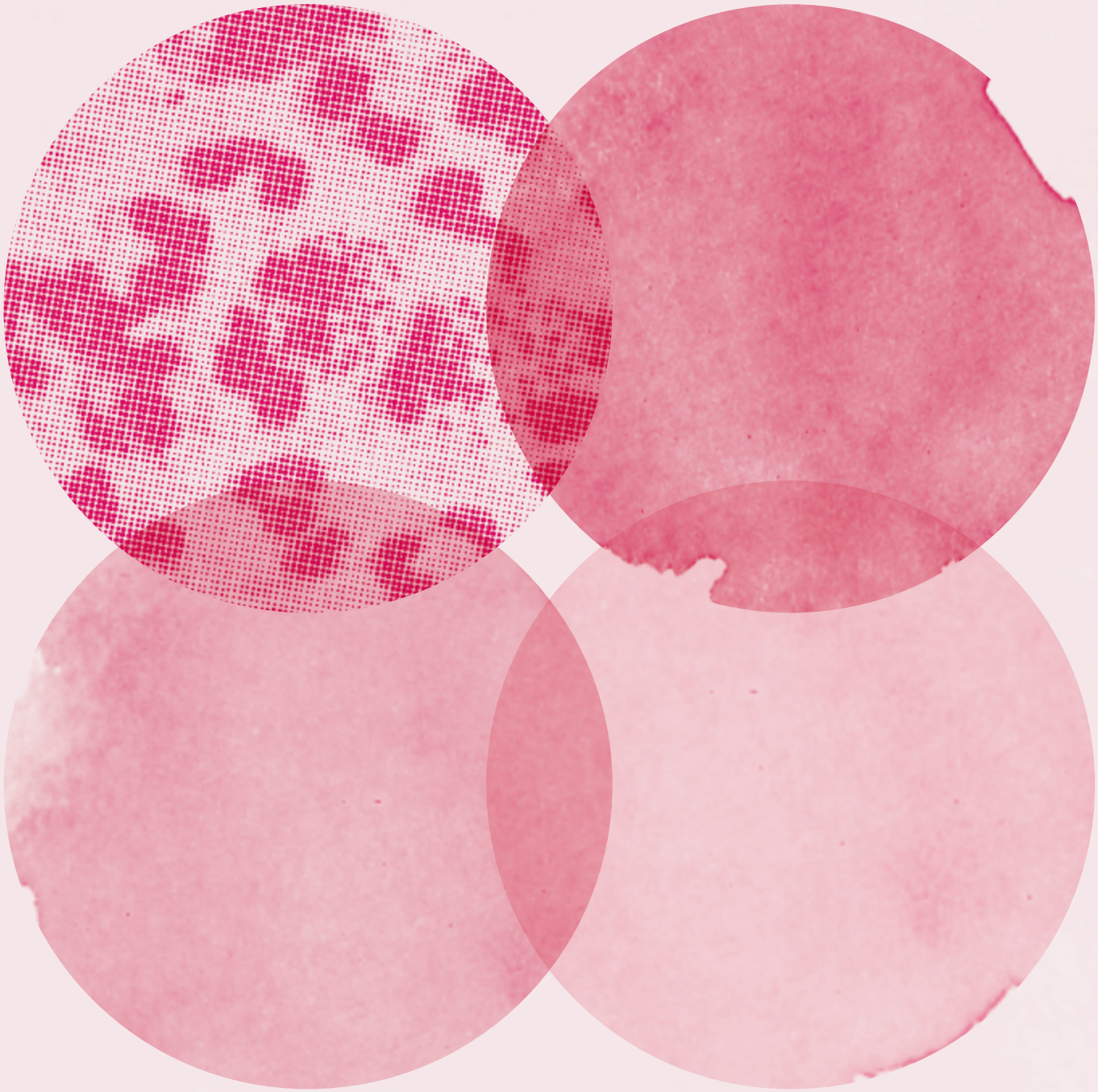
World Health Organization

WHO GUIDELINES FOR THE

Treatment of *Neisseria gonorrhoeae*

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



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

WHO GUIDELINES FOR THE

Treatment of *Neisseria gonorrhoeae*

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

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

1.Neisseria gonorrhoeae - drug therapy. 2.Gonorrhea - drug therapy. 3.Drug Resistance, Microbial. 4.Guideline. I.World Health Organization.

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RECOMMENDATION 1

Treatments for gonorrhoea (genital or cervix) among adults and adolescents, HIV-positive patients, men who have sex with men (MSM) or pregnant women	
Population:	Adults and adolescents with genital gonococcal infections, and people living with HIV, and key populations, including sex workers, MSM and pregnant women
Intervention:	Other treatments
Comparison:	Ceftriaxone
Main outcomes:	**Critical:** Microbiological cure, STI complications, clinical cure, transmission to partners, compliance, gonorrhoea antimicrobial in vitro resistance, side-effects (including allergy, toxicity) **Important:** HIV transmission and acquisition, quality of life
Setting:	Outpatients
Perspective:	Population
Background:	*Neisseria gonorrhoeae* are intracellular Gram-negative bacteria transmitted via sexual contact. They primarily infect the mucous membranes of the urethra, endocervix, rectum, pharynx, and conjunctiva. It is curable, but antimicrobial resistance has made the treatment of gonorrhoea more complicated than in past decades. The 2003 World Health Organization recommended ciprofloxacin 500 mg orally as a single dose, ceftriaxone 125 mg by intramuscular injection as a single dose, cefixime 400 mg orally as a single dose, or spectinomycin 2 g by intramuscular injection as a single dose. The Guideline Development Group (GDG) identified ceftriaxone 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:** The World Health Organization (WHO) recently reported that the global estimate of gonorrhoea is 0.8% (0.6–1.0%) and regional estimates range from 0.3% to 1.7%. Infection of the genital tract causes local inflammation that can result in dysuria, discharge, genital discomfort, and pain. In women, it may spread to the fallopian tubes and ovaries causing pelvic inflammatory disease (PID). Complications include infertility, chronic pelvic pain, and ectopic pregnancy and infection, which can result in considerable physical and emotional morbidity in addition to a significant financial burden on healthcare services. Complications of gonorrhoea are usually seen when the infection remains untreated for a prolonged period, or with inappropriate treatment, and are more common in settings where access to medical care is suboptimal. It has consistently been identified as a risk factor for incident HIV infection in both heterosexual and MSM populations. **Additional considerations:** Gonococcal resistance to many antibiotics is increasing and is cause for concern. It includes resistance to ceftriaxone, cefixime, azithromycin and ciprofloxacin.
Desirable effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • **Moderate** • Large • Varies • Don't know	**Research evidence:** For adults, adolescents, HIV-positive patients and MSM, 108 studies were found (including foreign languages articles): 14 randomized and 94 non-randomized studies (including 3 non-randomized studies with 2 or more groups and 91 non-randomized studies with 1 group). See the evidence profile below for the summary of the results. For pregnant women, 3 studies were included: 2 randomized and 1 non-randomized. The results from adults (non-pregnant people) were also used to inform the recommendations. See the evidence profile below for the summary of the results. **Additional considerations:** The GDG agreed that much of the data for effects of gonorrhoea treatments is dated with the emergence of resistance. This data would therefore be indirect today. The GDG also noted that there is little data comparing dual therapy to increased doses of single therapy. Dual therapy indicates that the same class of antibiotic should not be used for both drugs. Different dosages were assessed across studies, with little difference in effects. The cure rates of azithromycin 1 g or 2 g were similar. The cure rates of gentamicin and kanamycin were above 95%, but the cure rates varied across studies (and were fragile depending on which studies were included in the analysis), but this data is also dated. The cure rates were similar for cefixime 400 mg and 800 mg. The GDG noted that in many countries, doses much higher than what is considered standard are given. Therefore, standard doses as "minimum" should be described, but higher doses may be used in some cases. There was no data in high-risk groups (e.g. MSM or sex workers). Side-effects were generally non-serious. Side-effects are probably greater with azithromycin (1 or 2 g) and spectinomycin (2 g) than with ceftriaxone. The GDG agreed that when measured, the side-effects were trivial. There is global resistance to quinolones and emerging resistance to single therapies. Therefore, in order to successfully treat gonococcal infection with a single therapy, susceptibility should be known. Resistance to azithromycin is emerging, and resistance to gentamicin and kanamycin are not being measured. For pregnant women, doxycycline and tetracyclines cannot be used due to adverse effects.
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	
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:** There were no quantitative studies measuring patient values in gonococcal infections. 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 there would be no differences in the values and preferences between different populations.
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:** No research evidence. **Additional considerations:** The balance of benefits and harms for each drug was similar, and so no drug is favoured over the other. Due to emerging resistance to single therapies, dual therapy is probably favoured over single therapy.

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

Drug	Full dose treatment cost*	25% procurement	Service Delivery	Drugs+ service delivery
Ceftriaxone 250 mg IM	$0.57	$0.14	$10	$10.71
Azithromycin 1–2 g po	$0.377 (1*500 mg)	$0.094	$10	$10.94 (1 g) $11.88 (2 g)
Cefixime 400 mg po	$1.33	$0.33	$10	$11.63
Cefixime 400 mg po × 2	$2.33	$0.66	$10	$12.99
Cefixime 800mg po	$2.33	$0.66	$10	$12.99
Gentamicin 240 mg IM	–	–	–	–
Spectinomycin 2 g IM	–	–	–	–
Kanamycin 2 g	$1.18 (1*1 g)	$0.29	$10	$12.95
Ceftriaxone 125 mg IM	–	–	–	–

*Based on the *International drug price indicator guide* (MSH, 2015).

Evidence for other costs was not found, such as costs related to the drug management: delivery/dispensing, storing and ordering the medication, costs related to IM administration, and costs related to needle stick injuries to patients and personnel.

Additional considerations:
Costs of the treatments were similar, however, some countries may not be able to afford dual therapy (nor increased surveillance to determine if single therapy could be used). Users and prescribers perceive that azithromycin is more costly, but it is not. However, the GDG agreed that azithromycin is already recommended for treating chlamydia infection, and so it is relevant for treatment based on a syndromic approach also.

Certainty of evidence of

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

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

Research evidence:
No studies evaluating resource costs 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:
MEDLINE, Embase and the Cochrane Library for Economic Evaluation and Technology Assessment reports were searched, and 5 cost-effectiveness studies of uncomplicated gonorrhoea published before 2000 were found. These were not assessed but the cost factors were considered above.

A cost-effectiveness analysis published in 2000 estimated the cost and annual number of new HIV infections in the United States of America (USA). attributed to gonorrhoea. According to the model used in the analysis, the probability that a new case of gonorrhoea would facilitate a new case of HIV transmission from an HIV- infected person to his or her partner is 0.00066. When multiplied by the $195 000 lifetime cost of HIV treatment, these probabilities suggest that the cost of gonorrhoea-attributed HIV is US$129. The model used in this analysis also suggests that in 1996, 430 new cases of HIV were attributable to gonorrhoea and the cost to treat these cases of HIV disease over the patients' lifetime would be of US$83.8 million.

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:** No studies assessed equity issues. **Additional considerations:** Some countries have surveillance, but others do not, and the GDG agreed that guidance for surveillance is necessary. The GDG agreed that there may be a risk of equity being reduced with dual therapy, as the costs may be higher with dual versus single.
ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Reviews and studies specific to gonorrhoea treatment acceptability were identified through a search. A systematic review 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 (Nagarkar, 2015). Treatment may not be acceptable to patients due to the resources, 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 of doctors, stigma, shyness, and embarrassment. Cost of care and lack of faith in clinical care were also factors. There is some evidence from a review for acceptability of injections versus oral drugs in people with syphilis. Approximately 10–20% of people refused injections. The GDG noted that in practice, some health care providers are averse to providing injections, and there is the additional labour time and costs with intramuscular administration (Chauhan, 2006; Crowe, 1997; Kingston, 2004; Tayal, 2009). An overview of reviews of medication adherence (Ryan 2014) reported that adherence might be improved with simpler drug regimens. **Additional considerations:** Today, many people are already receiving dual therapy. Cefixime may have an advantage over ceftriaxone, as it does not need to be administered by injection.
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:** None

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 gonorrhoea (genital or cervix) among adults and adolescents, HIV-positive patients, MSM or pregnant women

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

The WHO STI guideline recommends that local resistance data should determine the choice of therapy (both for dual therapy or single therapy).
Good practice statement

In settings where local resistance data are not available, the WHO STI guideline suggests dual therapy over single therapy for people with genital or anorectal gonorrhoea.
Conditional recommendation, low quality evidence

WHO STI guideline suggests the following options:
Dual therapy (one of the following)
- Ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose
- Cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

Single therapy (one of the following based on recent local resistance data confirming susceptibility to the antimicrobial)
- Ceftriaxone 250 mg IM orally as single dose
- Cefixime 400 mg orally as single dose
- Spectinomycin 2 g IM orally as single dose

Remarks: Because of the emerging resistance data for gonococcal infections and reduced effectiveness of some drugs, good practice dictates that the choice of treatment depends on reliable local data on antimicrobial susceptibility. Alternative single-drug therapies have not been suggested, such as gentamicin or kanamycin, because surveillance data is lacking. Guidance for surveillance of antimicrobial resistance in *N. gonorrhoeae* is available from WHO. This recommendation applies to pregnant women who should be closely monitored. This recommendation applies to pregnant women who should be closely monitored.

Justification

Overall justification

In summary, there is low-quality evidence for benefits and harms of dual therapy compared to single therapy, but due to emerging resistance to single therapies and lack of local surveillance data in most regions, dual therapy is favoured over single therapy. Dual therapy is currently being used in some settings, appears to be acceptable, and the costs compared to effectiveness are not greater.

	Detailed justification *Balance of effects* The quality evidence for the effects of treatments for gonococcal infections is low. Evidence is available from 108 studies, including 14 randomized and 94 nonrandomized studies, which were conducted in a broad range of high-, middle- and low-income countries. Although high cure rates were shown (> 95%), the evidence is outdated, regionally specific, and therefore, considered indirect due to emerging resistance data. Available data on antimicrobial resistance in gonorrhoea revealed high rates of resistance to quinolones, emerging azithromycin resistance, and decreased susceptibility to ceftriaxone and cefixime. Low-quality evidence suggests similar cure rates with azithromycin at 1 g or 2 g single doses, but there is emerging resistance data for azithromycin from many countries. Cure rates for kanamycin and gentamycin vary and are based on older studies. Currently, there is little surveillance data for these two drugs. There are similar cure rates with cefixime at 400 mg or 800 mg single doses. The evidence for dual versus single therapy is low quality, as there are few studies evaluating different combinations with azithromycin. Side-effects of the drugs were often not measured, but when measured, were trivial. In particular, the evidence for differences in side-effects between 1 g or 2 g single doses of azithromycin is uncertain, but the GDG agreed that side-effects, such as nausea, could be greater with higher doses.
	Overall, the GDG therefore agreed that the success of the available treatments is based on in vitro susceptibility of gonococcal infections and should therefore be based on recent local surveillance data. Due to global resistance patterns, quinolones are no longer an option for treatment of gonococcal infections. The GDG agreed that dual therapy should be suggested due to the emergence of resistance and the paucity of surveillance data in most settings to guide decisions about susceptibility to single therapy. Additional studies comparing different combinations of dual therapy (such as gentamicin, ceftriaxone, cefixime, or gemifloxacin plus azithromycin) will inform recommendations in future. No studies were found that assessed patient values and preferences, acceptability, equity, or feasibility specific to gonococcal infections. There is some evidence from literature about acceptability of injections versus oral drugs in people with syphilis. Approximately 10–20% of people refused injections. The GDG also noted that in practice, some health care providers are averse to providing injections, and there is the additional labour time and costs with intramuscular administration. The GDG agreed that there is probably no variability in values placed on the outcomes. However, intramuscular injection may be less desirable than oral administration, and dual therapy is acceptable based on current use. Although azithromycin is perceived by some to require greater resources, the costs of the suggested treatments were similar. Since azithromycin is currently recommended for treatment of other sexually transmitted infections (e.g. chlamydia), it may provide additional benefit by treating possible co-infections. For pregnant women: The quality of evidence for the effects of treatments for genital and anorectal gonococcal infections in pregnant women is low. Evidence was reviewed from 3 studies, including 2 randomized and 1 non-randomized studies. When data for pregnant women was not available, evidence in non-pregnant adults was used to inform the recommendations.
Subgroup considerations	There was no to very little data for key populations. Therefore, recommendations were made based on the evidence for adults. This recommendation also applies to pregnant women, MSM and people living with HIV.
Implementation considerations	
Monitoring and evaluation	
Research priorities	While surveillance data should be collected including breakpoints for resistance, frequency of collection, number of isolates, and interpretation of local data, research into current and new drug options is needed. Appropriately designed randomized controlled trials (RCTs) on new drug options, dual therapy, and other alternatives such as gentamicin and kanamycin, should be conducted. Specifically, studies should compare different combinations of dual therapy (such as gentamicin, ceftriaxone, cefixime, or gemifloxacin plus azithromycin). Trials should include both men and women, and key populations, such as MSM and sex workers. In addition to commonly reported outcome (for example, cure and side-effects), important outcomes should be evaluated, including transmission of gonorrhoea to partners, HIV transmission and acquisition, quality of life, and gonorrhoea antimicrobial in vitro resistance. There is a need to understand the values and preference of patients, in particular values placed on burden of injection versus oral drug administration, which may also be reflected in compliance.

EVIDENCE PROFILE

In adults and adolescents, HIV-positive patients or men having sex with men (MSM) with uncomplicated genital (cervix, urethra) and anorectal gonococcal infections, what are the effects of ceftriaxone compared to other treatments?														
Outcomes	**AZM 1 g po × 1**	**AZM 2 g po × 1**	**CFX 400 mg po × 1**	**CFX 800 mg po × 1 (400 mg × 2)**	**SPC 2 g IM × 1**	**SPC 4 g IM × 1**	**GTM 240 mg IM × 1**	**CTX 125 mg IM × 1**	**Kanamycin 2 g IM × 1**	**CFX + AZM**	**CFX + DOX**	**CTX + AZM**	**CTX + DOX**	**CTX 250 mg IM × 1**
Microbiological cure by person–7 days or less	**RR 1.01 (0.99–1.04)** 10 more per 1000 (from 10 fewer to 39 more) 970 people per 1000 (0.95–0.98)	**990 people per 1000 (0.98–1.00)**	**RR 0.98 (0.96–1.01)** 20 fewer per 1000 (from 10 to 39 fewer) 970 people per 1000 (0.95–0.98)	**RR 1.00 (0.96–1.04)** 0 fewer per 1000 (from 39 fewer to 39 more) 970 people per 1000 (0.95–1.00)	**RR 1.00 (0.98–1.01)** 0 per 1000 (from 10 more to 20 fewer) For MSM RR 1.00 (0.87 to 1.16) 0 fewer per 1000 (from 127 more to 157 fewer)	**990 people per 1000 (0.97–1.01)**	**950 people per 1000 (0.94–0.97)**	**RR 1.00 (0.89–1.13)** 0 per 1000 (from 108 to 127 fewer) For MSM 970 people per 1000 (0.93–1.02)	**RR 0.92 (0.88–0.97)** 78 fewer per 1000 (from 29 to 118 fewer) 980 people per 1000 (0.96–0.99)	**No study found**	**No study found**	**910 people per 10005** (0.81–0.92)	**900 people per** 10005 (0.89–0.91)	**980 people per** 1000
Quality of evidence	⊕⊕⊕⊖ **moderate**[2] Imprecision ⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊕⊕⊖ **moderate**[2] Imprecision ⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊕⊕⊖ **moderate**[2] Imprecision ⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊕⊕⊕ **high** ⊕⊕⊖⊖ **low**[2] **Imprecision**	⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊖⊖⊖ **very low**[1,3] Risk of bias Indirect	⊕⊕⊖⊖ **low**[2] Imprecision ⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊕⊕⊖ **moderate**[2,3] Imprecision, Indirect ⊕⊖⊖⊖ **very low**[1,3] Risk of bias Indirect			⊕⊖ ⊖⊖ **very low**[1] Risk of bias	⊕⊖ ⊖⊖ **very low**[1] Risk of bias	
Microbiological cure by person – 8 days or more	RR 1.02 (0.99 to 1.05) 519 more per 1000 (from 127 more to 1000 more)		930 people per 1000 (0.78–1.08)			970 people per 1000 (0.96–0.98)	980 people per 1000 (0.96–1.00)					860 people per 0007 (0.81–0.92)	790 people per 0007 (0.75–0.83)	990 people per 1000
Quality of evidence	⊕⊕⊕⊖ **moderate**[2] Imprecision		⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊕⊕⊖ **moderate**[4] Imprecision		⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊖⊖⊖ **very low**[1] Risk of bias					⊕⊖ ⊖⊖ **very low**[1] Risk of bias	⊕⊖ ⊖⊖ **very low**[1] Risk of bias	

In adults and adolescents, HIV-positive patients or men having sex with men (MSM) with uncomplicated genital (cervix, urethra) and anorectal gonococcal infections, what are the effects of ceftriaxone compared to other treatments?

Outcomes	AZM 1 g po × 1	AZM 2 g po × 1	CFX 400 mg po × 1	CFX 800 mg po × 1 (400 mg × 2)	SPC 2 g IM × 1	SPC 4 g IM × 1	GTM 240 mg IM × 1	CTX 125 mg IM × 1	Kanamycin 2 g IM × 1	CFX + AZM	CFX + DOX	CTX + AZM	CTX + DOX	CTX 250 mg IM × 1
Microbiological cure by infection – 7 days or less	960 cures per 1000 (0.91 to 1.00)		RR 1.00 (0.97–1.04) 0 fewer per1000 (from 29 fewer to 39 more)	RR 0.96 (0.90–1.02) 39 fewer per 1000 (from 98 fewer to 20 more)	RR 1.00 (0.87–1.16) 0 fewer per 1000 (from 127 fewer to 157 more) For MSM 890 cures per 1000 (0.68 to 1.10)			RR 1.003 (0.94–1.07) 0 fewer per 1000 (from 59 fewer to 69 more)						990 cures per 1000
	⊕⊖⊖⊖ **very low**[1] Risk of bias		⊕⊕⊕⊖ **moderate**[2] Imprecision	⊕⊕⊕⊖ **moderate**[2] Imprecision	⊕⊕⊕⊖ **moderate**[2] Imprecision ⊕⊖⊖⊖ **very low**[1] Risk of bias			⊕⊕⊖⊖ **low**[2] Imprecision						
Microbiological by infection – 8 days or more	960 cures per 1000 (0.91 to 1.00)		980 cures per 1000 (0.96 to 0.99)											990 cures per 1000
Quality of evidence	⊕⊖⊖⊖ **very low**[1] Risk of bias		⊕⊖⊖⊖ **very low**[1] Risk of bias											
Clinical cure by person	990 cures per 1000 (0.97–1.00)				RR 1.00 (0.98–1.02) 0 fewer per 1000 (from 17 fewer to 17 more)			RR 1.00 (0.89–1.13) 0 fewer per 1000 (from 96 fewer to 113 more)	860 cures per 1000 (0.81–0.91)	No study found	No study found	No study found	No study found	870 cures per 1000
Quality of evidence	⊕⊖⊖⊖ **very low**[1] Risk of bias				⊕⊕⊕⊖ **moderate**[2] Imprecision			⊕⊕⊖⊖ **low**[2] Imprecision	⊕⊖⊖⊖ **very low**[1] Risk of bias					

In adults and adolescents, HIV-positive patients or men having sex with men (MSM) with uncomplicated genital (cervix, urethra) and anorectal gonococcal infections, what are the effects of ceftriaxone compared to other treatments?														
Outcomes	**AZM 1 g po × 1**	**AZM 2 g po × 1**	**CFX 400 mg po × 1**	**CFX 800 mg po × 1 (400 mg × 2**	**SPC 2 g IM × 1**	**SPC 4 g IM × 1**	**GTM 240 mg IM × 1**	**CTX 125 mg IM × 1**	**Kanamycin 2 g IM × 1**	**CFX + AZM**	**CFX + DOX**	**CTX + AZM**	**CTX + DOX**	**CTX 250 mg IM × 1**
Clinical cure by infection	1000 cures per 1000 (0.85–1.15)				RR 0.91 (0.55–1.52) 79 fewer per1000 (from 396 fewer to 458 more)									880 cures per 1000
Quality of evidence	⊕⊖⊖⊖ **very low**[1] Risk of bias				⊕⊕⊕⊖ **moderate**[2] Imprecision									
Side-effects (diarrhoea, nausea) disturbance/ pain)	RR 14.95 (6.23–35.89) 419 more per 1000 (from 157 more to 1000 more)		RR 3.33 (0.95–11.72) 70 more per 1000 (from 2 fewer to 322 more)	RR 4.38 (1.68–11.39) 101 more per 1000 (from 20 more to 312 more)	RR 10.63 (0.45–252.55) 289 more per 1000 (from 17 fewer to 1000 more)	10 per 1000 (0.00–0.01)	No events (0/385)	No events (0/154)	No events (0/564)	No study found	No study found	No study found	No study found	30 per 1000
Quality of evidence	⊕⊕⊕⊖ **moderate**[2,4] **Risk of bias Imprecision**		⊕⊕⊖⊖ **low**[2,4] **Risk of bias, Imprecision**	⊕⊕⊕⊖ **moderate**[4] Risk of bias	⊕⊕⊖⊖ **low**[2,4] **Risk of bias Imprecision**	⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊖⊖⊖ **very low**[1] Risk of bias					
Resistance	Resistance data from WHO surveillance and published literature. See end of document for summary.													
Complications	Not measured in studies instudies													
Transmission to partners	Not measured in studies													
Compliance	Not measured in studies													
HIV transmission and acquisition	Not measured in studies													
Quality of life	Not measured in studies													

Effects reported with 95% CI.
AZM: azithromycin; CFX: cefixime; CI: confidence interval; CTX: ceftriaxone; DOX: doxycycline; GTM: gentamicin; IM: intramuscular; KNM: kanamycin; po: by mouth; SPC: spectinomycin.

1. Results from single arm studies providing proportion of events were analysed; number of events was unadjusted for confounding factors.
2. Total numbers does not meet optimum sample size.
3. Data outdated and cure rates unclear due to unknown resistance patterns.
4. Subjective outcomes but no information provided regarding blinding.
5. Cure at day 30
6. Cure at day 60
7. Cure at day 90

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EVIDENCE PROFILE

In pregnant women with uncomplicated genital (cervix, urethra) and anorectal gonococcal infections, what are the effects of ceftriaxone compared to other treatments?						
Outcomes	**AZM 1–2 g po × 1 (not in pregnant women)**	**CFX 400 mg po × 1 (compared to 125 mg IM × 1)**	**CFX 800 mg po × 1 (400 mg × 2) (not in pregnant women)**	**CFX vs CFX + AZM**	**CTX + AZM**	**CTX 250 mg IM × 1**
Microbiological cure by person	**RR 1.01** (0.99–1.04) **10 more per 1000** (from 10 fewer to 38 more)	**RR 1.01** (0.93–1.10) **10 more per 1000** (from 66 fewer to 95 more)	**RR 1.00** (0.96–1.04) 0 fewer per 1000 (from 38 fewer to 38 more)	No study found	No study found	**960 pregnant women per 1000**
		950 pregnant women per 1000 (900–1000)				
Quality of evidence	⊕⊕⊕⊖ **moderate**[2] Imprecision	⊕⊕⊖⊖ **low**[1] Imprecision	⊕⊕⊕⊖ **moderate**[2] Imprecision			
Microbiological cure by infection	**960 cures per 1000** **(0.91–1.00)**	**RR 1.01** (0.93–1.10) **10 more per 1000** **(from 66 fewer to 95 more)**	**RR 0.96** (0.90–1.02) **38 fewer per 1000** **(from 96 fewer to 19 more)**			**950 cures per 1000**
Quality of evidence	⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊕⊖⊖ **low**[1] Imprecision	⊕⊕⊕⊖ **moderate**[1] Imprecision			
Microbiological cure by person (oropharyngeal)		**RR 1.00** (0.73–1.37) **0 fewer per 1000** (from 267 fewer to 366 more)				**990 pregnant women per 1000**
Quality of evidence		⊕⊕⊖⊖ **low**[1] Imprecision				
Maternal side-effects	**RR 14.95** (6.23–35.89) **419 more per 1000** (from 157 to 1000 more)	**30 per 1000 vomiting/diarrhoea** (–0.01–0.07)	**RR 4.38** (1.68–11.39) **101 more per 1000** (from 20 to 312 more)			**30 adults (non pregnant) per 1000**
Quality of evidence	⊕⊕⊕⊖ **moderate**[2,3] Risk of bias Imprecision	⊕⊖⊖⊖ **very low**[1] Risk of bias	⊕⊕⊕⊖ **moderate**[3] Risk of bias			

Fetal: Minor malformations or congenital anomalies		**RR 0.68** (0.28–1.66) **54 fewer babies per 1000** (from 122 fewer to 112 more) (including nevus, cleft palate, supernumerary nipple)				**170 babies per 1000**
Quality of evidence		⊕⊕⊖⊖ **low**[2] Imprecision				
Fetal: Major malformations	Not reported	Not reported	Not reported			**1 baby per 1000**
Quality of evidence						
Fetal: Small for date/ preterm delivery (< 37 weeks)	Not reported	**140 per 1000 babies** (0.06–0.21)	Not reported			**Not reported**
Quality of evidence		⊕⊖⊖⊖ **very low**[1] Risk of bias				
Fetal loss	Not reported	**10 per 1000 babies** (–0.02–0.04)	Not reported			**Not reported**
Quality of evidence		⊕⊖⊖⊖ **very low**[1] Risk of bias				
Resistance	Resistance data from WHO surveillance and published literature. See end of document for summary.					
Clinical cure	Not measured in studies.					
Complications	Not measured in studies.					
Transmission to partners	Not measured in studies.					
Compliance	Not measured in studies.					
HIV transmission and acquisition	Not measured in studies.					
Quality of life	Not measured in studies.					

Effects reported with 95% CI.
AZM: azithromycin; CFX: cefixime; CTX: ceftriaxone; DOX: doxycycline; GTM: gentamicin; IM: intramuscular; KNM: kanamycin; RR: relative risk; SPC: spectinomycin

1. Results from single arm studies providing proportion of events were analysed; number of events was unadjusted for confounding factors.
2. Total numbers does not meet optimum sample size.
3. Subjective outcomes but no information provided regarding blinding.

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RECOMMENDATION 2

Treatments for gonococcal oropharyngeal infections in adults and adolescents	
Population:	Adults and adolescents with gonococcal oropharyngeal infections, including people living with HIV, and key populations, including sex workers and men who have sex with men (MSM), and pregnant women
Intervention:	Other treatment
Comparison:	Ceftriaxone
Main outcomes:	**Critical:** Microbiological cure, Clinical cure, gonorrhoea antimicrobial in vitro resistance, compliance **Important:** STI complications, side-effects (including allergy, toxicity), quality of life, transmission to partners
Setting:	Outpatients
Perspective:	Population
Background:	Neisseria gonorrhoeae are intracellular Gram-negative bacteria transmitted via sexual contact. They primarily infect the mucous membranes of the urethra, endocervix, rectum, pharynx and conjunctiva. It is curable, but antimicrobial resistance makes the treatment of gonorrhoea more complicated than in past decades. Moreover, the oropharynx is thought to serve as an anatomic reservoir of infection that facilitates the gonococcus' acquisition of genes conferring antimicrobial resistance and promotes sustained gonococcal transmission in the population. The Guideline Development Group (GDG) identified ceftriaxone compared 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:** The World Health Organization (WHO) recently reported that the global estimate of gonorrhoea was 0.8% (0.6–1.0%) and regional estimates ranged from 0.3% to 1.7%. Complications of gonorrhoea are usually seen when infection remains untreated for a prolonged period, with inappropriate treatment, and are more common in settings where access to medical care is suboptimal. It has consistently been identified as a risk factor for incident HIV infection in both heterosexual and MSM populations. Oropharyngeal infection is common in MSM. Moreover, the oropharynx is thought to serve as an anatomic reservoir of infection that facilitates the gonococcus' acquisition of genes conferring antimicrobial resistance and promotes sustained gonococcal transmission in the population. It can result in considerable physical and emotional morbidity in addition to a significant financial burden on healthcare services. **Additional considerations:** The GDG agreed that there will likely not be testing for oropharyngeal infections, which are also asymptomatic and makes it difficult to distinguish between the type of infection. It is also difficult to determine infection by self-report.
Desirable effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** There are 28 studies: 8 randomized and 20 non-randomized studies (including 2 non-randomized studies with 2 or more groups and 18 non-randomized studies with 1 group) See evidence table below for a summary of the findings. **Additional considerations:** Similar treatments were provided to people with oropharyngeal infections as for anorectal infections (typically people had co-infection at other sites). As in studies for anorectal infection, there were few direct comparisons of dual versus single therapy. There is also the emerging resistance data and higher risk of treatment failure with oropharyngeal infections. The GDG also agreed that the consequences of treatment failure are more severe. The GDG identified that gonococcal infections obtain some of its resistance from commensal bacteria in the oropharynx. Spectinomycin may result in lower cure rates (75%, from 49% to 100%); and there was no data for the effects of gentamicin or kanamycin. Side-effects were based on data from treatment of genital and anorectal infections. Side-effects were not serious when occurring. Side-effects are probably greater with azithromycin (1 or 2 g) than with ceftriaxone. The GDG agreed that the side-effects were trivial. There is global resistance to quinolones and emerging resistance to single therapies. Therefore, in order to treat successfully with a single therapy, susceptibility should be known. There is also emerging resistance to azithromycin. Resistance to gentamicin or kanamycin is not currently being measured.
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	**Research evidence:** No research evidence was identified. **Additional considerations:** Evidence was also assessed as dated and may not be applicable with emerging resistance patterns.
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:** There were no quantitative studies measuring values and preferences in gonococcal infections. Qualitative studies suggested 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:** None
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:** No research evidence was identified. **Additional considerations:** The balance of benefits and harms for each drug was similar – with no drug favoured over another. Due to emerging resistance to single therapies, dual therapy is probably favoured over single therapy.

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

Drug	Full dose treatment cost*	25% procurement	Service Delivery	Drugs+ service delivery
Ceftriaxone 250 mg IM	$0.57	$0.14	$10	$10.71
Azithromycin 1–2 g po	$0.377 (1*500 mg)	$0.094	$10	$10.94 (1 g) $11.88 (2 g)
Cefixime 400 mg po	$1.33	$0.33	$10	$11.63
Cefixime 400 mg po × 2	$2.33	$0.66	$10	$12.99
Cefixime 800mg po	$2.33	$0.66	$10	$12.99
Gentamicin 240 mg IM	–	–	–	–
Spectinomycin 2 g IM	–	–	–	–
Kanamycin 2 g	$1.18 (1*1 g)	$0.29	$10	$12.95
Ceftriaxone 125 mg IM	–	–	–	–

*Based on the *International drug price indicator guide* (MSH, 2015)

Evidence for other costs was not found, such as costs related to the drug management: delivery/dispensing, storing and ordering the medication, costs related to the IM administration, lifetime medical cost of treating a person with HIV infection because of needle stick, syringes, injection time, needle disposal, cost related to accidental needle stick to medical personnel, hospital evaluation of needle stick.

Additional considerations:
Costs of the treatments were similar. However, some countries might not be able to afford dual therapy (nor increased surveillance to determine if single therapy could be used) or azithromycin. However, the GDG agreed that azithromycin is already recommended for use for chlamydia. This is also relevant for treatment based on a syndromic approach.

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:
There were no studies found that evaluated resource costs.

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:** Five cost-effectiveness studies in uncomplicated gonorrhoea published before 2000 were found; these were not assessed but the cost factors were considered above. A cost-effectiveness analysis published in 2000, estimated the annual number and cost of new HIV infections in the USA attributable to gonorrhoea. According to the model, the probability that a new case of gonorrhoea would facilitate a new case of HIV transmission from an HIV-infected person to his or her partner is 0.00066. When multiplied by the $195 000 lifetime cost of HIV treatment, these probabilities suggest that the gonorrhoea-attributable HIV cost is in US$129. The model suggests that in 1996, 430 new cases of HIV were attributable to gonorrhoea, and the cost to treat these cases of HIV disease over the patients' lifetime would be of US$83.8 million. **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:** No research evidence was identified. **Additional considerations:** Some countries have surveillance but others do not. The GDG agreed that guidance for surveillance is necessary. The GDG agreed that there may be a risk that equity could be reduced with dual therapy.

Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Reviews and studies specific to gonorrhoea treatment acceptability were identified through a search. A systematic review 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 (Nagarkar, 2015). Treatment may not be acceptable for 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 of doctors, stigma, shyness, and embarrassment. Cost of care and lack of faith in clinical care were also factors. There is some evidence from a review for acceptability of injections versus oral drugs in people with syphilis. Approximately 10% to 20% of people refused injections. The GDG noted that in practice, some health care providers are averse to providing injections, and there is the additional labour time and costs with intramuscular administration (Chauhan, 2006; Crowe, 1997; Kingston, 2004; Tayal, 2009). An overview of reviews of medication adherence (Ryan, 2014) reported that adherence may be improved with simpler drug regimens. **Additional considerations:** Today, many people are already receiving dual therapy. Cefixime may have an advantage over ceftriaxone as it does not need to be administered by injection.
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:** None

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 gonococcal oropharyngeal infections in adults and adolescents

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 gonococcal oropharyngeal infections, the WHO STI guideline suggests dual therapy over single therapy. *Conditional recommendation, IVery low quality evidence* WHO STI guideline suggests the following options: *Dual therapy* (one of the following) • Ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose • Cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose *Single therapy* (based on recent local resistance data confirming susceptibility to the antimicrobial) • Ceftriaxone 250 mg IM orally as single dose **Remarks:** Treatment failures have been observed after single-drug therapy for gonococcal oropharyngeal infections, and therefore, dual therapy is suggested over single therapy. This recommendation applies to pregnant women who should be closely monitored for complications.				
Justification	**Overall justification** In summary, there is very low quality evidence for benefits and harms of dual therapy compared to single therapy, but due to emerging resistance to single therapies and lack of local surveillance data in most regions, dual therapy is favoured over single therapy. Dual therapy is currently being used in some settings, appears to be acceptable, and the costs compared to effectiveness are no greater than single therapy. The recommendations for genital, anorectal infections and oropharyngeal infections are similar; however, single therapy with spectinomycin was less effective in oropharyngeal infections.				

Justification	**Detailed justification** *Balance of effects* The quality evidence for the effects of different treatments for oropharyngeal gonococcal infections is low and very low, and therefore, overall the evidence for this recommendation is very low. Evidence from 28 studies was identified: 8 randomized and 20 non-randomized studies (including 2 non-randomized studies with 2 or more groups and 18 non-randomized studies with one group). These studies were conducted in a broad range of high-, middle- and low-income countries. This evidence is outdated, regionally specific, and considered indirect due to emerging resistance data. The GDG agreed that the success of the available treatments is based on in vitro susceptibility of gonococcal infections and should therefore be based on recent local surveillance data. Similar treatments were provided to people with oropharyngeal infections and anorectal infections (typically people had co-infection at other sites). The data showed a higher risk of treatment failure with oropharyngeal infections, and the GDG agreed that the consequences of treatment failure are severe. Based on these considerations, the GDG agreed that treatment should be as aggressive for oropharyngeal infections as for anorectal infections. Low-quality evidence showed that spectinomycin may result in lower cure rates (75%, ranging from 49% to 100%). Data for the effects of gentamycin or kanamycin is not available. No studies were found to assess patient values and preferences, acceptability, equity, or feasibility. The GDG agreed that there is probably no variability in values. However, intramuscular injection may be less desirable than oral administration, and dual therapy is acceptable. Although azithromycin may be perceived to require greater resources, the costs were similar across different treatments.
Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research priorities	While surveillance data should be collected including breakpoints for resistance, frequency of collection, number of isolates, and interpretation of local data, research into current and new drug options is needed. Appropriately designed randomized controlled trials on new drug options, dual therapy, and other alternatives such as gentamicin and kanamycin, should be conducted. Specifically, studies should compare different combinations of dual therapy (such as gentamicin, ceftriaxone, cefixime, or gemifloxacin plus azithromycin). Trials should include both men and women, and key populations, such as MSM and sex workers. In addition to commonly reported outcome (for example, cure and side-effects), important outcomes should be evaluated, including transmission of gonorrhoea to partners, HIV transmission and acquisition, quality of life, and gonorrhoea antimicrobial in vitro resistance. There is a need to understand the values and preference of patients, in particular values placed on burden of injection versus oral drug administration, which may also be reflected in compliance.

EVIDENCE PROFILE

In adults and adolescents, with gonococcal oropharyngeal infections, what are the effects of ceftriaxone compared to other treatments?												
Outcomes	AZM 1–2 g po × 1	CFX 400 mg po × 1	CFX 800 mg po × 1 (400 mg × 2)	SPC 2 g IM × 1	SPC 4 g IM × 1	GTM 240 mg IM × 1	CTX 125 mg IM × 1	CFX + AZM	CFX + DOX	CTX + AZM	CTX + DOX	CTX 250 mg IM × 1
Microbiological cure by person	RR 1.00 (0.89–1.12) **0 fewer per 1000** (from 102 fewer to 112 more)	RR 1.16 (0.80–1.68) **149 more per 1000** (from 186 fewer to 632 more)	RR 1.00 (0.65–1.53) **0 fewer per 1000** (from 326 fewer to 493 more)	RR 0.56 (0.38–0.82) **409 fewer per 1000** (from 167 to 577 fewer)	750 people per 1000 (0.49–1.01)	No study found	RR 0.67 (0.17–2.67) **307 fewer per 1000** (from 772 fewer to 1000 more)	960 per 1000* (0.94–1.06)	710 per 1000* (0.67–1.33)	RR 0.97 (0.85–1.11) **28 fewer per 1000** (from 102 more to 140 fewer)	RR 0.93 (0.55–1.55) **65 fewer per 1000** (from 419 fewer to 512 more)	930 people per 1000
Quality of evidence	⊕⊕⊖⊖ low[1] Imprecision	⊕⊕⊖⊖ low[1] Imprecision	⊕⊕⊖⊖ low[1] Imprecision	⊕⊕⊖⊖ low[1] Imprecision	⊕⊖⊖⊖ Very low[2] Risk of bias		⊕⊕⊖⊖ low[1] Imprecision	⊕⊖⊖⊖ Very low[2] Risk of bias	⊕⊖⊖⊖ Very low[2] Risk of bias	⊕⊕⊖⊖ low[1] Imprecision	⊕⊕⊖⊖ low[1] Imprecision	
Microbiological cure by infections					RR 0.56 (0.27–1.14) **396 fewer per 1000** (from 126 more to 657 fewer)		990 people per 1000 (0.91–1.09)					900 people per 1000
Quality of evidence					⊕⊕⊖⊖ low[1] Imprecision		⊕⊖⊖⊖ Very low[2] Risk of bias					
Side-effects (diarrhoea, nausea, gastrointestinal disturbance/ pain)	RR 14.95 (6.23–35.89) **419 more per 1000** (from 157 more to 1000 more)	RR 3.33 (0.95–11.72) **70 more per 1000** (from 2 fewer to 322 more)	RR 4.38 (1.68–11.39) **101 more per 1000** (from 20 more to 312 more)	RR 10.63 (0.45–252.55) **289 more per 1000** (from 17 fewer to 1000 more)	10 per 1000 (0.00–0.01)	No events (0/385)	No events (0/154)	No events (0/53)	No study found	No study found	No study found	30 per 1000 (in adults with urogenital infections)
Quality of evidence	⊕⊕⊕⊖ moderate[2,3] Risk of bias Imprecision	⊕⊕⊖⊖ low[2,3] Risk of bias, Imprecision	⊕⊕⊕⊖ moderate[3] Risk of bias	⊕⊕⊖⊖ low[2,3] Risk of bias, Imprecision	⊕⊖⊖⊖ Very low[1] Risk of bias	⊕⊖⊖⊖ Very low[1] Risk of bias	⊕⊖⊖⊖ Very low[1] Risk of bias	⊕⊖⊖⊖ Very low[1] Risk of bias				

In adults and adolescents, with gonococcal oropharyngeal infections, what are the effects of ceftriaxone compared to other treatments?												
Outcomes	**AZM 1–2 g po × 1**	**CFX 400 mg po × 1**	**CFX 800 mg po × 1 (400 mg × 2**	**SPC 2 g IM × 1**	**SPC 4 g IM × 1**	**GTM 240 mg IM × 1**	**CTX 125 mg IM × 1**	**CFX + AZM**	**CFX + DOX**	**CTX + AZM**	**CTX + DOX**	**CTX 250 mg IM × 1**
Clinical cure	Not measured in studies											
Resistance	Resistance data from WHO surveillance and published literature. See end of document for summary.											
Complications	Not measured in studies											
Transmission to partners	Not measured in studies											
Compliance	Not measured in studies											
HIV transmission and acquisition	Not measured in studies											
Quality of life	Not measured in studies											

Effects reported with 95% CI.
AZM: azithromycin; CFX: cefixime; CI: confidence interval; CTX: ceftriaxone; DOX: doxycycline; GTM: gentamicin; IM: intramuscular; KNM: kanamycin; po: by mouth; RR: relative risk; SPC: spectinomycin
* Studies include MSM.

1. Total numbers do not meet optimum sample size.
2. Results from single arm studies providing proportion of events were analysed; number of events was unadjusted for confounding factors.
3. Subjective outcomes but no information provided regarding blinding.

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Included studies

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RECOMMENDATION 3

Treatments for people with treatment failure of *N. gonorrhoeae* (genital or oropharyngeal)	
Population:	People with gonococcal treatment failure
Intervention:	One treatment
Comparison:	Another treatment
Main outcomes:	**Critical:** Microbiological cure, compliance, STI complications, clinical cure, gonorrhoea antimicrobial in vitro resistance, transmission to partners, side-effects (including allergy, toxicity), HIV transmission and acquisition **Important:** Quality of life
Setting:	Outpatients
Perspective:	Population
Background:	*Neisseria gonorrhoeae* are intracellular Gram-negative bacteria transmitted via sexual contact. They primarily infect the mucous membranes of the urethra, endocervix, rectum, pharynx and conjunctiva. It is curable, but antimicrobial resistance makes the treatment of gonorrhoea more complicated than in past decades. *Neisseria gonorrhoeae* has developed various resistance mechanisms to previous and current therapeutic agents, including high-level resistance to the extended-spectrum cephalosporins (ESCs) cefixime and ceftriaxone. Associated with this, treatment failures with ESCs have recently been observed in the UK and other European countries. The treatment options, however, have diminished rapidly because of the emergence and worldwide spread of antimicrobial resistance (AMR) to all drugs previously used or considered first line. The Guideline Development Group (GDG) identified a combination of 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:** Since the last WHO guidelines, a high resistance level to fluoroquinolones has been observed. Increased resistance to most antibiotics used to treat gonococcal infections has also been observed, and concerns with "untreatable" gonococcal infection has been raised. **Additional considerations:** The GDG noted that suspected treatment failures could in fact be reinfections, and this pattern should be reflected in the guidelines. There is also concern about treatment failures with dual therapy. It was indicated that the current Global Action Plan does not say to re-treat with the same regimen in cases of potential reinfection.
Desirable effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • **Moderate** • Large • Varies • Don't know	**Research evidence:** No studies were found specifically evaluating the effects of treatments in people who had treatment failure. Most data is from individuals who failed in a study and the treatment (typically retreatment with the same medication) and success was reported for those individuals. Studies reported individuals who had failed with a variety of treatments. Most studies did not indicate if treatment failure was failure of cure due to the medication or reinfection.
Undesirable effects	**How substantial are the undesirable anticipated effects?** • Large • Moderate • Small • **Trivial** • Varies • Don't know	**Additional considerations:** The effects were not consistently larger or smaller across treatments. However, the GDG agreed that reinfection should be excluded before the treatment is switched. If there is the potential that reinfection has occurred, then the treatment should be repeated. Treatment of the partner and abstinence should be reinforced. If ceftriaxone was previously used, the dose could be increased, as with azithromycin. If treatment failure is confirmed or suspected and a non-WHO-recommended regimen was previously used, then a WHO-recommended regimen could be used. If a WHO recommended regimen was used, then alternative treatments could be used: if cefixime resistant, treat with ceftriaxone. Alternative therapies could include spectinomycin or gentamicin, which can be given with azithromycin at an increased dose, 2 g, if the previous dosage led to treatment failure. Since cure rates were low with spectinomycin for oropharyngeal infections, then gentamicin could be used for those infections. Using evidence from use of drugs in adults, when side-effects occurred, they were not serious. The GDG agreed that the side-effects were trivial.
Certainty of evidence	**What is the overall certainty of the evidence of effects?** • **Very low** • Low • Moderate • High • No included studies	**Research evidence:** No research evidence was identified. **Additional considerations:** None

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:** There were no quantitative studies measuring values and preferences in gonococcal infections. Qualitative studies suggested 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:** None
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:** No research evidence was identified. **Additional considerations:** As with gonococcal infections that did not fail treatment, the balance of benefits and harms for each drug was similar – with no drug favoured over another. Due to emerging resistance to single therapies, dual therapy is probably favoured over single therapy also for gonococcal infections that failed initial treatment.

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

Drug	Full dose treatment cost*	25% procurement	Service Delivery	Drugs+ service delivery
Ceftriaxone 250 mg IM	$0.57	$0.14	$10	$10.71
Azithromycin 1–2 g po	$0.377 (1*500 mg)	$0.094	$10	$10.94 (1 g) $11.88 (2 g)
Cefixime 400 mg po	$1.33	$0.33	$10	$11.63
Cefixime 400 mg po × 2	$2.33	$0.66	$10	$12.99
Cefixime 800mg po	$2.33	$0.66	$10	$12.99
Gentamicin 240 mg IM	–	–	–	–
Spectinomycin 2 g IM	–	–	–	–
Kanamycin 2 g	$1.18 (1*1 g)	$0.29	$10	$12.95
Ceftriaxone 125 mg IM	–	–	–	–

*Based on the *International drug price indicator guide* (MSH, 2015)

Evidence for other costs was not found, such as costs related to the drug management: delivery/dispensing, storing and ordering the medication, costs related to the IM administration, lifetime medical cost of treating a person with HIV infection because of needle sticks, syringes, injection time, needle disposal, cost related to accidental needle stick to medical personnel, hospital evaluation of needle stick.

Additional considerations:
Costs of the treatments were similar. However, some countries might not be able to afford dual therapy (nor increased surveillance to determine if single therapy could be used) or azithromycin. However, the GDG agreed that azithromycin is already recommended for use for chlamydia. This is also relevant for treatment based on a syndromic approach.

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 were found evaluating resource costs.

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:** Five uncomplicated gonorrhoea cost-effectiveness studies published before 2000 were found; these were not assessed, but the cost factors were considered above. A cost-effectiveness analysis published in 2000 estimated the annual number and cost of new HIV infections in the USA attributable to gonorrhoea. According to the model, the probability that a new case of gonorrhoea would facilitate a new case of HIV transmission from an HIV-infected person to his or her partner is 0.00066. When multiplied by the $195 000 lifetime cost of HIV treatment, these probabilities suggest that the gonorrhoea-attributable HIV cost is US$129. The model suggest that in 1996, 430 new cases of HIV were attributable to gonorrhoea, and the cost to treat these cases of HIV disease over the patients' lifetimes would be US$83.8 million. **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:** No studies assessed equity issues. **Additional considerations:** None
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** No studies assessed acceptability specific to retreatment **Additional considerations:** None
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:** None

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 retreatment of gonococcal treatment failure

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 gonococcal infections who have failed treatment, the WHO STI guideline suggests the following options:
	• If reinfection is suspected, re-treat with WHO-recommended regimen, reinforce sexual abstinence or condom use, and provide partner treatment.
	• If treatment failure occurred after treatment with a regimen not recommended by WHO, re-treat with WHO-recommended regimen.
	• If treatment failure occurred and resistance data are available, re-treat according to susceptibility.
	• If treatment failure occurred after treatment with a WHO-recommended single therapy, re-treat with WHO-recommended dual therapy.
	• If treatment failure occurred after a WHO-recommended dual therapy, re-treat with one of the following dual therapies:
	  • ceftriaxone 500 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
	  • cefixime 800 mg orally as a single dose PLUS azithromycin 2 g orally as a single dose
	  • gentamicin 240 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
	  • spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) PLUS azithromycin 2 g orally as a single dose.
	Conditional recommendation, very low quality evidence
	Remarks: Before retreatment, reinfection should be distinguished from treatment failure, resistance data should be obtained when possible, and the WHO-recommended regimens should be used.				

Justification	The quality of evidence is very low. The evidence is from 34 randomized and non-randomized studies that evaluated a treatment or many treatments and then reported on retreatment of individual cases who experienced treatment failure. No studies specifically recruited people who had treatment failure. Most studies reported the cases who failed treatment or had reinfection (a distinction was often not made). These studies also reported the drug used for initial treatment, the drug that was used for retreatment, and sometimes whether the case was cured. Cure rates for different drugs were not consistent across the studies. In summary, there is very low-quality evidence for the effects of specific drugs for people who failed treatment. Therefore, the recommendation was based on ensuring that retreatment is first according to WHO regimens, and if first treatment was according to WHO regimens, the suggestion was for increasing dosages.				

Subgroup considerations	
Implementation considerations	
Monitoring and evaluation	
Research priorities	Treatment failures should be consistently reported including treatment provided and outcome of treatment. Research on new treatment options is essential.

EVIDENCE PROFILE

Treatments for people who experienced treatment failure

Study	Number of patients with treatment failure	Treatment received first	Minimum inhibitory concentration (MIC)	Retreatment	Number of patients cured
Takahashi 2014	1	Azithromycin	For susceptibility ≤ 0.25 µg/mL and for resistance ≥ 1 µg/mL	Ceftriaxone	1
Ota 2009	5	Cefixime	Not mentioned	Cefixime	5
Ota 2009	4	Ofloxacin	Not mentioned	Ofloxacin	4
Ota 2009	1	Cefixime	Not mentioned	Cefixime	1
Habib 2004	2	Azithromycin	Not mentioned	Spectinomycin	2
Ramus 2001	2	Cefixime 400 mg po × 1	Not mentioned	Ceftriaxone 250 mg IM × 1	2
Ramus 2001	2	Ceftriaxone 125 mg IM × 1	Not mentioned	Ceftriaxone 250 mg IM × 1	2
Mroczkowski 1997	1	Cefixime	Resistant to cefixime > 0.25 µg/mL	Resistant to cefixime	0
Hira 1995	4	Gentamicin 280 mg IM × 1	Not mentioned	Sulfametrole (800 mg) + Trimethoprim (160 mg) × 2 days	4
Hira 1995	4	Kanamycin 2 g IM × 1	Not mentioned	Sulfametrole (800 mg) + Trimethoprim (160 mg) × 2 days	4
Mroczkowski 1993	1	Trospectomycin	2.0 µg/mL	Retreatment not mentioned	1 woman treated with trospectinomycin for endocervical pharyngeal gonorrhoea had her endocervical infection cured, but her oropharyngeal culture grew *N. gonorrhoeae* at follow-up
Mroczkowski 1993	2	Ceftriaxone	0.125 µg/mL	Retreatment not mentioned	2 treatment failures in the ceftriaxone group were observed with endocervical infections.

Study	Number of patients with treatment failure	Treatment received first	Minimum inhibitory concentration (MIC)	Retreatment	Number of patients cured
Cavenee 1993	1 treatment failure with rectum site of infection	Ceftriaxone 125 mg IM × 1	Not mentioned	Retreatment not mentioned	Did not mention cure
Cavenee 1993	4 treatment failures with cervix site of infection	Ceftriaxone 125 mg IM × 1	Not mentioned	Retreatment not mentioned	Did not mention cure
Cavenee 1993	4 treatment failures by person (all sites of infection)	Ceftriaxone 125 mg IM × 1	Not mentioned	Retreatment not mentioned	Did not mention cure
Cavenee 1993	1 treatment failure with pharynx site of infection	Spectinomycin 2 g IM × 1	Not mentioned	Retreatment not mentioned	Did not mention cure
Cavenee 1993	3 treatment failures with cervix site of infection	Spectinomycin 2 g IM × 1	Not mentioned	Retreatment not mentioned	Did not mention cure
Cavenee 1993	4 treatment failures by person (all sites of infection)	Spectinomycin 2 g IM × 1	Not mentioned	Retreatment not mentioned	Did not mention cure
Steingrimssoir 1990	1	Azithromycin 500 mg (double dose, bid)	≤ 0.5 mg/l	Spectinomycin	1
Steingrimssoir 1990	1	Azithromycin 1 g	0.125 mg/l	Retreatment not mentioned	Did not mention cure
Kouri 1989	5	Spectinomycin	< 1.0 µg /ml and resistance ≥ 1.0 µg/ml)	Spectinomycin	5
Pandhi 1989	4	Gentamicin 240 mg IM × 1	Not mentioned	Fortified procaine benzyl penicillin 4.8 mega unit along with 1 g of probenecid orally	4
Pabst 1989	1 treatment failure with cervical site of infection	Ceftriaxone 250 mg IM × 1	Not mentioned	Ceftriaxone	1
Pabst 1989	1 treatment failure with urethral site of infection	Ceftriaxone 250 mg IM × 1	Not mentioned	Ceftriaxone	1
Pabst 1989	2 treatment failures with all sites of infection	Ceftriaxone 250 mg IM × 1	Not mentioned	Ceftriaxone	2
Judson 1985	8 treatment failures with pharynx site of infection	Spectinomycin	12.5 to 32 µg/mL	Procaine penicillin	8
Kim 1984	44	Thiamphenicol	2 to 16 µg/mL	Spectinomycin	43 cure and 1 not cured with PPNG (Penicillinase producing *N. gonorrhoeae*)

Study	Number of patients with treatment failure	Treatment received first	Minimum inhibitory concentration (MIC)	Retreatment	Number of patients cured
Kim 1984	1 with PPNG (penicillin producing *N. gonorrhoeae*.	Spectinomycin	12.5 to 25 µg/mL	Retreatment not mentioned	Did not mention cure
Meheus 1984	13	Spectinomycin	Sensitive to 16 or 32 µg/ml	Procaine penicillin	7 were cured, and 6 were lost to follow-up.
Sands 1980	32	Tetracycline	Not mentioned	Spectinomycin 2 g IM × 1	32
Fluker 1980	3	Spectinomycin	20 mg/l or less	Retreatment not mentioned	Did not mention cure
Rajan 1979	7	Kanamycin 2 g x 1	Not mentioned	Spectinomycin hydrochloride 2 g IM x 1	7
Porter 1977	13 with urethral site of infection	Spectinomycin hydrochloride 2 g IM × 1	5 µg to 10 µg/ml	Tetracycline	13
Karney 1977	7 (oropharyngeal)	Spectinomycin hydrochloride 2 g IM × 1	Not clear	Retreatment not mentioned	Did not mention cure
McCann 1977	FOR male:				
McCann 1977	1	Spectinomycin hydrochloride 2 g IM × 1	Not clear	Spectinomycin	1
McCann 1977	4	Spectinomycin hydrochloride 2 g IM × 1	Not clear	Penicillin	4
McCann 1977	1	Spectinomycin and penicillin resistant	Not clear	Kanamycin	1
McCann 1977	3	Spectinomycin hydrochloride 2 g IM × 1	Not clear	Spectinomycin hydrochloride 2 g IM x 1	3
McCann 1977	1	Spectinomycin hydrochloride 2 g IM × 1	Not clear	Trimethoprim sulphamethoxazole	Loss of follow-up

Study	Number of patients with treatment failure	Treatment received first	Minimum inhibitory concentration (MIC)	Retreatment	Number of patients cured
McCann 1977	FOR female:				
McCann 1977	2	Spectinomycin hydrochloride 4 g IM × 1	Not clear	Spectinomycin hydrochloride 2 g IM x 1	2
McCann 1977	1	Spectinomycin hydrochloride 4 g IM × 1	Not clear	Kanamycin	1
McCann 1977	1	Spectinomycin hydrochloride 4 g IM × 1	Not clear	Penicillin	1
Holder 1972	1 with both the urethra and rectum site of infection	Spectinomycin hydrochloride 4 g IM × 1	Not clear	4–8 m.u. aqueous procaine penicillin G in a single injection.	1
Holder 1972	1 with both rectum site of infection	Spectinomycin hydrochloride 4 g IM x 1	Not clear	4–8 m.u. aqueous procaine penicillin G in a single injection.	1
Brown 1974	6	Spectinomycin	10 to 20 µg/ml	Not mentioned retreatment	Did not mention cure
Kousa 1974	14 (8 men and 6 women)	Spectinomycin	Treatment failures occurred among the patients with strains with MICs of spectinomycin of 7.5 to 15.0 µg/ml.	2 g spectinomycin may not be sufficient for strains less sensitive to penicillin; in such cases a dose of 4 g spectinomycin should be used.	All women were cured at 2nd follow-up visit.
Duncane 1972	Total treatment failure 8	Spectinomycin 2 g			
Duncane 1972	Re-treated 3	Spectinomycin 2 g	5.0 to 15 µg/ml	4.8 million units of aqueous procaine penicillin G	2
Duncane 1972	Re-treated 2	Spectinomycin 2 g	5.0 to 15 µg/ml	4 g of spectinomycin hydrochloride	0
Duncane 1972	Total treatment failures 5	Spectinomycin 4 g			
Duncane 1972	Re-treated 3	Spectinomycin 4 g	5.0 to 15 µg/ml	4.8 million units of aqueous procaine penicillin G	2
Duncane 1972	Re-treated 1	Spectinomycin 4 g	5.0 to 15 µg/ml	9 g tetracycline in divided doses	1

bid: twice daily; IM: intramuscular; po: by mouth.

ADDITIONAL STUDIES

Author, study year	Number of patients with treatment failure	Treatment received first	Minimum inhibitory concentration (MIC)	Retreatment	Number of patients cured
Unemo 2012* France	1 in Australia	Cefixime 200 mg po, 2 doses 6 hours apart	MIC 2 to 8 µg/ml	Gentamicin 160 mg IM	1
Unemo 2011* Austria	1	Cefixime 400 mg po × 1 × 7 days	MIC 1 mg/l	Azithromycin 2 g po x 1	1
Allen 2013	6 in Toronto	Cefixime 400 mg po	MIC of 0.12 µg/ml or greater	Ceftriaxone 250 mg IM	6
Allen 2013	3	Cefixime 400 mg po	MIC of 0.12 µg/ml or greater	Cefixime 800 mg po	3
Unemo 2012¶	1 pharyngeal in Slovenia	Ceftriaxone 250 mg IM x 1	MICs of 0.125 mg/l.	Ceftriaxone 250 mg IM x 1 + azithromycin 2 g oral x 1	1
Yokoi 2007¶	4 Japanese males	Cefixime 200 mg × 2 × 3 days	MIC of 0.50 to 1.0 µg/ml	Ceftriaxone 1 g IM x 1	3 cure; 1 loss to follow-up
Lewis 2013* South Africa	1	Cefixime 400 mg × 1 oral	MIC: 0.75 mg/L	Azithromycin 2 g po x 1	1
Lewis 2013	1	Cefixime 400 mg × 1 oral	MIC: 1 mg/L	Ceftriaxone 2 g IM x 1	1
Chen 2013* (research letter)	1 Pharyngeal	Ceftriaxone 500 mg IM × 1	MIC: 0.03– 0.06 µg/ml	Azithromycin 1 g	1
Ison 2011 in UK (Rapid communications)	1	Cefixime 400 mg × 1 oral	MIC: 0.25 mg/L	1st time re-treated with Azithromycin but were not cured; and 2nd time re-treated with Ceftriaxone 250 mg IM x 1 and cured	1
Soge 2012 Portland	1	Azithromycin 2 g orally	Pre-treatment azithromycin MIC of 1.0 µg/mL; post-treatment azithromycin MIC of 8.0 µg/mL	Cefpodoxime 400 mg and Azithromycin 1 g orally	1

IM: intramuscular; po: by mouth.

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Included studies: randomized and non-randomized studies

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ANTIMICROBIAL RESISTANCE IN NEISSERIA GONORRHOEAE

The data on gonococcal antimicrobial resistance from countries participating in the Gonococcal Antimicrobial Surveillance Programme (GASP) were used for recommendations 1, 2 and 3. The data from 2009 to 2013 were reported in the Global STI surveillance report. In addition, the results of searches for additional studies published between 2011 and 2015 that addressed resistance were used; these included in particular studies conducted in low- and middle-income countries.

Summary:

1. High rates of quinolone resistance
2. Increasing proportions of gonorrhoea isolates with elevated ceftriaxone minimum inhibitory concentration (MIC) values
3. Increasing proportion of gonorrhoea isolates resistant to azithromycin
4. Treatment failure to ceftriaxone and cefixime documented in some countries

Antimicrobial resistance from the GASP revealed the following:

Table 1. Number of countries reporting ≥ 5% of gonoccocal isolates with resistance to azithromycin and ciprofloxacin/quinolones and elevated minimum inhibitory concentrations of cefixime (0.25 µg/ml) or ceftriaxone (> 0.125 µg/ml), 2012–2013

Reported % resistant isolates	Africa (n=1)	Americas (n=11)	Eastern Mediterranean (n=1)	Europe (n=24)	South-East Asia (n=5)	Western Pacific (n=14)	Total (n=56)
Ceftriaxone/cefixime							
≥ 5% decreased susceptibility	0	1	0	9	0	4	14
Of which ≥ 10% decreased susceptibility	0	0	0		0	2	6
Azithromycin							
≥ 5% resistant isolates	1	1	–	13	0	1	15
Of which ≥ 10% resistant isolates	1	0	–	9	0	1	10
Ciprofloxacin/quinolones							
≥ 5% resistant isolates	1	10	–	24	5	15	55
50–90% resistant isolates	1	2	–	14	0	3	20
> 90% resistant isolates	0	0	–	1	5	6	12

Source: Report on the global sexually transmitted infection surveillance 2015. Geneva: World Health Organization; 2016 (in press).

Extended-spectrum cephalosporins

Since 2009, 46 countries have reported decreased susceptibility to extended-spectrum cephalosporins. Forty-nine countries reported data on the susceptibility of N. gonorrhoeae to extended-spectrum cephalosporins in 2012 and/or 2013, with 59% (29 of 49) countries reporting decreased susceptibility in 2012/2013.

In the European Region, which accounted for half of the reporting countries in 2012/2013, among the 23 countries reporting, less than 1% of isolates in the region overall exhibited decreased sensitivity to ceftriaxone. Nine countries in the region reported minimum inhibitory concentration (MICs) greater than 0.25 µg/ml for cefixime in 5% or more of isolates, with four countries reporting elevated minimum inhibitory concentrations in 10% or more. Only seven countries reported no decreased susceptibility to cefixime; among these, five countries reported decreased susceptibility in previous years, and one reported data for the first time in 2013.

Decreased susceptibility to ceftriaxone was reported by 10 of the 12 Western Pacific Region countries submitting data for 2012/2013, with four reporting decreased susceptibility in 5% or more of isolates: the cut-off for changing treatment guidelines. An additional three countries in the region reported at least 5% decreased susceptibility in past years. Only two countries reported no isolates with decreased susceptibility (New Caledonia and the Philippines) in any reporting year.

In the Region of the Americas, two countries reported decreased susceptibility to ceftriaxone – Canada and the USA – with Canada reporting over 5%. Decreased susceptibility to cefixime among less than 5% of isolates was also reported by Canada and the USA.

Ceftriaxone susceptibility data are more limited in the remaining regions. In the South-East Asia Region, only two countries reported ceftriaxone susceptibility data in 2012/2013. Of the seven countries that reported to GASP between 2009 and 2013, five reported some decreased susceptibility to ceftriaxone; among these, four reported decreased susceptibility in over 5% of isolates. Only one country in the African Region and one in the Eastern Mediterranean Region reported in 2012 and/or 2013, and neither reported decreased susceptibility to ceftriaxone. Of note, only four countries have reported from the African Region and two from the Eastern Mediterranean Region since 2009. Among these, only two countries reported decreased susceptibility to ceftriaxone: Côte d'Ivoire (> 10%) and South Africa (< 5%).

The first reported treatment failure to ceftriaxone was in Japan followed by additional treatment failures in Austria, Australia, Canada, France, Norway, Slovenia, South Africa, Sweden and the United Kingdom. Although the majority of reports are from developed countries, it can be assumed that these data represent only the tip of a silent epidemic of antimicrobial resistance as surveillance data from resource-constrained settings are scarce.

Azithromycin

Among 42 countries reporting azithromycin susceptibility in 2012/2013, 17 reported resistance in 5% or more of isolates. Across all regions, only seven countries reported no resistant isolates. The majority of countries reporting in 2012/2013 were in the European Region. Among the 24 countries reporting from the region, 13 reported 5% or more resistant isolates. Among these, nine countries reported over 10%, including Cyprus and Greece with over 20% resistance. Three countries in the European Region reported no resistant isolates; however, two of them reported resistance in previous years, and the third reported antimicrobial resistance (AMR) data for the first time in 2013.

Countries in Asia began reporting susceptibility data for azithromycin in 2011. In the four countries reporting from the South-East Asia Region between 2011 and 2013, three reported less than 5% resistant isolates, and one reported no resistant isolates. Among the nine Western Pacific Region countries that have submitted data, six reported resistant isolates with only one country reporting over 5% resistant isolates (Japan reported over 10% in both 2012 and 2013). Four countries reported from the Region of the Americas and all of them (including Canada and the USA) found isolates resistant to azithromycin; only one country (Chile) reported over 5% resistance. No countries reported data from the Eastern Mediterranean Region. The first country to report on AMR for azithromycin in the African Region was Côte d'Ivoire in 2013, which reported over 10% resistant isolates.

Quinolones

In 2012 and 2013, 56 countries reported susceptibility data for ciprofloxacin. High levels of resistance were reported from all regions with nearly every country reporting over 20% resistant isolates. Twelve countries, mostly in Asia, reported very high levels of resistance (over 90% of isolates). Only four countries reported less than 5% resistant isolates – Dominican Republic, Fiji, New Caledonia and Panama (although the Dominican Republic reported > 20% resistance in previous years (see Table 2).

Table 2: Reported percentage of gonoccocal isolates with resistance to azithromycin and ciprofloxacin/quinolones and elevated minimum inhibitory concentrations (MICs) of cefixime (> 0.25 µg/ml) or ceftriaxone (> 0.125 µg/ml), 2012 and 2013

Region and country	Ceftriaxone				Cefixime				Azithromycin				Quinolones/ciprofloxacin			
	2012		2013		2012		2013		2012		2013		2012		2013	
	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%
African Region																
Côte d'Ivoire			36	0.0							36	13.6			36	0.9
Region of the Americas																
Argentina	404	0.0	606	0.0		767		8.0			606	0.5	404	49.0	606	54.0
Chile	767	0.0	891	0.0							767	30.9	891	41.0		
Columbia	65		61	0.0							65	40.0	61	14.8		
Cuba	60	0.0	60	0.0							60	46.7	60	46.7		
El Salvador	21	0.0	20	0.0							21	0.0	20	20.0		
Panama	5	0.0									5	0.0				
Paraguay	18	0.0	46	0.0							18	66.7	46	58.7		
Venezuela	14	0.0											14	42.9		
Dominican Republic													4	0.0	2	0.0
Regional total	**1354**	**0.0**	**1684**	**0.0**					**767**	**8.0**	**606**	**0.5**	**1358**	**37.3**	**1686**	**45.1**
Canada	3036	5.5	3195	3.5	3036	2.2	3195	1.8	3036	0.9	3195	1.2	3036	28.5	3195	29.3
USA	5495	0.3	5945	0.1	5495	1.0	5495	0.4	5495	0.3	5945	0.6	5495	14.7	5945	16.1

Region and country	Ceftriaxone				Cefixime				Azithromycin				Quinolones/ciprofloxacin			
	2012		2013		2012		2013		2012		2013		2012		2013	
	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%
Eastern Mediterranean Region																
Morocco			35	0.0												
European Region																
Austria	107	0.0	109	0.0	107	4.7	109	6.4	107	2.8	109	5.5	107	73.8	109	71.6
Belarus	75	0.0	40	0.0	75	0.0	40	2.5	75	1.3	40	0.0	75	21.0	40	28.0
Belgium	107	0.0	110	0.0	107	0.9	110	6.4	107	1.9	110	1.8	107	56.1	110	56.4
Cyprus	3	0.0	9	0.0	3	0.0	9	0.0	3	0.0	9	33.3	3	100.0	9	88.9
Denmark	114	0.0	110	0.0	114	12.3	110	11.8	114	13.2	110	9.1	114	58.8	110	58.2
France	110	0.0	112	0.0	110	1.8	112	3.6	110	0.0	112	0.0	110	39.1	112	44.6
Germany	106	0.9	101	1.0	106	5.7	101	12.9	106	1.9	101	4.0	106	73.6	101	63.4
Greece	68	0.0	75	0.0	68	5.9	75	14.7	68	5.9	66	22.7	68	69.1	75	72.0
Hungary	79	0.0	88	0.0	79	6.3	88	6.8	79	0.0	88	2.3	79	65.8	88	68.2
Iceland			5	0.0			5	0.0			5	0.0			5	40.0
Ireland	80	1.3	103	0.0	80	3.8	103	0.0	80	8.8	103	2.9	80	22.5	103	26.2
Italy	100	0.0	100	0.0	100	6.0	100	0.0	100	2.0	100	1.0	100	65.0	100	63.0
Latvia	39	0.0	38	0.0	39	2.6	38	2.6	39	5.1	38	15.8	39	38.5	38	26.3
Malta	16	0.0	31	0.0	16	0.0	31	0.0	16	0.0	31	0.0	16	56.3	31	35.5

Region and country	Ceftriaxone				Cefixime				Azithromycin				Quinolones/ciprofloxacin			
	2012		2013		2012		2013		2012		2013		2012		2013	
	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%
The Netherlands	146	0.0	139	0.0	146	0.0	139	0.0	146	0.7	139	1.4	146	34.2	139	34.5
Poland	108	0.0			108	0.0			108	10.2			108	68.5		
Norway	110	0.0	112	0.0	110	5.5	112	4.5	110	12.7	112	10.7	110	55.5	112	79.5
Portugal	110	0.0	110	0.0	110	0.0	110	0.0	110	1.8	110	18.2	110	40.9	110	47.3
Russia	106	0.0							106	17.0			106	25.5		
Slovakia	108	0.0	110	0.0	108	3.7	110	4.5	108	2.8	110	1.8	108	53.7	110	47.3
Slovenia	47	2.1	73	0.0	47	4.3	73	1.4	47	14.9	73	0.0	47	40.4	73	63.0
Spain	105	0.0	119	5.0	105	15.2	119	15.1	105	9.5	119	8.4	105	58.1	119	65.5
Sweden	110	0.0	100	0.0	110	0.0	100	0.0	110	6.4	100	9.0	110	57.3	100	60.0
United Kingdom	262	0.0	240	0.0	262	0.0	240	0.8	262	1.9	240	0.4	262	27.9	240	32.1
Regional total	**2216**	**0.1**	**2034**	**0.3**	**2110**	**3.6**	**2034**	**0.9**	**2216**	**5.2**	**2025**	**5.3**	**2216**	**48.9**	**2034**	**52.4**
South-East Asia Region																
Bhutan									142	0.0	215	0.0	187	88.2	215	93.0
India	88	0.0	50	0.0					55	3.6	50	2.0	88	97.7	50	96.0
Pakistan													71	94.3		
Sri Lanka											113	1.8	48	95.8	113	97.3
Thailand	748	0.4	496	0.4					749	0.4	464	0.9	722	86.9	510	92.2
Regional total	**836**	**0.4**	**546**	**0.4**					**946**	**0.5**	**842**	**4.7**	**1116**	**88.9**	**888**	**93.2**

Region and country	Ceftriaxone				Cefixime				Azithromycin				Quinolones/ciprofloxacin			
	2012		2013		2012		2013		2012		2013		2012		2013	
	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%	No. of isolates	%
Western Pacific Region																
Australia (Urban)	4394	0.3	4658	0.6					4394	1.4	4658	2.2	4394	32.2	4658	35.8
Australia (Remote)	324	0.0	239	0.8					324	0.3	239	0.0	324	2.8	239	2.1
Brunei													204	83.8	102	70.6
Cambodia															7	100.0
China	1236	12.8											1236	99.6		
Fiji													168	0.0	120	0.0
Hong Kong	1149	5.5	1134	4.5					1149	4.2	1134	4.7	1149	96.1	1134	93.7
Japan	371	0.5	391	21.9					371	10.8	391	13.8	98	72.4	391	70.8
Korea			12	8.3					91	0.0			91	96.7	82	93.9
Mongolia			444	0.2							444	4.1	517	43.7	444	19.8
New Caledonia			140	0.0									150	0.7	140	0.7
New Zealand	401	0.3	384	1.0							74	0.0	345	41.7	384	35.4
Philippines	23	0.0	129	0.0							89	0.0	23	95.7	127	93.7
Singapore	160	0.0	55	1.8									160	71.9	160	83.1
Viet Nam			44	2.3					90	1.1	44	2.3	90	100.0	44	93.2
Regional total	**8058**	**3.0**	**7630**	**2.3**					**6419**	**2.4**	**7073**	**3.3**	**8949**	**52.4**	**8032**	**45.9**

Source: Report on the global sexually transmitted infection surveillance 2015. Geneva: World Health Organization; 2016 (in press).

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Extended-spectrum cephalosporins

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RECOMMENDATION 4

Treatment of gonococcal ophthalmia neonatorum	
Population:	Treating gonococcal neonatal ophthalmia
Intervention and comparison:	Ceftriaxone, kanamycin, spectinomycin
Main outcomes:	Microbiological cure Clinical cure Complications Side-effects (including allergy, toxicity, gastro) Antimicrobial resistance Compliance
Setting:	Out- and inpatient care
Perspective:	Population
Background:	Ophthalmia neonatorum is a form of conjunctivitis occurring in the neonatal period. It is the most common cause of acute ophthalmic disease in newborns. The most severe type of ophthalmia neonatorum is gonococcal that and may lead to blindness if diagnosis and treatment are attempted late. During the 19th century, the single greatest cause of blindness in newborns in Western countries was gonorrhoeal keratitis, until Crede introduced the use of 2% silver nitrate ophthalmic solution to the eyes of newborns. In 2003, WHO recommended ceftriaxone 50 mg/kg intramuscular (IM) injection, as a single dose, to a maximum of 150 mg. Alternative regimens where ceftriaxone is not available include: kanamycin 25 mg/kg IM as single dose, to a maximum of 75 mg or spectinomycin 25 mg/kg IM as a single dose, to a maximum of 75 mg.

ASSESSMENT

	Judgement	Research evidence
Problem	**Is the problem a priority?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** Gonococcal ophthalmia neonatorum is a serious condition. The reported incidence of this disease varies around the world. Identifying and treating the gonococcal ophthalmia neonatorum infection of newborns delivered to women with gonorrhoeal disease are important because it can result in corneal scarring, ocular perforation and blindness. **Additional considerations:** The GDG noted that most treatment of neonatal conjunctivitis would be syndromic as testing is rarely performed.
Desirable effects	**How substantial are the desirable anticipated effects?** • Trivial • Small • Moderate • **Large** • Varies • Don't know	**Research evidence:** Two randomized and 13 non-randomized studies were found. **Additional considerations:** There were 100% cure rates with all treatments, with the exception of penicillin (approximately 81–84% cure rates). There was little-to-no difference in adverse effects across treatments.
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	
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:** According to **indirect evidence** from **chlamydia-related economic evaluation studies**, the disutilities of different health states (utility loss due to the health states) are as follows: neonatal conjunctivitis: –0.03; neonatal pneumonia: –0.21 **Additional considerations:** None

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	
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	**Research evidence:** No research evidence was found. **Additional considerations:** The GDG noted that the treatments are relatively inexpensive when compared to the costs of long-term consequences of conjunctivitis.
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**	
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:** The major medical databases were searched (MEDLINE, Embase and the Cochrane Library for Economic Evaluation and Technology Assessment reports). Five cost-effectiveness studies on uncomplicated gonorrhoea published before 2000 were found; these were not assessed, but the cost factors were considered above. **Additional considerations:** The GDG agreed that there would be little difference in cost effectiveness across the different treatments. However, cost effectiveness may be lower with spectinomycin with reduced number of cures.

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:** None
Acceptability	**Is the intervention acceptable to key stakeholders?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** No research evidence was found. **Additional considerations:** Treatment options are already in use and acceptable.
Feasibility	**Is the intervention feasible to implement?** • No • Probably no • Probably yes • **Yes** • Varies • Don't know	**Research evidence:** No research evidence was found. **Additional considerations:** None

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 gonococcal neonatal ophthalmia						
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 ●	Strong recommendation against the intervention •
Recommendation	In neonates with gonococcal conjunctivitis, the WHO STI guidelines suggest one of the following treatment options: • Ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose • Kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose • Spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose *Conditional recommendation, very low quality evidence* **Remarks:** Due to the large net benefit with treatment, good practice dictates that neonates should be treated for gonococcal conjunctivitis. The choice of treatment may depend on the cost, quality of the drug in different resource settings, and on equity considerations. Side-effects should be monitored in neonates.					
Justification	There was very low-quality evidence for cure rates that were typically 100% for all treatments, with the exception of penicillin (approximately 81–84% cure rates). The quality of evidence was very low for little-to-no differences in adverse effects across treatments. No evidence is available for patient values and preferences. The costs for treatments were relatively low and similar, and most treatments are currently being used.					
Subgroup considerations						
Implementation considerations						
Monitoring and evaluation						
Research priorities	Resistance to treatment has not previously been reported.					

EVIDENCE PROFILE

Treatment of gonococcal ophthalmia neonatorum

Outcomes	Overall quality of evidence	CFT 50 mg/kg × 1 × 7 days IV	CFT 62.5 mg × 1	CFT 125 mg × 1	CEF 100 mg/kg	SPE 40 mg/kg	C-PEN (10 000 units per ml)	PEN 50 000 units/kg/day × 2 × 7 days IV
Microbiological cure	⊕⊖⊖⊖ **Very low**[1, 2]	1.00 (0.86 to 1.14)	1.00 (0.92 to 1.08)	1.00 (0.95 to 1.05)	1.00 (0.94 to 1.06)	0.97 (0.89 to 1.04)	0.81 (0.68 to 0.94	
Clinical cure	⊕⊖⊖⊖ **Very low**[1, 2]	0.97 (0.89 to 1.05)			1.00 (0.93 to 1.07)			0.84 (0.71 to 0.97)
Conjunctival scarring	⊕⊖⊖⊖ **Very low**[1, 2]	0 events						0.06 (−0.03 to 0.16)
Side-effects	⊕⊖⊖⊖ **Very low**[1, 2]			High dose is associated with few adverse effects.	No significant adverse effects	No significant adverse effects		No significant adverse effects
Compliance	In Singapore, occasionally parents were extremely reluctant to admit the child for inpatient treatment, and IM ceftriaxone would be adequate especially in cases where a follow-up visit for test of cure is not assured.							
Otitis media	One neonate with concurrent otitis media was treated with cefotaxime for 5 days							
Antimicrobial resistance	With ceftriaxone 62.5 mg × 1 treatment, penicillinase production was detected in 25% of strains and all isolates demonstrated very low minimal inhibitory concentrations (MICs) for ceftriaxone. Cefotaxime in a single IM dose of 100 mg/kg also showed no resistance to PPNG and non-PPNG strains.							

CFT: ceftriaxone; CEF: cefotaxime; C-PEN: crystalline penicillin eye-drops; IM: intramuscular; PEN: penicillin; SPE: spectinomycin

1. Results from single-arm studies providing proportion of events were analysed; number of events was unadjusted for confounding factors.
2. Sample size does not meet optimum minimum sample size criteria

Treatment of gonococcal ophthalmia neonatorum (continued)										
Outcomes	Overall quality of evidence	KNA 500 mg/kg × 1	KNA 100 mg + saline	KNA 75 mg + GN	KNA 75 mg + TCY	KNA 250 mg + 1% TCY	KNA 75 mg + saline	KNA 150 mg + saline	KNA 150 mg + GN	KNA 150 mg + CHL
Microbiological cure	⊕⊖⊖⊖ **Very low**[1,2]	1.00 (0.67 to 1.33)	0.99 (0.97 to 1.00)	1.00 (0.91 to 1.09)	1.00 (0.92 to 1.08)	0.96 (0.86 to 1.06)	0.89 (0.68 to 1.10)	1.00 (0.89 to 1.11)	1.00 (0.93 to 1.07)	1.00 (0.88 to 1.12)
Clinical cure	⊕⊖⊖⊖ **Very low**[1,2]					0.91 (0.82 to 1.00)				
Side-effects	⊕⊖⊖⊖ **Very low**[1,2]					4 of 70 cases had signs of mild congestion of palpebral conjunctivae on the 7th day	1 infant persistent with infection, pneumonia, sepsis, and a bilateral corneal ulcer developed			
Compliance	Not reported									
Otitis media	Not reported									
Antimicrobial resistance	For kanamycin and gentamicin, all strains were moderately sensitive. Over half of the isolates had a minimum inhibitory concentration of tetracycline of 2–4 mg/l.									

CHL: chloramphenicol drop; GN: gentamicin ointment; KNA: kanamycin; TCY: tetracycline drop

1. Results from single-arm studies providing proportion of events were analysed; number of events was unadjusted for confounding factors.
2. Sample size does not meet optimum minimum sample size criteria
3. Description of studies with single cases

Description of studies with single cases

Study year	Treatment	Outcomes	Cure	Not cure
Nsanze, 1996	Ceftriaxone 125 mg IM	Microbiological cure	1	0
Jarvis, 1987	Cephazolin (parenteral) and gentamicin eye drops;	Microbiological cure	1	0
	Penicillin G (100 000 U/kg/day) and gentamicin (6 mg/kg/day) IM	Microbiological cure	1	0
	Penicillin G (100 000 U/kg/day) IM	Microbiological cure	0	1
Lockie, 1986	Penicillin (topical) + penicillin (systematic)	Microbiological cure	0	2
	Penicillin (topical) + penicillin (systematic)	Microbiological cure	1	0
	Chloramphenicol (topical) cefoperazone 75 mg bid IM × 5 days & spectinomycin 40 mg/kg single IM (systematic)	Microbiological cure	1	0
	Gentamicin (topical) + kanamycin 25 mg bid IM × 7 days (systematic)	Microbiological cure	1	0
	Chloramphenicol (topical) + ampicillin (systematic)	Microbiological cure	1	0
	Chloramphenicol (topical) and single-dose spectinomycin 40 mg/kg single IM (systematic)	Microbiological cure	1	0
Ng, 1987	Ceftriaxone 50 mg/kg IM × 2	Microbiological cure	1	0
	Ceftriaxone 50 mg/kg IM × 3	Microbiological cure	2	0
	Kanamycin 500 mg IM × 1	Microbiological cure	2	0
Lepage, 1988	Cefotaxime 100 mg/kg	Clinical cure	9	0

bid: twice daily; IM: intramuscular

List of all treatments for gonococcal ophthalmia neonatorum from studies

Spectinomycin 40 mg/kg IM (single dose); cefotaxime 100 mg/kg IM (single dose); Penicillin G IM; Cefuroxime (single dose) IM Ceftriaxone 125 mg IM (single dose) Kanamycin 75 mg IM (single dose) + 1 % tetracycline ointment (4 × daily × 7 days) Kanamycin 75 mg IM (single dose) + 1% gentamicin ointment (4 × daily × 7 days)
Kanamycin 75 mg IM (single dose) + gentamicin ointment Kanamycin 75 mg IM (single dose) + saline wash Kanamycin 150 mg IM (single dose) + gentamicin ointment or kanamycin 150 mg IM (single dose) + saline wash Kanamycin 150 mg IM (single dose) + gentamicin ointment Kanamycin 150 mg IM (single dose) + chloramphenicol eye drops
Ceftriaxone 62.5 mg IM (single dose)
Cefotaxime 100 mg/kg IM single dose (without topical antibiotic therapy)
Cefotaxime 100 mg/kg IM single dose (without topical antibiotic therapy)
Kanamycin 100 mg IM + hourly ocular irrigation with saline)
Kanamycin 500 mg/kg IM × 1 Cefotaxime 100 mg/kg IM × 1 Ceftriaxone 50 mg/kg, 100 mg/kg, 150 mg/kg IM; (all combined with 1% kanamycin eye drops)
Penicillin (topical) + penicillin (systematic) Chloramphenicol (topical) + cefoperazone Gentamicin (topical) + kanamycin (systematic) Chloramphenicol (topical) + ampicillin (systematic) Chloramphenicol (topical) + spectinomycin (systematic) Chloramphenicol (topical) and single-dose spectinomycin (40 mg/kg) given intramuscularly (systematic)
Ceftriaxone 125 mg IM x 1 (30–40 mg/kg) (without topical antibiotic therapy)
Penicillin G (100 000 U/kg/day) IV followed by topical penicillin drops (100 000 U/ml) Cephazolin (parenteral) and topical gentamicin eye drops Penicillin G (100 000 U/kg/day) and gentamicin (6 mg/kg/day) IV
Kanamycin 250 mg IM stat + 1% tetracycline eye drops instilled every 4 hours for 7 days
Ceftriaxone 50 mg/kg/day 1 daily × 7 days IV (topical ofloxacin) vs penicillin 50 000 units/kg/day twice daily × 7 days IV (topical tobramycin + ofloxacin)
Local therapy as crystalline penicillin eye-drops (10 000 units per ml); Local + systematic therapy as crystalline penicillin eye-drops (10 000 units per ml) + intramuscular crystalline penicillin 100 000 units every 6 hours for 24 hours (i.e. a total of 400 000 units)
Ceftriaxone 50–125 mg IM in addition to tropical therapy.

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Patient values and preferences, acceptability and cost: other sexually transmitted infections

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RECOMMENDATIONS 5 AND 6

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 inpatient 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 *E. coli*, *Haemophilus*, **and** *Enterococcis*. There is no guidance in the 2003 WHO Guidelines that is specific to prevention of ophthalmia neonatorum. The Guideline Development Group (GDG) identified preventative medications for ophthalmia neonatorum due to 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:** Sixteen studies were included: 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 a 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 non-infectious conjunctivitis. The GDG noted that there have been incidences of using alcohol-based povidone iodine instead of water based, which has 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, and 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.
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:** None
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	**Ophthalmic ointment** / **Drug cost*** Erythromycin 0.5% / $0.74 Silver nitrate 1% / $7.30 Chloramphenicol / $0.2956 Tetracycline / $0.069 Povidone iodine / $0.01 *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.
Certainty of evidence of resources required	**What is the certainty of the evidence of resource requirements (costs)?** • Very low • Low • Moderate • High • **No included studies**	**Research evidence:** No research studies assessing other resource issues 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:** A cost analysis published in 2010 estimated costs of prophylaxis with povidone iodine 2.5%, erythromycin 0.5%, or azithromycin 1% in the 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, and therefore there is probably no impact on equity.
Acceptsbility	**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 efffects	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. Few data are available for the incidence of non-infectious conjunctivitis after prophylaxis or no prophylaxis. Low-quality evidence shows a slight reduction or little difference and indicates that between 4 and 50 per 1000 infants have non-infectious conjunctivitis after application of different prophylactic medications. 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 and 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 can provide protection.				
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 (0.25–50.99)	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 (0.14–1.08)	3 per 1000	2 fewer per 1000 (3 fewer to 0 fewer)
	47424 (1 non-RCTs)	⊕⊖⊖⊖ **very low**[3,4]	RR 3.27 (0.18–60.82)	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 (0.99–1.92)	28 per 1000	11 more per 1000 (0 fewer to 26 more)
	47424 (1 non-RCT)	⊕⊖⊖⊖ **very low**[4]	RR 0.24 (0.07–0.86)	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 (0.95–1.41)	78 per 1000	12 more per 1000 (4 fewer to 32 more)

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**
	47,424 (1 non-RCT)	⊕⊕⊖⊖ **low**[4]	RR 0.39 (0.24–0.63)	78 per 1000	47 fewer per 1000 (59 fewer to 29 fewer)
Incidence of non-infectious conjunctivitis					
	2041 (1 RCT)	⊕⊕⊖⊖ **low**[1,3]	RR 1.04 (0.84–1.30)	70 per 1000	3 more per 1000 (11 fewer to 21 more)
	47,424 (1 non-RCT)	⊕⊖⊖⊖ **very low**[3,4]	RR 0.53 (0.25–1.14)	70 per 1000	33 fewer per 1000 (53 fewer to 10 more)
Side-effects: 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 (0.34–1.89)	70 per 1000	14 fewer per 1000 (46 fewer to 62 more)

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 gonococcal conjunctivitis					
	10 946 (2 RCTs)	⊕⊖⊖⊖ **very low**[1,3]	RR 0.70 (0.16–3.12)	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 (0.52–1.57)	28 per 1000	3 fewer per 1000 (13 fewer to 16 more)
Incidence of infectious conjunctivitis: no study found					
Incidence of non-infectious conjunctivitis: no study found					
Side-effects: 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 (0.35–2.03)	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 (0.55–1.05)	28 per 1000	7 fewer per 1000 (13 fewer to 1 more)
Incidence of infectious conjunctivitis					

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%**
	2391 (2 RCTs)	⊕⊕⊖⊖ **low**[1,3]	RR 0.87 (0.71–1.07)	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 (0.21–1.28)	70 per 1000	34 fewer per 1000 (55 fewer to 20 more)
Side-effects: 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 (0.47–11.57)	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 (0.86–2.90)	90 per 1000	52 more per 1000 (13 fewer to 171 more)
Incidence of gonococcal conjunctivitis					
	14501 (5 RCTs)	⊕⊕⊖⊖ **low**	RR 1.39 (0.16–12.13)	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 (0.76–2.25)	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 (1.09–1.79)	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 (0.80–1.97)	18 per 1000	4 more per 1000 (3 fewer to 17 more)
Side-effects: 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 (0.97–4.17)	52 per 1000	53 more per 1000 (2 fewer to 164 more)

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 non-infectious conjunctivitis					
	394 (1 RCT)	⊕⊖⊖⊖ **very low**[1,2]	RR 20.17 (1.19–341.82)	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		

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 (0.60–6.29)	4 per 1000	4 more per 1000 (2 fewer to 23 more)
Incidence of chlamydial conjunctivitis					
	2005 (1 RCT)	⊕⊕⊖⊖ **low**[1]	RR 0.52 (0.38–0.71)	110 per 1000	53 fewer per 1000 (68 fewer to 32 fewer)
Incidence of infectious conjunctivitis					
	2005 (1 RCT)	⊕⊕⊖⊖ **low**[1]	RR 0.75 (0.61–0.92)	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 (0.55–0.89)	139 per 1000	42 fewer per 1000 (63 fewer to 15 fewer)
Side-effects: 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 (0.97–3.22)	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 (1.03–1.79)	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 (0.01–1.94)	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 ($P = 0.223$).		

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		
Incidence of chlamydial conjunctivitis					
	719 (1 RCT)	⊕⊖⊖⊖ **very low**[1,2]	RR 1.27 (0.26–6.24)	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 (0.65–3.69)	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 (0.95–1.74)	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).		

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 *N. gonorrhoeae* during delivery					
	138 (1 RCT)	⊕⊕⊖⊖ **low**[1,2]	RR 0.17 (0.07–0.41)	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 (0.17–0.60)	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 (0.06–0.31)	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 (0.04–3.12)	37 per 1000	24 fewer per 1000 (36 fewer to 78 more)
Incidence of infectious conjunctivitis					
	2579 (2 RCTs)	⊕⊕⊕⊖ **moderate**[3]	RR 0.27 (0.05–1.37)	75 per 1000	54 fewer per 1000 (71 fewer to 28 more)
Incidence of non-infectious conjunctivitis: no study found					
Side-effects: 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 (0.02–0.29)	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 (0.11–0.46)	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 (0.01–0.17)	20 per 1000	19 fewer per 1000 (20 fewer to 17 wer)
Incidence of chlamydial conjunctivitis					

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%
	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 1000 (58 fewer to 47 fewer)
Incidence of non-infectious conjunctivitis: no study found					
Side-effects: 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%). Culture was performed for 111 newborns (11.1%), 91 cases (9.1%) were positive and 20 newborns (2%) negative. Greatest number negative cultures were in normal saline group and erythromycin group stood second.		
Side-effects: 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					

1. Few events across studies
2. Sample size does not meet optimum minimum sample size criteria
3. 95% CI includes potential for fewer or greater "adverse 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.
5. The baseline risk for incidence of conjunctivitis represents the average risk of the control group patients through all the different comparisons
6. 95% CI includes potential for fewer or greater "cures".

Resistance to prophylaxis

Tetracycline may prove inconvenient as it may select resistant strains (Ison, 1988). Erythromycin 0.5% also selects resistant bacterial strains (Hedberg, 1990; Schwarcz, 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 from the District of Columbia.

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