ClinicalEvidence

Chlamydia (uncomplicated, genital)

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ABSTRACT

INTRODUCTION: Genital chlamydia is the most commonly reported bacterial sexually transmitted infection in developed countries. The majority of infections affect young adults under the age of 25 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of antibiotic treatment for men and non-pregnant women with uncomplicated genital chlamydial infection? What are the effects of antibiotic treatment for pregnant women with uncomplicated genital chlamydial infection? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2014 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 26 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions — for men and non-pregnant women: antibiotics (single-dose) and antibiotics (multiple-dose regimens); for pregnant women: antibiotics (single-dose), erythromycin or amoxicillin (multiple-dose regimens), and clindamycin (multiple-dose regimens).

QUESTIONS

INTERVENTIONS

Key points

- Genital chlamydia is caused by *Chlamydia trachomatis* (serotypes D-K), an obligate intracellular organism that is sexually transmitted. It infects the urethra and rectum in men and women, as well as the endocervix in women. It is defined as uncomplicated if it has not ascended to the upper genital tract or caused sexually acquired reactive arthritis.

  It is the most common bacterial sexually transmitted infection in developed countries. Over 200,000 chlamydia diagnoses were made in the UK in 2013, [1] [2] [3] with almost 70% of cases detected in young adults under the age of 25 years.

Infection is usually asymptomatic, particularly in women. Most people infected do not present for testing or treatment. Therefore, population rates based on routine surveillance data underestimate the true disease burden. The highest positivity rates are seen in sexually active 15- to 24-year-olds, with rates of 10% being observed.

If untreated, chlamydial infection may persist or resolve spontaneously, with the average duration of infection in women being 1.36 years.

If untreated, *Chlamydia* infection in women causes pelvic inflammatory disease (PID) in approximately 16% of women.This may result in infertility, ectopic pregnancy, or chronic pelvic pain.

Partner notification and treatment is an important part of effective management.

Young adults who test positive for chlamydia are at greater risk of re-testing positive within the next year. Repeated chlamydial infections have been shown to increase the risk of PID and its associated complications. Therefore, the National Chlamydia Screening Programme (NCSP) in England now recommends repeat testing at 3 months for positive individuals. [4]

- Multiple-dose regimens of tetracyclines (doxycycline or tetracycline) achieve microbiological cure in at least 95% of men and non-pregnant women with genital chlamydia.

  Erythromycin also seems beneficial as a multiple-dose regimen, but we don't know which regimen of erythromycin is more effective.

  Ciprofloxacin may be less effective at leading to microbiological cure compared with multiple-dose doxycycline. There were also a greater number of adverse effects with multiple-dose ciprofloxacin, most commonly gastrointestinal side effects.

  We don't know whether multiple-dose regimens of other antibiotics (such as other macrolides, quinolones, and penicillins) are effective, as we found few adequate studies.

- In men and non-pregnant women with uncomplicated genital chlamydia, one single dose of azithromycin seems as beneficial as a 7-day course of doxycycline and produces similar rates of adverse effects.

  Single-dose treatments have the obvious advantage of improving adherence.

  Treatment cure rates of over 95% have been reported. However, two recent randomised controlled treatment trials in men with urethritis suggest it may not be as effective in symptomatic men. [5] [6] [7] [8]

- In pregnant women, multiple-dose regimens of erythromycin or amoxicillin seem effective in treating chlamydial infection.

  One small study has also suggested that clindamycin and multiple-dose erythromycin are equally effective at curing infection, although the size of the study makes it hard to draw definitive conclusions.

- Single-dose azithromycin may be effective in treating chlamydia in pregnant women.

- In pregnant women, no antibiotic regimen has a microbiological cure rate of over 95%, and pregnant women should be offered a test of cure no sooner than 5 weeks after treatment was initiated to ensure that the infection has cleared.

Clinical context

DEFINITION

Genital chlamydia (*Chlamydia trachomatis* serotypes D-K) is a sexually transmitted infection (STI) that infects the urethra and rectum in men and women, as well as the endocervix in women. It can also infect other mucosal surfaces, including conjunctiva and nasopharynx. It is defined as an **uncomplicated** genital infection if it has not ascended to the upper genital tract or has not caused sexually acquired reactive arthritis. Infection in women is asymptomatic in the majority of cases but may cause non-specific symptoms, including vaginal discharge and intermenstrual and post-coital bleeding. Infection in men causes urethral discharge and urethral irritation or dysuria, but may also be asymptomatic in up to 50% of cases. [9] [10] **Complicated** chlamydial infection includes spread to the upper genital tract (causing pelvic inflammatory disease [PID] in women [see review on PID] and epididymo-orchitis in men), or development of sexually acquired reactive arthritis. [9] [10] Lymphogranuloma venereum (LGV) caused by *C trachomatis* serovars L1-3 (predominantly serovar L2) has also emerged as an important genital tract pathogen in men who have sex with men. [11] [12] In most cases, men infected with LGV present with symptomatic rectal disease. [13] [14] Interventions for complicated chlamydial infection (including LGV) are not included in this review.

INCIDENCE/ PREVALENCE

Genital chlamydia is the most common bacterial STI in developed countries. In 2013, more than 200,000 cases of chlamydia were reported to Public Health England. [1] Infection is most common in people under 25 years of age, with rates decreasing thereafter. [2] [3] In 15- to 24-year-olds, the chlamydia diagnosis rate was more than 2000 per 100,000 population in 2013, as a result of the National Chlamydia Screening Programme (NCSP). [15] Testing coverage in the NCSP in 2013 was 25% across England. [15]

AETIOLOGY/ RISK FACTORS

Infection is caused by the bacterium *C trachomatis* serotypes D-K. It is transmitted primarily through sexual intercourse, but also perinatally and through direct or indirect oculogenital transfer. Risk factors include age under 25 years, new partner or more than one partner in the past year, and failure to use condoms correctly. [10]

PROGNOSIS

In women, untreated chlamydial infection can ascend to the upper genital tract, causing PID in approximately 16% of women [16] (see review on PID). Tubal infertility has been found to occur in about 18% of women after a single episode of PID, [17] and the risk of ectopic pregnancy is increased six- to sevenfold. [18] [19] Ascending infection in men causes epididymitis, and there is mounting evidence that acute chlamydia infection is possibly associated with male infertility by direct effect on sperm production and maturation. [17] [20] [21] Mother-to-infant transmission can lead to neonatal conjunctivitis and pneumonitis. [9] Chlamydia may coexist with other genital infections, and may facilitate transmission of HIV infection. [9] [22] A recent modelling study, combining all the evidence on duration of infection in women, concluded that the mean duration of infection was 1.36 years, with nearly a quarter testing negative, as a result of clearance of 'passive' infection within a few weeks of testing positive, despite not being treated. [23] There is limited evidence regarding the duration of infection in men, although it is assumed to be similar in those who are asymptomatic. [24] Men and women who are chlamydia-positive are at high risk of retesting positive after treatment. [25] Therefore, the NCSP in England now recommends repeat testing at 3 months for positive individuals. [4] Although the assumption that positive tests for chlamydia after treatment are always due to re-infection, cure rates of less than 95% have been observed in prospective studies where repeat infection is unlikely, particularly with azithromyicin 1 gram. [4] [5] [7] [8] [26] [27] A large partner-treatment RCT found an 8% (95% CI 5% to 11%) failure rate in 289 women who had been sexually inactive 3 to 20 weeks after treatment. [28] A subset analysis of men enrolled in an RCT and who had tested positive for chlamydia found a positive-retest rate of 37% (25/68) in chlamydia-positive men with urethritis at a median of 43 days after treatment. [27] Interestingly, the proportion of men who tested positive for chlamydia at re-screening yet denied sexual exposure was 36% (9/25). The authors of the study concluded that this higher than expected rate of positive re-screening tests could have been the result of inaccurate reporting by the index patient or treatment failure. *C trachomatis* resistance to antibiotics seems to be rare. [26] However, due to technical difficulties, limited studies have been undertaken *in vivo*. At high multiplicities of infection (load), in-vitro persistence to antimicrobials (heterotypic resistance) can often be demonstrated. It has been proposed that people with high organism loads, which are associated with symptomatic infection and younger age, may be at increased risk of treatment failure. [26] All antibiotics seem to have lower efficacy in pregnant women, with no antibiotic regimen having a microbiological cure rate of over 95%. In pregnant women, a repeat test is recommended no sooner than 5 weeks after treatment, to ensure that the infection has cleared. [10] Partner notification and treatment is an important part of effective management (see our review on Partner notification). Innovative and effective partner treatment strategies have been associated with lower rates of re-infection. [25] [29]

AIMS OF INTERVENTION

To eradicate *C trachomatis*; to prevent the development of upper genital tract infection; to prevent further sexual transmission; and to prevent perinatal transmission, with minimal adverse effects of treatment.

OUTCOMES

Cure rates the primary outcome assessed in most trials is short-term **microbiological cure rate** (calculated as the percentage of people attending a follow-up visit at least 1 week, and usually <5 weeks, after the end of antibiotic treatment who had a negative test for *C trachomatis*), [30] which until recently usually used culture, which is less sensitive than nucleic acid amplification tests. However, because of the potentially prolonged life cycle of the organism, this may not indicate eradication of *C trachomatis*. [5] [31] Antibiotics that have cure rates higher than 95% in treatment studies are the first-line treatment of choice. [10] [32] Long-term cure rates (>5 weeks) have not been studied extensively in RCTs because of high default rates and difficulty in distinguishing persistent infection from re-infection. [6] It is beyond the scope of this review to assess the effectiveness of the listed interventions at reducing the risk of retesting positive at more than 5 weeks after treatment. Other outcomes assessed are **adverse effects**, including effects on the fetus. We present cure rates for pregnant women separately from those for men and non-pregnant women, because two important drug groups (tetracyclines and quinolones) are contraindicated in pregnancy.

METHODS

BMJ Clinical Evidence search and appraisal February 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2014, Embase 1980 to February 2014, and The Cochrane Database of Systematic Reviews 2014, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full

texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing more than 20 individuals, of whom at least 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open-label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were studied, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 22). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of antibiotic treatment for men and non-pregnant women with uncomplicated genital chlamydial infection?**

OPTION **ANTIBIOTICS (SINGLE DOSE) FOR MEN AND NON-PREGNANT WOMEN**

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- Single-dose azithromycin may be as effective as multiple-dose doxycycline and multiple-dose lymecycline at increasing microbiological cure rates in men and non-pregnant women with uncomplicated genital chlamydia.

Benefits and harms

Single-dose versus multiple-dose antibiotics:

We found one systematic review (search date 2001, 12 blinded and open-label RCTs, 1543 people) comparing azithromycin with doxycycline. [33] We found one additional RCT [34] and two subsequent RCTs. [7] [8]

Microbiological cure

Single-dose versus multiple-dose antibiotics Single-dose azithromycin may be as effective as multiple-dose doxycycline and multiple-dose lymecycline at increasing microbiological cure rates (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[33] Systematic review	People (aged >15 years) with genital chlamydia infection 12 RCTs in this analysis	**Microbiological cure** 853/884 (96%) with azithromycin 1 g (single dose) 645/659 (98%) with doxycycline (multiple dose) 100 mg (twice-daily) for 7 days Cure rates for single-dose azithromycin ranged from 81% to 100%; for multiple-dose doxycycline from 88% to 100%	Difference = +0.008 95% CI –0.007 to +0.022 P = 0.296	⟷	Not significant
[34] RCT	146 women (aged >18 years) with confirmed *Chlamydia trachomatis* infections of the cervix	**Microbiological cure , 15–35 days** 57/57 (100%) with azithryomycin 1 g (single dose) 63/63 (100%) with lymecycline (multiple dose) 300 mg (twice-daily) for 10 days	Significance not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[7] RCT **4-armed trial**	111 men (aged 16-45 years) with confirmed *C trachomatis* infection	**Microbiological cure , 15–45 days** 41/53 (77%) with azithromycin (single dose) with or without tinidazole (single dose) 55/58 (95%) with doxycycline (multiple dose) with or without tinidazole (single dose) The primary aim of the study was to determine whether the addition of tinidazole would be tolerable and more efficacious than treatment with either doxycycline or azithromycin alone	P = 0.011	○○○	doxycycline (multiple dose)
[8] RCT	101 men (aged >16 years) with confirmed *C trachomatis* infection	**Microbiological cure , 3 weeks** 86% with azithromycin (single dose) 90% with doxycycline (multiple dose) Absolute numbers not reported Azithromycin (single dose): n = 51 Doxycycline (multiple dose): n = 50	Significance not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] Systematic review	People (aged >15 years) with genital chlamydia infection 12 RCTs in this analysis	**Adverse effects** with azithromycin (single dose) with doxycycline (multiple dose) Cases of short-term adverse effects of both azithromycin and doxycycline were reported to be mild and the rates similar for both groups 1543 people included in this analysis			
[34] RCT	146 women (aged >18 years) with confirmed *C trachomatis* infections of the cervix	**Adverse effects** 6/72 (8%) with azithryomycin 1 g (single dose) 16/74 (22%) with lymecycline 300 mg (twice-daily) for 10 days Both groups reported experiencing diarrhoea, vomiting, nausea, genital candidiasis; however, women receiving azithromycin additionally reported experiencing palpitations, while those receiving lymecycline reported experiencing abdominal pains, genital pruritus, leukorrhoea, increased perspiration, back pain, withdrawal bleeding, fatigue, malaise, and urticaria	P = 0.04	○○○	azithromycin (single dose)

No data from the following reference on this outcome. [7] [8]

Comment: When taken as a directly observed treatment, the advantage of single-dose azithromycin over multiple-dose antibiotics is that adherence to treatment can be guaranteed. Concern has been raised, however, that azithromycin may be less than 95% effective in symptomatic men with urethritis, [5] which has been supported by a recent meta-analysis. [6] This may be because of an increased chlamydia load in men with urethritis. [5] [6]

OPTION ANTIBIOTICS (MULTIPLE-DOSE REGIMENS) OTHER THAN TETRACYCLINE, DOXYCYCLINE, OR ERYTHROMYCIN FOR MEN AND NON-PREGNANT WOMEN

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- We don't know how multiple-dose antibiotics (trovafloxacin, pivampicillin, sparfloxacin, clarithromycin, minocycline, and ofloxacin) and multiple-dose doxycycline compare at increasing cure. Cure rates were high for all antibiotics assessed.
- We don't know how multiple-dose rifampicin and multiple-dose tetracycline compare at increasing cure. Cure rates were high for both antibiotics.
- Roxithromycin and erythromycin may be equally effective at increasing cure rates.
- Multiple-dose lymecycline and multiple-dose doxycycline seem no more effective than single-dose azithromycin at increasing microbiological cure rates.

Benefits and harms

Multiple-dose antibiotics (other than tetracycline, doxycycline, ciprofloxacin, or erythromycin) versus tetracycline/doxycycline:

See Multiple-dose regimens of doxycycline or tetracycline for men and non-pregnant women, p 7 .

Multiple-dose antibiotics (other than tetracycline, doxycycline, ciprofloxacin, or erythromycin) versus ciprofloxacin:

See Multiple-dose regimens of ciprofloxacin for men and non-pregnant women, p 7 .

Multiple-dose antibiotics (other than tetracycline, doxycycline, ciprofloxacin, or erythromycin) versus erythromycin:

See Multiple-dose regimens of erythromycin for men and non-pregnant women, p 12 .

Multiple-dose antibiotics (other than tetracycline, doxycycline, ciprofloxacin, or erythromycin) versus single-dose antibiotics:

We found no systematic reviews or RCTs.

Comment: Most RCTs were conducted in STI clinics, where follow-up is difficult. [35] [36] [37] [38] Most RCTs were small (3 RCTs had <40 people with chlamydia), [39] [40] [41] and many antibiotic regimens were compared, so it is difficult to draw conclusions about relative efficacy. Only a few RCTs re-

ported that sexual partners of participants were offered treatment. Amoxicillin and ampicillin have not been adequately assessed in the treatment of genital chlamydia infection because in-vitro studies suggest that amoxicillin does not eradicate *Chlamydia trachomatis*, [10] [42] raising concern that infection may persist and recrudesce *in vivo*. A similar effect is presumed for ampicillin.

Clinical guide
Although there is limited evidence on the effects of ofloxacin (we found only one RCT), [40] ofloxacin is recommended as an alternative treatment in people in whom doxycycline and azithromycin are contraindicated. [10]

OPTION CIPROFLOXACIN (MULTIPLE-DOSE REGIMENS) FOR MEN AND NON-PREGNANT WOMEN

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- Multiple-dose ciprofloxacin may be less effective at increasing cure rates than multiple-dose doxycycline in men and non-pregnant women with uncomplicated genital chlamydia.

Benefits and harms

Multiple-dose ciprofloxacin versus multiple-dose doxycycline/tetracycline:
See Multiple-dose regimens of doxycycline or tetracycline for men and non-pregnant women, p 7 .

Multiple-dose ciprofloxacin versus multiple-dose erythromycin:
We found no systematic review or RCTs.

Multiple-dose ciprofloxacin versus other multiple-dose antibiotics (other than doxycycline, tetracycline, or erythromycin):
We found no systematic review or RCTs.

Multiple-dose ciprofloxacin versus single-dose antibiotics:
We found no systematic review or RCTs.

Comment: Most RCTs were conducted in STI clinics, where follow-up is difficult. Many antibiotic regimens were compared, so it is difficult to draw conclusions about relative efficacy. Only a few RCTs reported that sexual partners of participants were offered treatment.

Clinical guide
Ciprofloxacin is often prescribed for epididymo-orchitis, which can be caused by chlamydia. Ofloxacin is the preferred quinolone used for treatment of uncomplicated chlamydia, even though evidence is limited. In-vitro studies suggest that both treatments are suboptimal at eradicating infection compared with macrolide or doxycycline, but ofloxacin is more effective than ciprofloxacin. [43] More effective quinolones are available, such as moxifloxacin, but there is an increased risk of adverse effects even at small doses. [44]

OPTION DOXYCYCLINE OR TETRACYCLINE (MULTIPLE-DOSE REGIMENS) FOR MEN AND NON-PREGNANT WOMEN

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- Multiple-dose doxycycline may be more effective at increasing cure rates than multiple-dose ciprofloxacin for men and non-pregnant women with uncomplicated genital chlamydial infection. There were a greater number of adverse effects with multiple-dose ciprofloxacin.

- We don't know whether multiple-dose doxycycline is more effective than other multiple-dose antibiotics (trovafloxacin, pivampicillin, sparfloxacin, clarithromycin, minocycline, and ofloxacin) at increasing cure rates. Cure rates were high for all antibiotics assessed.
- We don't know whether multiple-dose tetracycline is more effective than multiple-dose rifampicin at increasing cure. Cure rates were high for both antibiotics.

Benefits and harms

Multiple-dose doxycycline versus multiple-dose ciprofloxacin:

We found two RCTs. [45] [46]

Microbiological cure

Multiple-dose doxycycline versus multiple-dose ciprofloxacin Multiple-dose doxycycline may be more effective at increasing cure rates than multiple-dose ciprofloxacin in men and non-pregnant women with uncomplicated genital chlamydia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[45] RCT **3-armed trial**	60 men with culture positive for *Chlamydia trachomatis* prior to treatment (subgroup of larger population of 178 men with non-gonococcal urethritis)	**Microbiological cure , 2 weeks** 9/9 (100%) with doxycycline 11/20 (55%) with ciprofloxacin 1.5 g 13/18 (72%) with ciprofloxacin 2 g Similar significant results were found at 4 weeks	P = 0.03 doxycycline *v* ciprofloxacin 1.5 g P = 0.14 doxycycline *v* ciprofloxacin 2 g	○○○	doxycycline
[46] RCT	200 people (>18 years) with confirmed *C trachomatis* infection	**Microbiological cure , 1 week** 87/97 (90%) with doxycycline 88/94 (94%) with ciprofloxacin See Further information on studies	Significance not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] RCT **3-armed trial**	162 men with non-gonococcal urethritis (60 men with culture positive for *C trachomatis* prior to treatment)	**Adverse effects** 10/52 (19%) with doxycycline 20/57 (35%) with ciprofloxacin 1.5 g 20/53 (38%) with ciprofloxacin 2 g The most common adverse effect was gastrointestinal side effects	P = 0.06 doxycycline *v* ciprofloxacin 1.5 g P = 0.05 doxycycline *v* ciprofloxacin 2 g	○○○	doxycycline

No data from the following reference on this outcome. [46]

Multiple-dose doxycycline versus multiple-dose erythromycin:

We found no systematic review or RCTs.

Multiple-dose doxycycline versus other multiple-dose antibiotics (other than tetracycline, ciprofloxacin, or erythromycin):

We found six RCTs. [39] [47] [40] [48] [35] [49]

Microbiological cure

Multiple-dose doxycycline versus other multiple-dose antibiotics (other than tetracycline, ciprofloxacin, or erythromycin)

We don't know whether multiple-dose doxycycline is more effective than other multiple-dose antibiotics (trovafloxacin, pivampicillin, sparfloxacin, clarithromycin, minocycline, and ofloxacin) at increasing cure rates in men and non-pregnant women with uncomplicated genital chlamydia. Cure rates were high for all antibiotics assessed (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[39] RCT	27 people (18–35 years) with confirmed *C trachomatis* infection (subgroup of larger population of 40 people with presumptive non-gonococcal urethral or endocervical infection)	**Microbiological cure , 1 week** 13/13 (100%) with doxycycline 14/14 (100%) with clarithromycin The cure rates remained the same 3 weeks post-treatment	Significance not reported		
[47] RCT	86 people (>16 years) with confirmed *C trachomatis* infection (subgroup of larger population of 253 people with non-gonococcal urethritis or mucopurulent cervicitis, or whose partner had either condition or a positive culture for *C trachomatis*)	**Microbiological cure , 2 weeks** 39/39 (100%) with doxycycline 100 mg (twice-daily) for 7 days 39/39 (100%) with minocycline 100 mg (nightly) for 7 days Similar non-significant results were found at 4 weeks	Significance not reported		
[40] RCT	28 men (18–37 years) with confirmed *C trachomatis* infection (subgroup of larger population of 114 men with uncomplicated urethritis)	**Microbiological cure , 28–35 days post-treatment commencement** 10/10 (100%) with doxycycline 100 mg (twice-daily) for 7 days 15/18 (83%) with ofloxacin 300 mg (twice-daily) for 7 days Similar non-significant results were found at 2 weeks	Reported as not significant P values not reported	⟷	Not significant
[48] RCT **3-armed trial**	223 men with confirmed *C trachomatis* infection (subgroup of larger population of 683 men with non-gonococcal urethritis)	**Microbiological cure , >17 days** 73/76 (96%) with doxycycline 100 mg (nightly) for 7 days 64/66 (97%) with sparfloxacin 200 mg for 1 day, then 100 mg for 6 days 59/67 (88%) with sparfloxacin 100 mg for 3 days, then placebo for 4 days	Significance not reported		
[35] RCT	633 people (16–60 years, mean age 35.1 years) with confirmed *C trachomatis* infection (subgroup of larger	**Microbiological cure , 31–39 days** 240/246 (98%) with doxycycline 246/265 (93%) with trovafloxacin	Significance not reported See Further information on studies		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	population of 977 people with uncomplicated chlamydial urethritis or cervicitis)				
[49] RCT	80 men with confirmed *C trachomatis* infection	**Microbiological cure , 2 weeks** 38/39 (97%) with doxycycline 200 mg for 1 day, then 100 mg for 8 days 37/40 (93%) with pivampicillin 700 mg (twice-daily) for 9 days Similar non-significant results were found at 4 weeks	Reported as not significant P values not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[47] RCT	237 people (aged 16 years or older) with non-gonococcal urethritis or mucopurulent cervicitis, or whose partner had either condition or a positive culture for *C trachomatis* (86 people with confirmed *C trachomatis* infection)	**Adverse effects** 64/126 (51%) with doxycycline 100 mg (twice-daily) for 7 days 33/111 (30%) with minocycline 100 mg (nightly) for 7 days Significant between-group differences in overall adverse effects were observed for subgroups of males (32/74 [43%] with doxycycline *v* 17/65 [26%] with minocycline; P = 0.05) and females (32/52 [62%] with doxycycline *v* 16/46 [35%] with minocycline; P = 0.009) 5 people withdrew (2 with minocycline and 3 with doxycycline); 1 person on minocycline developed severe depression and mood swings with headaches and bad dreams; 2 people on doxycycline had penile oedema, and numbness in extremities and lips, with some shortness of breath.	Significance not reported		
[47] RCT	253 people (aged 16 years or older) with non-gonococcal urethritis or mucopurulent cervicitis, or whose partner had either condition or a positive culture for *C trachomatis* (86 people with confirmed *C trachomatis* infection)	**Gastrointestinal upset** 49/126 (39%) with doxycycline 100 mg (twice-daily) for 7 days 20/111 (18%) with minocycline 100 mg (nightly) for 7 days Significant between-group differences in vomiting only were observed (9/126 [7%] with doxycycline *v* 0/111 [0%] with minocycline; P = 0.004)	P <0.001	○○○	minocycline
[48] RCT **3-armed trial**	683 men with non-gonococcal urethritis (223 men with confirmed *C trachomatis* infection)	**Severe adverse effects** 6% with doxycycline 200 mg for 7 days 3% with sparfloxacin 200 mg for 1 day, then 100 mg for 6 days	Significance not reported		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0% with sparfloxacin 100 mg for 3 days, then placebo for 4 days Absolute numbers not reported n = 230 doxycycline, n = 231 7-day sparfloxacin, n = 222 3-day sparfloxacin			
[48] RCT **3-armed trial**	683 men with non-gonococcal urethritis (223 men with confirmed *C trachomatis* infection)	**Gastrointestinal events** 47/230 (20%) with doxycycline 100 mg (nightly) for 7 days 25/231 (11%) with sparfloxacin 200 mg for 1 day, then 100 mg for 6 days 31/220 (14%) with sparfloxacin 100 mg for 3 days, then placebo for 4 days	Significance not reported		
[48] RCT **3-armed trial**	683 men with non-gonococcal urethritis (223 men with confirmed *C trachomatis* infection)	**Photophobia** 1/230 (0.4%) with doxycycline 100 mg (nightly) for 7 days 3/231 (1.3%) with sparfloxacin 200 mg for 1 day, then 100 mg for 6 days 1/220 (0.5%) with sparfloxacin 100 mg for 3 days, then placebo for 4 days	Significance not reported		

No data from the following reference on this outcome. [40] [35] [49]

Different regimens of multiple-dose doxycycline versus each other:

We found no RCTs comparing different regimens of doxycycline, but the most frequent schedule (in 3 RCTs) was 100 mg twice-daily for 7 days. [47] [40]

Multiple-dose tetracycline versus multiple-dose doxycycline, erythromycin, or ciprofloxacin:

We found no systematic review or RCTs.

Multiple-dose tetracycline versus other multiple-dose antibiotics (other than doxycycline, ciprofloxacin, or erythromycin):

We found one RCT. [41]

Microbiological cure

Multiple-dose tetracycline versus other multiple-dose antibiotics (other than doxycycline, ciprofloxacin, or erythromycin)

We don't know whether multiple-dose tetracycline is more effective than multiple-dose rifampicin at increasing cure rates in men and non-pregnant women with uncomplicated genital chlamydia. Cure rates were high for both antibiotics (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[41] RCT	633 men with confirmed *C trachomatis* infection (subgroup of larger population of men with non-gonococcal urethritis)	**Microbiological cure , 14–21 days** 19/19 (100%) with tetracycline hydrochloride 500 mg (4 times per day) for 7 days 14/18 (78%) with rifampicin 600 mg for 7 days	Significance not reported		

Adverse effects

No data from the following reference on this outcome. [41]

Multiple-dose doxycycline or tetracycline versus single-dose antibiotics:

See Single-dose antibiotics for men and non-pregnant women, p 4 .

Further information on studies

[46] At 3 weeks, follow-up was only 143/200 (72%). Microbiological cure was 70/72 (97%) with doxycycline and 65/71 (92%) with ciprofloxacin (significance not reported). We have not reported this in the tables due to the high attrition. The study concluded that overall "doxycycline proved more effective than ciprofloxacin ... although both treatment regimens were unsatisfactory".

[35] Subgroup analysis demonstrated differing response in males and females. Significant between-group differences were observed in men (101/102 [99%] with doxycycline *v* 89/100 [89%] with trovafloxacin, 95% CI –16.4 to –3.6, P = 0.003), while no significant differences were observed in women (139/144 [97%] with doxycycline *v* 157/165 [95%] with trovafloxacin, 95% CI –5.8 to +3.1, P value not reported).

Comment: Most RCTs were conducted in STI clinics, where follow-up is difficult. In one RCT of doxycycline with available data, more than 15% of randomised people were not included in the analysis. [35] Most RCTs were small (two RCTs had less than 40 people with chlamydia), [39] [41] and many antibiotic regimens were compared, so it is difficult to draw conclusions about relative efficacy. Only a few RCTs reported that sexual partners of participants were offered treatment.

Clinical guide

The studies included in this review, which investigated multiple-dose regimens, support the use of multiple-dose doxycycline as first-line in the treatment of uncomplicated genital chlamydial infection for men and non-pregnant women. [9]

OPTION ERYTHROMYCIN (MULTIPLE-DOSE REGIMENS) FOR MEN AND NON-PREGNANT WOMEN

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- Erythromycin and roxithromycin may be equally effective at increasing cure rates in men and non-pregnant women with uncomplicated genital chlamydia. Cure rates were similar for both antibiotics, but less than 95%.
- We don’t know which regimen of erythromycin is more effective at increasing cure rates. However, higher doses of erythromycin were associated with an increase in adverse effects.

Benefits and harms

Multiple-dose erythromycin versus multiple-dose doxycycline/tetracycline:

See Multiple-dose regimens of doxycycline or tetracycline for men and non-pregnant women, p 7 .

Multiple-dose erythromycin versus multiple-dose ciprofloxacin:

We found no systematic review or RCTs.

Multiple-dose erythromycin versus other multiple-dose antibiotics (other than ciprofloxacin, doxycycline, or tetracycline):

We found one RCT. [36]

Microbiological cure

Multiple-dose erythromycin versus other multiple-dose antibiotics (other than ciprofloxacin, doxycycline, or tetracycline) Erythromycin and roxithromycin may be equally effective at increasing cure rates in men and non-pregnant women with uncomplicated genital chlamydia. Cure rates were similar for both antibiotics (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[36] RCT	281 people with genitourinary chlamydia infections	**Microbiological cure , 3 weeks** 87/113 (77%) with erythromycin ethylsuccinate 500 mg (twice-daily) for 7 days 93/114 (82%) with roxithromycin 300mg for 7 days Subgroup analysis of men and women demonstrated no significant differences between erythromycin and roxithromycin (P values not reported) Attrition rate: 54/281 (19%)	Significance not reported		

Adverse effects

No data from the following reference on this outcome. [36]

Different regimens of multiple-dose erythromycin versus each other:

We found two RCTs. [37] [38] The first RCT compared 7 days with 4 days of treatment with erythromycin stearate 1 g-daily. [37] In the other RCT, erythromycin stearate 2 g-daily was compared with 1 g-daily for 7 days. [38]

Microbiological cure

Different regimens of multiple-dose erythromycin versus each other We don't know which regimen of erythromycin is more effective at increasing cure rates in men and non-pregnant women with uncomplicated genital chlamydia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[37] RCT	99 people with uncomplicated genitourinary *Chlamydia trachomatis* infection	**Microbiological cure , 2 weeks** 15/33 (45%) with erythromycin 500 mg (twice-daily) for 4 days 35/40 (88%) with erythromycin 500 mg (twice-daily) for 7 days Significant between-group differences were also observed for subgroups of males (P <0.05) and females (P <0.01) Attrition rate: 26/99 (26%) Similar significant results and attrition rate reported at 7 days	P <0.0005	○○○	erythromycin 7 days
[38] RCT	114 people with *C trachomatis* infections	**Microbiological cure , post-treatment** 33/45 (73%) with erythromycin 1 g (in 3 divided doses daily) for 7 days 28/31 (90%) with erythromycin 2 g (in 3 divided doses daily) for 7 days Attrition rate: 38/114 (33%)	Significance not reported		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[38] RCT	114 people with *C trachomatis* infections	**Gastrointestinal adverse effects** 16/47 (34%) with erythromycin 1 g (in 3 divided doses daily) for 7 days 30/42 (71%) with erythromycin 2 g (in 3 divided doses daily) for 7 days Gastrointestinal adverse effects included nausea, vomiting, diarrhoea, and abdominal pain, and were significantly more common in women than men (26/41 [63%] women *v* 20/48 [42%] men) P = 0.033	P = 0.0004	○○○	erythromycin 1 g
[38] RCT	114 people with *C trachomatis* infections	**Discontinuing treatment because of adverse effects** 2/47 (4%) with erythromycin 1 g (3 times daily) for 7 days 11/42 (26%) with erythromycin 2 g (3 times daily) for 7 days	P = 0.0037	○○○	erythromycin 1 g

No data from the following reference on this outcome. [37]

Multiple-dose erythromycin versus single-dose antibiotics:

We found no systematic reviews or RCTs.

Comment: Most RCTs were conducted in STI clinics, where follow-up is difficult. In the RCT of erythromycin versus roxithromycin, more than 15% of randomised participants were not included in the analysis. [36] Many antibiotic regimens were compared, so it is difficult to draw conclusions about relative efficacy. Only a few RCTs reported that sexual partners of participants were offered treatment.

Clinical guide

The studies included in this review do not provide evidence that erythromycin is more than 95% effective in the treatment for uncomplicated genital chlamydial infection. However, consideration must be given to the discontinuation rates due to gastrointestinal side effects at high doses.

QUESTION **What are the effects of antibiotic treatment for pregnant women with uncomplicated genital chlamydial infection?**

OPTION **ERYTHROMYCIN OR AMOXICILLIN (MULTIPLE-DOSE REGIMENS) FOR PREGNANT WOMEN**

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- Multiple-dose erythromycin and multiple-dose amoxicillin seem equally effective at increasing cure rates in pregnant women with uncomplicated genital chlamydia.

Benefits and harms

Multiple-dose erythromycin versus multiple-dose amoxicillin:

We found one systematic review (search date 2012, 11 blinded and open-label RCTs, 1449 people). [50]

Microbiological cure

Multiple-dose erythromycin versus multiple-dose amoxicillin Multiple-dose erythromycin and multiple-dose amoxicillin seem equally effective at increasing cure rates in pregnant women with uncomplicated chlamydia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[50] Systematic review	Pregnant women with confirmed *Chlamydia trachomatis* infections 3 RCTs in this analysis	**Failure to achieve microbiological cure** 28/191 (15%) with erythromycin 500 mg (4 times daily) for 7 days 17/199 (9%) with amoxicillin 500 mg (3 times daily) for 7 days	OR 0.54 95% CI 0.28 to 1.02 P = 0.059	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[50] Systematic review	Pregnant women with confirmed *C trachomatis* infections 3 RCTs in this analysis	**Adverse effects not leading to treatment discontinuation** 35/150 (23%) with erythromycin 500 mg (4 times daily) for 7 days 10/154 (6%) with amoxicillin 500 mg (3 times daily) for 7 days	OR 0.25 95% CI 0.13 to 0.48 P = 0.000027	●●○	amoxicillin
[50] Systematic review	Pregnant women with confirmed *C trachomatis* infections 4 RCTs in this analysis	**Adverse effects resulting in treatment discontinuation** 40/249 (16%) with erythromycin 500 mg (4 times daily) for 7 days 4/254 (2%) with amoxicillin 500 mg (3 times daily) for 7 days	OR 0.16 95% CI 0.09 to 0.30 P <0.00001	●●●	amoxicillin

Multiple-dose erythromycin versus multiple-dose clindamycin:

See Multiple-dose clindamycin for pregnant women, p 16 .

Multiple-dose erythromycin or amoxicillin versus single-dose antibiotics:

See Single-dose antibiotics for pregnant women, p 17 .

Comment: **Clinical guide**

The evidence included in this review supports the use of either multiple-dose erythromycin or amoxicillin in the treatment of uncomplicated genital chlamydia infection in pregnant women. However, neither treatment reaches the efficacy of more than 95% treatment success. Adverse effects (namely gastrointestinal disturbance) resulting in discontinuation was significantly greater in the erythromycin arm.

Re-testing after treatment is thus indicated due to high treatment failure rates.

OPTION CLINDAMYCIN (MULTIPLE-DOSE REGIMENS) FOR PREGNANT WOMEN

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- Multiple-dose clindamycin and multiple-dose erythromycin seem equally effective at increasing cure rates in pregnant women with uncomplicated genital chlamydia.

Benefits and harms

Multiple-dose clindamycin versus multiple-dose erythromycin:

We found one systematic review (search date 2012), which identified one RCT. [50]

Microbiological cure

Multiple-dose clindamycin compared with multiple-dose erythromycin We don't know how multiple-dose clindamycin and multiple-dose erythromycin compare at increasing cure rates in pregnant women with uncomplicated genital chlamydia (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[50] Systematic review	Pregnant women with confirmed *Chlamydia trachomatis* infections Data from 1 RCT	**Failure to achieve microbiological cure** 3/41 (7%) with clindamycin 6/37 (16%) with erythromycin 3-armed study; remaining arm evaluated placebo 135 women included in this analysis	OR 0.42 95% CI 0.11 to 1.68 P = 0.22	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [50]

Comment: **Clinical guide**
Clindamycin is a possible alternative for the treatment of chlamydia in pregnancy in women for whom macrolides are contraindicated.

OPTION ANTIBIOTICS (SINGLE DOSE) FOR PREGNANT WOMEN

- For GRADE evaluation of interventions for Chlamydia (uncomplicated, genital), see table, p 22 .
- Single-dose azithromycin seems more effective at increasing cure rates than multiple-dose erythromycin in pregnant women with uncomplicated genital chlamydia.
- We don't know whether single-dose azithromycin is more effective at increasing microbiological cure rates than multiple dose amoxicillin.
- Azithromycin should only be used in pregnancy if no adequate alternative is available (see Comments).

Benefits and harms

Single-dose antibiotics versus other single-dose antibiotics:

We found no systematic review or RCTs.

Single-dose azithromycin versus multiple-dose erythromycin:

We found two systematic reviews (search dates 2012; [50] 1991–2006 [51]), which identified the same five RCTs (4 non-blinded; 372 pregnant women). The RCTs identified by the reviews compared a single dose of azithromycin 1 g with erythromycin 500 mg four times daily for 7 days. [50] [51] However, the reviews included different RCTs in their meta-analysis and found slightly different results, and so we report data from both reviews here. [50] [51] The second review also analysed data from one RCT (47 women) that was published in only abstract form (conference proceeding). [51]

Microbiological cure

Single-dose azithromycin versus multiple-dose erythromycin Single-dose azithromycin seems more effective at increasing cure rates than multiple-dose erythromycin in pregnant women with uncomplicated genital chlamydia (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[50] Systematic review	Pregnant women with confirmed *Chlamydia trachomatis* infections 4 RCTs in this analysis	**Failure to achieve microbiological cure , 2–3 weeks** 11/145 (8%) with azithromycin 1 g (single dose) 27/145 (19%) with erythromycin (multiple dose) 500 mg (4 times daily) for 7 days	OR 0.38 95% CI 0.19 to 0.74 P = 0.005	●●○	azithromycin (single dose)
[51] Systematic review	Pregnant women with confirmed *C trachomatis* infections 4 RCTs in this analysis	**Microbiological cure , 2–6 weeks** 139/149 (93%) with azithromycin 1 g (single dose) 118/144 (82%) with erythromycin (multiple dose) 500 mg (3 or 4 times daily) for 7 days The review found no significant difference between azithromycin and erythromycin in rate of treatment success	OR 2.66 95% CI 0.69 to 10.29	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[50] Systematic review	Pregnant women with confirmed *C trachomatis* infections 4 RCTs in this analysis	**Fetal anomaly (not specified further)** 1/65 (2%) with azithromycin 1 g (single dose) 1/65 (2%) with erythromycin (multiple dose) 500 mg (4 times daily) for 7 days 289 women included in this analysis	OR 1.0 95% CI 0.06 to 16.16 P = 1.0	⟷	Not significant
[50] Systematic review	Pregnant women with confirmed *C trachomatis* infections 3 RCTs in this analysis	**Adverse effects resulting in treatment discontinuation** 1/80 (1%) with azithromycin 1 g (single dose) 13/80 (16%) with erythromycin (multiple dose) 500 mg (4 times daily) for 7 days	OR 0.15 95% CI 0.05 to 0.45 P = 0.00075	●●●	azithromycin (single dose)
[51] Systematic review	Pregnant women with confirmed *C trachomatis* infections 6 RCTs in this analysis	**Gastrointestinal adverse effects** 27/191 (14%) with azithromycin 1 g (single dose) 112/183 (61%) with erythromycin (multiple dose) 500 mg (3 or 4 times daily) for 7 days Gastrointestinal adverse effects included vomiting, nausea, anorexia, abdominal pain, and diarrhoea	OR 0.11 95% CI 0.07 to 0.18	●●●	azithromycin (single dose)

Single-dose azithromycin versus multiple-dose amoxicillin:

We found one systematic review (search date 2006, 2 RCTs, 149 women). [51]

Microbiological cure

Single-dose azithromycin versus multiple-dose amoxicillin We don't know whether single-dose azithromycin is more effective at increasing microbiological cure rates than multiple-dose amoxicillin in pregnant women with uncomplicated genital chlamydia (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Microbiological cure					
[52] RCT	110 pregnant women with confirmed *C trachomatis* infections In review [51]	**Treatment success (defined as microbiological cure and completion of all medication) , 4 weeks** 35/55 (64%) with azithromycin 1 g (single dose) 32/55 (58%) with amoxicillin 500 mg (multiple dose) (3 times daily) for 7 days	P = 0.56	⟷	Not significant
[53] RCT	39 pregnant women with confirmed *C trachomatis* infections In review [51]	**Failure to achieve microbiological cure** 1/19 (5%) with azithromycin 1 g (single dose) 3/15 (20%) with amoxicillin (multiple dose) 500 mg (3 times daily) for 7 days	P = 0.3	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [52] [53]

Comment:

Clinical guide

Azithromycin is the recommended first-line treatment for pregnant women with chlamydia in various countries. [9] [10] [54] However, in the UK, the use of azithromycin in pregnancy is 'off-label': the British National Formulary (BNF) recommends its use only if there is no alternative available. In pregnant women, erythromycin seems less effective than azithromycin and is more likely to be discontinued because of its GI adverse effects. Although there is no evidence that amoxicillin is less effective in pregnancy, amoxicillin and ampicillin have traditionally been used with caution to treat genital chlamydia. In-vitro studies suggest that amoxicillin does not eradicate *C trachomatis*, [10] raising concern that infection may persist and recrudesce *in vivo*, and thus studies on the effectiveness of ampicillin and amoxicillin in the treatment of chlamydia are limited. Azithromycin as a single-dose antibiotic is suitable when the recipient can be directly observed and compliance can be guaranteed. Animal studies and observational data have not indicated an increased risk of congenital malformations. [55] [56] In 2008, the National Teratology Information Service considered these data too limited to exclude a clinically important increase in risk, although a high risk of congenital malformations seemed unlikely. A large retrospective cohort study assessing nearly 1500 fetuses exposed to azithromycin found no evidence of an increased risk of major congenital malformations with azithromycin. [55] Considering these points, the approach advocated by the Scottish Intercollegiate Guidelines Network would appear pragmatic; taking compliance, tolerability, and efficacy into account, azithromycin 1 g as a single oral dose is recommended for uncomplicated genital chlamydial infection in pregnancy after discussion of the balance of benefits and risks with the patient. [54] It is important to ensure that the discussion with the patient regarding any off-label use of a drug is documented.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antibiotics (single dose) for men and non-pregnant women Two RCTs added. [7] [8] Categorisation unchanged (beneficial).

Antibiotics (single dose) for pregnant women One systematic review updated. [50] Categorisation unchanged (likely to be beneficial).

Clindamycin (multiple-dose regimens) for pregnant women One systematic review updated. [50] Categorisation unchanged (unknown effectiveness).

Erythromycin or amoxicillin (multiple-dose regimens) for pregnant women One systematic review updated. [50] Categorisation unchanged (likely to be beneficial).

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Disclaimer

GRADE **Evaluation of interventions for Chlamydia (uncomplicated, genital).**

Important outcomes			Microbiological cure						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of antibiotic treatment for men and non-pregnant women with uncomplicated genital chlamydial infection?									
15 (1877) [33] [34] [7] [8]	Microbiological cure	Single-dose versus multiple-dose antibiotics	4	–2	0	0	0	Low	Quality points deducted for inclusion of non-blinded RCTs and for no statistical assessment in 2 studies
2 (190) [45] [46]	Microbiological cure	Multiple-dose doxycycline versus multiple-dose ciprofloxacin	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor follow-up
6 (877) [39] [47] [40] [48] [35] [49]	Microbiological cure	Multiple-dose doxycycline versus other multiple-dose antibiotics (other than tetracycline, ciprofloxacin, or erythromycin)	4	–2	0	–1	0	Very low	Quality points deducted for poor follow-up and no statistical assessment; directness point deducted for broad range of antibiotics assessed against doxycycline
1 (38) [41]	Microbiological cure	Multiple-dose tetracycline versus other multiple-dose antibiotics (other than doxycycline, ciprofloxacin, or erythromycin)	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and no statistical assessment
1 (227) [36]	Microbiological cure	Multiple-dose erythromycin versus other multiple-dose antibiotics (other than ciprofloxacin, doxycycline, or tetracycline)	4	–2	0	0	0	Low	Quality points deducted for poor follow-up and no statistical assessment
2 (149) [37] [38]	Microbiological cure	Different regimens of multiple-dose erythromycin versus each other	4	–3	0	0	0	Very low	Quality points deducted for sparse data, poor follow-up, and no statistical assessment
What are the effects of antibiotic treatment for pregnant women with uncomplicated genital chlamydial infection?									
3 (390) [50]	Microbiological cure	Multiple-dose erythromycin versus multiple-dose amoxicillin	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of non-blinded RCTs
1 (78) [50]	Microbiological cure	Multiple-dose clindamycin versus multiple-dose erythromycin	4	–2	0	0	0	Low	Quality points deducted for method of randomisation not specified and sparse data
at least 4 (at least 290) [50] [51]	Microbiological cure	Single-dose azithromycin versus multiple-dose erythromycin	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of non-blinded RCTs
2 (144) [52] [53]	Microbiological cure	Single-dose azithromycin versus multiple-dose amoxicillin	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and inclusion of non-blinded RCTs; directness point deducted for composite outcome in 1 RCT

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.