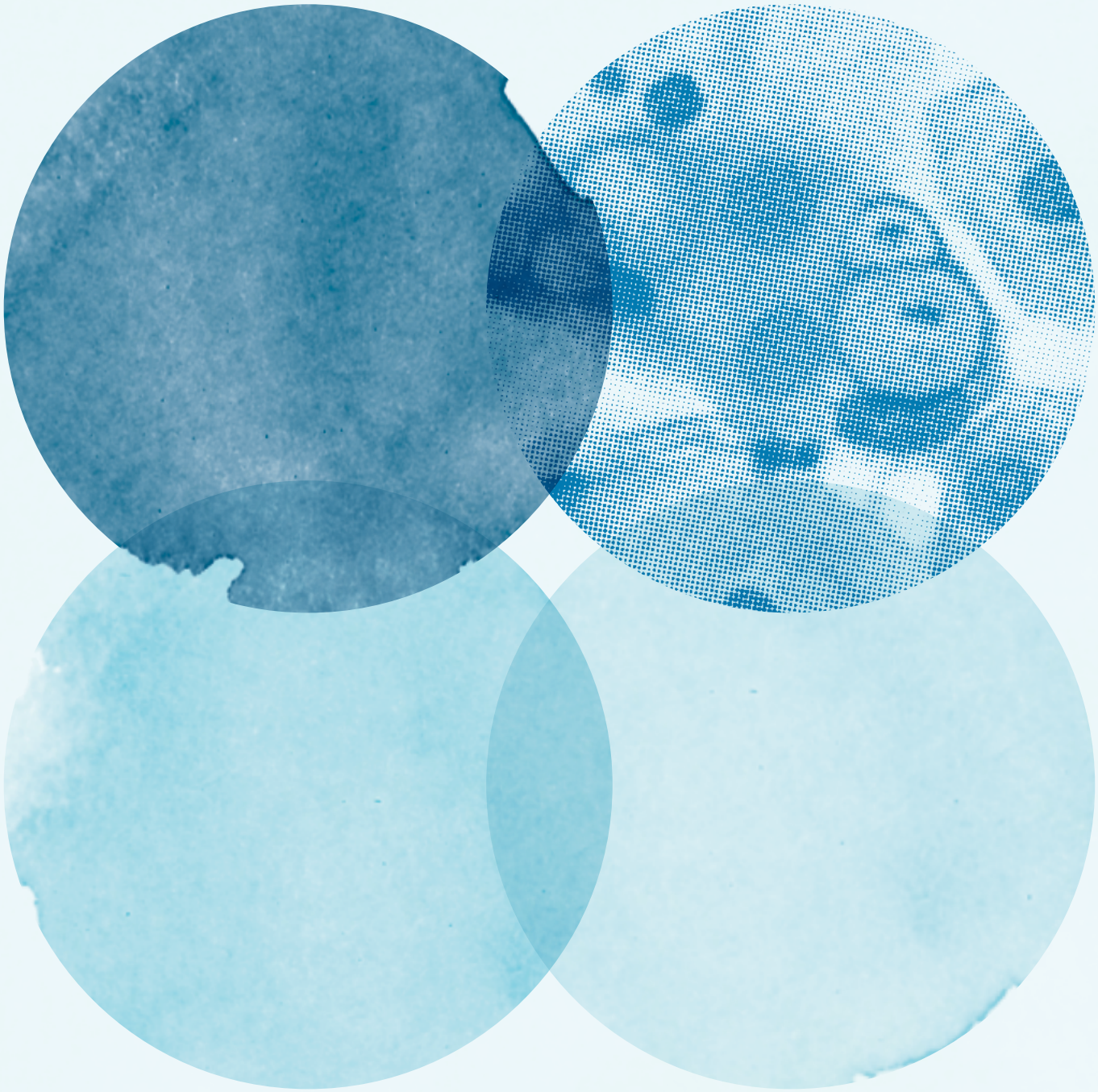
World Health Organization

WHO GUIDELINES FOR THE

Treatment of *Chlamydia trachomatis*



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CONTENTS

CONTENTS (CONTINUED)

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immune deficiency syndrome
AMR	antimicrobial resistance
DALY	disability-adjusted life year
DFA	direct fluorescent antibody
DOI	declaration of interests
ELISA	enzyme-linked immunosorbent assays
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GUD	genital ulcer disease
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRP	UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction
HSV-2	herpes simplex virus type 2
LGV	lymphogranuloma venereum
MSH	Management Sciences for Health
MSM	men who have sex with men
NAATs	nucleic acid amplification tests (NAATs)
PICO	population, intervention, comparator, outcome
POCT	point-of-care test
STI	sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
WHO	World Health Organization

WHO GUIDELINES FOR THE TREATMENT OF *CHLAMYDIA TRACHOMATIS*

EXECUTIVE SUMMARY

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting quality of life and causing serious morbidity and mortality. STIs have a direct impact on reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect impact through their role in facilitating sexual transmission of human immunodeficiency virus (HIV) and thus they also have an impact on national and individual economies. More than a million STIs are acquired every day. In 2012, an estimated 357 million new cases of curable STIs (gonorrhoea, chlamydia, syphilis and trichomoniasis) occurred among 15–49 year-olds worldwide, including 131 million cases of chlamydial infection.

Chlamydial infection, caused by *Chlamydia trachomatis*, is the most common bacterial STI and results in substantial morbidity and economic cost worldwide. Occurring most commonly among young sexually active adults, *C. trachomatis* causes cervicitis in women and urethritis in men, as well as extra-genital infections, including rectal and oropharyngeal infections. Asymptomatic infections are common in both men and women. Untreated chlamydial infection may cause severe complications in the upper reproductive tract, primarily in young women, including ectopic pregnancy, salpingitis and infertility. Lymphogranuloma venereum (LGV), caused by a more invasive serovar of *C. trachomatis*, is increasingly prevalent among men who have sex with men (MSM) in some settings. Maternal infection is associated with serious adverse outcomes in neonates, such as preterm birth, low birth weight, conjunctivitis, nasopharyngeal infection and pneumonia. *C. trachomatis* can be diagnosed by culture, direct immunofluorescence assays (DFAs) and enzyme-linked immunosorbent assays (ELISAs), but nucleic acid amplification tests (NAATs) are preferred due to their superior performance characteristics.

RATIONALE FOR THE GUIDELINES

Since the publication of the World Health Organization (WHO) Guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management. These guidelines provide updated treatment recommendations for common infections caused by *C. trachomatis* based on the most recent evidence; they form one of several modules of guidelines for specific STIs. Other modules will focus on treatments for *Neisseria gonorrhoeae* (gonorrhoea), herpes simplex virus type 2 (HSV-2; genital herpes) and *Treponema pallidum* (syphilis). In addition, future work will provide guidance for syphilis screening and treatment of pregnant women, STI syndromic approach, clinical management, STI prevention, and treatments of other STIs. It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols, adapting this guidance to the local epidemiological situation and antimicrobial susceptibility data.

OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of infection with *C. trachomatis*; and
- to support countries to update their national guidelines for treatment of chlamydial infection.

METHODS

These guidelines were developed following the methods outlined in the 2014 WHO handbook for guideline development. The Guideline Development Group (GDG) included international STI experts, clinicians, researchers and programme managers. The GDG prioritized questions and outcomes related to treatment of chlamydial infections to include in this update, and a methodologist and a team of systematic reviewers from McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy, independently conducted systematic reviews of the effectiveness of different treatments for chlamydial infections. The evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented to the GDG. Conflicts of interest were managed according to WHO guidelines and declared before the recommendations were discussed and finalized. Research implications were also developed by the GDG.

RECOMMENDATIONS

The current guidelines provide nine treatment recommendations for genital infections and LGV caused by *C. trachomatis*. The recommendations summarized in Table 1 apply to adults, adolescents (10–19 years of age), people living with HIV and key populations, including sex workers, MSM and transgender persons. Specific recommendations have also been developed for genital chlamydial infection in pregnant women and for prophylaxis and treatment of ophthalmia neonatorum caused by *C. trachomatis*.

Table 1. Summary of recommendations for treatment of chlamydial infections

Recommendations	Strength of recommendation and quality of evidence
Uncomplicated genital chlamydia	
Recommendation 1 The WHO STI guideline suggests treatment with one of the following options: • azithromycin 1 g orally as a single dose • doxycycline 100 mg orally twice a day for 7 days or one of these alternatives: • tetracycline 500 mg orally four times a day for 7 days • erythromycin 500 mg orally twice a day for 7 days • ofloxacin 200–400 mg orally twice a day for 7 days. *Remarks:* While good practice based on evidence of large net benefit dictates that patients should be treated for chlamydial infection, the choice of treatment may depend on the convenience of dosage, the cost and quality of the medicines in different settings, and equity considerations. When high value is placed on reducing costs, doxycycline in a standard dose may be the best choice; when high value is placed on convenience, azithromycin in a single dose may be the best choice. A delayed-release doxycycline formulation may be an alternative to twice daily dosing of doxycycline, but the high cost of the delayed-release formulation may prohibit its use. Note that doxycycline, tetracycline and ofloxacin are contraindicated in pregnant women (see recommendations 3a–3c).	*Conditional recommendation, moderate quality evidence*
Anorectal chlamydial infection	
Recommendation 2 The WHO STI guideline suggests treatment with doxycycline 100 mg orally twice a day for 7 days over azithromycin 1 g orally as a single dose. *Remarks:* This recommendation applies to people with known anorectal infection and to people with suspected anorectal infections with genital co-infection. Clinicians should ask men, women and key populations (e.g. men who have sex with men, transgender persons and female sex workers) about anal sex and treat accordingly. Doxycycline should not be used in pregnant women because of adverse effects (see recommendations 3a–3c).	*Conditional recommendation, low quality evidence*

Genital chlamydial infection in pregnant women	
Recommendation 3a The WHO STI guideline recommends treatment with azithromycin over erythromycin. **Recommendation 3b** The WHO STI guideline suggests treatment with azithromycin over amoxicillin. **Recommendation 3c** The WHO STI guideline suggests treatment with amoxicillin over erythromycin. Dosages: • azithromycin 1 g orally as a single dose • amoxicillin 500 mg orally three times a day for 7 days • erythromycin 500 mg orally twice a day for 7 days. *Remarks:* Azithromycin is the first choice of treatment but may not be available in some settings. Azithromycin is less expensive than erythromycin and since it is provided as a single dose, may result in better adherence and therefore better outcomes.	*Strong recommendation, moderate quality evidence* *Conditional recommendation, low quality evidence* *Conditional recommendation, low quality evidence*
Lymphogranuloma venereum (LGV)	
Recommendation 4 The WHO STI guideline suggests treatment with doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 3 weeks. *Remarks:* Good practice dictates effective treatment of LGV, in particular for men who have sex with men and for people living with HIV. When doxycycline is contraindicated, azithromycin should be provided. When neither treatment is available, erythromycin 500 mg orally four times a day for 21 days is an alternative. Doxycycline should not be used in pregnant women because of adverse effects (see recommendations 3a–3c).	*Conditional recommendation, very low quality evidence*
Ophthalmia neonatorum	
Recommendation 5 In neonates with chlamydial conjunctivitis, the WHO STI guideline recommends treatment with azithromycin 20 mg/kg/day orally, one dose daily for 3 days, over erythromycin 50 mg/kg/day orally, in four divided doses daily for 14 days. *Remarks:* This is a strong recommendation given the potential for the risk of pyloric stenosis with the use of erythromycin in neonates. In some settings, azithromycin suspension is not available and therefore erythromycin may be used. Side-effects should be monitored with the use of either medication.	*Strong recommendation, very low quality evidence*

Recommendation 6 For all neonates, the WHO STI guideline recommends topical ocular prophylaxis for the prevention of gonococcal and chlamydial ophthalmia neonatorum. **Recommendation 7** 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 • silver nitrate 1% solution • chloramphenicol 1% eye ointment. *Remarks:* Recommendations 6 and 7 apply 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 medication. 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.**	*Strong recommendation, low quality evidence* *Conditional recommendation, low quality evidence*

OVERVIEW OF THE GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs

STI EPIDEMIOLOGY AND BURDEN

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting quality of life and causing serious morbidity and mortality. STIs have a direct impact on reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect impact through their role in facilitating sexual transmission of human immunodeficiency virus (HIV) and thus they also have an impact on national and individual economies. The prevention and control of STIs is an integral component of comprehensive sexual and reproductive health services that are needed to attain the related targets under Sustainable Development Goal (SDG) No. 3 (Ensure healthy lives and promote well-being for all at all ages), including: target 3.2 – to end preventable deaths of newborns and children under 5 years of age; target 3.3 – to end the epidemics of AIDS and other communicable diseases; target 3.4 – to reduce premature mortality from noncommunicable diseases and promote mental health and well-being; target 3.7 – to ensure universal access to sexual and reproductive health-care services; and target 3.8 – to achieve universal health coverage.

Worldwide, more than a million curable STIs are acquired every day. In 2012, there were an estimated 357 million new cases of curable STIs among adults aged 15–49 years worldwide: 131 million cases of chlamydia, 78 million cases of gonorrhoea, 6 million cases of syphilis and 142 million cases of trichomoniasis *(1)*. The prevalence of some viral STIs is similarly high, with an estimated 417 million people infected with herpes simplex virus type 2 (HSV-2) *(2)*, and approximately 291 million women harbouring human papillomavirus (HPV) at any point in time *(3)*. The burden of STIs varies by region and gender, and is greatest in resource-poor countries.

When left undiagnosed and untreated, curable STIs can result in serious complications and sequelae, such as pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, fetal loss and congenital infections. In 2012, an estimated 930 000 maternal syphilis infections resulted in 350 000 adverse pregnancy outcomes, including stillbirths, neonatal deaths, preterm births and infected infants *(4)*. Curable STIs accounted for the loss of nearly 11 million disability-adjusted life years (DALYs) in 2010 *(5)*. The psychological consequences of STIs include stigma, shame and loss of self-worth. STIs have also been associated with relationship disruption and gender-based violence *(6)*.

Both ulcerative and non-ulcerative STIs are associated with a several-fold increased risk of transmitting or acquiring HIV *(7, 8)*. Infections causing genital ulcers are associated with the highest HIV transmission risk; in addition to curable ulcer-causing STIs (e.g. syphilis and chancroid), highly prevalent HSV-2 infections substantially increase that risk *(9)*. Non-ulcerative STIs, such as gonorrhoea, chlamydia and trichomoniasis, have been shown to increase HIV transmission through genital shedding of HIV *(10)*. Treating STIs with the right medicines at the right time is necessary to reduce HIV transmission and improve sexual and reproductive health *(11)*. Efforts should therefore be taken to strengthen STI diagnosis and treatment.

WHY NEW GUIDELINES FOR THE PREVENTION, TREATMENT AND MANAGEMENT OF STIs?

Since the publication of the World Health Organization (WHO) Guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and advancements in prevention, diagnosis and treatment necessitate changes in STI management. Indeed, 88% of countries have updated their national STI guidelines or recommendations since 2006 *(12)*. Updated global guidance reflecting the most recent evidence and expert opinion is therefore needed to assist countries to incorporate new developments into an effective national approach to the prevention and treatment of STIs.

There is an urgent need to update global treatment recommendations to effectively respond to the changing antimicrobial resistance (AMR) patterns of STIs, especially for *Neisseria gonorrhoeae*. Effective treatment protocols that take into account global and local resistance patterns are essential to reduce the risk of further development of AMR. High-level gonococcal resistance to quinolones, a previously recommended first-line treatment, is widespread and decreased susceptibility to the extended-spectrum (third-generation) cephalosporins, another first-line treatment for gonorrhoea, is on the rise *(13)*. Low-level resistance to Trichomonas vaginalis has also been reported for nitroimidazoles, the only available treatment. Resistance to azithromycin has been reported in some strains of *Treponema pallidum* and treatment failures have been reported for tetracyclines and macrolides in the treatment of *Chlamydia trachomatis (14, 15)*.

A WHO STI expert consultation recommended updating the WHO 2003 guidelines for the first- and second-line treatments for *C. trachomatis*, increasing the dosage of ceftriaxone to 250 mg for treatment of *N. gonorrhoeae* with continued monitoring of antimicrobial susceptibility, and consideration of whether azithromycin (2 g, single dose) should be recommended in early syphilis *(16)*.

The epidemiology of STIs is changing, with viral pathogens becoming more prevalent than bacterial etiologies for some conditions; this means that updated information is required to inform locally appropriate prevention and treatment strategies. An increasing proportion of genital ulcers are now due to viral infections as previously common bacterial infections, such as chancroid, approach elimination in many countries *(16, 17)*. As recommended during the STI expert consultation, treatment guidelines for genital ulcer disease (GUD) should be updated to include HSV-2 treatment and a longer treatment duration for HSV-2 should be explored. In addition, suppressive therapy for HSV-2 should be considered in areas with high HIV prevalence *(16)*. The chronic, lifelong nature of viral infections also requires that renewed attention be paid to developing effective prevention strategies, including expanding accessibility to available vaccines for HPV and development of new vaccines for HSV-2.

In the 2003 WHO guidelines, a syndromic approach was recommended for the management of STIs. The approach guides the diagnosis of STIs based on identification of consistent groups of symptoms and easily recognized signs and indicates treatment for the majority of organisms that may be responsible for producing the syndrome. The syndromic management algorithms need to be updated in response to the changing situation. In addition to changes to the GUD algorithm, other syndromes need to be re-evaluated, particularly vaginal discharge. The approach to syndromes for key populations also needs to be updated. For example, addition of a syndromic management algorithm for anorectal infections in men who have sex with men (MSM) and sex workers is urgently needed since a substantial number of these infections go unrecognized and untreated in the absence of guidelines *(16)*.

New rapid, point-of-care diagnostic tests (POCTs) are changing STI management. Rapid syphilis diagnostic tests are now widely available, making syphilis screening more widely accessible and allowing for earlier initiation of treatment for those who test positive. Efforts are under way to develop POCTs for other STIs that will augment syndromic management of symptomatic cases and increase the ability to identify asymptomatic infections *(12)*. Updated guidelines are needed that incorporate rapid tests into syndromic management of STIs and provide algorithms for testing and screening *(16)*.

Although recent technological advances in diagnostics, therapeutics, vaccines and barrier methods offer better opportunities for the prevention and care of STIs, access to these technologies is still limited, particularly in areas where the burden of infection is highest. For optimal effectiveness, global guidelines for the management of STIs need to include approaches for settings with limited access to modern technologies, as well as for settings in which these technologies are available.

It is strongly recommended that countries take updated global guidance into account as they establish standardized national protocols, adapting this guidance to the local epidemiological situation and antimicrobial susceptibility data. Standardization ensures that all patients receive adequate treatment at every level of health-care services, optimizes the training and supervision of health-care providers and facilitates procurement of medicines. It is recommended that national guidelines for the effective management of STIs be developed in close consultation with local STI, public health and laboratory experts.

APPROACH TO THE REVISION OF STI GUIDELINES

To ensure effective treatment for all STIs, WHO plans a phased approach to updating the STI guidelines to address a range of infections and issues. Four phases have been proposed by the WHO STI Secretariat and agreed upon by the STI Guideline Development Group (GDG) members (see Annex A for members of these groups). Table 2 summarizes the proposed phases and timeline.

Table 2: Phases for development of the STI guidelines

Phases	Topics	Timeframe
Phase 1	Treatment of specific STIs: *Chlamydia trachomatis* (chlamydia), *Neisseria gonorrhoeae* (gonorrhoea), HSV-2 (genital herpes) and *Treponema pallidum* (syphilis) Syphilis screening and treatment of pregnant women STI syndromic approach Clinical management package	November 2013 – April 2016 May 2016 – December 2017
Phase 2	STI prevention: condoms, behaviour change communication, biomedical interventions and vaccines	2017–2018
Phase 3	Treatment of specific STIs and reproductive tract infections (RTIs) not addressed in Phase 1: Trichomonas vaginalis (trichomoniasis), bacterial vaginosis, Candida albicans (candidiasis), Hemophilus ducreyi (chancroid), Klebsiella granulomatis (donovanosis), human papillomavirus (HPV; genital warts/cervical cancer), Sarcoptes scabiei (scabies) and Phthirus pubis (pubic lice)	2017–2018
Phase 4	STI laboratory diagnosis and screening	2017–2018

Phase 1 will focus on treatment recommendations for specific STIs as well as other important and urgent STI issues. Recommendations for the treatment of specific infections will be developed and published as independent modules:

- *Chlamydia trachomatis* (chlamydia)
- *Neisseria gonorrhoeae* (gonorrhoea)
- HSV-2 (genital herpes)
- *Treponema pallidum* (syphilis)
- Syphilis screening and treatment of pregnant women.

In addition, guidelines for the STI syndromic approach and a clinical management package will be developed later in Phase 1. Phase 2 will focus on guidelines for STI prevention. The independent Phase 1 and 2 modules will later be consolidated into one document and published as comprehensive WHO guidelines on STI case management. Phase 3 will address treatment of additional infections, including Trichomonas vaginalis (trichomoniasis), bacterial vaginosis, Candida albicans (candidiasis), Hemophilus ducreyi (chancroid), Klebsiella granulomatis (donovanosis), HPV (genital warts/cervical cancer), Sarcoptes scabiei (scabies) and Phthirus pubis (pubic lice). Phase 4 will provide guidance on laboratory diagnosis and screening of STIs.

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01 INTRODUCTION

1.1 EPIDEMIOLOGY, BURDEN AND CLINICAL CONSIDERATIONS

Chlamydial infection, caused by *Chlamydia trachomatis*, is the most common bacterial sexually transmitted infection (STI) and results in substantial morbidity and economic cost worldwide. The World Health Organization (WHO) estimates that in 2012, 131 million new cases of chlamydia occurred among adults and adolescents aged 15–49 years worldwide, with a global incidence rate of 38 per 1000 females and 33 per 1000 males. The estimated 128 million prevalent cases of chlamydia result in an overall prevalence of 4.2% for females and 2.7% for males, with the highest prevalence in the WHO Region of the Americas and the WHO Western Pacific Region *(1)*. In many countries, the incidence of chlamydia is highest among adolescent girls aged 15–19 years, followed by young women aged 20–24 years. The three biovars of *C. trachomatis*, each consisting of several serovars or genotypes, cause genital infections, lymphogranuloma venereum (LGV: a genital ulcer disease [GUD] that affects lymphoid tissue), and trachoma (eye infection).

CLINICAL PRESENTATION

Genital infections due to *C. trachomatis* are asymptomatic in approximately 70% of women and 50% of men *(2)*. Symptoms of uncomplicated chlamydial infection in women include abnormal vaginal discharge, dysuria, and post-coital and intermenstrual bleeding. Common clinical signs on speculum examination include cervical friability and discharge. Symptomatic men usually present with urethral discharge and dysuria, sometimes accompanied by testicular pain. If left untreated, most genital infections will resolve spontaneously with no sequelae but they may result in severe complications, mainly in young women. Infection can ascend to the upper reproductive tract and can cause pelvic inflammatory disease, ectopic pregnancy, salpingitis and tubal factor infertility in women *(3)* and epididymitis in men *(4)*. The risk of complications may increase with repeated infection.

Infections at non-genital sites are common. Rectal infection may manifest as a rectal discharge, rectal pain or blood in the stools, but is asymptomatic in most cases. Oropharyngeal infections can manifest as pharyngitis and mild sore throat, but symptoms are rare.

Chlamydial infection in pregnancy is associated with preterm birth and low birth weight. Infants of mothers with chlamydia can be infected at delivery, resulting in neonatal conjunctivitis and/or nasopharyngeal infection *(3)*. Symptoms of ophthalmia include ocular discharge and swollen eyelids. In newborns, nasopharyngeal infection can lead to pneumonitis.

LGV, caused by a more invasive serovar of *C. trachomatis*, affects the submucosal connective tissue and can spread to regional lymph nodes. It commonly presents as a unilateral, tender inguinal or femoral lymph node and a genital ulcer or papule *(5)*. Anorectal exposure may result in proctitis, rectal discharge, pain, constipation or tenesmus. Left untreated, LGV can lead to rectal fistula or stricture.

LABORATORY DIAGNOSIS

There have been major developments in the diagnosis of *C. trachomatis* in the last 10–20 years. Although *C. trachomatis* can be diagnosed by culture, direct immunofluorescence assays (DFAs), and laboratory-based and point-of-care enzyme-linked immunosorbent assays (ELISAs), nucleic acid amplification tests (NAATs) are strongly recommended due to their superior performance characteristics. NAATs are highly sensitive and specific and can be used for a wide range of samples, including urine and vulvovaginal, cervical and urethral swabs. Several commercial NAATs using different technologies are available. The increased sensitivity of NAATs compared with other diagnostic tests, such as culture and antigen detection methods (DFA and ELISA), allows testing of non-invasive specimens, which can be collected conveniently at the primary level of care. Commercially available NAATs are not yet licensed for the diagnosis of extra-genital samples but have shown to be reliable for detection of chlamydial infection in rectal and pharyngeal swabs. Several commercially available tests for chlamydia are combined with tests for gonorrhoea. Further information is available in the WHO publication on laboratory diagnosis of STIs including HIV *(6)*.

1.2 RATIONALE FOR NEW RECOMMENDATIONS

The guidelines for treatment of chlamydial infections need to be updated to respond to the changes in epidemiology and antimicrobial susceptibility for chlamydia that have occurred since the previous WHO Guidelines for the management of sexually transmitted infections were published in 2003 *(7)*. LGV is increasingly prevalent among men who have sex with men (MSM) in some settings, and treatment failure has been reported with tetracycline and macrolides in approximately 10% of cases *(8)*. Moreover, the 2003 WHO STI guidelines are the only international guidelines that still recommend treating chlamydial infections with amoxicillin or tetracycline. As recommended by the WHO STI expert consultation in 2008, the first- and second-line treatment recommendations for *C. trachomatis* needed to be reviewed and revised based on the most recent available evidence.

1.3 OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of infection with *C. trachomatis*; and
- to support countries to update their national guidelines for treatment of chlamydial infection.

1.4 TARGET AUDIENCE

These guidelines are primarily intended for health-care providers at all levels (primary, secondary and tertiary) of the health-care system involved in the treatment and management of people with STIs in low-, middle- and high-income countries. They are also intended for individuals working in sexual and reproductive health programmes, such as HIV/AIDS, family planning, maternal and child health and adolescent health, to ensure appropriate STI diagnosis and management.

The guidelines are also useful for policy-makers, managers, programme officers and other professionals in the health sector who are responsible for implementing STI management interventions at regional, national and subnational levels.

1.5 STRUCTURE OF THE GUIDELINES

These guidelines provide evidence-based recommendations for the treatment of specific clinical conditions caused by *C. trachomatis*. These guidelines provide direction for countries as they develop national treatment recommendations; however, national guidelines should also take into account the local pattern of AMR, as well as health service capacity and resources.

Updated treatment recommendations based on the most recent evidence are included for the most important common conditions caused by *C. trachomatis*. Recommendations were not updated for rare conditions and other conditions for which no new information has become available since the 2003 WHO STI guidelines were issued.

Treatment recommendations for the following conditions caused by *C. trachomatis* are included in these guidelines:

- uncomplicated genital infections
- anorectal infections
- uncomplicated genital infections in pregnant women
- LGV
- ophthalmia neonatorum (treatment and prophylaxis).

02 METHODS

These guidelines were developed following the methods outlined in the 2014 edition of the WHO handbook for guideline development *(9)* (see Annex B for a detailed description).

2.1 GUIDELINE DEVELOPMENT GROUP (GDG)

To update the WHO guidelines for the prevention, treatment and management of STIs, a GDG was established, comprising 33 international STI experts, including clinicians, researchers and programme managers (Annex A). A core subgroup to focus on the guidelines related to chlamydia was created within the GDG, to provide more intensive feedback throughout the process (Annex A). The GDG participated in meetings and teleconferences to prioritize the questions to be addressed, discuss the evidence reviews and finalize the recommendations. The GDG reviewed and approved the final version of the guidelines.

2.2 QUESTIONS AND OUTCOMES

In December 2013 the first GDG meeting was held to identify and agree on the key PICO (population, intervention, comparator, outcome) questions that formed the basis for the systematic reviews and the recommendations. Following this meeting, a survey of GDG members was conducted to prioritize the questions and outcomes according to clinical relevance and importance. Six PICO questions were identified for the update on the treatment of genital and anorectal chlamydial infections, treatment of LGV, and prevention and treatment of neonatal ophthalmia (see Annex B). These questions pertained to adults and other special populations, namely adolescents, pregnant women, people living with HIV, and populations at high risk of acquiring and transmitting STIs, such as men who have sex with men (MSM) and sex workers. Only outcomes that were ranked as critical or important to patients and decision-making were included: clinical and microbiological cure, and adverse effects (including maternal and fetal effects in pregnant women).

2.3 REVIEWS OF THE EVIDENCE

The systematic reviews for each priority question were conducted by McMaster University, the WHO Collaborating Centre for Evidence-Informed Policy. Evidence for desirable and undesirable outcomes, patient values and preferences, resources, acceptability, equity and feasibility were reviewed from published and unpublished literature. Comprehensive searches for previously conducted systematic reviews, randomized controlled trials and non-randomized studies were performed from March to October 2015. Additional searches were conducted to identify studies on patient values and preferences (e.g. qualitative research designs) and resource implications (e.g. cost of interventions, cost–benefit and cost–effectiveness studies). Two members of the Systematic Review Team screened studies, extracted and analysed the data, and assessed the quality/certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[1]

1 For more information, see: http://www.gradeworkinggroup.org/

The quality/certainty of the evidence was assessed at four levels:

- High – We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate – We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low – Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low – We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

In addition, the direct costs of medicines were estimated using the 2014 Management Sciences for Health (MSH) International drug price indicator guide *(10)*. References for all the reviewed evidence are listed in Annex C. All evidence was summarized in GRADE evidence profiles and in evidence-to-decision tables (see Web annexes D and E).

2.4 MAKING RECOMMENDATIONS

Recommendations were developed during a second meeting of the GDG in October 2015, which was facilitated by two co-chairs, one with expertise in GRADE and the other with clinical STI expertise. The methodologist presented the GRADE evidence profiles and evidence-to-decision frameworks at the meeting. When formulating the recommendations, the GDG considered and discussed the desirable and undesirable effects of the interventions, the value placed on the outcomes, the associated costs and use of resources, the acceptability of the interventions to all stakeholders (including people affected by STIs), the impact on health equity and the feasibility of implementation. Treatments were judged according to the above criteria and final decisions and guideline recommendations were agreed. The discussion was facilitated by the co-chairs with the goal of reaching consensus across the GDG. Disagreements among the GDG members were noted in the evidence-to-decision framework for each judgement. In the case of failure to reach consensus for a recommendation, the planned procedure was for the GDG to take a vote and record the results. However, no votes were taken because the GDG reached consensus during discussion for all of the recommendations. Following the meeting, the recommendations were finalized via teleconference and final approval was obtained from all GDG members electronically. These guidelines were subsequently written up in full and then peer reviewed. The External Review Group approved the methods and agreed with the recommendations made by the GDG (members are listed in Annex A).

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations are presented using the wording "The WHO STI guideline recommends…", while conditional recommendations are worded as "The WHO STI guideline suggests…" throughout the guidelines. The implications of the differing strengths of recommendations for patients, clinicians and policy-makers are explained in detail in Table 3.

Table 3. Implications of strong and conditional recommendations using the GRADE approach

Implications	Strong recommendation "The WHO STI guideline recommends..."	Conditional recommendation "The WHO STI guideline suggests..."
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

2.5 MANAGEMENT OF CONFLICTS OF INTEREST

Management of conflicts of interest was a key priority throughout the process of guideline development. WHO guidelines for declaration of interests (DOI) for WHO experts were implemented *(11)*. DOI statements were obtained from all GDG members prior to assuming their roles in the group. At the GDG meetings (December 2013 and October 2015), the members disclosed their interests, if any, at the beginning of the meeting. Their DOI statements are summarized in Web annex F.

After analysing each DOI, the STI team concluded that no member had financial or commercial interests related to STI treatment. Other notified interests were minor; they were either not related to STI or were non-commercial grants or interests. The STI team concluded that there were no significant conflicts of interest that would exclude any member from participating fully in the guideline development process. Therefore, options for conditional participation, partial or total exclusion of any GDG member were not discussed.

03 DISSEMINATION, UPDATING AND IMPLEMENTATION OF THE GUIDELINES

3.1 DISSEMINATION

These guidelines will be made available as a printed publication, as a download on the website of the WHO Department of Reproductive Health and Research (where there will also be links to all supporting documentation)[2], and in the WHO Reproductive Health Library (RHL)[3]. The recommendations will also be available in a guideline application ("app") created with the GRADEpro GDT software. The guidelines will be announced in the next edition of the RHL newsletter and in the Reproductive Health and Research departmental newsletter, and other relevant organizations will be requested to copy the announcement in their respective newsletters.

WHO headquarters will work with WHO's regional offices and country offices to ensure that countries receive support in the adaptation, implementation and monitoring of these guidelines using the WHO Department of Reproductive Health and Research guidance on Introducing WHO's reproductive health guidelines and tools into national programmes *(12)*.

All levels of WHO (headquarters, regional offices and country offices) will work with regional and national partners – including the United Nations Population Fund (UNFPA), the United Nations Children's Fund (UNICEF), the Joint United Programme on HIV/AIDS (UNAIDS), nongovernmental organizations (NGOs) and other agencies implementing sexual and reproductive health and STI services – to ensure that the new recommendations are integrated and implemented in sexual and reproductive health, family planning, and maternal, neonatal, child and adolescent health services. Reference to this document will be made within other relevant WHO guidelines. These guidelines will also be disseminated at major conferences related to STIs and HIV and the aforementioned programme areas.

3.2 UPDATING THE GUIDELINES AND USER FEEDBACK

A system of monitoring relevant new evidence and updating the recommendations as new findings become available will be established within a year of implementing the guidelines. An electronic follow-up survey of key end-users of the STI guidelines will be conducted after the release of the guidelines. The results of the survey will be used to identify challenges and barriers to the uptake of the guidelines, to evaluate their usefulness for improving service delivery, and to identify topics or gaps in treatment that need to be addressed in future editions.

3.3 IMPLEMENTATION OF THE WHO GUIDELINES FOR THE TREATMENT OF *C. TRACHOMATIS*

ADAPTATION, IMPLEMENTATION AND MONITORING

These guidelines provide recommendations for treatment of chlamydial infection based on the best global evidence available at the time of compilation. However, the epidemiology and AMR of STIs vary by geographical location and are constantly changing, sometimes rapidly. It is recommended that countries conduct good quality studies to gather the information needed to adapt these guidelines to the local STI situation as they update their national guidelines. In areas lacking local data as a basis for adaptation, the recommendations in these guidelines can be adopted as presented.

2 These guidelines and all supporting documents will be available at: www.who.int/reproductivehealth/publications/rtis/chlamydia-treatment-guidelines/en/

3 RHL is available at: http://apps.who.int/rhl/en/

For further guidance on adaptation, implementation and monitoring of national guidelines please refer to Introducing WHO's reproductive health guidelines and tools into national programmes: principles and processes of adaptation and implementation *(12)*.

In adapting the guidelines for national use, recommended treatments should have an efficacy of at least 95%. The criteria to be considered for the selection of medicines are listed in Box 1. Recommended medicines should meet as many of the criteria as possible, taking into account local availability, efficacy, route and frequency of administration.

BOX 1. CRITERIA FOR THE SELECTION OF MEDICINES FOR THE TREATMENT OF STIS

- High efficacy (at least 95% cure rate)
- High quality (potent active ingredient)
- Low cost
- Low toxicity levels
- Organism resistance unlikely to develop or likely to be delayed
- Single dose
- Oral administration
- Not contraindicated for pregnant or lactating women

Appropriate medicines should be included in the national essential medicines lists. When selecting medicines, consideration should be given to the competencies and experience of health-care providers.

IDENTIFYING AND PROCURING STI DRUGS

It is important not only to identify medicines that will be recommended as first-line treatment for STIs but also the estimated quantities of the medicines that will be required. Quantifying medication needs is important in order to estimate costs, to reconcile financial requirements with available budget, and to make orders in advance so that the unit and freight costs can be minimized.

In order to estimate the quantity of medicines needed, it will be necessary to review the medicines that are recommended for treatment, their unit prices, the quantity required per treatment and the epidemiological information on the prevalence of infection. One can estimate medicine needs by multiplying the estimated number of cases by the total quantity of medicine specified for treatment of one case. These figures can be derived from health centres providing care but they must be verified to avoid wasteful over-ordering.

Budgeting for medicines is critical. If the national ministry of health does not provide medicines for free and the patient cannot afford to buy the medicines, then there will essentially be no possibility of curtailing the spread of infection and the occurrence of complications. At the national level it is important that decision-makers, politicians and fiscal controllers understand the need to subsidize STI medicines. Low-cost STI medicines can be obtained through international vendors of generic products, non-profit organizations with procurement schemes such as UNICEF, UNFPA and UNHCR, and through joint medicine procurement schemes. By way of such schemes, national programmes can join other national programmes to jointly procure medicines, thus reducing the overall costs by sharing the overhead costs and taking advantage of discounts for purchasing in bulk. Placing STI medicines on national lists of essential medicines increases the likelihood of achieving a supply of these medicines at low cost.

04 RECOMMENDATIONS FOR TREATMENT OF CHLAMYDIAL INFECTIONS

The following nine recommendations apply to adults, adolescents (10–19 years of age), people living with HIV, and key populations, including sex workers, men who have sex with men (MSM) and transgender persons. Specific recommendations have also been developed for ophthalmia neonatorum caused by C. trachomatis.

4.1 UNCOMPLICATED GENITAL CHLAMYDIA

RECOMMENDATION 1

For people with uncomplicated genital chlamydia, the WHO STI guideline suggests one of the following options:

- azithromycin 1 g orally as a single oral dose
- doxycycline 100 mg orally twice a day for 7 days

or one of these alternatives:

- tetracycline 500 mg orally four times a day for 7 days
- erythromycin 500 mg orally twice a day for 7 days
- ofloxacin 200–400 mg orally twice a day for 7 days.

Conditional recommendation, moderate quality evidence

Remarks: While good practice based on evidence of large net benefit dictates that patients should be treated for chlamydial infection, the choice of treatment may depend on the convenience of dosage, the cost and quality of the medicines in different settings, and equity considerations. When high value is placed on reducing costs, doxycycline in a standard dose may be the best choice; when high value is placed on convenience, azithromycin in a single dose may be the best choice. A delayed-release formulation of doxycycline may be an alternative to twice daily dosing of doxycycline, but the high cost of the delayed-release formulation may prohibit its use. Note that doxycycline, tetracycline and ofloxacin are contraindicated in pregnant women (see recommendations 3a–3c).

Research implications: The potential for resistance to azithromycin, doxycycline and other treatment options should be investigated. Future research could compare these treatments and recommended dosages in randomized controlled trials measuring important outcomes such as clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastrointestinal effects), compliance, quality of life, HIV transmission and acquisition, and partner transmission of chlamydia. Studies are also needed that evaluate amoxicillin (500 mg three times a day for 7 days).

SUMMARY OF THE EVIDENCE

Evidence from a Cochrane systematic review was used. This review included 25 randomized studies comparing tetracycline, quinolones and macrolides. There are no data available for amoxicillin. Overall, there is moderate to low quality evidence for most comparisons of treatments. Moderate quality evidence shows trivial differences between azithromycin 1 g and doxycycline 100 mg orally twice a day for 7 days in the numbers of people microbiologically cured and experiencing adverse events. There were 10 fewer people per 1000 cured with azithromycin versus doxycycline, ranging from 38 fewer to 10 more (risk ratio [RR] 0.99; 95% confidence interval [CI] 0.96 to 1.10). In addition, there were 3 more adverse events per 1000 people with azithromycin versus doxycycline, ranging from 42 fewer to 64 more (RR 1.02; 95% CI 0.72 to 1.43). Similar results are shown in a recently published randomized study. Delayed-release doxycycline hyclate probably leads to little to no difference in the proportion of people microbiologically cured but probably has fewer side-effects than standard dose doxycycline. Ofloxacin may result in fewer cures but also slightly fewer adverse events compared to doxycycline. When comparing multiple high doses of azithromycin (1 g weekly for 3 weeks) to a single dose, more people may be cured but

there are no data for adverse events related to very high doses. Higher doses of any tetracycline compared with lower doses may lead to more cures but will probably also lead to more adverse events. Tetracyclines compared with quinolones may lead to fewer cures but also slightly fewer adverse events. Erythromycin compared with quinolones may lead to fewer cures and more adverse events.

There is no evidence relating to patient values and preferences but the Guideline Development Group (GDG) agreed that there is probably no variability in the values people place on the outcomes. Research related to other conditions indicates that adherence may be improved with simpler medication regimens. The GDG therefore agreed that azithromycin may be more acceptable to patients since it is a single dose regimen (a majority of the GDG members considered single-dose regimens to be preferable for patient compliance over multi-dose regimens). There is little to no evidence for equity issues and feasibility. Resistance in other infections (e.g. gonorrhoea and Mycoplasma genitalium) that often co-occur with chlamydia may restrict the use of some medicines, such as ofloxacin. For many of these medicines, costs may differ between countries; in places with high incidence of chlamydia, the cost differences between azithromycin and doxycycline may be large due to greater numbers of people requiring treatment.

In summary, there was moderate quality evidence for trivial differences in benefits and harms between azithromycin and doxycycline, and although the cost of azithromycin is higher, the single dose may make it more convenient to use than doxycycline. While the differences are also trivial with the other medicines, the evidence is low quality and these are therefore provided as alternatives, with the exception of delayed-release doxycycline, which is currently expensive.

See Annex C for list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence profiles and evidence-to-decision frameworks (pp. 3-22).

4.2 ANORECTAL CHLAMYDIAL INFECTION

RECOMMENDATION 2

In people with anorectal chlamydial infection, the WHO STI guideline suggests using doxycycline 100 mg orally twice daily for 7 days over azithromycin 1 g orally single dose.

Conditional recommendation, low quality evidence

Remarks: This recommendation applies to people with known anorectal infection and to people with suspected anorectal infections with genital co-infection. Clinicians should ask men, women and key populations (e.g. men who have sex with men [MSM], transgender persons and female sex workers) about anal sex and treat accordingly. Doxycycline should not be used in pregnant women because of adverse effects (see recommendations 3a–3c).

Research implications: The global incidence of chlamydial anorectal infections should be determined. More research is necessary on the effects of treatments used for anorectal infections, particularly azithromycin, which is currently not on the WHO essential medicines list for anorectal chlamydial infections *(13)*. Effects should be assessed in both men and women, and in key populations (e.g. MSM, transgender persons and female sex workers).

SUMMARY OF THE EVIDENCE

There is low quality evidence from eight non-randomized studies (five direct comparisons and three single-arm studies) that evaluated doxycycline and azithromycin (see Web annexes D and E). There are no data for amoxicillin, erythromycin and quinolones. Evidence showed that there may be 200 fewer microbiological cures per 1000 people with azithromycin compared with doxycycline (RR 0.80; 95% CI 0.71 to 0.91). Evidence from studies of genital infections shows little to no difference in side-effects with these treatments (RR 1.02; 95% CI 0.72 to 1.43). Although there are fewer women than men in the studies, the evidence suggested little difference in effects between men and women. There is no evidence relating to patient values and preferences, but the GDG agreed that there are no known reasons to suspect values would vary for different people. There is little to no evidence for acceptability, but research in other conditions indicates that adherence may be improved with simpler medication regimens. There is also little to no evidence for equity issues and feasibility, but azithromycin is more expensive and typically the cost is transferred to consumers. The GDG agreed that equity may vary between the medicines depending on the population: in some populations, azithromycin may be more acceptable since it is a single-dose treatment, and some people may experience stigma related to visibility of a multi-dose regimen with doxycycline. Therefore, suggesting doxycycline over azithromycin could create inequity for people sensitive to stigma related to multi-dose regimens. Azithromycin is currently not listed as an essential medicine for anorectal chlamydial infection.

In summary, doxycycline may result in more cures, but although it is less expensive than azithromycin, azithromycin may be better accepted due to the single-dose treatment.

See Annex C for list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence profiles and evidence-to-decision frameworks (pp. 23-35).

4.3 CHLAMYDIAL INFECTION IN PREGNANT WOMEN

RECOMMENDATION 3A

In pregnant women with genital chlamydial infection, the WHO STI guideline recommends using azithromycin over erythromycin.

Strong recommendation, moderate quality evidence

RECOMMENDATION 3B

In pregnant women with genital chlamydial infection, the WHO STI guideline suggests using azithromycin over amoxicillin.

Conditional recommendation, low quality evidence

RECOMMENDATION 3C

In pregnant women with genital chlamydial infection, the WHO STI guideline suggests using amoxicillin over erythromycin.

Conditional recommendation, low quality evidence

Dosages:

- azithromycin 1 g orally as a single dose
- amoxicillin 500 mg orally three times a day for 7 days
- erythromycin 500 mg orally twice a day for 7 days.

Remarks: Azithromycin is the first choice of treatment but may not be available in some settings. Azithromycin is less expensive than erythromycin and since it is provided as a single dose, may result in better adherence and therefore better outcomes.

Research implications: Research in pregnant women comparing these treatments and the recommended dosages should be conducted. Although these medicines are relatively safe in pregnancy, maternal and fetal complications (e.g. adverse pregnancy outcomes, fetal defects) with the use of these treatments for STIs and other infections should be monitored, collected and analysed to inform updated recommendations in the future. When conducting these studies, costs and acceptability of the treatments could be measured.

SUMMARY OF THE EVIDENCE

Overall, there is moderate to low quality evidence from 14 randomized controlled trials, two non-randomized comparative studies and two large cohort studies assessing the effects of azithromycin, erythromycin and amoxicillin in pregnant women with chlamydial infections. The differences in benefits between these different treatments are small, and wide confidence intervals included the possibility of greater or lesser benefits with azithromycin compared to other medicines. Moderate quality evidence found that there are probably 94 more people microbiologically cured per 1000 with azithromycin versus erythromycin (RR 1.11; 95% CI 0.94 to 1.30), and low-quality evidence found that there may be 72 more people cured per 1000 with azithromycin versus amoxicillin (RR 1.09, 95%CI 0.93 to 1.28). There are probably 40 fewer people microbiologically cured per 1000 with erythromycin versus amoxicillin (RR 0.95; 95% CI 0.88 to 1.02). There may be slightly fewer side-effects with azithromycin compared with erythromycin or amoxicillin (approximately 50/1000 fewer), but there may be substantially more side-effects with erythromycin versus amoxicillin (approximately 400/1000 more).

Much of the evidence was uncertain for fetal outcomes as it came from indirect comparisons in large cohort studies. There were few events, and confidence intervals around the small differences included the potential for fewer or more events between comparisons.

In summary, the GDG agreed that azithromycin is preferred over erythromycin because of greater effectiveness and lower cost, and preferred over amoxicillin due to greater effectiveness. Azithromycin may also be more acceptable due to single dosage; however, it may not be available in all settings due to misconceptions that it is costly. Amoxicillin is preferred over erythromycin as it is less costly and may result in greater benefits and fewer side-effects.

See Annex C for list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence profiles and evidence-to-decision frameworks (pp. 36-51).

4.4 LYMPHOGRANULOMA VENEREUM (LGV)

RECOMMENDATION 4

In adults and adolescents with LGV, the WHO STI guideline suggests using doxycycline 100 mg orally twice daily for 21 days over azithromycin 1 g orally, weekly for 3 weeks.

Conditional recommendation, very low quality evidence

Remarks: Good practice dictates treatment of LGV, in particular for men who have sex with men (MSM) and for people living with HIV. When doxycycline is contraindicated, azithromycin should be provided. When neither treatment is available, erythromycin 500 mg orally four times a day for 21 days is an alternative. Doxycycline should not be used in pregnant women because of adverse effects (see recommendations 3a–3c).

Research implications: Additional research for each of the treatments and the dosages recommended is needed, in particular for erythromycin and azithromycin. Randomized controlled trials should be conducted, measuring critical and important outcomes, such as clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastrointestinal effects), quality of life, HIV transmission and acquisition, compliance and LGV transmission to partners. The effects of shorter courses of treatment should also be investigated.

SUMMARY OF THE EVIDENCE

There is very low quality evidence from 12 non-randomized studies with no comparisons between treatments. These studies assessed treatment with azithromycin and doxycycline for 21 days, and erythromycin for 14 days. Evidence for doxycycline showed that there may be large benefits (clinical and microbiological cure rates greater than 90%) and trivial side-effects (e.g. persistent mucous membrane abnormalities, perirectal abscess and allergy). The effects of azithromycin and erythromycin were uncertain, with only 14 people receiving azithromycin and 31 people receiving erythromycin in the studies. Side-effects are likely trivial and similar to the side-effects of these treatments in people with other chlamydial infections. There is no evidence relating to patient values and preferences, but the GDG agreed that there are no known reasons to suspect values would vary for different people. There is little to no evidence for acceptability, but research in other conditions indicates that adherence may be improved with simpler medication regimens. There is little evidence for equity issues and feasibility, but the GDG agreed that these may be dependent on individuals and countries. Data for medicine prices and procurement indicate that doxycycline is cheaper than azithromycin and erythromycin, although the latter medicines are still inexpensive.

In summary, there is very low quality evidence for all medicines for treatment of LGV. The evidence suggests large benefits with doxycycline over azithromycin, and the effects of erythromycin are unknown. In addition, doxycycline is the least expensive.

See Annex C for list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence profiles and evidence-to-decision frameworks (pp. 52-63).

4.5 OPHTHALMIA NEONATORUM

RECOMMENDATION 5

In neonates with chlamydial conjunctivitis, the WHO STI guideline recommends using oral azithromycin 20 mg/kg/day orally, one dose daily for 3 days, over erythromycin 50 mg/kg/day orally, in four divided doses daily for 14 days.

Strong recommendation, very low quality evidence

Remarks: This is a strong recommendation given the potential for the risk of pyloric stenosis with the use of erythromycin in neonates. In some settings, azithromycin suspension is not available and therefore erythromycin may be used. Side-effects should be monitored with the use of either medication.

Research implications: Additional research should be conducted to determine the effects of these medicines to treat ophthalmia neonatorum. The effects of other medications such as trimethoprim should also be investigated. Pyloric stenosis should be monitored or research conducted to evaluate this risk with the medicines suggested.

SUMMARY OF THE EVIDENCE

There is low quality evidence for a cure rate of 98% with erythromycin 50 mg/kg/day for 14 days, and uncertain effects on the cure rate for azithromycin given the small numbers of neonates receiving azithromycin in the study (see Web annexes D and E). There is very low quality evidence for 7 more instances of pyloric stenosis per 1000 with erythromycin. The GDG regarded the risk of pyloric stenosis as a serious adverse effect of erythromycin use in children. There are no data evaluating pyloric stenosis due to use of azithromycin. There are also no data assessing the effects of

trimethoprim. There is no evidence for variation in patient values and preferences, but compliance with treatments ranged from 77% to 89%. The costs for treatments are relatively low and similar, and most treatments are currently being used.

In summary, azithromycin is preferred over erythromycin because of the potential risk of serious adverse events with erythromycin, and there are no data for trimethoprim.

See Annex C for list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence profiles and evidence-to-decision frameworks (pp. 64-74).

RECOMMENDATION 6

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

RECOMMENDATION 7

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: Recommendations 6 and 7 apply 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 medication. Caution should be taken to avoid touching eye tissue when applying the topical treatment and to provide a water-based solution of povidone iodine. Alcohol-based povidone iodine solution must not be applied. The topical application should be administered immediately after birth.

Research implications: 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 medications is needed, in particular comparisons with chloramphenicol.

SUMMARY OF THE EVIDENCE

Overall, the quality of evidence is low to very low from 16 studies: 15 randomized studies and one non-randomized study with two comparison groups. There are few available data for the effects of chloramphenicol. Large benefits were reported for prophylaxis compared with no prophylaxis, in particular in babies born to women with known infection (approximately 70% reduction in conjunctivitis with prophylaxis using different medications). The benefits with different medications are similar; however, the low to very low quality evidence indicates that the benefits of tetracycline hydrochloride, erythromycin or povidone iodine may be slightly greater than for 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 relating to 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, and these benefits outweigh the risk of non-infectious conjunctivitis due to prophyalaxis with any of the topical medications. Some topical medications may provide greater protection (tetracycline hydrochloride, erythromycin or povidone iodine), but all are feasible to provide.

See Annex C for list of references of reviewed evidence, and Web annex D for details of the evidence reviewed, including evidence profiles and evidence-to-decision frameworks (pp. 75-96).

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ANNEX A:
STI GUIDELINE DEVELOPMENT TEAMS

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ANNEX B: DETAILED METHODS FOR GUIDELINE DEVELOPMENT

QUESTIONS AND OUTCOMES

To determine which recommendations to update, in December 2013 the World Health Organization (WHO) Department of Reproductive Health and Research reviewed current recommendations of key international guidelines:

- Sexually transmitted diseases treatment guidelines, 2010, Department of Health and Human Services, United States Centers for Disease Control and Prevention (CDC)[4];
- United Kingdom national guidelines for the management of sexually transmitted infections, British Association for Sexual Health and HIV (BASHH), 2006–2011;[5]
- Canadian guidelines on sexually transmitted infections, Public Health Agency of Canada, 2013–2014;[6]
- European sexually transmitted infections guidelines, International Union of Sexually Transmitted Infections (IUSTI);[7]
- National management guidelines for sexually transmissible infections, Sexual Health Society of Victoria, Australia, 2008;[8]
- National guideline for the management and control of sexually transmitted infections (STIs), National Department of Health, South Africa, 2009;[9] and
- National guidelines on prevention, management and control of reproductive tract infections including sexually transmitted infections, Ministry of Health and Family Welfare, Government of India, August 2007.[10]

Based on the review, four proposed categories of sexually transmitted infection (STI) conditions were prioritized:

a. STI conditions included in the 2003 WHO STI guidelines[11] that were selected by the GDG to be reviewed and updated in the new WHO STI guidelines. These are important and common conditions.

b. STI conditions not included in the 2003 WHO STI guidelines that were selected by the GDG to be reviewed and added in the new WHO STI guidelines. These are important and common conditions.

c. STI conditions included in the 2003 WHO STI guidelines that were not updated but were selected by the GDG to be included in the new WHO STI guidelines. These STI conditions are rare and diagnosis is not often made in the majority of settings, or it is unlikely that there is new information available as a basis for making any changes to the 2003 WHO STI recommendations.

d. STI conditions not included in the 2003 WHO STI guidelines that are part of other national guidelines, but were not selected by the GDG to be included in the new WHO STI guidelines. These conditions are rare and difficult to diagnose in the majority of settings, or it is unlikely that new research or information has become available; there are existing recommendations for these conditions that can be applied in other settings (e.g. reference hospitals that manage complicated conditions).

A meeting was held in December 2013, at which the Guideline Development Group (GDG) discussed and decided on the initial list of population, intervention, comparator and outcome (PICO) questions identified by WHO. After the meeting, surveys pertaining to each of the four STI topic areas (i.e. gonorrhoea, chlamydia, syphilis and herpes simplex virus type 2 [HSV-2]) were administered among subgroups of the GDG members with expertise relating to the relevant STIs. The goal of the surveys was to rank the population, interventions and outcomes for each specific STI condition by importance. The surveys required the members of the STI subgroups to rank the population, interventions and outcomes on a scale of 1 to 9, from lowest to highest priority.

4 Available at: http://www.cdc.gov/std/treatment/2010/std-treatment-2010-rr5912.pdf

5 Available at: http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx?hkey=072c83ed-0e9b-44b2-a989-7c84e4fbd9de

6 Available at: http://www.phac-aspc.gc.ca/std-mts/sti-its/cgsti-ldcits/index-eng.php

7 Available at: http://www.iusti.org/regions/europe/euroguidelines.htm

8 Melbourne Sexual Health Centre Treatment Guidelines, available at: http://mshc.org.au/HealthProfessional/MSHCTreatmentGuidelines/tabid/116/Default

9 Lewis DA, Maruma E. Revision of the national guideline for first-line comprehensive management and control of sexually transmitted infections: what's new and why? South Afr J Epidemiol Infect. 2009;24(2):6-9 (http://apps.who.int/medicinedocs/documents/s18369en/s18369en.pdf, accessed 14 June 2016).

10 Available at: http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/legaldocument/wcms_117313.pdf

11 Guidelines for the management of sexually transmitted infections. Geneva: World Health Organization; 2003 (http://www.who.int/hiv/pub/sti/en/STIGuidelines2003.pdf, accessed 30 May 2016).

Four different priority STI surveys were conducted, and each survey attained a 90–100% response rate from the STI subgroup members. The survey results for priority populations, interventions and outcomes were analysed. Populations, interventions and outcomes with an average rating of 7 to 9 were considered "critical"; those with an average rating of 4 to 6 were considered "important"; and those with an average rating of 1 to 3 were considered "not important" and were thus not covered in the guidelines. Some questions that scored less than 7 were kept for consistency.

The number of comparisons in each question was also reduced; only "critical" interventions were compared with each other and with important interventions. Thus, "important" interventions were not compared to each other.

A revised list of questions was then compiled and all members of the full STI GDG were requested to review the priority questions. The priority questions were then revised based on this feedback.

Six questions were identified for the update of the chlamydial infections guideline. Each question is framed using the PICO format (population, intervention, comparator and outcome). Each question corresponds to a recommendation.

PRIORITY QUESTIONS AND OUTCOMES FOR *CHLAMYDIA TRACHOMATIS*

1. Uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents

Population	Intervention	Comparator	Outcome
Adults and adolescents with uncomplicated genital (cervix, urethra) chlamydial infections	Azithromycin 1 g orally x 1 dose Doxycycline 100 mg twice daily x 7 days	Doxycycline extended release (ER) 200 mg daily x 7 days Erythromycin 500 mg orally, four times daily x 7 days Erythromycin ethylsuccinate (ES) 800 mg orally, four times daily x 7 days Erythromycin 500 mg orally, twice daily x 10–14 days Amoxicillin 500 mg orally, thrice daily x 7 days Quinolones	**Critical:** Clinical cure, microbiological cure, STI complications, side-effects (including allergy, toxicity, gastro), compliance **Important:** Quality of life, HIV transmission and acquisition, partner transmission

2. Uncomplicated anorectal chlamydial infections in adults and adolescents, excluding lymphogranuloma venereum (LGV)

Population	Intervention	Comparator	Outcome
Adults and adolescents with uncomplicated anorectal chlamydial infections (excluding LGV)	Azithromycin 1 g orally x 1 dose Doxycycline 100 mg twice daily x 7 days	Doxycycline (ER) 200 mg daily x 7 days Erythromycin 500 mg orally, four times daily x 7 days Erythromycin ES 800 mg orally, four times daily x 7 days Erythromycin 500 mg orally, twice daily x 10–14 days Amoxicillin 500 mg orally, thrice daily x 7 days Quinolones	**Critical:** Clinical cure, microbiological cure, STI complications, side-effects (including allergy, toxicity, gastro), compliance **Important:** Quality of life, HIV transmission and acquisition, partner transmission

3a–c. Chlamydia in pregnancy

Population	Intervention	Comparator	Outcome
Pregnant women with chlamydia	Azithromycin 1 g orally x 1 dose Erythromycin 500 mg orally, four times daily x 7 days	Amoxicillin 500 mg orally, thrice daily x 7 days Erythromycin 500 mg orally, twice daily x 14 days Erythromycin 250 mg orally, four times daily x 14 days Erythromycin ES 800 mg orally, four times daily x 7 days Erythromycin ES 400 mg orally, four times daily x 14 days	**Critical:** Fetal outcomes (e.g. teratogenicity, toxicity), fetal loss, prematurity/low birth weight, chorioamnionitis, infant pneumonitis/neonatal ophthamia, postpartum endometritis, microbiological cure, side-effects (including allergy, toxicity, gastro), clinical cure (symptoms), compliance **Important:** HIV acquisition, quality of life, transmission to partner

4. Lymphogranuloma venereum (LGV) in all populations

Population	Intervention	Comparator	Outcome
Adults and adolescents with LGV	Doxycycline 100 mg twice daily x 21 days Azithromycin 1 g orally once a week x 1–3 weeks	Doxycycline 100 mg twice daily x 14 days Erythromycin base 500 mg orally, four times daily x 21 days	**Critical:** Clinical cure, microbiological cure **Important:** STI complications, side-effects (including allergy, toxicity, gastro), quality of life, HIV transmission and acquisition, compliance, LGV transmission to partner

5. Ophthalmia neonatorum treatment

Population	Intervention and comparator	Outcome
Neonates with neonatal conjunctivitis	Erythromycin in 4 divided doses orally, daily x 14 days: 20 mg/kg/day, 30 mg/kg/day, or 50 mg/kg/day Azithromycin 20 mg/kg/day orally, daily x 3 days Trimethoprim 40 mg + sulfa 200 mg orally, twice daily x 14 days	**Critical:** Clinical cure, microbiological cure, Complications, side-effects (including allergy, toxicity, gastro), antimicrobial resistance, compliance

6 and 7. Ophthalmia neonatorum prophylaxis

Population	Intervention and comparator	Outcome
Neonates at risk for ophthalmia neonatorum	Ophthalmic ointment in each eye at the time of delivery: Erythromycin 0.5% Silver nitrate 1% Chloramphenicol Tetracycline 1% Povidone iodine 2.5%	**Critical:** Absence of conjunctivitis, keratitis, complications, blindness, corneal scarring, antimicrobial resistance

REVIEWS OF THE EVIDENCE

SEARCH FOR EVIDENCE FOR EFFECTS OF INTERVENTIONS

To avoid duplication of reviews that have been previously published, evidence was searched using a hierarchical approach. The team first searched for synthesized evidence then searched the primary studies for all the factors needed to complete the evidence-to-decision framework for each question (i.e. benefits and harms, patient values, acceptability, feasibility, equity and costs).

The hierarchical approach consisted of identifying pre-existing synthesized evidence, including from previously published guidelines that included systematic reviews of the literature. When synthesized evidence about benefits and harms for an intervention was not available or the synthesized evidence was not up to date, a new systematic review of randomized controlled trials (RCTs) and non-randomized studies was conducted.

The search strategies were developed by an information specialist trained in systematic reviews. The strategies included the use of keywords from the controlled vocabulary of the database and text words based on the PICO questions. There were no restrictions based on language, publication status or study design. RCTs were included for critical and important outcomes, and non-randomized studies for critical outcomes when no evidence was available from RCTs. Additional strategies included contacting Cochrane review groups and authors of study protocols.

The Cochrane Library suite of databases (Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment [HTA] database and the American College of Physicians [ACP] Journal Club) was searched for published systematic reviews and protocols from 2004 to 2015.

Search strategy:

1. chlamydia.mp.
2. trachomatis.mp.
3. ct infection*.tw.
4. or/1-3

Primary studies were searched for in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase databases. Search end dates for each PICO question varied between March and October 2015 (see list below). The strategies included searching for subject headings and text words that included chlamydia and specific interventions (e.g. medication names and classes). Additional strategies included checking reference lists and consulting with the GDG for any missed articles. We searched for RCTs for critical and important outcomes, and non-randomized studies for critical outcomes when no evidence was available from RCTs.

Search end dates:

- Uncomplicated genital (cervix, urethra) chlamydial infections in adults and adolescents: up to March 2015
- Uncomplicated anorectal chlamydial infections (excluding LGV) in adults and adolescents: up to June 2015
- Chlamydia in pregnancy: up to 1 June 2015; up to 1 December 2015 for non-randomized comparative studies
- Lymphogranuloma venereum in all populations: up to June 2015
- Ophthalmia neonatorum treatment: up to May 2015
- Ophthalmia neonatorum prevention: up to October 2015.

SCREENING STUDIES, DATA EXTRACTION AND ANALYSIS

Two researchers independently screened titles and abstracts of systematic reviews identified through database searching to determine studies eligible for inclusion in the analysis. Disagreements were resolved by discussing study inclusion with a third member of the research team. Data were extracted using a pilot-tested form for patient characteristics (including the subgroups identified by the GDG), diagnosis, treatment (dose, schedule, etc.), setting, follow-up and outcomes. Two investigators independently abstracted data. Risk of bias of each study was also assessed using risk of bias tools appropriate for RCTs (http://handbook.cochrane.org/chapter_8/8_assessing_risk_of_bias_in_included_studies.htm) and using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I; previously called ACROBAT) tool to assess non-randomized studies (www.riskofbias.info).

To measure the treatment effect, the data were analysed using RevMan 5.2.[12]

For dichotomous outcomes, we calculated relative risks with 95% confidence intervals (e.g. risk ratios and odds ratios) by pooling results from RCTs and pooling results from non-randomized studies using the random effects model. Moderate to high heterogeneity (I2 > 50%) was explored. Effects were converted to absolute effects using the calculated relative effect and a representative baseline risk (agreed upon by the GDG). When non-randomized studies with one group were included, a pooled proportion of an event (and confidence intervals) were calculated across the studies using the generic inverse variance. For continuous outcomes, a mean difference or a standardized mean difference (when studies used different scales to measure an outcome) was calculated. When possible, the forest plots of the meta-analyses were made available to the GDG.

When data could not be pooled across studies, narrative synthesis methods were used (see http://methods.cochrane.org/sites/methods.cochrane.org/files/Mckenzie.pdf). Results were presented in tables (e.g. median effects with interquartile ranges), or were narratively described by direction of the effect or by statistical significance as reported in the primary study.

PATIENT VALUES AND PREFERENCES, ACCEPTABILITY, EQUITY AND FEASIBILITY

Studies on patient values and preferences, acceptability, equity and feasibility were searched for and screened using two methods. First, while screening studies for the effects of treatments and costs, two investigators identified studies of potential relevance in these areas. Secondly, a separate search was conducted in MEDLINE, Embase and PsycINFO from January 2000 to July 2015. Text words and keywords for the different STIs were used in combination with words such as "preference", "adherence", "satisfaction", "attitudes", "health utilities" and "value", "equity" and "feasibility". The results included 2563 unique references. Two investigators screened the studies, and 162 studies were identified for full text retrieval. Any study design was included that addressed equity or feasibility. In addition, when adherence was measured in RCTs or non-randomized studies, the data were collected, synthesized and presented in the evidence profiles for each PICO question.

The following study designs were included:

a. Patient utilities and health status values studies: These studies examine how patients value alternative health states and their experiences with treatment. The measurement techniques used can include: standard gamble, time trade-off, visual analogue scale, or mapping results based on generic surveys (EuroQol five dimensions health questionnaire [EQ-5D] or the 36-Item Short Form Health Survey [SF-36]) or specific measurement (e.g. St George Respiratory Questionnaire) of health-related quality of life.

b. Studies of patients' direct choices when presented with decision aids: These studies examine the choices patients make when presented with decision aids for management options (i.e. probabilistic trade-off techniques).

c. Studies on non-utility measurement of health states: These studies quantitatively examine patients' views, attitudes, satisfaction or preferences through questionnaires or scales; these are neither utility studies nor studies of patients' responses to decision aids. Patients are asked about how desirable or aversive a particular outcome is for them. This category includes some studies that use questionnaires or scales.

d. Qualitative studies: These studies explore patients' views, attitudes, satisfactions or preferences related to different treatment options based on qualitative research methods including focus group discussions, interviews, etc.

12 RevMan (Computer Program). Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration; 2012.

From the search, we included 17 studies reporting information relating to different STIs. In many instances, data for all infections informed the evidence for chlamydia specifically.

RESOURCES

We searched the published literature for evidence on use of resources and obtained data on direct costs of medicines.

Based on the list of possible treatments identified by the GDG, an estimate of the cost associated with each alternative was calculated. This costing estimate refers only to the actual market price of the medication and does not include the costs of other resources that could be involved, such as syringes, injection time or needle disposal.

Data were presented in a table and included: treatment, dose per day, treatment duration, days, medicine cost per dose, medicine cost per full course of treatment, and 25% of procurement costs (as defined in the 2014 MSH International drug price indicator guide)[13]. A final price for a full course of treatment for each medicine by dosage was calculated as the number of doses per day, multiplied by the number of days of the treatment, plus 25% of the procurement costs for the medicines used. The unit price of the medicine was obtained from the median prices provided in the 2014 MSH International drug price indicator guide and information available on the Internet. In order to determine a precise and reliable estimate, the price per unit (all expressed in US dollars) was provided only when the information available matched the dosage of interest (grams per pill or 1000 units per vial). No calculations were made based on assumptions about the cost per unit of hypothetical packaging not listed in the directory.

The major medical databases were also searched (MEDLINE, Embase and the Cochrane Library for Economic Evaluation and Technology Assessment reports) from January 2005 to July 2015. Three studies addressed the cost-effectiveness of different treatment strategies for chlamydia. In addition, while screening studies for the effects of treatments, two investigators also identified studies of potential relevance for costs, and abstracted data regarding possible resources to be considered during the decision-making process.

13 International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Science for Health; 2015 (http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2014.pdf, accessed 3 June 2016).

APPLYING THE GRADE APPROACH TO MAKING THE RECOMMENDATIONS

EVIDENCE PROFILES

An evidence profile was made for each PICO question using the GRADEpro software (www.gradepro.org). Each profile included the critical and important outcomes, the relative and absolute effects, and the quality of evidence according to the GRADE domains (see the GRADE handbook)[14]. Briefly, the GRADE approach assesses the quality of evidence for treatment interventions using well-established criteria for the design, risk of bias, inconsistency, indirectness, imprecision, effect size, dose–response curve and other considerations that may affect the quality of the evidence. Two investigators used the GRADE approach to assess the quality and level of certainty of the evidence. The evidence profiles for each recommendation are available in Web annex D.

EVIDENCE-TO-DECISION FRAMEWORKS

Evidence-to-decision frameworks were also developed using GRADEpro software (www.gradepro.org). Evidence-to-decision frameworks present the desirable and undesirable effects of the interventions, the value of the outcomes, the costs and resource use, the acceptability of the interventions to all stakeholders, the impact on health equity, and the feasibility of implementation (i.e. the GRADE criteria for making decisions). The evidence-to-decision frameworks are based on a population perspective for these recommendations. All GRADE criteria were considered from this perspective.

MAKING THE RECOMMENDATIONS

In October 2015, the GDG met to make the recommendations. This meeting was facilitated by two co-chairs – one with expertise in GRADE and the other with clinical expertise of chlamydia. During the meeting, the evidence profiles and evidence-to-decision frameworks were presented by the methodologists. The GDG discussed each GRADE criterion and judged which intervention was favoured. Then a final decision and guideline recommendation was developed. The goal was to arrive at agreement across all members of the GDG and this was facilitated by the chairpersons through discussion. When there was disagreement for a criterion, it was noted in the evidence-to-decision framework for the relevant judgement. If there was disagreement for any of the final recommendations, the plan was for the GDG to vote and the numbers to be recorded. Because there was no disagreement for any of the final recommendations, however, votes were not taken or reported in these guidelines.

The GDG made a strong or conditional recommendation for or against each intervention and described special circumstances in the remarks. Research implications were also developed and presented, based on the gaps identified in the evidence. Following the meeting, the recommendations were finalized via teleconference, and final approval was obtained from the GDG members electronically. All decisions and discussions from the GDG for each recommendation are available in the evidence-to-decision frameworks in Web annex D.

14 Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook. Hamilton, Ontario: McMaster University and Evidence Prime Inc.; 2013 (http://gdt.guidelinedevelopment.org/central_prod/_design/client/handbook/handbook.html, accessed 31 May 2016).

ANNEX C:
LISTS OF REFERENCES FOR REVIEWED EVIDENCE

RECOMMENDATION 1

Treatments for adults and adolescents with uncomplicated genital (cervix, urethra) chlamydial infections

Systematic review

1. Páez-Canro C, Martinez-Martinez F, Alzate JP, Lethaby A, Gaitán HG. Antibiotics for treating genital *Chlamydia trachomatis* infection in men and non-pregnant women (protocol). Cochrane Database Syst Rev. 2013;(12):CD010871.

Included studies

1. Bowie WR, Yu JS, Fawcett A, Jones HD. Tetracycline in nongonococcal urethritis. Comparison of 2 g and 1 g daily for seven days. Br J Vener Dis. 1980;56(5):332-6.
2. Campbell WF, Dodson MG. Clindamycin therapy for *Chlamydia trachomatis* in women. Am J Obstet Gynecol. 1990;162(2):343-7.
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Patient values and preferences, acceptability and cost: other sexually transmitted infections and conditions

1. Kingston M, Carlin E. Treatment of sexually transmitted infections with single-dose therapy: a double-edged sword. Drugs. 2002;62(6):871-8.

2. Nagarkar A, Mhaskar P. A systematic review on the prevalence and utilization of health care services for reproductive tract infections/sexually transmitted infections: evidence from India. Indian J Sex Transm Dis. 2015;36(1):18-25. doi:10.4103/0253-7184.156690.

3. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. Cochrane Database Syst Rev. 2014;4:CD007768.

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RECOMMENDATION 2

Treatments in adults and adolescents with uncomplicated anorectal chlamydial infections (excluding lymphogranuloma venereum

Systematic review

1. Kong FY, Tabrizi SN, Fairley CK, Vodstrcil LA, Huston WM, Chen M, et al. The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis. J Antimicrob Chemother. 2015;70(5):1290-7. doi:10.1093/jac/dku574.

Included studies

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

1. Nagarkar A, Mhaskar P. A systematic review on the prevalence and utilization of health care services for reproductive tract infections/sexually transmitted infections: evidence from India. Indian J Sex Transm Dis. 2015;36(1):18-25. doi:10.4103/0253-7184.156690.
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RECOMMENDATIONS 3A, 3B, 3C

Treatments in pregnant women with chlamydial infections

Systematic review

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Additional references

1. Amin A, Garcia Moreno C. Addressing gender-based violence to reduce risk of STI and HIV. Sex Transm Infect. 2013;89(Suppl 1):A8.
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RECOMMENDATION 4

Treatments for adults and adolescents with lymphogranuloma venereum

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RECOMMENDATION 5

Treatment of chlamydial ophthalmia neonatorum

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RECOMMENDATIONS 6 AND 7

Prevention of gonococcal and chlamydial ophthalmia neonatorum

Systematic reviews

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