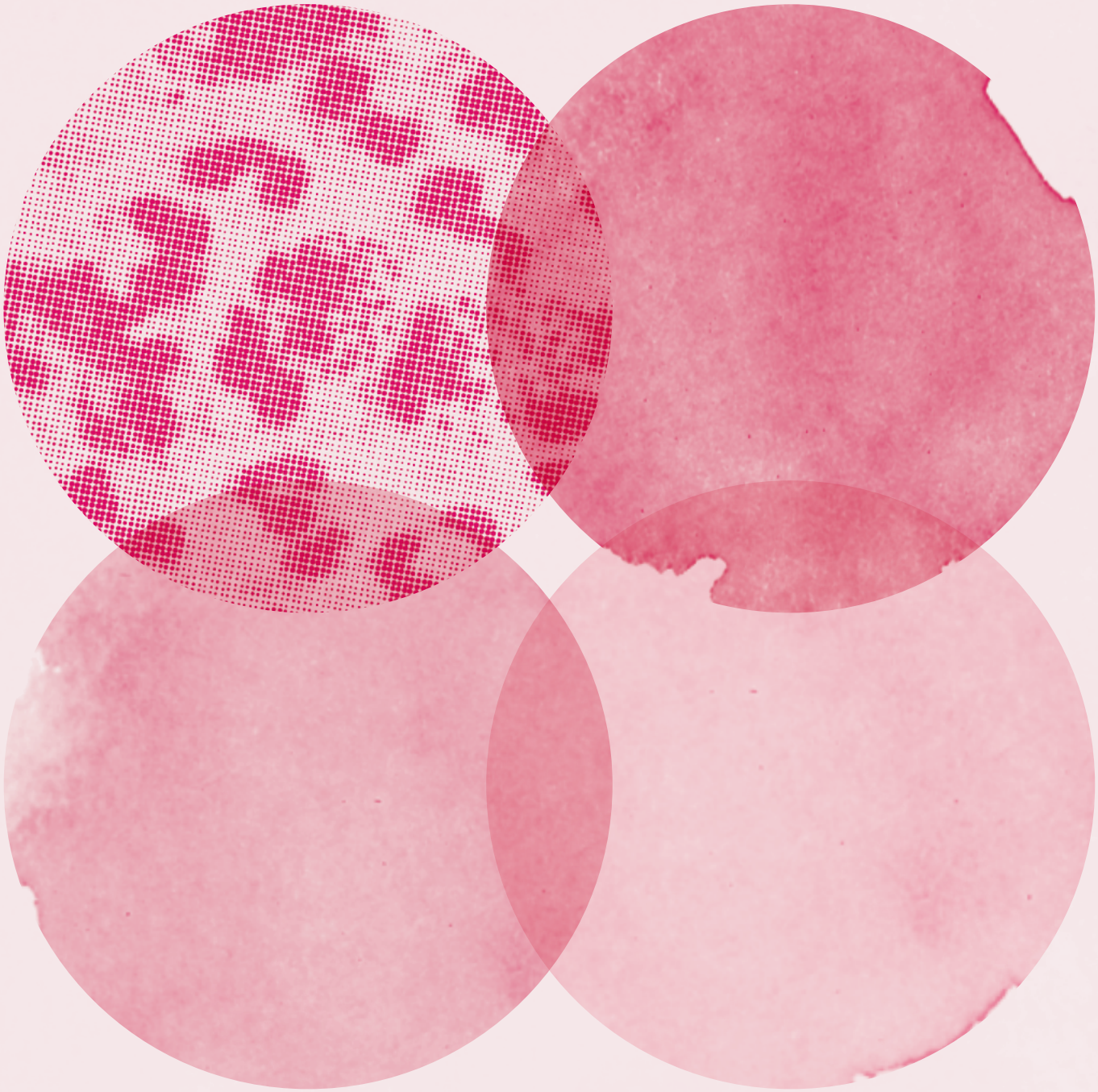
World Health Organization

WHO GUIDELINES FOR THE

Treatment of *Neisseria gonorrhoeae*



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CONTENTS

CONTENTS (CONTINUED)

Web annexes available at:
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Web annex D: Evidence profiles and evidence-to-decision frameworks
Web annex E: Systematic reviews for gonorrhoea guidelines
Web annex F: Summary of conflicts of interest

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immune deficiency syndrome
AMR	antimicrobial resistance
DALY	disability-adjusted life years
DOI	declaration of interests
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
HPV	human papillomavirus
HRP	WHO Special Programme of Research, Development and Research Training in Human Reproduction
HSV-2	herpes simplex virus type 2
IM	intramuscular
MSH	Management Sciences for Health
MSM	men who have sex with men
NAATs	nucleic acid amplification tests
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 *NEISSERIA GONORRHOEAE*

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 78 million cases of gonorrhoea.

Gonorrhoea, caused by *Neisseria gonorrhoeae*, is the second most common bacterial STI and results in substantial morbidity and economic cost worldwide. Uncomplicated gonococcal infection commonly manifests as urethritis in men and may cause mucopurulent cervicitis in women. Rectal and pharyngeal infections in both men and women are largely asymptomatic. Gonococcal infections are often asymptomatic in women; the lack of discernible symptoms results in unrecognized and untreated infection that may lead to serious complications, including pelvic inflammatory disease, ectopic pregnancy and infertility. Untreated urethral infection in men can lead to epididymitis, urethral stricture and infertility. Infants of mothers with gonococcal infection can contract neonatal conjunctivitis, which may lead to blindness if left untreated.

Neisseria gonorrhoeae can be diagnosed by culture or nucleic acid amplification tests (NAATs), and by Gram stain in men with urethritis. In settings without available laboratory diagnostic support, diagnosis is often made clinically, based on the presence of symptoms such as vaginal and urethral discharge. The treatment of gonococcal infections is complicated by the rapidly changing antimicrobial susceptibility patterns of *N. gonorrhoeae*, raising concerns about the eventual development of untreatable gonococcal infections with serious sexual and reproductive health consequences.

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. There is an urgent need to update treatment recommendations for gonococcal infections to respond to changing antimicrobial resistance (AMR) patterns of *N. gonorrhoeae*. High-level resistance to previously recommended quinolones is widespread and decreased susceptibility to the extended-spectrum (third-generation) cephalosporins, another recommended first-line treatment in the 2003 guidelines, is increasing and several countries have reported treatment failures. These guidelines for the treatment of common infections caused by *N. gonorrhoeae* form one of several modules of guidelines for specific STIs. Other modules will focus on treatments for Chlamydia trachomatis (chlamydia), 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 for 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 *N. gonorrhoeae*; and
- to support countries to update their national guidelines for treatment of gonococcal 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 gonococcal 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 gonorrhoea. 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

These guidelines provide six treatment recommendations for specific conditions caused by *N. gonorrhoeae*. The recommendations summarized in Table 1 for sexually transmitted gonococcal infections apply to all adults and adolescents (10–19 years of age), including people living with HIV and key populations, including sex workers, men who have sex with men and transgender persons and pregnant women. Specific recommendations are also provided for prophylaxis and treatment of ophthalmia neonatorum caused by *N. gonorrhoeae*. Notable changes from the 2003 WHO STI guidelines include the following: quinolones are no longer recommended for the treatment of gonorrhoea due to the reported high level of resistance; there are now recommendations for oropharygeal infections, and retreatment of gonococcal infections after treatment failure; dual therapy is a preferred option for treatment of gonococcal infections over single therapy; single therapy is based on local resistance data and changes have been made to some dosages; and new topical medications have been suggested for prophylaxis of ophthalmia neonatorum.

Table 1. Summary of recommendations for treatment of gonococcal infections

Recommendations	Strength of recommendation and quality of evidence
Genital and anorectal gonococcal infections	
Recommendation 1 The WHO STI guideline recommends that local resistance data should determine the choice of therapy (both for dual therapy and single therapy). In settings where local resistance data are not available, the WHO STI guideline suggests dual therapy over single therapy for people with genital or anorectal gonorrhoea. The WHO STI guideline suggests the following options: *Dual therapy* (one of the following) • ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose • cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose *Single therapy* (one of the following, based on recent local resistance data confirming susceptibility to the antimicrobial) • ceftriaxone 250 mg IM as a single dose • cefixime 400 mg orally as a single dose • spectinomycin 2 g IM as a single dose. *Remarks*: Because of the emerging resistance data for gonococcal infections and reduced effectiveness of some medicines, good practice dictates that the choice of treatment depends on reliable local data on antimicrobial susceptibility. Alternative single-medicine therapies, such as gentamicin or kanamycin, have not been suggested due to lack of surveillance data. Guidance for surveillance of antimicrobial resistance in *N. gonorrhoeae* is available from WHO.[1] This recommendation applies to pregnant women, who should be closely monitored for complications.	*Good practice statement* *Conditional recommendation, low quality evidence*

1 UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. Strategies and laboratory methods for strengthening surveillance of sexually transmitted infection 2012. Geneva: World Health Organization; 2012 (http://www.who.int/reproductivehealth/publications/rtis/9789241504478/en/, accessed 25 May 2016).

Oropharyngeal gonococcal infections	
Recommendation 2 In adults and adolescents with gonococcal oropharyngeal infections, the WHO STI guideline suggests dual therapy over single therapy. The WHO STI guideline suggests the following options: *Dual therapy* (one of the following) • ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose • cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose *Single therapy* (based on recent local resistance data confirming susceptibility to the antimicrobial) • ceftriaxone 250 mg IM as single dose. *Remarks*: Treatment failures have been observed after single therapy for gonococcal oropharyngeal infections and therefore dual therapy is suggested over single therapy. This recommendation applies to pregnant women, who should be closely monitored for complications.	*Conditional recommendation, very low quality evidence*
Retreatment of gonococcal infections after treatment failure	

Recommendation 3
 	
In people with gonococcal infections who have failed treatment, the WHO STI guideline suggests the following options.
• If reinfection is suspected, re-treat with a WHO-recommended regimen, reinforce sexual abstinence or condom use, and provide partner treatment.
• If treatment failure occurred after treatment with a regimen not recommended by WHO, re-treat with a WHO-recommended regimen.
• If treatment failure occurred and resistance data are available, re-treat according to susceptibility.
• If treatment failure occurred after treatment with a WHO-recommended single therapy, re-treat with WHO-recommended dual therapy.
• If treatment failure occurred after a WHO-recommended dual therapy, re-treat with one of the following dual therapies:
  – ceftriaxone 500 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
  – cefixime 800 mg orally as a single dose PLUS azithromycin 2 g orally as a single dose
  – gentamicin 240 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
  – spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) PLUS azithromycin 2 g orally as a single dose.
 	
Remarks: Before retreatment, reinfection should be distinguished from treatment failure, resistance data should be obtained when possible, and the WHO-recommended regimens should be used.
	Conditional recommendation, very low quality evidence

Gonococcal ophthalmia neonatorum	
Recommendation 4 In neonates with gonococcal conjunctivitis, the WHO STI guideline suggests one of the following treatment options: • ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose • kanamycin 25 mg/kg (maximum 75 mg) IM as a single dose • spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose. *Remarks*: Due to the large net benefit with treatment, good practice dictates that neonates should be treated for gonococcal conjunctivitis. The choice of treatment may depend on the cost and quality of the medicine in different settings and on equity considerations. Side-effects should be monitored in neonates.	*Conditional recommendation, very low quality evidence*
Recommendation 5 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 6 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. *Remarks*: Recommendations 5 and 6 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.**	*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 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

Gonorrhoea, caused by *Neisseria gonorrhoeae*, is the second 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, 78 million new cases occurred among adolescents and adults aged 15–49 years worldwide with a global incidence rate of 19 per 1000 females and 24 per 1000 males. The estimated 27 million prevalent cases of gonorrhoea in 2012 translates to a global prevalence of gonorrhoea of 0.8% among females and 0.6% among males aged 15–49 years, with the highest prevalence in the WHO Western Pacific and African Regions (1). Co-infection with Chlamydia trachomatis is detected in 10–40% of people with gonorrhoea (2–5).

CLINICAL PRESENTATION

Uncomplicated gonococcal infection commonly manifests as urethritis in men with symptoms of urethral discharge and dysuria. On examination, the urethral discharge may range from scanty and mucoid to copious and purulent. Gonorrhoea is often asymptomatic in women; less than half of infected women complain of non-specific symptoms such as abnormal vaginal discharge, dysuria, lower abdominal discomfort and dyspareunia. The most common clinical signs are vaginal discharge and cervical friability due to mucopurulent cervicitis. Rectal infections in men and women are largely asymptomatic; occasionally patients complain of rectal and anal pain or discharge. Pharyngeal infections are mainly asymptomatic, but mild sore throat and pharyngitis may occur.

In the majority of women with gonorrhoea, the lack of discernible symptoms results in unrecognized and untreated infections. Untreated infections usually resolve spontaneously but may lead to serious complications such as pelvic inflammatory disease, including endometritis, salpingitis and tubo-ovarian abscess, which can lead to ectopic pregnancy and infertility. Untreated urethral infection in men can lead to epididymitis, urethral stricture and infertility. The risk of complications increases with repeated infection.

Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis manifesting as purulent ocular discharge and swollen eyelids. Untreated conjunctivitis may lead to scarring and blindness.

LABORATORY DIAGNOSIS

N. gonorrhoeae can be diagnosed by culture or nucleic acid amplification tests (NAATs) and, in some instances, Gram stain. NAATs are highly sensitive and specific diagnostic tests that can be conducted on a wide range of samples, including urine, vulvovaginal, cervical and urethral swabs. NAATs have a sensitivity of over 90%, which is higher than for culture (> 85%). The sensitivity varies by NAAT type and is frequently lower for rectal and pharyngeal samples. The lower specificity (98.1–99.7%) of some, particularly early generation, NAATs may result in low positive predictive values, especially in low-prevalence populations, due to cross-reaction with other species of Neisseria. A drawback of currently available commercial NAATs is their inability to provide information on antimicrobial susceptibility. Cultures should be done in parallel with NAATs to allow for susceptibility testing.

Specimens from all cases of suspected gonococcal infection should be collected for microbiological culture and antimicrobial susceptibility testing, to the extent possible considering local availability of resources.

Microbiological cultures of *N. gonorrhoeae* are specific and cheap, with a reasonable sensitivity of 85–95% for urethral and endocervical infection. Optimal isolation of *N. gonorrhoeae* requires good specimen collection, timely inoculation into adequate and appropriate culture media, proper transportation and appropriate incubation.

Gram-stained smears can provide a presumptive diagnosis of gonorrhoea, especially among symptomatic men with urethritis. In low-income settings, Gram stains may provide a less expensive alternative to NAATs for symptomatic men. However, only 50–70% of asymptomatic infections in men are positive on Gram stain. Gram stain diagnosis for cervical and rectal infection is less reliable and pharyngeal samples should not be analysed.

Since laboratory diagnostic tests are not available in the majority of countries, diagnosis is often made clinically, based on the presence of symptoms such as vaginal and urethral discharge. Presumptive treatment is sometimes provided to those at high risk of gonococcal infection, if indicated based on local epidemiological patterns.

1.2 RATIONALE FOR NEW RECOMMENDATIONS

Gonococcal treatment guidelines need to be updated in response to the changing antimicrobial susceptibility patterns of *N. gonorrhoeae*. Increased resistance to most antibiotics used to treat gonococcal infections has been reported worldwide, raising concerns about the eventual development of untreatable gonococcal infections with serious sexual and reproductive health consequences (6). The previous WHO Guidelines for the management of sexually transmitted infections, published in 2003 (7), include ciprofloxacin as a first-line treatment for gonorrhoea, even though high levels of resistance to quinolones are reported in most countries and these medicines have been withdrawn from all international guidelines. Decreased susceptibility to the extended spectrum (third-generation) cephalosporins, another recommended first-line treatment in the 2003 guidelines, is becoming more widespread and several countries have reported treatment failures. Treatment recommendations must therefore be updated urgently to reflect the actual antimicrobial resistance (AMR) patterns of STIs, delay the further development of resistance to cephalosporins and to include treatment options for cases of cephalosporin treatment failure.

1.3 OBJECTIVES

The objectives of these guidelines are:

- to provide evidence-based guidance on treatment of infection with *N. gonorrhoeae*; and
- to support countries to update their national guidelines for treatment of gonococcal 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 *N. gonorrhoeae*. 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 *N. gonorrhoeae*. Recommendations were not updated for rare conditions and other conditions for which no new information became available since the 2003 WHO STI guidelines were issued.

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

- genital and anorectal infections
- oropharyngeal infections
- persistent infection due to treatment failure
- 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 (8) (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 gonorrhoea 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, anorectal and oropharyngeal gonococcal infections, management of treatment failure, 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 resources (e.g. cost of intervention, cost-benefits 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.[2]

2 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 edition of the Management Sciences for Health (MSH) International drug price indicator guide (9). 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 (10). 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)[3], and in the WHO Reproductive Health Library (RHL)[4]. 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 (11).

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 STI 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 *N. GONORRHOEAE*

ADAPTATION, IMPLEMENTATION AND MONITORING

These guidelines provide recommendations for treatment of gonorrhoea 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.

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

4 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 (11).

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 medications 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 MEDICINES

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.

STI TREATMENT FOR KEY POPULATIONS

Key populations are at increased risk of transmitting and acquiring STIs, including *N. gonorrhoeae*. It is critical to increase access to STI services including treatment for specific STIs for key populations and people living with HIV. The following WHO guidelines provide recommendations and guidance on increasing access to and delivering STI services for key populations.

- Implementing comprehensive HIV/STI programmes with sex workers: practical approaches from collaborative interventions (12)
- Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (13)
- Implementing comprehensive HIV and STI programmes with men who have sex with men: practical guidance for collaborative interventions (14)
- Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (15).

04 RECOMMENDATIONS FOR TREATMENT OF GONOCOCCAL INFECTIONS

The following six 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 *N. gonorrhoeae*.

4.1 GENITAL AND ANORECTAL GONOCOCCAL INFECTIONS

RECOMMENDATION 1

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

Good practice statement

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

Conditional recommendation, low quality evidence

The WHO STI guideline suggests the following options:

Dual therapy (one of the following)

- ceftriaxone 250 mg intramuscular (IM) as a single dose PLUS azithromycin 1 g orally as a single dose
- cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

Single therapy (one of the following, based on recent local resistance data confirming susceptibility to the antimicrobial)

- ceftriaxone 250 mg IM as a single dose
- cefixime 400 mg orally as a single dose
- spectinomycin 2 g IM as a single dose.

Remarks: Because of the emerging resistance data for gonococcal infections and reduced effectiveness of some medicines, good practice dictates that the choice of treatment depends on reliable local data on antimicrobial susceptibility. Alternative single-medicine therapies, such as gentamicin or kanamycin, have not been suggested due to lack of surveillance data. Guidance for surveillance of antimicrobial resistance (AMR) in *N. gonorrhoeae* is available from WHO (16). This recommendation applies to pregnant women, who should be closely monitored.

SUMMARY OF THE EVIDENCE

The quality of the evidence for the effects of treatments for gonococcal infections is low. Evidence is available from 108 studies, including 14 randomized and 94 non-randomized studies, which were conducted in a broad range of high-, middle- and low-income countries. Although high cure rates were shown (> 95%), the evidence is outdated and regionally specific, and therefore is considered to be indirect due to emerging resistance data. Available data on AMR in *N. gonorrhoeae* revealed high rates of resistance to quinolones, emerging azithromycin resistance and decreased susceptibility to ceftriaxone and cefixime. Low quality evidence suggests similar cure rates with azithromycin using single doses of 1 g or 2 g, but there are data on emerging resistance for azithromycin from many countries. Cure rates for kanamycin and gentamycin vary and are based on older studies. Currently, there is little surveillance data for these two medicines. There are similar cure rates with cefixime using single doses of 400 mg or 800 mg. The evidence for dual versus single therapy is low quality, as there are few studies evaluating different combinations with azithromycin. Side-effects of the medicines were often not measured, but when measured were trivial. In particular, the evidence for differences in side-effects between 1 g or 2 g single doses of azithromycin is uncertain, but the Guideline Development Group (GDG) agreed that side-effects, such as nausea, could be greater with higher doses.

Overall, the GDG therefore agreed that the success of the available treatments is based on in vitro susceptibility of gonococcal infections, and should therefore be based on recent local surveillance data. Due to global resistance patterns, quinolones are no longer an option for treatment of gonococcal infections. The GDG agreed that dual therapy should be suggested due to the emergence of resistance and the paucity of surveillance data in most settings to guide decisions about susceptibility to single therapy. Additional studies comparing different combinations of dual therapy (such as gentamicin, ceftriaxone, cefixime or gemifloxacin plus azithromycin) will inform recommendations in future.

No studies were found that assessed patient values and preferences, acceptability, equity or feasibility specific to gonococcal infections. There is some evidence from the literature about acceptability of injections versus oral medications in people with syphilis. Approximately 10–20% of people refused injections. The GDG also noted that some health-care providers are, in practice, averse to providing injections, and that additional labour time and costs are associated with IM administration. The GDG agreed that there is probably no variability in the values people place on the outcomes. However, IM injection may be less desirable among patients than oral administration, and dual therapy is acceptable to patients based on current use. Although azithromycin is perceived by some GDG members to require greater resources, the costs of the suggested treatments were similar. Since azithromycin is currently recommended for treatment of other STIs (e.g. chlamydia), it may provide additional benefit by treating possible co-infections.

For pregnant women: The quality of evidence for the effects of treatments for genital and anorectal gonococcal infections in pregnant women is low. Evidence was reviewed from three studies, including two randomized studies and one non-randomized study. When data for pregnant women were not available, evidence in non-pregnant adults was used to inform the recommendations.

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

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. 1-24).

4.2 OROPHARYNGEAL GONOCOCCAL INFECTIONS

RECOMMENDATION 2

In adults and adolescents with gonococcal oropharyngeal infections, the WHO STI guideline suggests dual therapy over single therapy.

Conditional recommendation, very low quality evidence

The WHO STI guideline suggests the following options:

Dual therapy (one of the following)

- ceftriaxone 250 mg IM as a single dose PLUS azithromycin 1 g orally as a single dose
- cefixime 400 mg orally as a single dose PLUS azithromycin 1 g orally as a single dose

Single therapy (based on recent local resistance data confirming susceptibility to the antimicrobial)

- ceftriaxone 250 mg IM as single dose.

Remarks: Treatment failures have been observed after single therapy for gonococcal oropharyngeal infections and therefore dual therapy is suggested over single therapy. This recommendation applies to pregnant women, who should be closely monitored for complications.

SUMMARY OF THE EVIDENCE

The quality of the evidence for the effects of different treatments for oropharyngeal gonococcal infections is low and very low, and therefore, overall, the evidence for this recommendation is very low. Evidence from 28 studies was identified: eight randomized and 20 non-randomized studies (including two non-randomized studies with two or more groups, and 18 non-randomized studies with one group). These studies were conducted in a broad range of high-, middle- and low-income countries. This evidence is outdated and regionally specific, and therefore is considered to be indirect due to emerging resistance data. The GDG agreed that the success of the available treatments is based on in vitro susceptibility of gonococcal infections, and should therefore be based on recent local surveillance data. Similar treatments were provided to people with oropharyngeal infections and anorectal infections (typically people had co-infection at other sites). The data showed a higher risk of treatment failure with oropharyngeal infections, and the GDG agreed that the consequences of treatment failure are severe. Based on these considerations, the GDG agreed that treatment should be as aggressive for oropharyngeal infections as for anorectal infections. Low quality evidence showed that spectinomycin may result in l ower cure rates (75%, ranging from 49% to 100%). Data for the effects of gentamycin or kanamycin are not available.

No studies were found to assess patient values and preferences, acceptability, equity or feasibility. The GDG agreed that there is probably no variability in values. However, IM injection may be less desirable than oral administration, and dual therapy is acceptable. Although azithromycin may be perceived by health-care providers, programme managers, policy-makers and funders to require greater resources, in fact the costs were similar across different treatments.

In summary, there is very low quality evidence for benefits and harms of dual therapy compared to single therapy, but due to emerging resistance to single therapies and lack of local surveillance data in most regions, dual therapy is favoured over single therapy. Dual therapy is currently being used in some settings and it appears to be acceptable, and the costs compared to effectiveness are not greater than single therapy. The recommendations for genital, anorectal and oropharyngeal infections are similar; however, single therapy with spectinomycin was less effective in oropharyngeal infections.

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. 25-38).

4.3 RETREATMENT OF GONOCOCCAL INFECTIONS AFTER TREATMENT FAILURE

RECOMMENDATION 3

In people with gonococcal infections who have failed treatment, the WHO STI guideline suggests the following options.

- If reinfection is suspected, re-treat with a WHO-recommended regimen, reinforce sexual abstinence or condom use, and provide partner treatment.
- If treatment failure occurred after treatment with a regimen not recommended by WHO, re-treat with a WHO-recommended regimen.
- If treatment failure occurred and resistance data are available, re-treat according to susceptibility.
- If treatment failure occurred after treatment with a WHO-recommended single therapy, re-treat with WHO-recommended dual therapy.
- If treatment failure occurred after a WHO-recommended dual therapy, re-treat with one of the following dual therapies:
  - ceftriaxone 500 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
  - cefixime 800 mg orally as a single dose PLUS azithromycin 2 g orally as a single dose
  - gentamicin 240 mg IM as a single dose PLUS azithromycin 2 g orally as a single dose
  - spectinomycin 2 g IM as a single dose (if not an oropharyngeal infection) PLUS azithromycin 2 g orally as a single dose.

Conditional recommendation, very low quality evidence

Remarks: Before retreatment, reinfection should be distinguished from treatment failure, resistance data should be obtained when possible, and the WHO-recommended regimens should be used.

SUMMARY OF THE EVIDENCE

The quality of the evidence is very low. The evidence is from 34 randomized and non-randomized studies that evaluated a treatment or many treatments and then reported on retreatment of individual cases of treatment failure. No studies specifically recruited people who had treatment failure. Most studies reported on cases of treatment failure or reinfection (a distinction was often not made). These studies also reported the medicine used for initial treatment, the medicine used for retreatment, and sometimes reported whether or not the case was cured. Cure rates for different medicines were not consistent across the studies.

In summary, there is very low quality evidence for the effects of specific medicines for people who fail treatment. Therefore, the recommendation was based on first determining whether or not the initial treatment was according to a WHO-recommended regimen; if it was not, then retreatment is suggested according to a WHO-recommended regimen; but if the initial treatment was according to a WHO-recommended regimen, then the suggestion for retreatment is for increasing dosages.

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. 39-63).

4.4 OPHTHALMIA NEONATORUM

RECOMMENDATION 4

In neonates with gonococcal conjunctivitis, the WHO STI guideline suggests one of the following treatment options:

- ceftriaxone 50 mg/kg (maximum 150 mg) IM as a single dose
- kanamycin 25 mg /kg (maximum 75 mg) IM as a single dose
- spectinomycin 25 mg/kg (maximum 75 mg) IM as a single dose.

Conditional recommendation, very low quality evidence

Remarks: Due to the large net benefit of treatment, good practice dictates that neonates should be treated for gonococcal conjunctivitis. The choice of treatment may depend on the cost and quality of the medicine in different settings and on equity considerations. Side-effects should be monitored in neonates.

SUMMARY OF THE EVIDENCE

The evidence is from two randomized and 13 non-randomized studies. There was very low quality evidence for cure rates, which were typically 100% for all treatments, with the exception of penicillin (81–84%). The quality of evidence was very low for adverse effects across treatments, generally indicating little to no difference among treatments. No evidence is available for patient values and preferences. The costs for treatments were relatively low and similar, and most treatments are currently being used.

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. 64-75).

RECOMMENDATION 5

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 6

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 5 and 6 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.

SUMMARY OF THE EVIDENCE

Overall, the quality of the evidence is low to very low from 16 studies: 15 randomized studies and one non-randomized study with two comparison groups. There are few 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 of treatment 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 for patient values and preferences, but the GDG agreed that there would likely be little difference in the high value placed on avoiding long-term consequences of both gonococcal and chlamydial conjunctivitis. The GDG also agreed that there would be little effect on acceptability, equity and feasibility, as prophylaxis is currently used in many countries. The GDG reported that alcohol-based povidone iodine has erroneously been used as prophylaxis resulting in serious harm to babies. Silver nitrate is the most expensive prophylaxis option.

In summary, there are large benefits for prophylaxis to prevent ophthalmia neonatorum, and these benefits outweigh the risk of non-infectious conjunctivitis due to prophylaxis 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. 76-93).

05 RESEARCH IMPLICATIONS

While surveillance data should be collected – including breakpoints for resistance, frequency of collection, number of isolates, and interpretation of local data – research into current and new medicine options is needed for genital, anorectal and oropharyngeal infections. This research is essential in light of the increasing antimicrobial resistance (AMR) to currently recommended treatments. Appropriately designed randomized controlled trials should be conducted on new medicine options, dual therapy and other alternatives, such as gentamicin and kanamycin. Specifically, studies should compare different combinations of dual therapy (such as gentamicin, ceftriaxone, cefixime or gemifloxacin plus azithromycin). Trials should include both men and women, and key populations, such as MSM and sex workers. In addition to commonly reported outcomes (e.g. cure and side-effects), other important outcomes should be evaluated, including transmission of gonorrhoea to partners, HIV transmission and acquisition, quality of life, and gonorrhoea antimicrobial in vitro resistance.

Treatment failure has been particular poorly researched. Although it is difficult to recruit a whole study population who had treatment failure, studies that conduct follow-up with patients who had treatment failure should improve their reporting. Studies should distinguish between cases of treatment failure and reinfection, and should report the first treatment, the follow-up treatment and the outcome. Related to cause of treatment failure, studies should explore and report the susceptibility of the organism in those who have experienced treatment failure.

Regarding the prevalence and treatment of ophthalmia neonatorum, there is little research into the risk of resistance to medications that are currently available. 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. The prevalence of gonococcal ophthalmia should be determined given the high prevalence of maternal gonorrhoea in some settings.

There is very little research into the values that people place on outcomes such as cure, burden of disease or risk of transmission. There is also little research specifically for people with gonococcal infections and their preferences for treatments, in particular their preference for injection versus oral administration of medicine, which may also be reflected in compliance in the context of randomized controlled trials.

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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)[5];
- United Kingdom national guidelines for the management of sexually transmitted infections, British Association for Sexual Health and HIV (BASHH), 2006–2011;[6]
- Canadian guidelines on sexually transmitted infections, Public Health Agency of Canada, 2013–2014;[7]
- European sexually transmitted infections guidelines, International Union of Sexually Transmitted Infections (IUSTI);[8]
- National management guidelines for sexually transmissible infections, Sexual Health Society of Victoria, Australia, 2008;[9]
- National guideline for the management and control of sexually transmitted infections (STIs), National Department of Health, South Africa, 2009;[10] 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.[11]

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[12] 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).

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

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

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

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

9 Melbourne Sexual Health Centre Treatment Guidelines, available at: http://mshc.org.au/HealthProfessional/MSHCTreatmentGuidelines/tabid/116/Default.aspx#.V06yFJMrKV4

10 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).

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

12 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).

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.

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 priority questions were identified for the update on gonorrhoea treatment. Each question is framed using the PICO format (population, intervention, comparator and outcome). Each question corresponds to a recommendation.

1(a). Uncomplicated genital (cervix, urethra) and anorectal gonococcal infections in adults and adolescents, HIV-positive patients, and in men who have sex with men (MSM)

Population	Intervention	Comparator	Outcome
Adults and adolescents, HIV-positive patients, MSM with uncomplicated genital (cervix, urethra) and anorectal gonococcal infections	Ceftriaxone ≥ 250 mg IM x 1	*Single therapy:* Azithromycin 1–2 g orally x 1 Cefixime 400 mg orally x 1 Cefixime 800 mg orally x 1 Cefixime 400 mg orally x 2 Gentamicin 240 mg IM x 1 Spectinomycin 2 g IM x 1 Kanamycin 2 g IM x 1 Quinolones (just in vitro resistance data) Ceftriaxone 125 mg IM x 1 *Dual therapy versus single therapy:* Multiple combinations of cefixime + doxycycline (or azithromycin) versus cefixime alone Multiple combinations of ceftriaxone + doxycycline (or azithromycin) versus ceftriaxone alone	**Critical:** Microbiological cure, STI complications, clinical cure, transmission to partners, compliance, N. gonorrhoeae antimicrobial in vitro resistance, side-effects (including allergy, toxicity) **Important:** HIV transmission and acquisition, quality of life

IM: intramuscular.

1(b). Uncomplicated genital (cervix, urethra) and anorectal gonococcal infections in pregnant women

Population	Intervention	Comparator	Outcome
Pregnant women with uncomplicated genital (cervix, urethra) and anorectal gonococcal infections	Ceftriaxone ≥ 250 mg IM x 1	*Single therapy:* Cefixime 800 mg orally x 1 Cefixime 400 mg orally x 2 Azithromycin 1–2 g orally x 1 Cefixime 400 mg orally x 1 *Dual therapy versus single therapy:* Cefixime + azithomycin versus cefixime alone Ceftriaxone + azithomycin versus ceftriaxone alone	**Critical:** Microbiological cure, fetal/neonatal outcomes (toxicity, teratogenicity, fetal loss, purulent conjunctivitis, polyarthritis, STI transmission, premature rupture of membranes, small for gestational age babies, chorioamionitis), compliance, maternal outcomes (including postpartum endometritis), STI complications, N. gonorrhoeae antimicrobial in vitro resistance, side-effects (including allergy, toxicity), clinical cure, transmission to partners **Important:** HIV transmission and acquisition, quality of life

2. Gonococcocal oropharyngeal infections in adults and adolescents

Population	Intervention	Comparator	Outcome
Adults and adolescents with gonoccocal oropharyngeal infections	Ceftriaxone ≥ 250 mg IM x 1	*Single therapy:* Ceftriaxone 125 mg IM x 1 Cefixime 400 mg orally x 1 Cefixime 800 mg orally x 1 Cefixime 400 mg orally x 2 Gentamicin 240 mg IM x 1 Azithromycin 2 g orally x 1 *Dual therapy:* Azithromycin 1 g orally x 1 PLUS one of the following: ceftriaxone 500 mg IM x 1; ceftriaxone 250 mg IM x 1; ceftriaxone 125 mg IM x 1; cefixime 400 mg orally x 1; cefixime 800 mg orally x 1; cefixime 400 mg orally x 2; or gentamicin 240 mg IM x 1	**Critical:** Microbiological cure, clinical cure, N. gonorrhoeae antimicrobial in vitro resistance, compliance **Important:** STI complications, side-effects (including allergy, toxicity), quality of life, transmission to partners

3. Treatment failure of *N. gonorrhoeae* (genital or oropharyngeal) to cephalosporins in adults and adolescents

Population	Intervention and comparator	Outcome
Adults and adolescents with treatment failure of N. gonorrhoeae (genital or oropharyngeal) to cephalosporins	Gentamicin 240 mg IM + azithromycin 2 g orally x 1 Gentamicin 240 mg IM + azithromycin 1 g orally x 1 Spectinomycin 2 g IM + azithromycin 2 g orally x 1 Gemifloxacin 320 mg orally + azithromycin 2 g orally x 1 Ceftriaxone 1 g IM + azithromycin 2 g orally x 1 Gentamicin 240 mg IM + spectinomycin 2 g IM x 1 Azithromycin 2 g orally x 1	**Critical:** Microbiological cure, compliance, STI complications, clinical cure, N. gonorrhoeae antimicrobial in vitro resistance, transmission to partners, side-effects (including allergy, toxicity), HIV transmission and acquisition **Important:** Quality of life

4. Treatment of ophthalmia neonatorum in neonates

Population	Intervention and comparator	Outcome
Neonates with neonatal conjunctivitis	Ceftriaxone 50 mg/kg IM x 1 or x 2 or x 3 Cefotaxime 100 mg/kg IM x 1 Spectinomycin 25 mg/kg IM x 1 Kanamycin 25 mg/kg IM x 1, Kanamycin + gentamicin ointment Kanamycin + tetracycline drop	**Critical:** Clinical cure, microbiological cure, complications, side-effects (including allergy, toxicity, gastro), antimicrobial in vitro resistance, compliance

5 and 6. Prevention of ophthalmia neonatorum in neonates

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 in vitro resistance

REVIEW 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. gonorrhoea.mp.
2. gonorrhea.mp.
3. gonococcal.mp.
4. 1 or 2 or 3
5. ophthalmia neonatorum.mp.
6. 4 or 5

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 gonorrhoea 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) and anorectal gonococcal infections in adults and adolescents, HIV-positive patients, and MSM: up to March 2015
- Uncomplicated genital (cervix, urethra) and anorectal gonococcal infections in pregnant women: up to March 2015
- Gonoccocal oropharyngeal infections in adults and adolescents: up to March 2015
- Treatment failure of *N. gonorrhoeae* (genital or oropharyngeal) to cephalosporins in adults and adolescents: up to March 2015
- Treatment ophthalmia neonatorum in neonates: up to September 2015
- Prevention of ophthalmia neonatorum in neonates: 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.[13]

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.

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

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.

From the search, we included 17 studies reporting information relating to different STIs. In many instances, data for all infections informed the evidence for gonorrhoea 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)[14]. 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/WHO 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. Six studies addressed the cost-effectiveness of different treatment strategies for gonorrhoea. In addition, while screening studies for the effects of treatments, two investigators also identified studies of potential relevance for costs. No studies were identified for resource use relating to treatment of gonococcal infections.

14 International drug price indicator guide, 2014 edition (updated annually). Medford (MA): Management Sciences for Health; 2015 (http://erc.msh.org/dmpguide/pdf/DrugPriceGuide_2014.pdf, accessed 6 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)[15]. 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.

15 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 gonorrhoea (genital or cervix) among adults and adolescents, HIV positive patients, men who have sex with men (MSM) or pregnant women

Systematic reviews

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Included studies: randomized and non-randomized studies

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Systematic review for pregnant women

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

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

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Patient values and preferences, acceptability and cost: other conditions

Systematic reviews

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 Journal of Sexually Transmitted Diseases. 2015;36(1):18-25. doi:10.4103/0253-7184.156690.
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Included studies

1. Dixon-Woods M, Stokes T, Young B, Phelps K, Windridge K, Shukla R. Choosing and using services for sexual health: a qualitative study of women's views. Sex Transm Infect. 2001;77(5):335-9.

For references on antimicrobial resistance in *Neisseria gonorrhoeae*, please see p. 48-49.

RECOMMENDATION 2

Treatments for gonococcal oropharyngeal infections in adults and adolescents

Systematic review

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Included studies: randomized and non-randomized studies

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

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

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Patient values and preferences, acceptability and cost: other conditions

Systematic reviews

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Included studies

1. Dixon-Woods M, Stokes T, Young B, Phelps K, Windridge K, Shukla R. Choosing and using services for sexual health: a qualitative study of women's views. Sex Transm Infect. 2001;77(5):335-9.

For references on antimicrobial resistance in *Neisseria gonorrhoeae*, please see p. 48-49.

RECOMMENDATION 3

Treatments for people with treatment failure of *N. gonorrhoeae* (genital or oropharyngeal)

Included studies: randomized and non-randomized studies

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15. McCann JS, Horner T, Shepherd I, Quin N, Dougan H. Spectinomycin hydrochloride (Trobicin) in the treatment of gonorrhoea. Ir Med J. 1977;70(3):86-8.
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Patient values and preferences, acceptability and cost: specific to gonorrhoea infections

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ANTIMICROBIAL RESISTANCE IN *NEISSERIA GONORRHOEAE*

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Ceftriaxone and cefixime resistance:

N. gonorrhoeae strains with high ceftriaxone MIC values have been reported in Japan (H041 strain), France and Spain (F89 strain), and Australia (A8806 strain):

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RECOMMENDATION 4

Treatment of gonococcal ophthalmia neonatorum

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RECOMMENDATIONS 5 AND 6

Prevention of gonococcal and chlamydial ophthalmia neonatorum

Systematic reviews

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