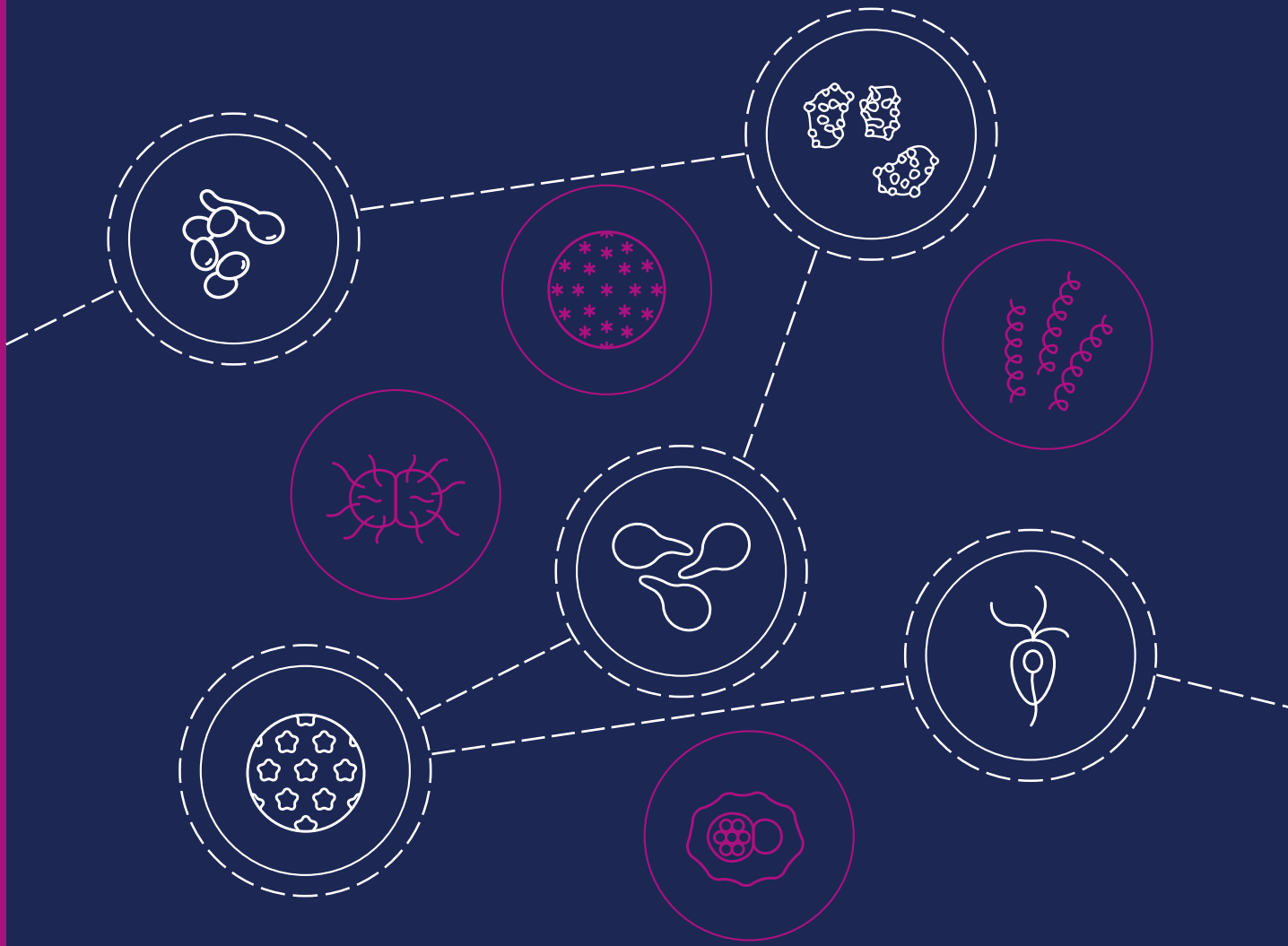
Recommendations for the treatment of *Trichomonas vaginalis*, *Mycoplasma genitalium*, *Candida albicans*, bacterial vaginosis and human papillomavirus (anogenital warts)



World Health Organization

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Abbreviations

AMR	antimicrobial resistance
AWaRe	WHO's Access, Watch and Reserve antibiotic categorization
BV	bacterial vaginosis
ERG	External Review Group
GARDP	Global Antibiotic Research and Development Partnership
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HPV	human papillomavirus
HR	high-risk
IARC	International Agency for Research on Cancer
JoRRP	juvenile onset RRP
LR	low-risk
NAAT	nucleic acid amplification test
PCR	polymerase chain reaction
PICO	population, intervention, comparison, outcome
PrEP	pre-exposure prophylaxis
RRP	recurrent respiratory papillomatosis
SGLT2	sodium-glucose co-transporter-2
STI	sexually transmitted infection
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNFPA	United Nations Population Fund
UNHCR	United Nations High Commissioner for Refugees
UNICEF	United Nations Children’s Fund
VLP	viral-like particle
VVC	vulvovaginal candidiasis

Executive summary

The global burden of sexually transmitted infections (STIs) is high, with over 30 pathogens, including bacteria, viruses and parasites, known to be transmitted through sexual contact. Recent World Health Organization (WHO) estimates for 2020 suggest that there were 374 million new cases of four curable STIs (gonorrhoea, chlamydia, syphilis and trichomoniasis) among people aged 15–49 years, including 156.3 million new cases of trichomoniasis, 128.5 million new cases of chlamydia, 82.4 million new cases of gonorrhoea, and 7.1 million new cases of syphilis, or approximately 1 million new curable STIs every day.[1]

These guidelines focus on the treatment for infections caused by *Trichomonas vaginalis*, *Mycoplasma genitalium* and *Candida albicans,* and treatment for the conditions of bacterial vaginosis and anogenital warts. Trichomoniasis, caused by the protozoan *Trichomonas vaginalis*, is the most common non-viral STI worldwide, is one of the most common causes of abnormal vaginal discharge and can lead to urethritis. *Mycoplasma genitalium* causes urethritis and cervicitis and is a particular concern due to significant antibiotic resistance (particularly to macrolides), which complicates the management and control of this infection as well as other STIs, and increases the risk of persistent infection and transmission. *Candida albicans*, a fungal infection which causes vulvovaginitis candidiasis, and bacterial vaginosis are the other two most common causes of abnormal vaginal discharge, which are not considered to be STIs, despite the potential for transmission between sexual partners. Finally, anogenital warts are prevalent and caused by certain common types of human papillomavirus (HPV), which is a common STI.

WHO has set ambitious targets in the recent *Global health sector strategies for HIV, viral hepatitis and STIs for the period 2022–2030*. To achieve these targets, such as 90% of girls fully vaccinated with the HPV vaccine by 15 years of age, the strategy highlights the importance of making STI prevention, diagnosis and treatment services more easily accessible.

The treatment of STIs is complicated by the rapidly changing antimicrobial susceptibility patterns of various sexually transmitted pathogens to available antibiotics, including *N. gonorrhoeae* and *M. genitalium*, with concerns about the eventual development of untreatable infections with serious sexual and reproductive health consequences. Certain antibiotics, including azithromycin, have been classified as highly susceptible to antimicrobial resistance, such that their use needs to be reserved for certain pathogens, including *M. genitalium*.

The recommendations in these guidelines support the provision of appropriate treatment for *T. vaginalis, M. genitalium, C. albicans,* bacterial vaginosis and anogenital warts, based on the best available evidence. They align with the WHO's Access, Watch and Reserve (AWaRe) antibiotic categorization, promoting accessibility and antibiotic stewardship. These recommendations complement the 2021 WHO publication *Guidelines for the management of symptomatic sexually transmitted infections* and will be included within the forthcoming edition of WHO's consolidated guidelines for the prevention, diagnosis, treatment and care of STIs.

The objectives of these present guidelines are:

- to provide evidence-informed guidance on treating infection with *T. vaginalis, M. genitalium* and *C. albicans*;
- to provide evidence-informed guidance on treatment of bacterial vaginosis and of anogenital warts, which are caused by certain types of HPV; and
- to support countries and national programmes in updating their national guidelines with a view to reaching the 2030 targets of the global health sector strategy on STIs.

1 The most up-to-date STI estimates are always made available at this page of the WHO Global Sexually Transmitted Infections Programme's website: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/stis/strategic-information.

These guidelines are intended for policy-makers, programme managers, health workers and any other public health professionals responsible for planning or implementing STI services, whether they are stand-alone services or integrated with other health services. These guidelines will also be a resource for donor and development agencies, international, nongovernmental, civil society and community-based organizations, and those working with or led by key populations and the communities affected the most by STIs, including HIV.

These guidelines were developed following the methods outlined in the 2014 *WHO handbook for guideline development*. Multiple systematic reviews were conducted to address the guideline objectives. The members of the STI Guideline Development Group reviewed the evidence and made recommendations. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the evidence and formulate the recommendations. The External Review Group reviewed the guidelines prior to submission to the WHO Guidelines Review Committee.

New treatment recommendations

These guidelines provide new treatment recommendations for *Trichomonas vaginalis, Mycoplasma genitalium*, *Candida albicans*, bacterial vaginosis and anogenital warts. The recommendations apply to all adults and adolescents (aged 10–19 years) diagnosed with these infections, whether symptomatic or asymptomatic, including pregnant and breastfeeding women (with some exceptions specified within the recommendations), people living with HIV and key populations (men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers and transgender people).

Table 1. Summary of the recommendations on treatment of *Trichomonas vaginalis* (trichomoniasis infections) (see further detail in section 3.1)

Recommendation	Strength of recommendation and certainty of evidence
Trichomoniasis infections	
For adults and adolescents (including pregnant women) with *Trichomonas vaginalis* (trichomoniasis) infections, **WHO suggests**: • metronidazole 400 mg or 500 mg orally twice daily for 7 days. Where adherence to multiple doses is a serious concern, **WHO suggests** one of the following options: • metronidazole 2 g orally as a single dose; or • tinidazole 2 g orally as a single dose (except during pregnancy). *Remarks:* • Secnidazole 2 g orally as a single dose (except during pregnancy) or ornidazole 1.5 g orally as a single dose (except during pregnancy) could be used as substitutes if metronidazole or tinidazole are not available.	**Conditional recommendation,** moderate certainty in evidence of effects (*new 2023)*

Table 2. Summary of the recommendations on treatment of *Mycoplasma genitalium* infections (see further detail in section 3.2)

Recommendations	Strength of recommendation and certainty of evidence
***Mycoplasma genitalium* infections**	
WHO recommends that the choice of therapy for *Mycoplasma genitalium* infections should be informed by an individual resistance profile, surveillance data or suspected resistance based on typical prescribing practices (antibiotic consumption) for other infections.	**Good practice statement** *(new 2023)*
In settings with high or suspected high resistance to macrolides (e.g. where azithromycin is frequently used) or when testing shows *Mycoplasma genitalium* resistant to macrolides, **WHO suggests**: • doxycycline 100 mg orally twice daily for 7 days to reduce bacterial load, followed by moxifloxacin 400 mg orally once daily for 7 days. In settings with low or suspected low resistance to macrolides or when testing shows *Mycoplasma genitalium* susceptible to macrolides, **WHO suggests**: • doxycycline 100 mg orally twice daily for 7 days to reduce bacterial load, followed by azithromycin 1 g orally once for 1 day (initial dose) then 500 mg once daily for 3 days. If azithromycin or moxifloxacin are not available, or there is confirmed or suspected high resistance to both, the **WHO suggests** one of the following options: • minocycline 100 mg orally twice daily for 14 days; • sitafloxacin 200 mg orally once daily for 7 days; or • pristinamycin 1 g orally four times a day for 10 days. *Remarks:* • If treatment for suspected chlamydial infection (doxycycline 100 mg orally twice daily for 7 days) was provided, retreatment with doxycycline to reduce bacterial load prior to use of moxifloxacin or azithromycin is not required. • When individual resistance profiles or surveillance data are unavailable, the likelihood of resistance may be based on typical prescribing practices (antibiotic consumption); for example, resistance to macrolides such as azithromycin is more likely in areas where azithromycin is typically prescribed for treatment of infections, or more likely in certain subpopulations such as men who have sex with men. • The use of doxycycline, moxifloxacin, minocycline and sitafloxacin are contraindicated during pregnancy and breastfeeding; therefore, only use pristinamycin.	**Conditional recommendation**, low certainty in evidence of effects *(new 2023)*

Table 3. Summary of the recommendations on treatment of *Candida albicans* (candidiasis infections) (see further detail in section 3.3)

Recommendations	Strength of recommendation and certainty of evidence
Candidiasis infections (vulvovaginal candidiasis)	
For adults and adolescents with *Candida albicans* (candidiasis) infection, **WHO suggests** one of the following options: • fluconazole 150–200 mg orally as a single dose; • clotrimazole 500 mg intravaginally as a single dose, or 200 mg intravaginally once daily for 3 days, or 10% cream intravaginally once; • miconazole 1200 mg intravaginally as a single dose or 400 mg intravaginally once daily for 7 days; • econazole 150 mg intravaginally as a single dose; or • nystatin 100 000 units intravaginally twice daily for 15 days. For pregnant women, **WHO suggests** one of the following options: • clotrimazole 100 mg intravaginally once daily for 7 days or 1% cream intravaginally once daily for 7 days; or • nystatin 100 000 units intravaginally twice daily for 15 days. *Remarks:* • The choice of treatment may depend on preferences for intravaginal (which may also reduce vulval itching and soreness) or oral administration, and the cost in different settings. • If an individual does not respond to treatment, refer to a specialist for further assessment and management.	**Conditional recommendation**, low certainty in evidence of effects *(new 2023)*

Table 4. Summary of the recommendations on treatment of bacterial vaginosis (see further detail in section 3.4)

Recommendations	Strength of recommendation and certainty of evidence
Bacterial vaginosis (vaginal infection)	
Recommendation For adults and adolescents (including pregnant women) with bacterial vaginosis, **WHO suggests**: • metronidazole 400 mg or 500 mg orally twice daily for 7 days. If oral metronidazole is not available, adherence to multiple doses is a serious concern, or if vaginal creams are preferred, **WHO suggests** one of the following options: • metronidazole 0.75% gel intravaginally for 7 days; • tinidazole 2 g orally as a single dose (except during pregnancy); • clindamycin 300 mg twice daily for 7 days; • clindamycin 2% gel (5 g) intravaginally once daily for 7 days; or • secnidazole 2 g orally as a single dose.	**Conditional recommendation**, moderate certainty in evidence of effects for metronidazole, low certainty in evidence of effects for clindamycin and secnidazole, very low certainty in evidence of effects for tinidazole *(new 2023)*

Table 5. Treatment of anogenital warts caused by human papillomavirus (HPV) (see further detail in section 3.5)

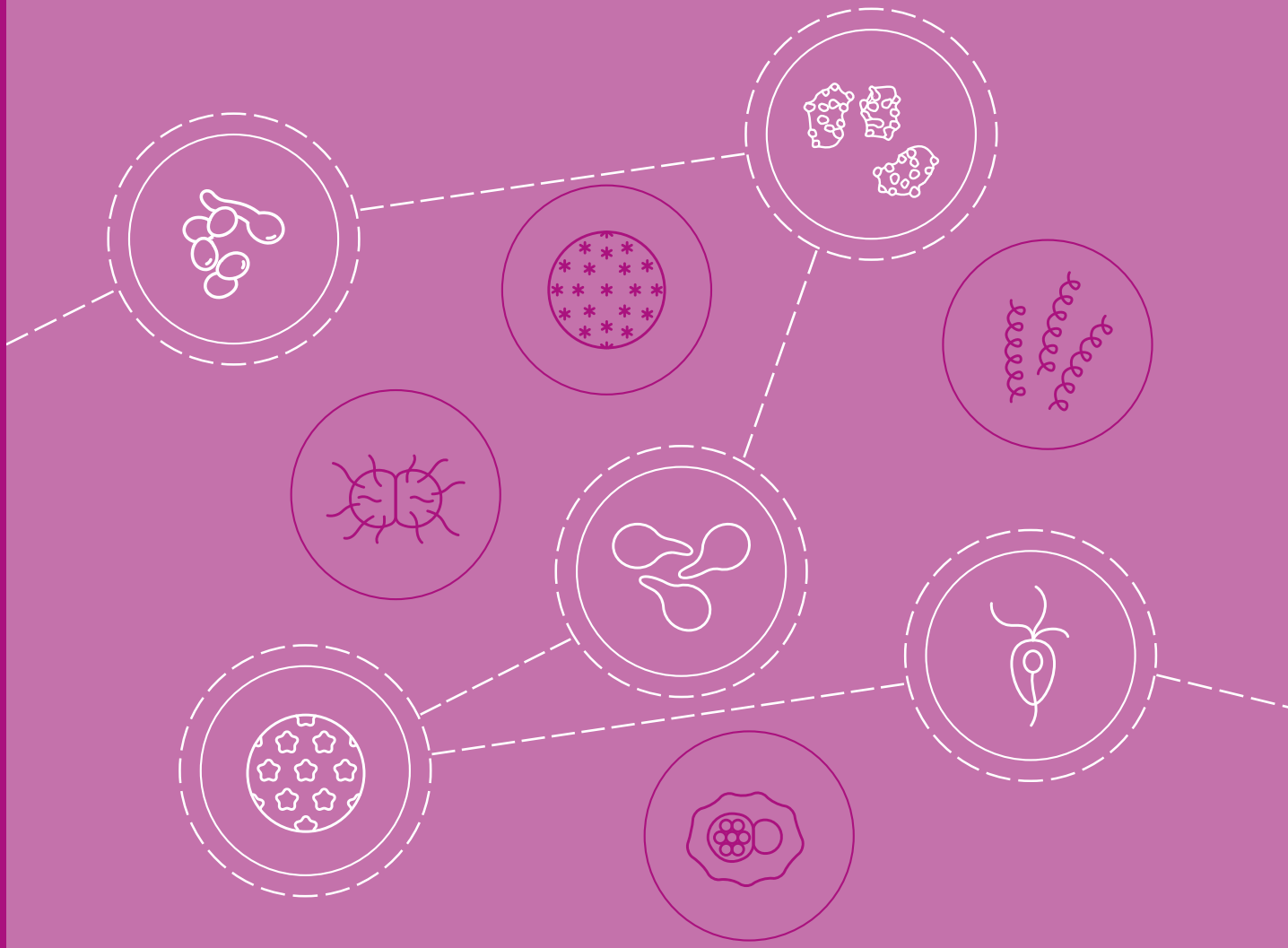
Recommendations	Strength of recommendation and certainty of evidence
Uncomplicated external anogenital warts caused by HPV	
Recommendation For adults and adolescents with uncomplicated external anogenital warts, **WHO suggests** one of the following options, which are self-applied: • podophyllotoxin 0.5% solution or 0.5–1.5% cream twice daily for 3 days, followed by 4 days of no treatment (this cycle can be repeated up to four times) (except during pregnancy); or • imiquimod cream 3.75% or 5% applied overnight three times a week for up to 16 weeks (except during pregnancy). When treatment has failed, depending on available resources, **WHO suggests** the following options: • electrosurgery/electrocautery; • CO_2 laser therapy; • trichloroacetic acid 80% (except during pregnancy); or • cryotherapy. *Remarks:* • The choice of treatment should be guided by factors such as the thickness and size of the anogenital warts, as well as anatomical location. • Response to treatment can vary, therefore close monitoring is essential. Additionally, while podophyllin resin (10–25%, applied by a health worker and washed off after 2–4 hours, and repeated once weekly, if necessary) is less effective than other treatments, it may be an alternative when other options are not available; however, close monitoring is essential. • Podophyllotoxin solution or cream, imiquimod cream, trichloroacetic acid and podophyllin resin are contraindicated during pregnancy. If necessary, cryotherapy is the safest option during pregnancy.	**Conditional recommendation,** moderate certainty in evidence of effects *(new 2023)*

Box 1. The WHO Access, Watch, Reserve (AWaRe) categorization of the antibiotics recommended in these guidelines

Access group	Watch group	Reserve group
Clindamycin	Azithromycin	–
Doxycycline	Minocycline	
Metronidazole	Moxifloxacin	
Ornidazole	Pristinamycin	
Secnidazole	Sitafloxacin	
Tinidazole		

Source: The WHO AWaRe (access, watch, reserve) antibiotic book. Geneva: World Health Organization; 2022 (*https*://apps.who.int/iris/handle/10665/365237).

1. Introduction



1. Introduction

1.1 Epidemiology, burden and global targets

The global burden of sexually transmitted infections (STIs) is high, with over 30 pathogens, including bacteria, viruses and parasites, known to be transmitted through sexual contact. Recent World Health Organization (WHO) estimates for 2020 suggest that there were 374 million new cases of four curable STIs (gonorrhoea, chlamydia, syphilis and trichomoniasis) among people aged 15–49 years, including 156.3 million new cases of trichomoniasis, 128.5 million new cases of chlamydia, 82.4 million new cases of gonorrhoea, and 7.1 million new cases of syphilis *(1)*, or approximately 1 million new curable STIs every day.

STIs are a major public health problem worldwide, reducing quality of life and causing serious morbidity and mortality. STIs directly affect reproductive and child health through infertility, cancers and pregnancy complications, and they have an indirect impact on health more broadly through their role in facilitating sexual transmission of HIV.

Population groups that are especially vulnerable to STIs include sex workers and their clients, gay men and other men who have sex with men, transgender people, people who inject drugs, people in prisons and other closed settings, young people, mobile populations and people affected by conflict and civil unrest *(1)*.

To end STIs as public health concerns by 2030, WHO has set ambitious targets within the recent *Global health sector strategies on HIV, viral hepatitis and STIs for the period 2022–2030*, including a 90% reduction in both gonorrhoea and syphilis infections and 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by 15 years of age by 2030 *(2)*. To achieve these targets, the strategy highlights the importance of making STI prevention, diagnosis and treatment services more easily accessible.

These guidelines focus on the treatment for infections caused by *Trichomonas vaginalis*, *Mycoplasma genitalium* and *Candida albicans*, and treatment for the conditions of bacterial vaginosis and anogenital warts (caused by certain types of HPV).

Trichomonas vaginalis is a flagellated protozoan parasite occurring in the human urogenital tract, and it is the etiological agent of trichomoniasis, the most common worldwide non-viral STI. *T. vaginalis* is transmitted during sexual intercourse, and humans are the only known host. In women, infection with *T. vaginalis* results in vaginitis and potentially also cervicitis and pelvic inflammatory disease. Additionally, *T. vaginalis* in pregnancy is associated with an increased risk of preterm birth, preterm premature rupture of membranes and small-for-gestational-age infants. Furthermore, *T. vaginalis* infection increases the risk of HIV acquisition *(3)*, and increased shedding of HIV has also been documented in seminal fluid of men with *T. vaginalis* infection who are also living with HIV *(4)*.

Mycoplasmas are members of the Mollicutes class of bacteria, and are the smallest known free-living micro-organisms – intermediate in size between bacteria and viruses *(5)*. The lack of a rigid cell wall makes these bacteria resistant to β-lactam antibiotics, such as penicillins, cephalosporins and carbapenems, which act on the bacterial cell wall. *Mycoplasma genitalium* is commonly found in the human urogenital tract– as are *Mycoplasma hominis* and the two ureaplasma species (*Ureaplasma urealyticum* and *Ureaplasma parvum) (6)*. In population-based studies, *M. genitalium* is found in up to 10% of sexually active men and women, and the prevalence is as high as 20% in key populations, such as men who have sex with men and sex workers *(7-9)*.

Vulvovaginal candidiasis (VVC) is one of the most common causes of vulvovaginitis, affecting approximately 70–75% of women at some point or multiple times during their lifetime *(10)*. In about 90% of cases, VVC is caused by the fungus *Candida albicans,* while non-*albicans* species account for the remaining 10% *(11)*. Candidiasis is often of endogenous origin and generally not considered to be an STI, despite the potential transmission of *Candida* species (spp.) between sexual partners.

Bacterial vaginosis (BV) arises from an imbalance within the vaginal microbiome and, globally, it is the most common cause of vaginal discharge. The prevalence of BV varies by world region, with recent estimates ranging from 23% to 29% among women of reproductive age *(12)*. BV is associated with an increased risk of gynaecological and obstetric sequelae, including preterm delivery and spontaneous abortion, as well as an increased risk of acquisition and transmission of HIV and other STIs *(13-15)*. Although the exact causative agents remain uncertain, BV is often associated with an overgrowth of specific pathogens, such as *Gardnerella* spp. There is an association between BV and having new or multiple male sexual partners, having any female sexual partners, and lack of condom use, indicating that sexual transmission is possible, but the condition is not regarded as an STI *(17, 18)*.

Infection with certain types of HPV causes anogenital warts, also known as condylomata acuminata, which are benign growths characterized by exophytic, papular or flat lesions in the anogenital area. HPV types 6 and 11 are responsible for approximately 90% of anogenital warts *(19, 20)*. While these lesions typically do not pose problems due to their size, the primary concerns are cosmetic, and frequent recurrence of the warts often necessitates repetitive treatment procedures. In countries where HPV vaccination has been implemented using a vaccine that covers HPV6 and HPV11, the incidence of genital warts has significantly decreased *(21-23)*.

1.2 Rationale for the new treatment recommendations

To reduce STIs and prevent complications, the provision of high-quality prevention, diagnosis and treatment services is essential. This requires the development of evidence-based guidelines on treatment and comprehensive case management, including screening, diagnosis, treatment and care. Correct and effective treatment of STIs, ideally given and taken on the same day, at the first contact between patients and health workers, is an important public health measure in the control of STIs since it endeavours to break the chain of transmission of the infection without delay.

Effective, accessible and affordable treatment is crucial for managing infections caused by *T. vaginalis, M. genitalium* and *C. albicans*, as well as management of bacterial vaginosis and anogenital warts. Relevant treatment choices for these infections were last updated in WHO's 2003 publication, *Guidelines for the management of sexually transmitted infections (24)*, and were also described in the recent 2021 guidelines for the management of symptomatic STIs *(25)*. There is a critical need to review and update these guidelines based on evidence obtained from more recent surveillance and research, reflecting the emergence of new diagnostic and therapeutic technologies and addressing the growing challenge of antimicrobial resistance.

M. genitalium is the most concerning of these pathogens due to its significant antibiotic resistance, particularly to macrolides and also fluoroquinolones. This resistance complicates the management and control of this infection as well as other STIs (e.g. *Chlamydia trachomatis*), and increases the risk of persistent infection and transmission. Additionally, it is strongly associated with serious reproductive health issues such as non-gonococcal urethritis, cervicitis, pelvic inflammatory disease and infertility. Bacterial vaginosis, *T. vaginalis* and *C. albicans* are significant due to being the most common causes of vaginal discharge. Finally, anogenital warts are prevalent and attributed to certain common types of HPV, which is a common STI. Developing evidence-based treatment recommendations for these infections and their associated conditions is essential.

1.3 Objectives

The objectives of these guidelines are:

- to provide evidence-informed guidance on treating infection with *T. vaginalis, M. genitalium* and *C. albicans*;
- to provide evidence-informed guidance on treatment of bacterial vaginosis, and of anogenital warts, which are caused by certain types of HPV; and
- to support countries and national programmes in updating their national guidelines with a view to reaching the 2030 targets of the global health sector strategy on STIs.

1.4 Target audience

These guidelines are intended for STI prevention and control programme managers at the national level and for frontline health workers in primary, secondary and tertiary health facilities involved in treating and managing people with STIs. The recommendations and guidance are also important for health workers, including lay providers and community health workers, responsible for offering and providing STI services outside of formal health facilities. These guidelines will be relevant for implementers of STI and HIV services (including providers of pre-exposure prophylaxis [PrEP] for HIV), sexual and reproductive health (SRH) services and maternal and child health (MCH) services. They will also be relevant to nongovernmental and community-based organizations, including those working with or led by key populations and the communities affected the most by STIs, including HIV. These guidelines can be used to support the planning, implementation, and monitoring and evaluation of such services, and can also be used as an advocacy tool in seeking the financial and human resources required to deliver adequate, acceptable and equitable STI services and care for everyone who needs them.

The recommendations are also important for persons with or at greater risk of acquiring STIs, including HIV, such as members of key populations (men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers and transgender people), people who use PrEP for HIV, and other vulnerable population groups, such as pregnant women, adolescents in high HIV/STI burden settings, Indigenous populations, refugees and people in humanitarian settings.

1.5 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations.

- These guidelines will contribute to the achievement of key global goals, including the Sustainable Development Goals, and relevant national-level goals and targets.
- The guidelines are based on a public health approach to scaling up the provision of services and care for people with STIs, with the aim of reaching everyone, including vulnerable populations and key populations, with relevant interventions, including, for example, targeted STI screening and antimicrobial resistance monitoring (in accordance with WHO guidance).
- The adaptation and implementation of the guidelines should be accompanied by efforts to promote and protect the human rights of people receiving STI services, including preventing stigma and discrimination, promoting gender equity, and ensuring that the use of services is always voluntary and never mandatory or coerced.
- The implementation of the recommendations in these guidelines should be informed by the local context, including the epidemiology of STIs, the availability of resources and commodities for diagnosis and treatment of STIs, the capacity of the health system and anticipated cost–effectiveness of the various interventions.
- The adaptability built into these guidelines is intended to promote accessibility, acceptability and

effectiveness of STI services through public and private health-care systems, including at community health centres and other primary care facilities providing services for STIs, such as clinics for maternal and child health, antenatal care, family planning and other sexual and reproductive health services. As such, these guidelines should form part of a broader package of service-delivery approaches, including linkage to prevention, testing, treatment and care services.

- The guidelines provide direction for acceptable and effective STI services for populations identified as being especially vulnerable to or at higher risk of STIs, including those living with HIV infection, and aim to improve health outcomes at the population level.
- The guidelines also followed the guiding principles of the WHO Model List of Essential Medicines (known as the Essential Medicines List or EML), including to prevent the emergence and spread of antibiotic resistance, as well as the principles of parsimony, feasibility and alignment with the WHO List of Critically Important Antimicrobials for Human Medicine, including the WHO Access, Watch and Reserve (AWaRe) antibiotic categorization (Table 1.1).

Table 1.1 WHO Access, Watch and Reserve (AWaRe) antibiotic categorization

Access group	Watch group	Reserve group
• first or second choice antibiotics • offer the best therapeutic value, while minimizing the potential for resistance	• first or second choice antibiotics • only indicated for specific, limited number of infective syndromes • more prone to be a target of antibiotic resistance and thus prioritized as targets of stewardship programmes and monitoring	• "last resort" • highly selected patients (life-threatening infections due to multidrug-resistant bacteria) • closely monitored and prioritized as targets of stewardship programmes to ensure their continued effectiveness

Source: adapted from AWaRe – the WHO antibiotic categorization website *(26)*.

1.6 Structure of the guidelines

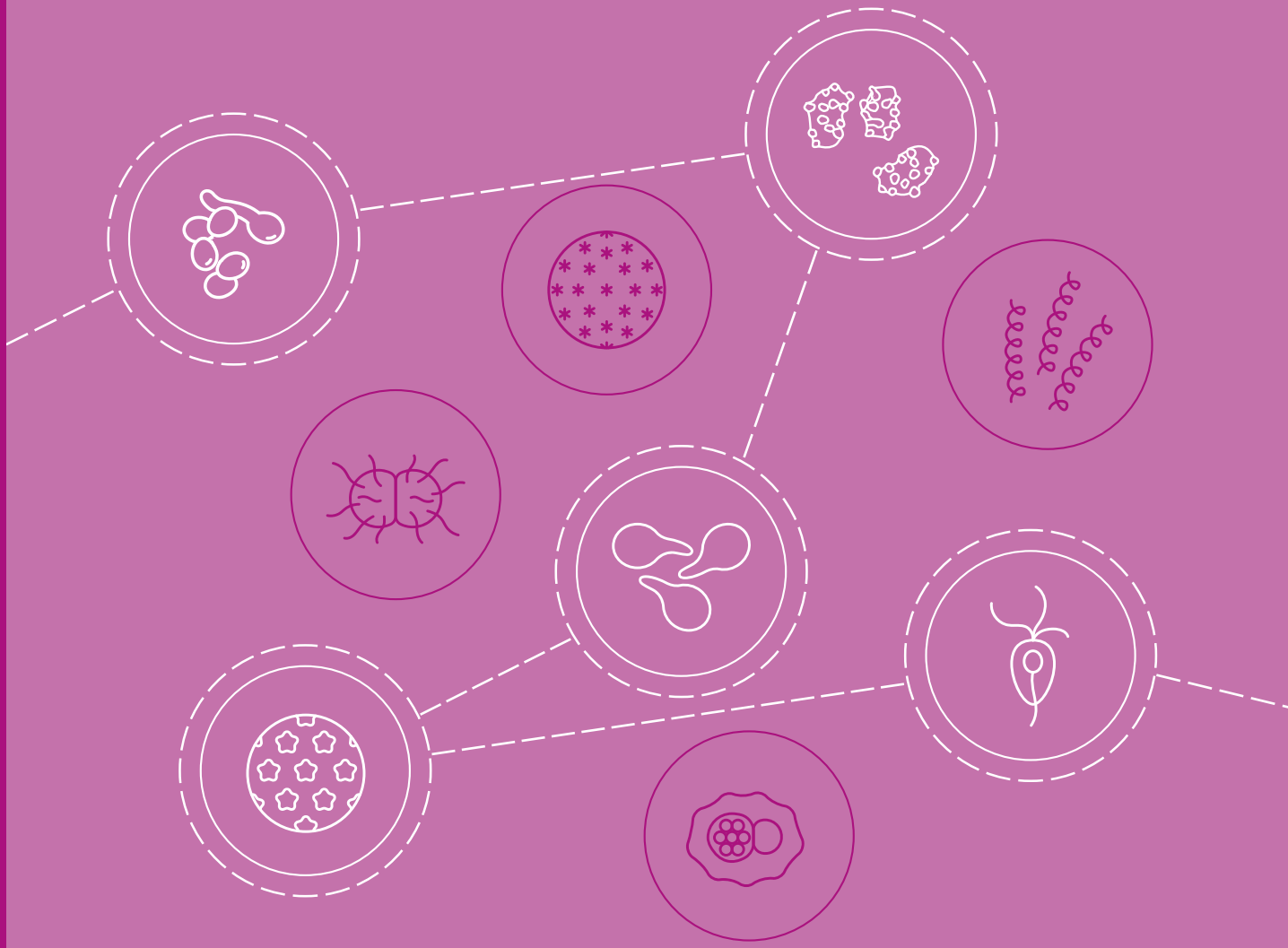
Following on from the introduction presented here, the next chapter presents the methods for the development of these guidelines, and Chapter 3 provides the evidence-informed treatment recommendations, which are intended to become subsections of the forthcoming edition of consolidated guidelines for the prevention, diagnosis, treatment and care of STIs.

The treatment recommendations presented are based on the most recent evidence and are for the most important conditions caused by *T. vaginalis* (section 3.1), *M. genitalium* (section 3.2) and *C. albicans* (section 3.3), and for bacterial vaginosis (BV) (section 3.4) and anogenital warts (section 3.5).

While these guidelines and recommendations provide direction for countries as they develop and update their national treatment guidelines and recommendations, countries should also consider the local pattern of antimicrobial resistance as well as health service capacity and resources.

Chapter 3 continues with discussion of implementation considerations, and notes of research needs relating to treatment for all five conditions. Finally, Chapter 4 describes WHO's plans for guideline dissemination and updating.

2. Methods



2. Methods

2.1 Overview

These guidelines were developed in accordance with procedures in the *WHO handbook for guideline development (27)*.

The Guideline Development Group (GDG) identified key questions and systematic reviews were conducted or updated to develop evidence summaries for each question. Evidence was assessed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach *(27)*.

The GDG developed the recommendations by considering the certainty of evidence for the effects, the balance between desirable and undesirable effects, values and preferences, acceptability, feasibility and resource needs across a variety of settings. Information on each of these aspects was included in evidence-to-decision tables, which were shared in advance with the GDG members for their feedback and used in meetings to support the judgements of the GDG in making WHO recommendations. Consistent with previous WHO guidelines, these guidelines are based on a public health approach.

The following sections provide further details on each aspect of the guideline development process.

2.2 Roles of groups involved in developing the guidelines

Five main groups were formed to guide and implement the guideline development process, coordinated by the WHO Secretariat. Each group played a specific role, as described below. Annex 1 lists the members of these groups and other contributors and their affiliations.

- **WHO Steering Committee.** This group, which is responsible for the overall coordination of the guideline development process, was led by the Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes (HHS). Participants included WHO staff members from the HHS Department and from the Department of Sexual and Reproductive Health and Research, the Department of Surveillance, Prevention and Control and the Department of Access to Medicines and Health Products. The Steering Committee also included WHO technical staff members from every WHO region.
- **Guideline Development Group (GDG).** This group comprised non-United Nations/non-WHO experts, health professionals and representatives of groups most affected by the recommendations in the guidelines. The 34 GDG members formulated the WHO recommendations and good practice statements, including any implementation and service-delivery considerations. They also reviewed and approved the final content of these guidelines. The GDG comprised 34 members, with a balanced representation of geographical regions, gender and backgrounds, including academia and research, programme implementation and policy and community organizations and networks. The group members were selected in coordination with the WHO Steering Committee and WHO country and regional offices. The Steering Committee reviewed curricula vitae, declarations of interest and confidentiality agreements. The proposed membership list was posted for public review and comment, and then finalized.
- **External Review Group (ERG).** The members were responsible for peer reviewing these guidelines. This group was selected in consultation with the WHO Steering Committee to assure geographical and gender balance. It comprised 15 peer reviewers from academia, policy and research institutions, programme implementation and community organizations, and representatives of networks of key and vulnerable populations.

- **External evidence reviewers, led by a methodologist**. With oversight by the guideline methodologist and with input from members of the WHO Steering Committee and GDG, an independent team of external experts conducted systematic reviews of the effects of interventions based on the selected key questions for the guidelines. In addition, evidence on values and preferences, feasibility and cost–effectiveness was compiled and summarized for each question.
- **External partners and observers**. Representatives of the Global Antibiotic Research and Development Partnership (GARDP), Unitaid, United Nations Population Fund (UNFPA) and the United States Centers for Disease Control and Prevention (CDC) attended the GDG meeting as observers. These organizations have a long history of collaboration with WHO's HHS Department.

All members of the GDG, ERG and other non-WHO staff participating in the meetings and/or other guideline development processes submitted declaration of interests forms and confidentiality statements to WHO. All of the declarations were reviewed by WHO and no conflicts of interest sufficient to preclude any GDG member from participating fully in the development of the guidelines were found. Annex 2 provides a full compilation and a summary of the declarations of interests.

2.3 Scope and questions

In December 2013, the first GDG meeting was held to identify and agree on the key questions of potential importance for these guidelines, including specification of the population, intervention, comparator(s) and outcome(s) (PICO questions). Following this meeting, a survey of GDG members was conducted to set priorities among the selected questions and outcomes of interest, based on clinical relevance and importance.

PICO questions were prioritized if they pertained to adults and other special populations: adolescents, pregnant women, people living with HIV and populations disproportionately affected by STIs, including key populations.

Recommendations for managing infections caused by *T. vaginalis*, *M. genitalium* and *C. albicans*, and for the management of bacterial vaginosis and of anogenital warts, which are caused by certain types of human papillomavirus (HPV), were prioritized among other prioritized topics. The PICO components of all PICO questions addressed in these guidelines are provided in Table 2.1.

2.4 Review of the evidence

Comprehensive searches were conducted to gather existing systematic reviews, and to gather randomized and non-randomized studies addressing the benefits and harms, the values and preferences of service users, resource use, acceptability, equity and feasibility of the interventions. The searches were performed from the date of the last search conducted for each previously published systematic review, or since inception if no review, and up to May 2022 (for Web Annexes A and D), September 2022 (for Web Annex E) or August 2023 (for Web Annexes B and C), depending on the topic and the available evidence. Detailed methods of the systematic reviews are available for *T. vaginalis* (Web Annex A), *M. genitalium* (Web Annex B), *C. albicans* (Web Annex C), bacterial vaginosis (Web Annex D) and anogenital warts (Web Annex E).

Evidence for the effects of interventions was synthesized statistically when possible, and then assessed using the GRADE approach based on the domains for risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose response and opposing confounding *(27)*.

Certainty of the evidence for effects was assigned to one of the four grades of evidence defined by the GRADE Working Group:

Table 2.1 Population, intervention, comparator and outcome (PICO) components of all PICO questions prioritized for these guidelines

	Population	Intervention or Comparator(s)	Critical outcomes
New treatment recommendations			
Trichomonas vaginalis	Adults and adolescents (including pregnant women)	Any dose, single- or multi-day regimen of metronidazole, tinidazole and secnidazole	Microbiological cure Adverse effects (including maternal and fetal effects) Transmission to partners Compliance HIV transmission and acquisition Quality of life
Mycoplasma genitalium		Any dose of azithromycin, moxifloxacin, doxycycline, josamycin, pristinamycin; or treatment guided by antimicrobial resistance (AMR) susceptibility testing	
Candida albicans		Fluconazole 150 mg single oral dose compared with clotrimazole, econazole, fenticonazole, itraconazole, miconazole or nystatin at different doses or by different routes of administration	
Bacterial vaginosis		Any dose, single or multi-day regimen of metronidazole, clindamycin, tinidazole and secnidazole	
Anogenital warts, caused by human papillomavirus (HPV)		Different doses or different routes of administration for podophyllotoxin solution or cream, imiquimod cream, sinecatechins (polyphenon E), trichloroacetic acid 80%, podophyllin, thermocoagulator and electrosurgery (i.e. electrocautery, cryotherapy or CO2 laser therapy)	

- High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Evidence summary of findings tables (also called evidence profiles) and the evidence-to-decision frameworks (i.e. tables to facilitate decision-making for the updated recommendations) were drafted in advance of the GDG meeting using the GRADEpro software (see the first section of Web Annexes A–E for the evidence-to-decision frameworks for each recommendation).

2.5 Making recommendations

A virtual GDG meeting was organized in May 2023 to support the development of the recommendations. The GDG reviewed the tables in the evidence-to-decision frameworks and evidence profiles and made judgements about the effects of treatment. Based on the discussions, the GDG made decisions on whether to make strong or conditional recommendations (see descriptions below) for or against an intervention. The GDG members

arrived at agreement by consensus and so there was no need for voting. The recommendations and evidence-to-decision frameworks were finalized electronically via email and presented during a follow-up GDG meeting in December 2023.

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. The strength of the recommendations reflects the degree of confidence of the GDG that the desirable consequences (e.g. beneficial health outcomes) of the recommendations outweigh the undesirable consequences (e.g. adverse effects) and takes into account other criteria, such as resources, acceptability, equity and feasibility. According to this assessment, the strength of recommendations is graded into two categories:

1. A strong recommendation is one for which the GDG was confident that the desirable consequences of adhering to the recommendation outweigh the undesirable consequences.
2. A conditional recommendation is one for which the GDG concluded that the desirable consequences of adhering to the recommendation probably outweigh the undesirable consequences but was not confident about these trade-offs *(27)*.

Table 2.2 explains the implications of the differing strengths of recommendations for patients, clinicians and policy-makers.

Good practice statements were made when the GDG agreed that it was necessary to provide guidance but a review of the literature was not warranted because the balance of desirable and undesirable consequences of an intervention was unequivocal and no other criteria would lead to a different assessment. Remarks were added to the recommendations or good practice statements to explain the recommendation and/or describe any relevant conditions. Implementation considerations were added to provide further information for the possible application of the recommendation.

WHO then drafted the full guidelines and circulated them electronically to the WHO Steering Committee, the GDG and the ERG for comments and feedback in February 2024. All the input was then considered and addressed as appropriate in the revised draft, followed by submission to the WHO Guidelines Review Committee for approval. Final editing prior to publication did not affect the recommendations that had been formulated.

Table 2.2 Implications of differing strengths of GRADE recommendations

Implications	Strong recommendation The WHO recommends…	Conditional recommendation The WHO suggests…
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	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. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	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 the involvement of various stakeholders.

GRADE: Grading of Recommendations Assessment, Development and Evaluation

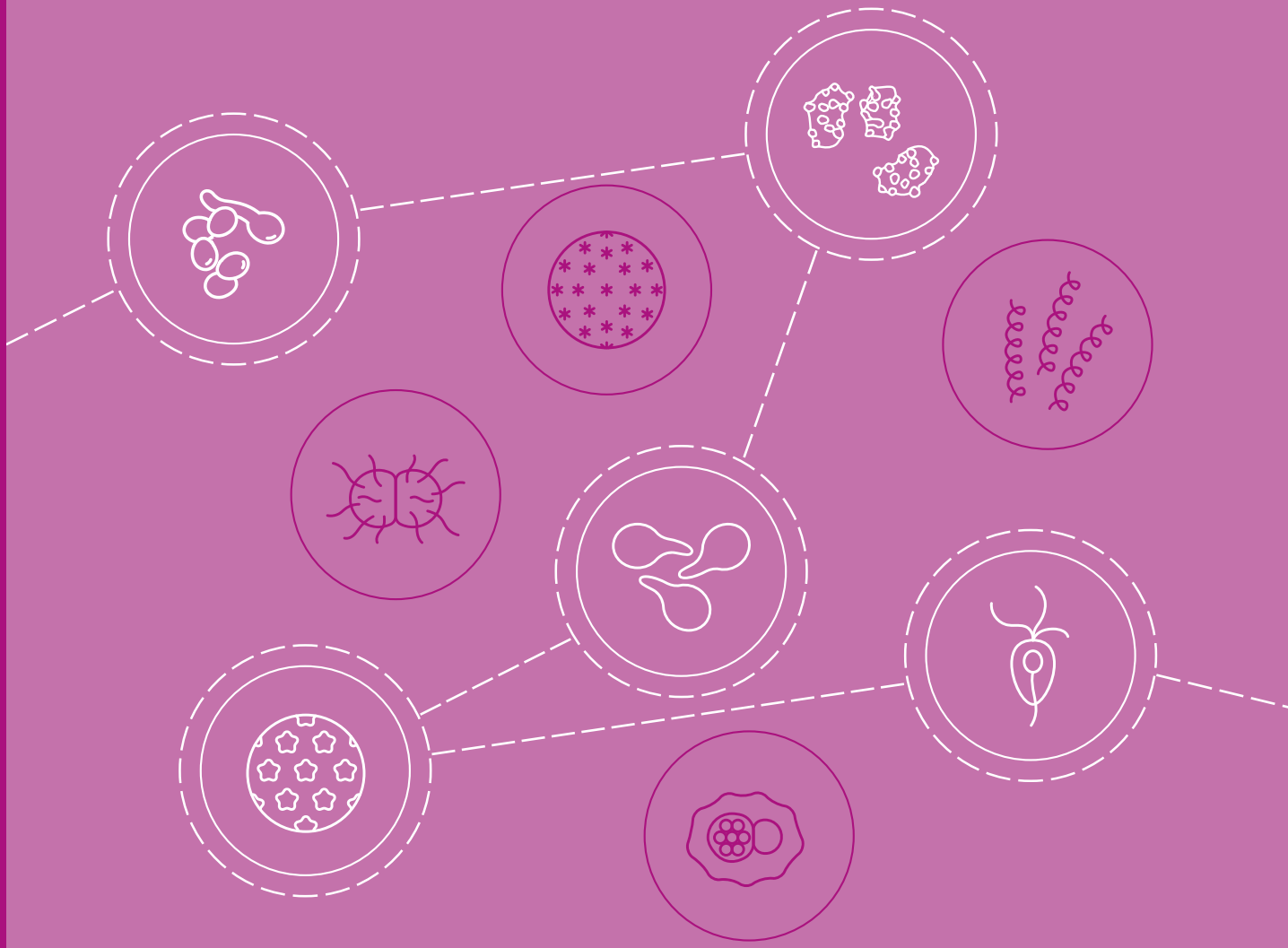
Source: WHO, 2014 *(27)*.

2.6 Managing conflicts of interest

Managing conflicts of interest was a key priority throughout the process of developing the guidelines. WHO guidelines for declaration of interests for WHO experts were implemented. Declarations of interest statements were obtained from all members of the GDG and the ERG before they assumed their role. At the beginning of the GDG meetings, including subgroup meetings, the members disclosed their declared interests. The declarations of interest statements are summarized in a table as suggested by the WHO Guidelines Review Committee (Annex 2).

Eleven members of the STI GDG members declared interests. All were deemed to have full participation as conflict was not related to treatment for these infections or related conditions.

3. New treatment recommendations



3. New treatment recommendations

This section provides treatment recommendations for infections caused by *Trichomonas vaginalis, Mycoplasma genitalium* and *Candida albicans*, whether symptomatic or asymptomatic, and treatment recommendations for bacterial vaginosis (BV) and anogenital warts, which are caused by certain types of human papillomavirus (HPV). The recommendations apply to all adults and adolescents (aged 10–19 years), including during pregnancy and breastfeeding (with some exceptions specified), and including people living with HIV and key populations, which are defined groups that, due to specific higher risk behaviours, are at increased risk of HIV irrespective of the epidemic type or local context. Key populations include men who have sex with men, people who inject drugs, people in prisons and other closed settings, sex workers and transgender people.

3.1 *Trichomonas vaginalis* (trichomoniasis)

3.1.1 Description

T. vaginalis is a motile, ovoid, pear-shaped, flagellated protozoan. In size, *T. vaginalis* averages 26 µm (21–32 µm) in total length, 9.5 µm (7.4–11.4 µm) in body length and 6.8 µm (5.3–7.7 µm) in body width, with a range of variation as indicated, depending on the prevailing physicochemical conditions, such as pH, temperature and ionic strength *(28)*. It is sexually transmitted and it specifically infects the vagina, the urethra and paraurethral glands in women and the urethra and the subpreputial sac in men.

Epidemiology

In 2020, WHO estimated that 156.3 million new cases of *T. vaginalis* occurred globally among adults aged 15–49 years. Prevalence of *T. vaginalis* is highest in Africa (12.0% and 1.3% for women and men, respectively), while the lowest prevalence is found in Europe (1.7% and 0.2%), in women and men, respectively *(1)*.

T. vaginalis infection, whether symptomatic or not, should be considered pathogenic in both women and men. The infection may be asymptomatic in at least 50% of women and in up to 70–80% of men *(29)*. *T. vaginalis* may cause an abnormal vaginal discharge (trichomoniasis) in women, and clearance is unlikely without treatment. *T. vaginalis* has serious negative reproductive health outcomes in women; adverse birth outcomes, including low birth weight, preterm delivery and preterm premature rupture of membranes have been documented. Infection with *T. vaginalis* can result in pelvic inflammatory disease and an increased risk of acquisition of HIV infection *(3, 30)*. There are also reports showing an association between *T. vaginalis* and cervical carcinogenesis in sexually active women. Furthermore, the associated risk increases in women co-infected with *T. vaginalis* and HPV. Consequently, more data and follow-up of women and men with *T. vaginalis* infections are needed to establish more concretely whether *T. vaginalis* is a risk factor for cervical cancer *(31-33)*.

Up to 72% of men who are sexual partners of women with *T. vaginalis* will have urethral colonization, but they may clear the organism without treatment, or remain as a reservoir for infection with *T. vaginalis (4, 34, 35)*. The degree to which men are impacted by *T. vaginalis* infection is becoming better appreciated with the use of more sensitive diagnostic tests, such as molecular tests. Some studies have determined that the prevalence of *T. vaginalis* in men ranges from 4% in asymptomatic men to 20% in men with symptoms of urethritis *(36, 37)*. In addition to non-gonococcal urethritis, *T. vaginalis* can also cause prostatitis and reduced fertility (impaired sperm function) in men *(4)*. *T. vaginalis* infection has also been associated with increased HIV shedding in seminal fluid, which may increase the risk of transmission of HIV to sexual partners *(38, 39)*.

While uncommon, perinatal transmission of *T. vaginalis* can lead to vaginal and respiratory infections in newborn babies *(40, 41)*. Non-sexual transmission of *T. vaginalis* is rare, but it has been reported in young girls who have self-reported no sexual activity. In the different settings of such reports, non-sexual transmission of *T. vaginalis* was associated with contaminated moist wash clothes, toilet seats, specula, shared bathing water and sharing of bath implements *(42-44)*. However, detection of *T. vaginalis* in young girls should be carefully assessed to exclude sexual abuse.

Clinical features

About 50–85% of women with *T. vaginalis* infection may be asymptomatic *(45, 46)*. Among these asymptomatic women, 30–50% will develop symptoms within the subsequent six months *(47)*. For symptomatic women, the primary concern is usually an abnormal vaginal discharge, which may be described as yellow and may appear purulent. Half of symptomatic women also report vulval itching. Vulval erythema and oedema may be noted on examination.

On speculum examination, a vaginal discharge, classically described as yellow or greenish, sometimes with a frothy appearance, may be seen. There may be vaginitis as shown by erythema of the vaginal mucosa. The cervix may have punctate haemorrhages, known as the "strawberry cervix". The visualization of a "strawberry cervix", albeit uncommon, is highly indicative of *T. vaginalis* infection.

Over 50% of men with *T. vaginalis* infection are asymptomatic, likely due to a low parasite burden. Symptomatic men complain of a clear or mucopurulent urethral discharge and dysuria. Studies estimate the incubation period for urethritis caused by *T. vaginalis* in men to be 3–9 days *(4, 37)*.

Diagnosis

Four main diagnostic assays exist to detect *T. vaginalis*, namely, wet mount smear microscopy, antigen detection assays, culture and nucleic acid amplification tests (NAATs) *(48)*.

A wet mount is usually used because it is quick, inexpensive and easy to perform. However, the slide needs to be read within 10 minutes of sample collection to successfully identify the motile trichomonads. Non-motile cells are not reliable for diagnosing trichomoniasis *(49)*.

The use of antigen detection assays is limited by the need for specialized equipment and the cost of reagents. Several of these assays are intended for use only in symptomatic women, making them less useful than other options *(48)*.

The sensitivity of *T. vaginalis* culture is about 70% compared with NAATs and can take up to seven days to confirm or refute a diagnosis. Hence, culture is no longer widely performed for the diagnosis of trichomoniasis.

With the introduction of NAATs, identification of *T. vaginalis* has improved and this has helped identify infection in asymptomatic individuals, thus permitting treatment to prevent onward transmission. Currently, NAATs have the highest sensitivity of all diagnostic methods to detect *T. vaginalis*. In women, vaginal swabs are the samples of choice for testing, but endocervical samples and urine can also be used in some assays. In men, urine and urethral swabs can be used. Given that residual genital samples collected for NAAT-based chlamydia and gonorrhoea diagnosis can also detect *T. vaginalis*, integrating *T. vaginalis* testing into existing testing programmes for *N. gonorrhoeae* and *C. trachomatis* is advisable. However, the use of NAATs as rapid point-of-care tests is not yet widespread at health facilities.

Sexual partners of persons with *T. vaginalis* infection should be treated, either after testing them (if possible) and screening them for other STIs, or by offering presumptive treatment for *T. vaginalis*. Although infection in men is traditionally thought to be benign and self-limited, it is important to ensure that all male sexual partners of women diagnosed with *T. vaginalis* are assessed because a high proportion of them are also generally infected.

3.1.2 Treatment for trichomoniasis infections

The following recommendations apply to adults and adolescents, including pregnant women, people living with HIV and key populations.

Recommendation on treatment of trichomoniasis infections (new 2023)

For adults and adolescents (including pregnant women) with *Trichomonas vaginalis* (trichomoniasis) infections, **WHO suggests:**

- metronidazole 400 mg or 500 mg orally twice daily for 7 days.

When adherence to multiple doses is a serious concern, **WHO suggests** one of the following options:

- metronidazole 2 g orally as a single dose; or
- tinidazole 2 g orally as a single dose (except during pregnancy).

Conditional recommendation, moderate certainty in evidence of effects.

Remarks:

- Secnidazole 2 g orally as a single dose (except during pregnancy) or ornidazole 1.5 g orally as a single dose (except during pregnancy) could be used as substitutes if metronidazole or tinidazole are not available.

Summary of the evidence

Four systematic reviews (including over 20 randomized and non-randomized studies) were found that assessed the benefits and harms of different doses of metronidazole, tinidazole and secnidazole *(50-53).* The searches were updated to May 2022 but this did not identify any additional studies. Additional details are available in the evidence-to-decision framework and systematic review in Web Annex A.

Effects

There is moderate certainty in the evidence showing that there is likely a smaller number of treatment failures with multiple doses (9%) compared with a single dose of metronidazole (15%) *(50, 51)*. When comparing metronidazole to tinidazole (both as a single 2 g dose), a systematic review found that there are likely slightly more treatment failures (6% more; moderate-certainty evidence) and adverse events (17% more; low-certainty evidence) with metronidazole than with tinidazole *(53)*. There is very low certainty in the evidence for tinidazole at multiple doses; only one study comparing it to multiple doses of metronidazole was found and no failures occurred out of 40 women. Very few studies have compared secnidazole to other treatments, but a recent systematic review reporting the number of treatment failures with secnidazole suggests, with very low certainty, that the number may be similar to metronidazole and tinidazole, but the adverse events may be higher. Overall, the small but greater benefits (fewer treatment failures) with multiple doses of metronidazole and the greater value placed on these benefits outweighed the trivial differences in harms compared with single doses of metronidazole or tinidazole.

Acceptability, costs, equity and feasibility

Other factors did not change the balance favouring multiple doses of metronidazole. Both multiple- and single-dose regimens were considered to be acceptable and feasible since multiple-dose regimens are commonly used for other infections. However, since there are small differences in treatment failures, a single dose of metronidazole or tinidazole could be provided when adherence is a serious concern. The differences in costs between multiple- and single-dose regimens are negligible. Tinidazole may be more expensive, but this is unlikely to impact equity.

3.2 *Mycoplasma genitalium*

3.2.1 Description

M. genitalium is a sexually transmitted bacterium with a characteristic flask shape on electron microscopy. It has the smallest known genome capable of self-replication. Mycoplasmas are members of the Mollicutes class of bacteria, which have no cell wall and usually range in size from 300 to 400 nanometres, making them the smallest known free-living micro-organisms – intermediate in size between bacteria and viruses *(5).* The lack of a rigid cell wall makes these bacteria resistant to ß-lactam antibiotics, such as penicillins, cephalosporins and carbapenems, which act on the bacterial cell wall. *Mycoplasma genitalium* is commonly found in the human urogenital tract – as are *Mycoplasma hominis* and two ureaplasma species (*Ureaplasma urealyticum* and *Ureaplasma parvum) (6)*. These bacteria were only discovered in 1981, and completely sequenced in 1995. They are fastidious in their growth requirements, due to their very small genome.

Epidemiology

In population-based studies, *M. genitalium* is found in up to 10% of sexually active men and women, and up to 20% in key populations, such as men who have sex with men and sex workers *(7-9)*. Ureaplasmas, on the other hand, can be found in the cervix or vagina in up to 80% of sexually active, asymptomatic women, and *M. hominis* in up to 50%. Consequently, *M. hominis* and the ureaplasmas are viewed as commensals rather than pathogenic infections *(54)*.

M. genitalium has been strongly associated with non-gonococcal urethritis, epididymitis and chronic prostatitis in men, and with cervicitis, pelvic inflammatory disease and bacterial vaginosis in women. The use of quantitative polymerase chain reaction (PCR) assays for *M. genitalium* has shown increased DNA loads in urine in men with non-gonococcal urethritis than in urine from those men without non-gonococcal urethritis *(55)*. *M. genitalium* infection has been documented as a risk factor for HIV infection *(56, 57)*.

Clinical features

Infections with *M. genitalium* in men are usually asymptomatic and there are limited data on the natural history of infection with *M. genitalium*. Estimations from existing data suggest that about 5% of men infected with *M. genitalium* will develop non-gonococcal urethritis. However, asymptomatic infections are common, having a similar frequency to that of chlamydial infections *(58, 59)*. In some men with acute epididymitis, the presence of *M. genitalium* has been identified as the cause.

In women, vaginal discharge and lower abdominal pain due to pelvic inflammatory disease have been associated with *M. genitalium.*

Diagnosis

Routine screening for *M. genitalium* is not recommended, except when needed to assess recurrent symptomatic episodes. Appropriate diagnosis of *M. genitalium* is by molecular biology techniques, such as PCR, and should ideally include macrolide resistance testing *(48)*. Culture methods are labour-intensive and take several months, making culture inappropriate for the diagnosis of *M. genitalium (60)*. There are no effective serological assays, antigen detection assays or rapid diagnostic tests currently available for *M. genitalium (48)*.

For laboratory-based NAAT testing for *M. genitalium*, the specimen must be collected from the relevant anatomical site where symptoms are occurring and carefully preserved and transported to the laboratory. Specimens and their transport medium should not contain any inhibitory substances for NAATs. It should be noted that the organism load of *M. genitalium* is 100-fold lower than that of *C. trachomatis* and, as such, transport systems that dilute the specimen unnecessarily should be avoided *(48)*.

3.2.2 Treatment for *Mycoplasma genitalium*

The following recommendations apply to adults and adolescents, including people living with HIV and key populations.

Good practice statement on treatment of *M. genitalium* infection (new 2023)

WHO recommends that the choice of therapy for *Mycoplasma genitalium* infections should be informed by an individual resistance profile, surveillance data or suspected resistance based on typical prescribing practices (antibiotic consumption) for other infections.

Recommendation on treatment of *M. genitalium* infection (new 2023)

In settings with high or suspected high resistance to macrolides (e.g. where azithromycin is frequently used) or when testing shows *Mycoplasma genitalium* resistant to macrolides, **WHO suggests:**

- doxycycline 100 mg orally twice daily for 7 days to reduce the bacterial load, followed by moxifloxacin 400 mg orally once daily for 7 days.

In settings with low or suspected low resistance to macrolides or when testing shows *Mycoplasma genitalium* susceptible to macrolides, **WHO suggests:**

- doxycycline 100 mg orally twice daily for 7 days to reduce the bacterial load, followed by azithromycin 1 g orally once for 1 day (initial dose) then 500 mg once daily for 3 days.

If azithromycin or moxifloxacin are not available, or there is confirmed or suspected high resistance to both, **WHO suggests** one of the following options:

- minocycline 100 mg orally twice daily for 14 days;
- sitafloxacin 200 mg orally once daily for 7 days; or
- pristinamycin 1 g orally four times a day for 10 days.

Conditional recommendation, low certainty in evidence of effects

Remarks:

- If treatment for suspected chlamydial infection (doxycycline 100 mg orally twice daily for 7 days) was provided, retreatment with doxycycline to reduce bacterial load prior to use of moxifloxacin or azithromycin is not required.
- When individual resistance profiles or surveillance data are unavailable, the likelihood of resistance may be based on typical prescribing practices (antibiotic consumption); for example, resistance to macrolides such as azithromycin is more likely in areas where azithromycin is typically prescribed for treatment of infections, or more likely in certain subpopulations such as men who have sex with men.
- The use of doxycycline, moxifloxacin, minocycline and sitafloxacin are contraindicated during pregnancy and breastfeeding; therefore, only use pristinamycin.

Summary of the evidence

A review was conducted of surveillance data, case reports for resistance, and primary studies about different medications and regimens to treat *M. genitalium* published up to August 2023. Additional details are available in the evidence-to-decision framework and systematic review in Web Annex B.

Antimicrobial resistance (macrolide resistance)

A systematic review of 59 studies found that the global prevalence of mutations associated with macrolide resistance (e.g. azithromycin) increased from 10% before 2010 to 51% in 2017 and varied across countries and regions *(61)*. In addition, the global prevalence of mutations associated with fluoroquinolone resistance (e.g. moxifloxacin) was 7.7% over time. This review also found that in men who have sex with men, there

was a greater proportion with macrolide resistance than fluoroquinolone resistance, and greater macrolide resistance than in heterosexual men, based on data from 21 countries. However, a recently published study based on four regions in the USA did not find higher rates of macrolide resistance in men who have sex with men compared with heterosexual men *(62)*.

Overall, the Guideline Development Group (GDG) agreed that antibiotic resistance determines the choice of medication, suggesting that first administering doxycycline (before administering azithromycin or moxifloxacin) may mitigate macrolide resistance. However, not all services would have the resources or facilities to test for resistance or collect surveillance data. Instead, prescribing practices in a region or country could provide an estimate of individual resistance or susceptibility.

Effects

Evidence from primary studies involving more than 1000 individuals indicates cure rates of 80–100% with azithromycin or moxifloxacin when *M. genitalium* is susceptible *(63-68)*. Two studies reported a low incidence of selection of macrolide resistance when doxycycline was administered prior to azithromycin *(69, 70)*. Another recent comparative study in 383 people found that the number of people cured was similar with doxycycline (100 mg twice daily for 7 days) followed by either azithromycin or moxifloxacin (but dependent on resistance) *(71)*. There are fewer studies evaluating pristinamycin, minocycline or sitafloxacin, but studies found somewhat similar cure rates, ranging from 70% to 100% *(69, 72-76)*. Although adverse events have been underreported, many drug regulatory agencies recommend limiting fluoroquinolone (e.g. moxifloxacin) use due to serious side-effects.

Acceptability, costs, equity and feasibility

The GDG acknowledged that acceptability, feasibility, equity and cost considerations are unlikely to significantly influence the choice of medication.

3.3 *Candida albicans* (candidiasis)

3.3.1 Description

Vulvovaginal candidiasis (VVC) affects approximately 70–75% of women at some point or multiple times during their lifetime *(10)*. It is caused by the fungus *Candida albicans* in approximately 90% of cases, while the non-*albicans* species cause the rest of VVC – *C. glabrata* in about 8% of cases and other non-*albicans* species in the remainder of cases (e.g. *C. tropicalis*, *C. krusei* and *C. parapsilosis) (11)*. Although men can be colonized with *Candida* species (spp.) and male sexual partners of women with candidiasis are transiently colonized, *Candida* balanitis and balanoposthitis in men are not recognized as STIs *(77)*. *Candida* yeasts may be detected in 20–30% of asymptomatic nonpregnant women of childbearing age *(78)*. The detection of *Candida* yeasts in asymptomatic women does not necessarily require treatment.

Pathogenesis

For *Candida* spp. to colonize the vagina, they must first adhere to the vaginal epithelial cells and then grow, proliferate and germinate before finally invading the vulvovaginal epithelium and causing symptomatic inflammation.

The symptoms of VVC are a result of several factors leading to an imbalanced vaginal microbiota. In addition, host predisposing factors and genetics as well as the strains of *Candida* spp. involved play a role. When *Lactobacilli* spp., which acidify the vaginal milieu by producing lactic acid and hydrogen peroxide (both of which inhibit growth of *Candida* spp.), are reduced in number, a disturbed microbiota results, leading to *Candida* adherence to the mucosal epithelium and abnormal growth of the yeast, resulting in symptomatic VVC *(79)*. In addition to the damage caused by the fungus itself, the host response also plays an important role – some women develop a local mucosal overreaction of innate immunity to the recruited neutrophils, contributing to inflammatory symptoms.

The important predisposing factors for colonization by *Candida* spp. and inflammation include the following:

- changes in estrogen levels associated with the menstrual cycle, pregnancy, hormone replacement and oral contraceptives;
- use of therapies, such as antibiotics, that disrupt the Lactobacillus-dominated microbiota;
- diabetes mellitus, especially if taking sodium-glucose co-transporter-2 (SGLT2) inhibitors *(80)*; and
- immunosuppression associated with HIV infection and transplantation.

Furthermore, since up to 30% of women are without predisposing factors, other factors – such as genetic background and ethnicity and the types of *Candida* strains circulating – play a role in idiopathic recurrent VVC *(81, 82)*.

Since candidiasis is usually of endogenous origin, it is not considered to be an STI, although *Candida* spp. may be transmitted between sexual partners.

Clinical features

VVC presents with pruritus (itching) or with a burning sensation of the vulva and vaginal soreness or irritation. Other clinical manifestations include pain during sexual intercourse (dyspareunia) and dysuria. The discharge, if present, is typically curdy, white, creamy and thick. The discharge is not always curd-like (sometimes described as being like cottage cheese) but can vary from watery to homogeneously thick. If a speculum examination is performed, the vaginal wall is found to be erythematous and an adherent discharge may be seen, either curd-like or homogeneously white. The cervix typically looks normal.

Recurrent VVC is defined as three or more episodes of symptomatic VVC in a period of 12 months. Self-reporting captured by surveys and other data have indicated VVC prevalence in 5–9% of women *(83, 84)*.

In the male genital tract, candidal infection causes balanitis, defined as inflammation of the glans penis. If the prepuce is also involved, it is referred to as balanoposthitis. Balanitis is generally sexually acquired. Often, it is associated with the presence of diabetes.

Taking SGLT2 inhibitors increases the risk of genital mycotic infections by 1.5–3 times over a five-year period, which respond reasonably adequately to treatment without need to discontinue the treatment for diabetes *(85-87)*.

Diagnosis

Microscopy: Vaginal pH in most women with candidiasis remains normal, typically between 4 and 4.5. Microscopy of a wet mount preparation or a Gram stain of vaginal secretions from the walls of the vagina will demonstrate Gram-positive *Candida* spp. A 10% potassium hydroxide preparation is also useful in identifying budding yeasts and/or pseudohyphae. It should be remembered that non-*albicans Candida* spp. generally do not form any traditional hyphae.

Culture methods: *Candida* culture on Sabouraud dextrose agar with chloramphenicol or chromogenic agar is recommended for the isolation of *Candida* spp. After inoculation of the specimen, the plates are incubated for two days at 36 °C. Microscopy can then be used to confirm the presence of yeast cells *(48)*.

Molecular testing of *Candida* species: Although molecular tests for *Candida* spp. exist, their role in the diagnosis of VVC is not yet clearly defined. As is also the case with molecular tests for STIs, any future exclusive use of NAATs for the diagnosis of VVC, without the use of culture methods, will preclude antimicrobial susceptibility testing, which is important in monitoring antimicrobial resistance in *Candida* spp. *C. albicans* is found as a commensal in several body locations, such as the skin, the genital tract and the gastrointestinal tract, but it can be an opportunistic pathogen whenever the immune status of the host or its microbiota becomes disturbed, causing extensive local or systemic disease. Surveillance data document that approximately two thirds of invasive candidal infections are caused by species other than *C. albicans*, which are generally associated with greater antifungal resistance than *C. albicans (88)*; nevertheless, vigilance for antimicrobial resistance emerging in *C. albicans* is important.

3.3.2 Treatment for vulvovaginal candidiasis

The following recommendations apply to adults and adolescents, including people living with HIV and key populations. A separate recommendation is made for treatment during pregnancy.

Recommendation on treatment of *C. albicans* (new 2023)

For adults and adolescents with *Candida albicans* (candidiasis) infections, **WHO suggests** one of the following options:

- fluconazole 150–200 mg orally as a single dose;
- clotrimazole 500 mg intravaginally as a single dose, or 200 mg intravaginally once daily for 3 days, or 10% cream intravaginally once;
- miconazole 1200 mg intravaginally as a single dose or 400 mg intravaginally once daily for 7 days;
- econazole 150 mg intravaginally as a single dose; or
- nystatin 100 000 units intravaginally twice daily for 15 days.

For pregnant women, **WHO suggests** one of the following options:

- clotrimazole 100 mg intravaginally once daily for 7 days or 1% cream intravaginally once daily for 7 days; or
- nystatin 100 000 units intravaginally twice daily for 15 days.

Conditional recommendation, low certainty in evidence of effects

Remarks:

- The choice of treatment may depend on preferences for intravaginal (which may also reduce vulval itching and soreness) or oral administration, and the cost in different settings.
- If an individual does not respond to treatment, refer to a specialist for further assessment and management.

Summary of the evidence

Six relevant systematic reviews of randomized controlled trials (RCTs) were found that assessed the benefits and harms of different treatments at different doses for women with uncomplicated VVC *(89, 90)*, in addition to a network meta-analysis *(91)*, a review in pregnant women *(92)*, a review with clotrimazole comparisons only *(93)*, and a review in people living with HIV *(94)*. The searches were updated to May 2022 without identifying any additional RCTs. Additional details are available in the evidence-to-decision framework and systematic review in Web Annex C.

Effects

Based on these reviews, there is low-certainty evidence for little to no difference in microbiological cures (0–4% difference) and adverse events (0–5% difference) when comparing fluconazole 150 mg as a single dose with other medicines taken either as a single dose or for 3 days, such as clotrimazole, fenticonazole, miconazole or itraconazole *(89, 93)*. However, there may be greater cures and fewer adverse events with a single dose of econazole 150 mg intravaginally compared with fluconazole, but the certainty of the evidence is also low. In pregnant women, clotrimazole for 6–7 days may result in greater cures than nystatin *(92, 93)*. The review in people living with HIV found no RCTs comparing different treatments. Overall, the balance of benefits and harms when comparing the different medicines at different doses did not favour one treatment over the other, with the exception of clotrimazole compared with nystatin, where the former was favoured.

Acceptability, costs, equity and feasibility

All recommended medication regimens were determined by the GDG to be acceptable, feasible and with negligible cost differences, and the choice would probably result in little impact on equity. There is some evidence that patients may prefer to take the medicines orally *(89)*. The GDG also noted that some medicines, such as fluconazole, clotrimazole and miconazole (and nystatin when others are not available), are likely the most commonly used and preferred.

3.4 Bacterial vaginosis

3.4.1 Description

Bacterial vaginosis (BV) is a genital condition in which there is a dysbiosis of the vaginal microbiome. Dysbiosis is typified by an alteration of the microbiome, resulting in changes in its functional composition and metabolic activity. For example, if there is a dysbiosis of the intestinal flora, there may be abdominal pain, diarrhoea or bloating of the abdomen. However, altered flora may cause no symptoms in some people. In the case of BV, women affected may complain of an abnormal, malodorous vaginal discharge or they may report no symptoms at all.

Epidemiology

BV is the most common cause of vaginal discharge globally among women of childbearing age. The prevalence of BV varies across countries and population groups. A recent systematic review and meta-analysis reported that the prevalence of BV among women of reproductive age varies among regions, ranging from 23% to 29%, with the following regional prevalence estimates: 23% in Europe and Central Asia, 24% in East Asia and Pacific, 24% in Latin America and the Caribbean, 25% in the Middle East and North Africa, 25% in sub-Saharan Africa, 27% in North America and 29% in South Asia *(12)*.

Pathogenesis

BV is characterized by a change in the vaginal ecosystem from a pattern in which *Lactobacillus* spp. are predominant to a pattern of mixed bacteria, which includes *Gardnerella* spp., *Prevotella* spp., *Fannyhessea vaginae*, *Mobiluncus* spp., *Megasphaera* spp. and *Sneathia* spp. *(48)*. The vaginal microbiome predominated by the lactic-acid-producing lactobacilli has a vaginal pH of less than 4.5, which is normally maintained at this level until menopause. In BV, the vaginal pH is greater than 4.5 *(77)*.

BV is associated with an increased risk of gynaecological and obstetric sequelae, including preterm delivery and spontaneous abortion, as well as an increased risk of acquisition and transmission of HIV and other STIs *(13, 15)*. *Gardnerella* spp. are key founder organisms in BV, displaying the greatest propensity to adhere to vaginal epithelial cells and initiate biofilm formation. *Gardnerella* spp. and *Prevotella* spp. produce virulence factors such as sialidases, which degrade the cervicovaginal mucus, enhancing biofilm formation and facilitating attachment of other BV-associated bacteria, resulting in the pathogenic process producing the symptoms and signs of BV. Some BV-associated bacteria produce volatile amines, which are responsible for the malodour of the discharge. The loss of lactic-acid-producing lactobacilli causes elevation in vaginal pH.

Although BV is not considered to be a sexually transmitted syndrome, epidemiological and molecular data collectively indicate that sexual transmission is likely to be involved in the acquisition and recurrence of BV. There is an association of BV with inconsistent condom use and a new sexual partner or an increased number of sexual partners, and it has an epidemiological profile consistent with an STI by meta-analysis. Molecular data support exchange of the genital microbiota between sexual partners, with the urethral and penile microbiota of males being more similar to the vaginal microbiota of a female partner than a non-partner. Men with a high prevalence and abundance of penile BV-associated bacteria are more likely to have a female partner with microscopically confirmed BV, and male circumcision reduces the prevalence and abundance of BV-associated bacteria in men and also reduces the risk of BV in female sexual partners *(48)*.

Among a cohort of biological females with female partners (women who have sex with women), incident BV occurred at a median of four days following sexual activity, with an increase in the relative abundance of *Gardnerella* spp., and other anaerobic bacteria associated with BV *(95)*.

Clinical features

In about 90% of symptomatic women, there is a complaint of a white vaginal discharge that can be seen on the vulva, and of an accompanying abnormal vaginal odour. Some women have only a mild vaginal discharge, which they may consider normal.

On external visual examination and digital examination of the vagina, the thin, white, homogeneous discharge may be observed externally on the posterior fourchette of the vulva or the labia. If a speculum examination is feasible, the homogeneous discharge may be observed to be adherent to the vaginal wall, while the cervix is usually normal in appearance.

Diagnosis

pH and KOH testing: The vaginal pH is greater than 4.5, and an amine odour can be sensed spontaneously or after addition of a drop of 10% potassium hydroxide to vaginal fluid on a slide (KOH test/whiff test). However, examination during menses, within a day of sexual intercourse, after recent douching or when the woman is using antimicrobial agents can affect the clinical and laboratory assessments for BV. The pH paper may provide an inaccurate reading if it samples water used to lubricate the speculum or if it samples cervical secretions, which are relatively alkaline. The amine smell, described as smelling fishy, is subjective as some people cannot discern the smell.

Microscopy: If a microscope is available at the point of care, a wet mount test for clue cells can be done. Clue cells are vaginal epithelial squamous cells coated with coccobacilli, with an absence of rods of lactobacilli. When visualized, the presence of clue cells on microscopy is one of the diagnostic criteria for BV. The identification of clue cells requires adequate training and good microscopy knowledge and skills.

If BV is present, microscopic examination of a Gram-stained vaginal smear collected with a swab from the vagina reveals large numbers of Gram-positive and Gram-negative cocci with reduced or absent lactobacilli (Gram-positive bacilli).

Diagnosis using Amsel's criteria: According to this method, diagnosis of BV requires at least three of the following to be present:

- a homogenous adherent whitish-grey vaginal discharge,
- pH of greater than 4.5,
- the release of amine odour from the vaginal fluid when mixed with 10% potassium hydroxide (the KOH test/whiff test), and
- the identification of "clue cells" on microscopic examination.

Grading using laboratory-based assessment: Where facilities are available for a laboratory-based assessment, more quantitative tests can be performed to grade BV as mild or severe, using the Ison-Hay criteria. The method compares the relative proportions of the different bacterial morphotypes and grades them as follows.

- Grade I (normal flora), with lactobacilli predominating or the only morphotypes present,
- Grade II (intermediate flora), with reduced lactobacilli and a mixed bacterial flora, and
- Grade III (BV), mixed bacterial flora with few or absent lactobacilli morphotypes.

Nugent's score: Another method for diagnosing BV using a Gram stain visualized under the microscope is Nugent's score – a method of classifying BV based on scoring of vaginal bacterial morphotypes, which requires good microscopy skills. The resulting Nugent's score ranges from 0 to 10, calculated from a weighted combination of the following: large Gram-positive rods (lactobacilli); small Gram-negative or Gram-variable

rods (e.g. *Gardnerella* spp. or other anaerobes); and curved Gram-negative or Gram-variable rods (e.g. *Mobiluncus* spp.). Each of these three groups is quantitatively weighted and interpretation is given as follows:

- score of 7–10 is diagnostic of BV,
- score of 4–6 is considered an intermediate microbiota, and
- a score 0–3 is considered a normal vaginal microbiota.

Point-of-care tests: Point-of-care tests (known as POC tests or POCTs), other than microscopy, are available to use either at the bedside or within a laboratory setting with appropriately trained technicians. These tests include:

- oligonucleotide probes for detection of high concentrations of *Gardnerella* spp. per millilitre of vaginal fluid; and
- tests that detect bacterial enzymes, such as sialidase, an enzyme produced by some BV-associated bacteria, including *Gardnerella* spp.

Molecular testing: Molecular assays for BV exist; they are based on detection of ribonucleic acid (RNA) markers from *Gardnerella* spp. and other anaerobic bacteria present in BV. These tests use either clinician-collected or patient-collected vaginal samples *(48)*.

3.4.2 Treatment of bacterial vaginosis

The following recommendations apply to adults and adolescents, including pregnant women, people living with HIV and key populations.

Recommendation on treatment of bacterial vaginosis (new 2023)

For adults and adolescents (including pregnant women) with bacterial vaginosis, **WHO suggests:**

- metronidazole 400 mg or 500 mg orally twice daily for 7 days.

If oral metronidazole is not available, adherence to multiple doses is a serious concern, or if vaginal creams are preferred, **WHO suggests** one of the following options:

- metronidazole 0.75% gel intravaginally for 7 days;
- tinidazole 2 g orally as a single dose (except during pregnancy);
- clindamycin 300 mg twice daily for 7 days;
- clindamycin 2% gel (5 g) intravaginally once daily for 7 days; or
- secnidazole 2 g orally as a single dose.

Conditional recommendation, moderate certainty in evidence of effects for metronidazole, low certainty in evidence of effects for clindamycin and secnidazole, very low certainty in evidence of effects for tinidazole

Summary of the evidence

Five systematic reviews that assessed the benefits and harms of different doses of metronidazole, tinidazole, clindamycin or secnidazole for the treatment of BV were found, and the searches were updated to May 2022 without identifying additional studies. Additional details are available in the evidence-to-decision framework and systematic review in Web Annex D.

Effects

There is moderate certainty in the evidence from a network meta-analysis showing that there is likely a moderate increase in the number of people cured with metronidazole or clindamycin (oral or intravaginally) compared with no treatment (ranging from 150 to 320 per 1000 more people) *(96)*. When directly comparing the treatments to each other, there may be little to no difference in cures or failures, discontinuation, or adverse events with clindamycin (oral or intravaginal), metronidazole (oral or intravaginal) or tinidazole (oral

2 g single dose) *(97)*. A review in pregnant women found that metronidazole and clindamycin also likely result in a moderate increase in cures when compared with no treatment, and there may be little to no difference between the two treatments *(98)*. Two other reviews addressed the use of secnidazole (oral 2 g single dose) and found that there may be an increase in the number of cures when compared with no treatment (which is similar to other treatments), and little to no difference in treatment failures or adverse effects between secnidazole 2 g single dose and metronidazole orally or intravaginally. Overall, there may be trivial differences between the various treatments for BV.

Another review assessed adverse pregnancy outcomes when taking metronidazole versus not taking it during pregnancy in RCTs and observational studies *(99)*. The meta-analyses of RCTs found little difference in pregnancy outcomes between the groups, but observational studies suggest the risk of spontaneous abortion may be increased when taking metronidazole during the first trimester of pregnancy, but this evidence is uncertain. Overall, there is little to no risk of adverse pregnancy outcomes with metronidazole.

Acceptability, costs, equity and feasibility

Metronidazole may be cheaper than other treatments and more available. However, given that intravaginal treatments and single-dose treatments result in similar benefits and harms, these treatments may be an alternative to metronidazole when adherence to multiple doses is a serious concern, when intravaginal treatment is preferred, or when metronidazole is not available.

3.5 Anogenital warts caused by human papillomavirus

3.5.1 Description

Anogenital warts are caused by types of HPV which infect the anogenital mucosa. Papillomaviruses are small, non-enveloped, icosahedral, species-specific viruses that have a diameter of 52–55 nanometres, with a circular and supercoiled double-stranded DNA genome. Papillomavirus isolates are described as "types" which have been detected in mammals and birds. They include human papillomaviruses (HPVs), which only infect humans. HPVs are epitheliotropic, infecting epithelial and mucosal surfaces. Various genotypes have tropism for infection at specific anatomical sites.

Genotyping is done to classify HPVs because they cannot be propagated by *in vitro* culture. HPVs fall into specific genera, with the alpha (α), beta (β) and gamma (γ) papillomaviruses being the largest groups. The α-papillomaviruses are important in mucosal infections, while the remainder cause cutaneous infections.

More than 200 HPV types have been identified to date, of which 40 are known specifically to infect the anogenital mucosa *(100)*. The anogenital HPVs are further subdivided into low-risk (LR) and high-risk (HR) or oncogenic types, based on their relative risk for causing cancer *(101)*. The HR HPVs are found in low- and high-grade lesions, as well as cancers of the cervix and a proportion of other anogenital sites, such as the vulva, vagina, anus and penis.

LR HPV types are typically found in low-grade intraepithelial lesions (non-precancerous lesions and now recognized as the viral cytopathic effect of infection), as well as in anogenital warts. HPV type 6 and HPV type 11 (HPV6 and HPV11) account for approximately 90% of genital warts and the rare *(102)*, but serious, recurrent respiratory papillomatosis (RRP).

The International Agency for Research on Cancer (IARC) classifies 12 HPV types as oncogenic (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) *(103)*. HPV16 is the most oncogenic HPV type, responsible for the highest proportion of cancer cases among all HPV types. Collectively, HPV16 and HPV18 are consistently responsible for approximately 70% of all cervical cancer cases worldwide. HR HPVs, especially HPV16, also have a causal role in other HPV-related anogenital cancers as well as some oropharyngeal cancers, particularly those of the tonsils and back of tongue.

Pathogenesis

HPV infection does not result in viraemia. At the cervix, HPV infection results in abnormalities of the superficial layers, known as the HPV-related cytopathic effect.

In a minority of cases, ranging from 5% to 10%, there is persistence of HPV infections, which is a prerequisite for the development of precursor lesions such as high-grade squamous intraepithelial lesions (HSILs), the true precursor lesions of cancer *(104)*. Without ablative treatment, a proportion will progress to cancer after some 10–20 years in persons with normal immunity, but may progress to cancer as quickly as 5–10 years in persons with weakened immunity, such as those with untreated HIV infection. Cofactors for persistence and cancer development include cigarette smoking, early age of sexual debut and infection with HPV, immunosuppression including HIV infection, and other host factors related to the immune response *(105, 106)*.

Epidemiology

Most genital HPV infections are sexually acquired (genital skin to genital skin or mucosa). Although common, they are usually transient and cleared by a healthy host immune system. It is estimated that the global risk of acquiring HPV at some point in one's life is 60% to 80% *(107)*. Peak ages of acquisition occur shortly after onset of sexual activity. In women, HPV genoprevalence increases rapidly with the onset of sexual debut, increasing with age then declines to a lower plateau after the 30s. In contrast, in males, HPV remains at a plateau once acquired. Higher numbers of sexual partners increases the risk of infection for both sexes, while male circumcision has a protective effect for transmission.

Among women with normal cervical cytology, a meta-analysis of over a million women showed global prevalence of HPV of almost 12%, with the highest prevalence at 24% being seen in women in sub-Saharan Africa *(108)*.

The estimated HPV attributable fraction for each of the following HPV-related cancers is 100% for the cervix, 88% for the anus, 78% for the vagina, 50% for the penis, 31% for the oropharynx and 25% for the vulva *(109, 110)*. Furthermore, in countries with high prevalence of HIV, up to 60% of cervical cancer cases are associated with coinfection with both HPV and HIV *(111)*.

Clinical features

Anogenital warts, also known as condylomata acuminata, are benign exophytic, papular or flat growths that may occur anywhere in the anogenital region. The incubation period between incident genital HPV infection and the appearance of warts is highly variable, but has been found to be shorter in women (median 2.9 months) than men (median 11.0 months) *(112)*. Most are caused by HPV6 and HPV11. Existing anogenital warts may enlarge considerably during pregnancy or may appear for the first time during pregnancy, and there may be a risk of causing obstructive labour. There is a higher prevalence of genital warts in immunosuppressed persons living with HIV infection.

The rare recurrent respiratory papillomatosis (RRP) caused by HPV6 and HPV11 typically has papillomas occurring in the upper respiratory tract, but the lower respiratory tract may also be involved, resulting in significant morbidity and mortality. Lesions on the larynx result in voice changes and can lead to obstruction of the airways. The patterns of RRP include juvenile-onset RRP (JoRRP), where the virus is transmitted at birth from mother to child with presentation typically occurring in the child between the ages of 1 and 4, and adult-onset RRP with HPV presumed to be sexually acquired, possibly through oro-genital sex, or possibly from latent HPV infection transmitted early in life *(113)*.

With the introduction of prophylactic vaccination with a vaccine that covers HPV6 and HPV11, the incidence of JoRRP has reduced significantly *(114)*, as has the incidence of genital warts.

Diagnosis

The diagnosis of genital warts is made upon finding flat, papular or pedunculated growths on the anogenital skin or mucosa during medical examination. HPV-related cancers may present with abnormal bleeding, discharge and/or non-healing lesions or ulcers.

Since HPV cannot be cultured conventionally, testing relies on molecular methods. Testing is done for epidemiologic surveillance as well as for clinical applications in some instances. Testing for epidemiologic purposes require type-specific assays with high analytic sensitivity.

Testing in clinical settings is used as a marker of underlying disease or as a predictor of incipient disease and matched to disease end-points. The use of molecular testing in clinical settings requires that laboratories use clinically validated assays, and it has been shown that self-collected genital samples are as effective as clinician-collected cervical samples for this purpose. Since cancer precursors are associated only with high-risk HPV types, there are no clinical indications for low-risk HPV screening.

Prevention

Prophylactic vaccination

The creation of viral-like particles (VLPs) – self-assembled macromolecules in recombinant systems that mimic the infectious virus in size and shape – has led to the success of prophylactic HPV vaccines. VLPs are highly immunogenic, eliciting high-titre, type-specific, neutralizing antibodies. Prophylactic HPV vaccines have proven safe and efficacious against HPV-related infections and diseases, such as cervical precancerous lesions and neoplasia itself, in phase 3 clinical trials *(22)*. They provide protection and immunogenicity for at least 12–15 years. The duration of protection offered by HPV vaccination continues to be monitored. Vaccines are most effective before sexual debut but also offer benefits to adults, protecting against infection, genital warts and anal canal disease *(115)*.

Cervical screening

Screening for precancerous lesions has been a cornerstone of cervical cytology (traditionally using the Papanicolaou [Pap] smear, and more recently using liquid-based cytology as an alternative), and this performs well when repeated every 2–3 years, provided there is a robust sampling system, sample conveyance, and assessment by an experienced pathologist. Thus, the success of the cervical screening is dependent on high-quality assurance and control, and requires appropriate follow-up and treatment of precancerous lesions. Other screening methods, such as visual inspection with acetic acid (VIA), are subjective and require ongoing supervision and quality assurance. HPV testing offers better specificity, and its negative predictive value means that women who test negative only need to be retested after a minimum interval of five years *(116, 117)*. The effectiveness of HPV screening for the prevention of anal and oropharyngeal cancers is under evaluation.

3.5.2 Treatment for external uncomplicated anogenital warts caused by HPV

The following recommendations apply to adults and adolescents, including pregnant women, people living with HIV and key populations.

Recommendation on treatment of anogenital warts caused by HPV (new 2023)

For adults and adolescents with uncomplicated external anogenital warts, **WHO suggests** one of the following options, which are self-applied:

- podophyllotoxin 0.5% solution or 0.5–1.5% cream twice daily for 3 days, followed by 4 days of no treatment (this cycle can be repeated up to four times) (except during pregnancy); or
- imiquimod cream 3.75% or 5% applied overnight three times a week for up to 16 weeks (except during pregnancy).

When treatment has failed, depending on available resources, **WHO suggests** the following options:

- electrosurgery/electrocautery;
- CO_2 laser therapy;
- trichloroacetic acid 80% (except during pregnancy); or
- cryotherapy.

Conditional recommendation, moderate certainty in evidence of effects

Remarks:

- The choice of treatment should be guided by factors such as the thickness and size of the anogenital warts, as well as anatomical location.
- Response to treatment can vary, therefore close monitoring is essential. Additionally, while podophyllin resin (10–25%, applied by a health worker and washed off after 2–4 hours, and repeated once weekly, if necessary) is less effective than other treatments, it may be an alternative when other options are not available; however, close monitoring is essential.
- Podophyllotoxin solution or cream, imiquimod cream, trichloroacetic acid and podophyllin resin are contraindicated during pregnancy. If necessary, cryotherapy is the safest option during pregnancy.

Summary of the evidence

Two relevant high-quality network meta-analyses and a systematic review were found that assessed the benefits and harms of different treatments for uncomplicated external anogenital warts *(118-120)*. Since their publication, three RCTs were found *(121-123)*, and the results were similar to those from the syntheses. Additional details are available in the evidence-to-decision framework and systematic review in Web Annex E.

Effects

There is moderate certainty in the evidence showing that there is likely complete lesion response to treatment ranging from 380 to 710 per 1000 people in comparison to 100 with no treatment. When comparing treatments, the lowest number of responses was with podophyllin 20%, and the highest number was with electrosurgery/electrocautery. The studies provided little information about the size, anatomical location or thickness of the warts, but the GDG agreed that response to treatment is likely associated with these factors and may be influenced by HIV status and use of antiretroviral therapy. Few studies provided data for adverse effects. Compared with no treatment, there may be greater erythema, oedema and itching with some creams/solutions; and watery discharge and some initial pain on treatment are likely to result from cryotherapy and CO_2 laser therapy. However, these adverse effects will improve/resolve within days, or up to a week. Given the moderate benefits that are valued more than the small, transient harms, treatment is favoured.

Acceptability, costs, equity and feasibility

Despite the lack of evidence for the costs, acceptability or feasibility of the options, the GDG agreed that creams and solutions may be more preferred and feasible over other treatments, such as cryotherapy, electrotherapy or laser therapy, and that costs and availability will vary in different countries and settings. Therefore, the GDG agreed that multiple options should be recommended to ensure equity and access to acceptable treatment, and that follow-up should be provided when options with fewer benefits are used.

3.6 Implementation considerations

3.6.1 Adapting, implementing and monitoring

These guidelines provide treatment recommendations for *T. vaginalis, M. genitalium, C. albicans,* bacterial vaginosis and anogenital warts, based on the best evidence available at the time of compilation. However, the epidemiology and the patterns of antimicrobial resistance vary geographically and need to be monitored, including for *M. genitalium*. In areas lacking local, national or regional data as a basis for adaptation, the recommendations in these guidelines can be adopted as presented since they have been assessed globally before being included in these guidelines and were developed with a view to being applicable to most settings.

When the guidelines are adapted for national use, the medication regimens that are included should have an efficacy of at least 95% and should also meet as many of the other criteria listed in Box 3.1 as possible. The selected medicines also need to be locally available, and the competencies and experience of local health workers should be considered.

Box 3.1 Criteria for selecting medicines for treating STIs to include in national guidelines

- 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 regimen
- Oral administration
- Not contraindicated for pregnant or lactating women

Appropriate medicines should also be included in national lists of essential medicines.

3.6.2 Identifying and procuring STI medicines

Identifying the medicines that will be recommended as first-line treatment for STIs is important, but so are the estimated quantities of the medicines that will be required. Quantifying medicine needs is an important part of estimating costs, to reconcile financial requirements with the available budget. Budgeting appropriately for medicines is critical. If the national health ministry does not provide medicines without user charges and the people who need the medicines cannot afford them, then there will essentially be no way to curtail the spread of infection and the occurrence of complications, which put more strain on the health system and national economy. Decision-makers, politicians and fiscal controllers at the national level should therefore understand the need to subsidize STI medicines.

Estimation of quantities is also key information as a basis for placing advance orders of medicines, with a view to minimizing the unit and freight costs. Estimating the quantity of medicines needed requires reviewing the medicines, their unit prices, the quantity required per treatment and the epidemiological information on the prevalence of infection. Medicine needs can be estimated by multiplying the estimated number of cases by the average quantity of medicine required for treating one case. These figures can be derived from health centres providing care but must be verified to avoid waste caused by excessive ordering (considering the limitations of shelf life and storage requirements).

Low-cost STI medicines can be obtained through international vendors of generic products and non-profit organizations with procurement schemes such as UNICEF, UNFPA and the United Nations High Commissioner

for Refugees (UNHCR). In addition, through joint medicine procurement schemes, national programmes from two or more countries can agree 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.

3.6.3 STI services for key populations

Adaptation and implementation of these guidelines should be accompanied by efforts to promote and protect the human rights of people who need services for STI care. This includes ensuring that stigma and discrimination are prevented in providing such services, while promoting gender equity, and ensuring that the use of services is voluntary. As key populations are disproportionately affected by STIs, it is critical to increase access to STI services, including treatment for specific STIs, for people living with HIV and key populations. Recommendations and guidance are provided in WHO's 2022 *Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations (124)*. In addition, the following WHO guidance documents provide additional implementation considerations for increasing access to and effectively delivering STI services for key populations.

- *Implementing comprehensive HIV and STI programmes with sex workers: practical approaches from collaborative interventions (125)*;
- *Implementing comprehensive HIV and STI programmes with men who have sex with men: practical guidance for collaborative interventions (126)*;
- *Implementing comprehensive HIV and STI programmes with transgender people: practical guidance for collaborative interventions (127)*; and
- *Implementing comprehensive HIV and HCV programmes with people who inject drugs: practical guidance for collaborative interventions (128)*.

3.6.4 Ensuring early and effective treatment

The following should be considered:

- promoting good STI health-care-seeking behaviour;
- providing access to high-quality care for STIs;
- providing immediate STI treatment;
- offering partner notification and treatment services;
- screening for STIs in population groups at higher risk, including key populations, and providing immediate treatment;
- introducing and/or strengthening case-finding for STIs, including HIV and viral hepatitis where resources permit and the epidemiology calls for it; and
- availability of laboratory or point-of-care diagnostics for detection and management of STIs.

3.7 Research needs

3.7.1 Trichomoniasis

There was only very low-certainty evidence about the effects of tinidazole as a single dose and for secnidazole or ornidazole. Therefore, RCTs are needed to compare these medicines and regimens to multiple doses of metronidazole.

3.7.2 *M. genitalium*

Monitoring for macrolide and quinolone resistance is not yet uniform across all countries. Therefore, there is a need for global epidemiological surveillance to monitor the prevalence of *M. genitalium* and its resistance to antimicrobials. It is also recommended to conduct RCTs that compare alternative regimens to moxifloxacin, and RCTs to assess monotherapy against sequential therapies and to evaluate different sequential therapies. In addition, the development and evaluation of new antimicrobial agents for treating *M. genitalium* are necessary.

3.7.3 Candidiasis

There were few direct comparisons of longer duration clotrimazole (e.g. 7 days or more) and therefore RCTs comparing these regimens to the recommended medication regimens are needed. Antifungal resistance profiles are also needed, particularly in immunocompromised individuals. While antifungal resistance is relatively uncommon, resistance to azoles seems to be increasing, evidencing the need for more robust and systematic surveillance as well as management of treatment failures *(129)*.

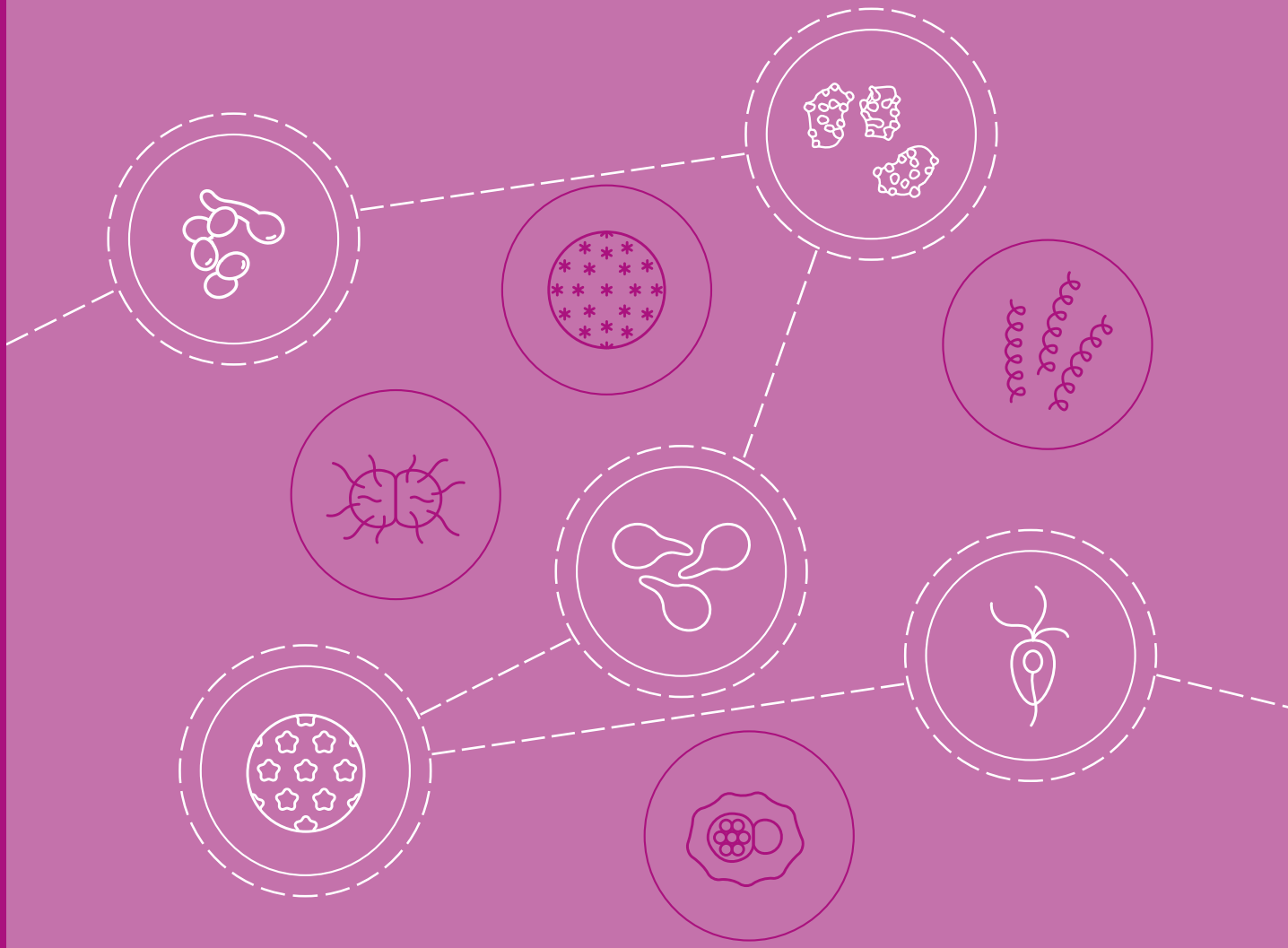
3.7.4 Bacterial vaginosis

Due to the low certainty about the effects of tinidazole compared with metronidazole, RCTs are needed. In addition, studies of different approaches to the management of recurrent bacterial vaginosis are needed.

3.7.5 Anogenital warts

Outcomes such as quality of life and preferences for creams/solutions and other treatments (at the patient and health system level) should be assessed and documented, and cost–effectiveness studies should be conducted. Additional research is needed in people living with HIV and other immunocompromised groups. Further consideration is needed about the risk of airborne HPV dispersal in airways of health workers after providing ablations *(130)*.

4. Disseminating and updating the guidelines



4. Disseminating and updating the guidelines

4.1 Dissemination

These guidelines will be made available on the WHO website at https://www.who.int/health-topics/sexually-transmitted-infections – click on "Guidelines" (there will also be links to other supporting documents).

WHO headquarters will work with WHO regional offices and country offices to ensure that countries receive support in adapting, implementing these guidelines, and monitoring their utility.

Every level of WHO (headquarters, regional offices and country offices) will work with regional and national partners – including UNFPA, UNICEF, UNAIDS, international and national nongovernmental organizations and other agencies implementing HIV, STI and sexual and reproductive health services – to ensure an integrated approach to preventing and controlling STIs. WHO will advocate that these external partners support the dissemination and implementation of these guidelines.

These guidelines will also be disseminated at conferences related to HIV, STIs and sexual and reproductive health, and through electronic media. These recommendations will also be included in the WHO's forthcoming *Consolidated guidelines for the prevention, diagnosis, treatment and care of STIs*.

The WHO AWaRe list will need to be revised to align with the treatment recommendations in these guidelines. Revisions will ensure that the recommendations are consistent across WHO products.

4.2 Updating the STI guidelines and user feedback

A system of monitoring relevant new evidence and updating the recommendations in these guidelines will be established and mechanisms for disseminating the new information put into operation. These mechanisms will include electronic communications. An electronic follow-up survey of key end-users of these guidelines will be conducted a year after they have been disseminated. 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 the delivery of STI services, and to identify new topics or gaps in treatment that need to be addressed in future editions.

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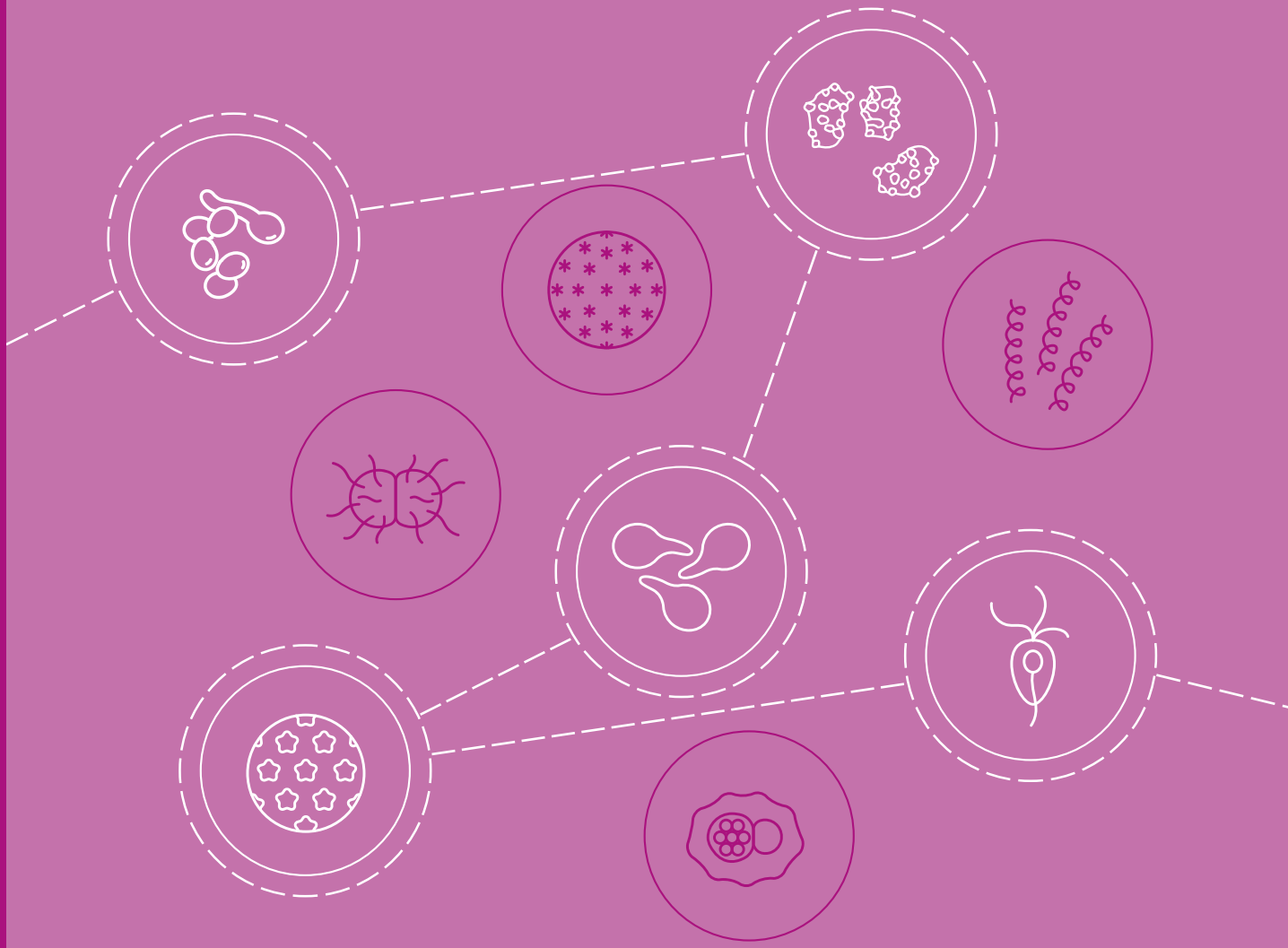

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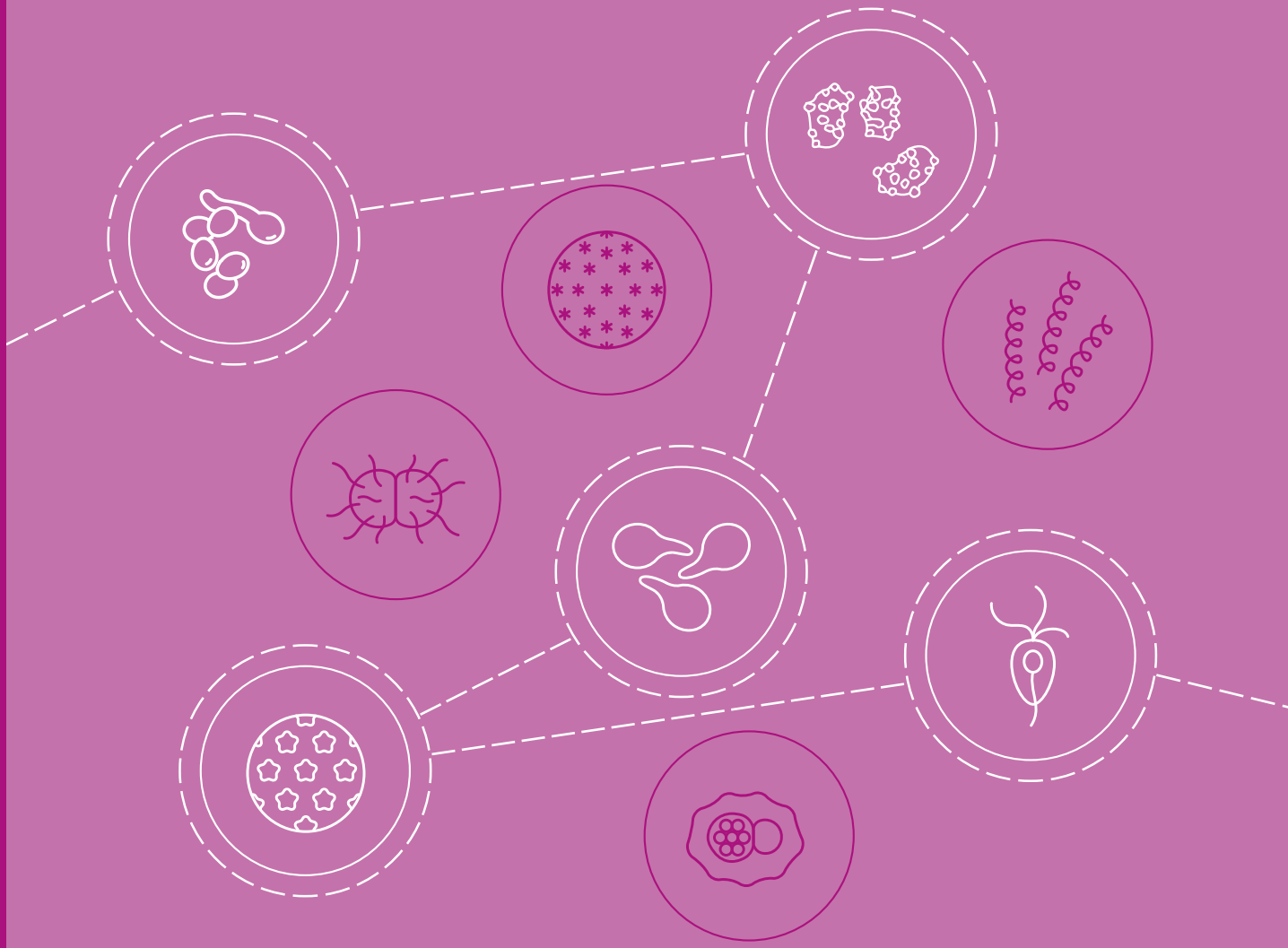
Annex 1.
Contributors to the guidelines



Annex 1.
Contributors to the guidelines

STI Guideline Development Group

Laith Abu Raddad
Director
WHO Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, STIs, and Viral Hepatitis
Weill Cornell Medical College
Doha, Qatar

Yaw Adu-Sarkodie
Professor of Clinical Microbiology
Kwame Nkrumah University of Science and Technology
Kumasi, Ghana

Mircea Betiu
Associate Professor
Nicolae Testimitanu State University of Medicine and Pharmacy
Chisinau, Republic of Moldova

Catriona Bradshaw
Professor of Sexual Health
Melbourne Sexual Health Centre
School of Translational Medicine
Monash University and Alfred Hospital
Melbourne, Australia

Xiang-Sheng Chen
Deputy Director
National Center for AIDS/STD Control and Prevention
Nanjing, China

Chido Dziva Chikwari
Assistant Professor of Epidemiology
London School of Hygiene & Tropical Medicine and The Health Research Unit Zimbabwe
Biomedical Research and Training Institute
Harare, Zimbabwe

Amina El Kettani
Medical Officer
Direction de l'Epidémiologie et de Lutte Contre les Maladies
Ministry of Health
Rabat, Morocco

Patricia Garcia
Professor
Universidad Peruana Cayetano Heredia
Lima, Peru

William M. Geisler
Clinical Associate Director and Medical Scientist
University of Alabama at Birmingham
Birmingham, United States of America (USA)

Kristina Grabbe
Jhipiego
USA

Kimberly Green
Global Program Director, Primary Health Care
PATH
Hanoi, Viet Nam

Somesh Gupta
Dermatologist
All India Institute of Medical Sciences
New Delhi, India

Edward W. Hook III
Director, Division of Infectious Diseases
University of Alabama at Birmingham
Birmingham, USA

Rena Janamnuaysook
Program Manager, Implementation Science
Institute of HIV Research and Innovation
Bangkok, Thailand

Nathalie Kapp
Chief Medical Adviser
International Planned Parenthood Federation
London, United Kingdom of Great Britain and Northern Ireland

Hamida Khattabi
Independent consultant
Rabat, Morocco

Rossaphorn Kittyaowamarn
Chief of Bangrak STIs Center
Bureau of AIDS, TB and STIs
Department of Diseases Control
Ministry of Public Health
Nonthaburi, Thailand

Jeffrey D. Klausner
Professor of Medicine and Public Health
UCLA David Geffen School of Medicine
Los Angeles, USA

Ranmini Kularatne
Clinical Microbiologist
Labtests
Auckland, New Zealand

Peter Kyambadde
Executive Director
Most at Risk Populations Initiative (MARPI)
National Coordinator, Key Populations/STI Program
Ministry of Health
Kampala, Uganda

David Lewis
Director
Western Sydney Sexual Health Centre
Sydney, Australia

Philippe Mayaud
Professor of Infectious Diseases and Reproductive Health
London School of Hygiene and Tropical Medicine
London, United Kingdom

Saiqa Mullick
Director, Implementation Science
Wits Reproductive Health and HIV Institute
Johannesburg, South Africa

Francis Ndowa
Physician
Skin and Genito-Urinary Medicine Clinic
Harare, Zimbabwe

Lilani Rajapaksa
Consultant Venereologist
Ministry of Health
Colombo, Sri Lanka

Kees Rietmeijer
Medical Director
Denver STD Prevention Training Center
Denver Public Health Department
Denver, USA

Danvic Rosadiño
Program and Innovations Director
LoveYourself Inc.
Manila, Philippines

Jonathan Ross
Consultant Physician
University Hospitals Birmingham NHS Foundation Trust
Birmingham, United Kingdom

Anna Shapiro
Policy Officer
Global Network of Sex Work Projects
Edinburgh, United Kingdom

Daniel Simões
Strategic Information Manager
Coalition Plus
Lisbon, Portugal

Jane Thiomi
GBV and HIV Prevention Manager
LVCT Health
Nairobi, Kenya

Jane Tomnay
Director
Centre for Excellence in Rural Sexual Health
The University of Melbourne
Melbourne, Australia

Magnus Unemo
Associate Professor in Medical Microbiology and Molecular Biology
Örebro University Hospital
Örebro, Sweden

Bea Vuylsteke
Institute of Tropical Medicine
Antwerp, Belgium

Judith Wasserheit
Professor of Global Health and Medicine
University of Washington
Seattle, USA

Observers

Laura Bachman
Chief Medical Officer
Division of STD Prevention
Centers for Disease Control and Prevention
Atlanta, USA

Azadeh Baghaki
Strategy Manager
Unitaid
Geneva, Switzerland

Lindley Barbee
Clinical Team Lead
Division of STD Prevention
Centers for Disease Control and Prevention
Atlanta, USA

Francis Kakooza
Head, Global Health Security Department
Infectious Diseases Institute
Makerere University
Kampala, Uganda

Fernando Pascal Martinez
Research and Development Access
Development Lead
Global Antibiotic Research and
Development Partnership
Barcelona, Spain

Tim Sladden
Senior Advisor, Sexual and Reproductive Health
United Nations Population Fund
New York, USA

External Review Group

Henry J. C. de Vries
Amsterdam Sexual Health Clinic
Amsterdam, Kingdom of the Netherlands

Hans Benjamin Hampel
University of Zurich
Zurich, Switzerland

Kausar Jabeen
Professor and Consultant Microbiologist, Pathology
and Laboratory Medicine
The Aga Khan University
Karachi, Pakistan

Monica Lahra
WHO Collaborating Centre for STIs and
Antimicrobial Resistance
Prince of Wales Hospital
Sydney, Australia

Pham Thi Lan
National Hospital of Dermatology and Venereology
Hanoi Medical University
Hanoi, Viet Nam

Ahmed Latif
Public health consultant
Brisbane, Australia

Ioannis Mameletzis
Consultant
Kyiv, Ukraine

Angelica Espinosa Miranda
Coordinator of Surveillance of STIs
Ministry of Health
Brasília, Brazil

Koleka Mlisana
Executive Manager, Academic Affairs, Research and
Quality Assurance
National Health Laboratory Service
Johannesburg, South Africa

Lori Newman
Medical Officer
National Institutes of Health
Washington, DC, USA

Catherine Ngugui
Head, National AIDS and STI Control
Ministry of Health
Nairobi, Kenya

Remco Peters
University of Pretoria
Pretoria, South Africa

Reshmie Ramautarsing
Physician
Institute of HIV Research and Innovation
Bangkok, Thailand

Pachara Sirivongrangson
Ministry of Public Health
Bangkok, Thailand

Janet Wilson
Consultant in Genito-Urinary Medicine
Leeds Teaching Hospitals NHS Trust
Leeds, United Kingdom

Methodologist and evidence review team

Methodologist

Maria Ximena Rojas Reyes
Institut d'Recerca Hospital de la Santa Creu i Sant Pau
Barcelona, Spain

Systematic review team

For treatment recommendations:
Nancy Santesso (lead), Angela Barbara and **Meha Bhatt**
Michael G. DeGroote Cochrane Canada Centre
McMaster University
Hamilton, Canada

WHO Secretariat and Steering Committee

Members based at WHO headquarters (Geneva, Switzerland)

Avni Amin
Technical Officer
Department of Sexual and Reproductive Health and Research (SRH)

Arif Al-Hamad
Technical Officer
Department of Surveillance, Prevention and Control
Antimicrobial Resistance (AMR) Division

Kingsley Asiedu
Department of Neglected Tropical Diseases

Rachel Baggaley
Unit Head, Testing, Prevention and Populations
Department of Global HIV, Hepatitis and Sexually Transmitted Infection Programmes (HHS)

Magdalena Barr-DiChiara
Technical Officer
Department of HHS

Maeve Brito de Mello
Technical Officer
Department of HHS

Meg Doherty
Director
Department of HHS

Sami Gottlieb
Medical Officer
Department of SRH

Benedikt Huttner
Team Lead
Department of Access to Medicines and Health Products

Cheryl Johnson
Technical Officer
Department of HHS

James Kiarie
Unit Head
Department of SRH

Ismail Maatouk
Technical Officer
Department of HHS

Daniel Marcano-Zamora
Technical Officer
Department of Surveillance, Prevention and Control
AMR Division

Gitau Mburu
Scientist
Department of SRH

Daniel McCartney
Consultant
Department of HHS

Antons Mozalevskis
Technical Officer
Department of HHS

Yamuna Mundade
Programme Manager
Department of HHS

Morkor Newman Owiredu
Medical Officer
Department of HHS

Anne-Laure Page
Scientist
Regulation and Prequalification

Jane Rowley
Technical Officer
Department of HHS

Özge Tunçalp
Medical Officer
Department of Maternal, Newborn, Child and Adolescent Health and Ageing

Igor Toskin
Scientist
Department of SRH

Annette Verster
Technical Officer
Department of HHS

Marco Vitoria
Medical Officer
Department of HHS

Teodora Wi[a]
Lead, Sexually Transmitted Infections
Department of HHS

Members based at WHO regional offices

[a] Overall coordinator of the STI guidelines.

Viatcheslav Grankov
Unit Lead, Joint Infectious Diseases
WHO Regional Office for Europe

Joumana Hermez
Regional Adviser
WHO Regional Office for the Eastern Mediterranean

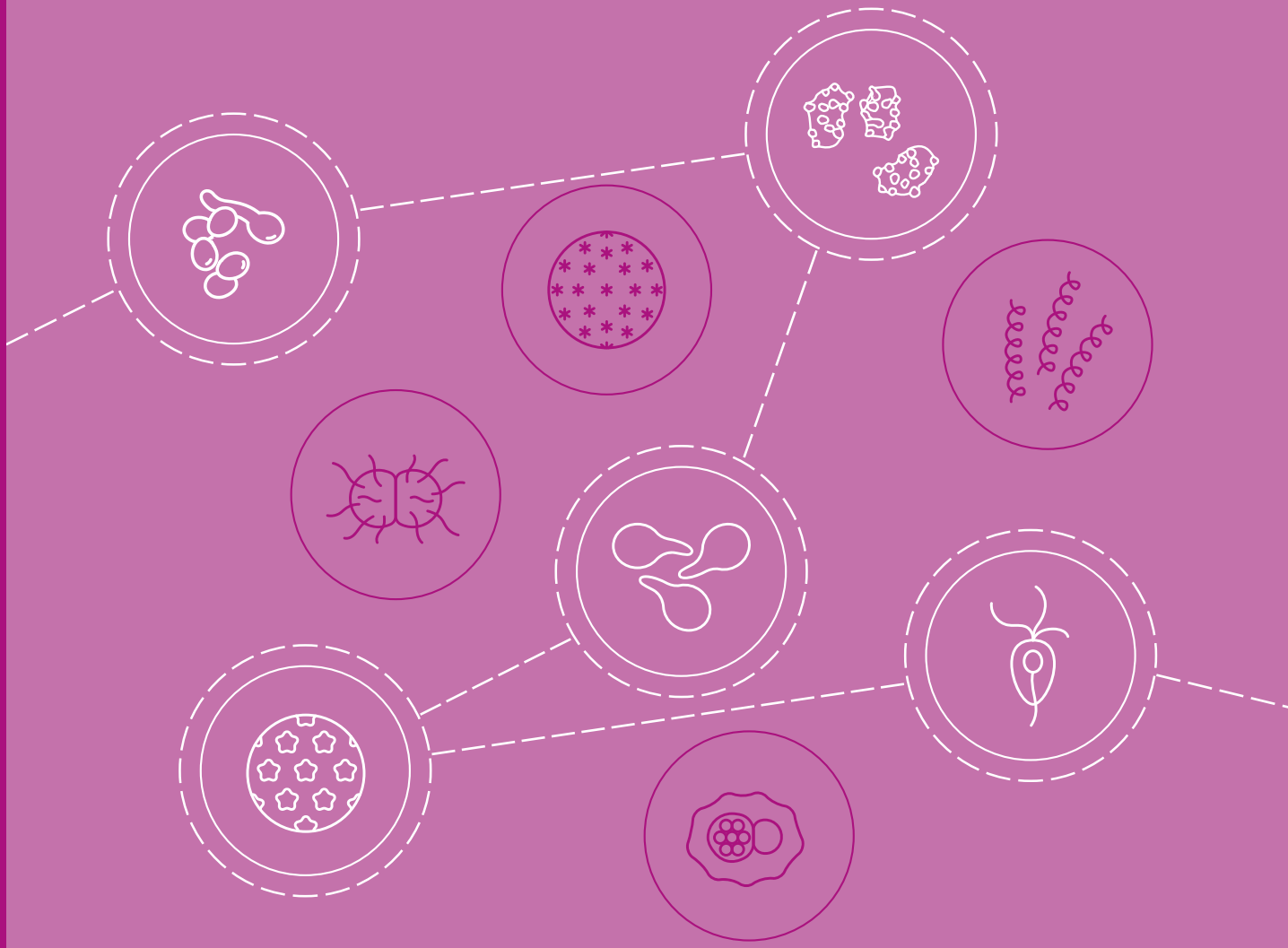
Kiyohika Izumi
Medical Officer
WHO Regional Office for the Western Pacific

Agnes Shetty
Medical Officer, HIV/AIDS Treatment and Care
WHO Regional Office for Africa

Ruben Mayorga Sagastume
Unit Chief, HIV, Hepatitis, Tuberculosis and STIs
WHO Regional Office for the Americas

Polin Chan
Regional Advisor, Hepatitis, HIV and STIs
WHO Regional Office for South-East Asia

Annex 2.
Declarations of interests and management of conflicts of interest



STI Guideline Development Group members

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan*
Laith Abu Raddad (Weill Cornell Medical College, Qatar)	–	–	–	–	–	–	Full participation
Yaw Adu-Sarkodie (Kwame Nkrumah University of Science and Technology, Ghana)	–	–	–	–	–	–	Full participation
Mircea Betiu (Nicolae Testimitanu State University of Medicine and Pharmacy, Republic of Moldova)	–	–	–	–	–	–	Full participation
Catriona Bradshaw (Monash University and Alfred Hospital, Australia)	Funding from Abbott to support development of STI testing recommendations in countries across the Asia-Pacific region (A$ 3800).	Australian Research Council Grant to Monash University that contains contributions from the Government, two diagnostic companies (SpeeDx and Cepheid) and nongovernmental organizations including the Global Antibiotic Research and Development Partnership (GARDP) to support work on the development of resistance diagnostics and antimicrobial resistance (AMR) (A$ 1.5 million). Diagnostic kits and GeneXpert platform donated for use in specific investigator-initiated research.	–	–	–	–	Full participation – not related to STI treatment
Xiang-Sheng Chen (National Center for AIDS/STD Control and Prevention, China)	–	–	–	–	–	–	Full participation

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan*
Chido Dziva Chikwari (Biomedical Research and Training Institute, Zimbabwe)	–	–	–	–	–	–	Full participation
Amina El Kettani (Ministry of Health, Morocco)	–	–	–	–	–	–	Full participation
Patricia Garcia (Universidad Peruana Cayetano Heredia, Peru)	–	–	–	–	–	–	Full participation
William M. Geisler (University of Alabama at Birmingham, United States of America [USA])	–	Research support from Hologic for study of *M. genitalium* prevalence and resistance in the USA (US$ 240 920).	–	–	–	–	Full participation – not related to STI treatment
Kimberly Green (PATH, Viet Nam)	–	Funding from USAID for STI screening among key populations as part of PrEP; funding from The Hepatitis Fund for triple elimination including syphilis screening (US$ 50 000).	–	–	–	–	Full participation – not related to STI treatment
Somesh Gupta (All India Institute of Medical Sciences, India)	–	–	–	–	–	–	Full participation
Edward W. Hook III (University of Alabama at Birmingham, USA)	–	Member of advisory board for Visby Diagnostics (US$ 10 000) and Talsis Diagnostics.	–	–	–	–	Full participation – not related to STI treatment
Rena Janamnuaysook (Institute of HIV Research and Innovation, Thailand)	–	–	–	–	–	–	Full participation

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan*
Nathalie Kapp (International Planned Parenthood Federation, United Kingdom of Great Britain and Northern Ireland)	–	–	–	–	–	–	Full participation
Hamida Khattabi (Independent consultant, Morocco)	–	–	–	–	–	–	Full participation
Rossaphorn Kittyaowamarn (Ministry of Public Health, Thailand)	–	Multicentre randomized, open-label, non-inferiority trial to evaluate the efficacy and safety of single-dose oral Zoliflodacin for treatment of patients with uncomplicated gonorrhoea (GARDP).	–	–	–	–	Full participation –related to gonorrhoea treatment only
Jeffrey D. Klausner (University of California, Los Angeles, USA)	Consulting with Diagnostics Direct (< US$ 5000) and Visby (< US$ 5000).	Research support from Cepheid for donated research supplies and loaned research equipment (US$ 10 000).	–	–	–	–	Full participation – not related to STI treatment
Ranmini Kularatne (Labtests, New Zealand)	–	–	–	–	–	–	Full participation
Peter Kyambadde (Ministry of Health, Uganda)	–	–	–	–	–	–	Full participation
David Lewis (Western Sydney Sexual Health Centre, Australia)	–	–	–	–	–	–	Full participation
Philippe Mayaud (London School of Hygiene & Tropical Medicine, United Kingdom)	–	Research support from Abbott Diagnostics for sample collection for development of diagnostic tests for *N. gonorrhoeae* and *C. trachomatis* (US$ 350 000).	–	–	–	–	Full participation – not related to STI treatment

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan*
Saiqa Mullick (Wits Reproductive Health and HIV Institute, South Africa)	–	Wits RHI is awaiting a potential donation of long-acting cabotegravir (CAB-LA) from the drug developer for a planned implementation science study. Wits RHI has also been involved in the clinical trials of CAB-LA; however, funding was not received directly from the product developer. Wits RHI runs various clinical trial (where Saiqa Mullick is not a principal investigator) with multiple donors but no profit is made from any of these trials/projects.	–	–	–	–	Full participation – not related to STI treatment
Francis Ndowa (Skin and Genito-Urinary Medicine Clinic, Zimbabwe)	–	–	–	–	–	–	Full participation
Lilani Rajapaksa (Ministry of Health, Sri Lanka)	–	–	–	–	–	–	Full participation
Kees Rietmeijer (Denver Public Health Department, USA)	–	Past consulting with Sentient (ceased 2023), and WHO (ceased 2022).	–	–	–	–	Declared. None are active. Full participation.
Danvic Rosadiño (LoveYourself Inc., Philippines)	–	–	–	–	–	–	Full participation
Jonathan Ross (University Hospitals Birmingham NHS Trust, United Kingdom)	Consultancy advice in relation to clinical trials (GSK plc.)	Research payments to his employer for his role as principal investigator for clinical trial.	Investments (participant and his wife) in GSK and AstraZeneca		–	–	Declared. Finance not significant. Full participation.

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan*
Anna Shapiro (Global Network of Sex Work Projects, United Kingdom)	–	–	–	–	–	–	Full participation
Daniel Simões (Coalition Plus, Portugal)	–	Consultant with European AIDS Treatment Group.	Member of Country Support core team (trainer) with the Center of Excellence for Health Immunity and Infections.	–	–	–	Full participation
Jane Thiomi (LVCT Health, Kenya)	–	–	–	–	–	–	Full participation
Jane Tomnay (University of Melbourne, Australia)	–	–	–	–	–	–	Full participation
Magnus Unemo (Örebro University Hospital, Sweden)	–	–	–	–	–	–	Full participation
Bea Vuylsteke (Institute of Tropical Medicine, Belgium)	–	–	–	–	–	–	Full participation
Judith Wasserheit (University of Washington, USA)	–	–	–	–	–	–	Full participation
Observers							
Laura Bachman (Centers for Disease Control and Prevention, USA)	–	–	–	–	–	–	NA

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan*
Azadeh Baghaki (Unitaid, Switzerland)	–	–	–	–	–	–	NA
Lindley Barbee (Centers for Disease Control and Prevention, USA)	–	Previous research support from Hologic, Nabriva, SpeeDx (ended 30 June 2022).	–	–	–	–	NA
Francis Kakooza (Makerere University, Uganda)	–	–	–	–	–	–	NA
Fernando Pascal Martinez (Global Antibiotic Research and Development Partnership, Spain)	–	–	–	–	–	–	NA
Tim Sladden (United Nations Population Fund, USA)	–	–	–	–	–	–	NA

External Review Group members

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan
Henry J.C. de Vries (Amsterdam Sexual Health Clinic, Kingdom of the Netherlands)	–	–	–	–	–	–	Full participation
Hans Benjamin Hampel (University of Zurich, Switzerland)	–	–	–	–	–	–	Full participation
Kausar Jabeen (The Aga Khan University, Pakistan)	–	–	–	–	–	–	Full participation
Monica Lahra (Prince of Wales Hospital, Australia)	–	–	–	–	–	–	Full participation
Pham Thi Lan (Hanoi Medical University, Viet Nam)	–	–	–	–	–	–	Full participation
Ahmed Latif (public health consultant, Australia)	–	–	–	–	–	–	Full participation
Ioannis Mameletzis (consultant, Ukraine)	–	–	–	–	–	–	Full participation
Angelica Espinosa Miranda (Ministry of Health, Brazil)	–	–	–	–	–	–	Full participation
Koleka Mlisana (National Health Laboratory Service, South Africa)	–	–	–	–	–	–	Full participation
Lori Newman (National Institutes of Health, USA)	–	–	–	–	–	–	Full participation

Name	1. Employment and consulting	2. Research support	3. Investment interests	4. Intellectual property	5. Public statements and positions	6. Tobacco products	Conflicts and management plan
Catherine Ngugui (Ministry of Health, Kenya)	–	Research support from GARDP, Drugs for Neglected Diseases Initiative (DNDI) and the Ministry of Health for a study on prevalence of *C. trachomatis* and *N. gonorrhoeae* infections among pregnant women and key populations in Kenya (US$ 40 000; ceased 2022).	–	–	Former Director of National AIDS and STI Control in Kenya	–	None are active. Full participation.
Remco Peters (University of Pretoria, South Africa)	–	Research support from the Foundation for Innovative New Diagnostics (FIND) for evaluation of lateral flow assay for point-of-care detection of *N. gonorrhoeae* (US$ 645 000). Support from the South African Medical Research Council for project of AMR and molecular typing of *N. gonorrhoeae* isolates in the Eastern Cape province, South Africa (US$ 50 000, ceased March 2023)	–	–	–	–	Full participation – not related to STI treatment
Reshmie Ramautarsing (Institute of HIV Research and Innovation, Thailand)	–	–	–	–	–	–	Full participation
Pachara Sirivongrangson (Ministry of Public Health, Thailand)	Consulting work for GARDP (US$ 10 000)	–	–	–	–	–	Full participation
Janet Wilson (Leeds Teaching Hospitals NHS Trust, United Kingdom)	–	–	–	–	–	–	Full participation

For more information, please contact:

World Health Organization
Global HIV, Hepatitis and Sexually Transmitted Infections Programmes
20 Avenue Appia
1211 Geneva 27
Switzerland

Email: hiv-aids@who.int
Website: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/
www.who.int

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