



World Health  
Organization

**GUIDELINES**



**GUIDELINES FOR THE  
MANAGEMENT OF  
SYMPTOMATIC SEXUALLY  
TRANSMITTED INFECTIONS**

JUNE 2021



**GUIDELINES FOR THE  
MANAGEMENT OF  
SYMPTOMATIC SEXUALLY  
TRANSMITTED INFECTIONS**

JUNE 2021

Guidelines for the management of symptomatic sexually transmitted infections

ISBN 978-92-4-002416-8 (electronic version)

ISBN 978-92-4-002417-5 (print version)

© World Health Organization 2021

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (<http://www.wipo.int/amc/en/mediation/rules/>).

**Suggested citation.** Guidelines for the management of symptomatic sexually transmitted infections. Geneva: World Health Organization; 2021. Licence: **CC BY-NC-SA 3.0 IGO**.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at <http://apps.who.int/iris>.

**Sales, rights and licensing.** To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

**Third-party materials.** If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

**General disclaimers.** The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Design and layout by 400 Communications.

# CONTENTS

<b>Acknowledgements</b>	<b>vi</b>
<b>Abbreviations and acronyms</b>	<b>viii</b>
<b>Executive summary</b>	<b>ix</b>
<b>1. Summary of recommendations</b>	<b>1</b>
1.1 Recommendations for the management of urethral discharge	1
1.2 Recommendations for the management of vaginal discharge	2
1.3 Recommendations for the management of lower abdominal pain among women	4
1.4 Recommendations for the management of genital ulcer disease, including anorectal ulcers	6
1.5 Recommendations for the management of anorectal discharge	8
<b>2. Introduction and overview of the development of WHO guidelines for the management of symptomatic sexually transmitted infections</b>	<b>9</b>
2.1 Epidemiology and global burden of sexually transmitted infections	9
2.2 STIs and HIV	10
2.3 Objectives and rationale for developing the guidelines	12
2.4 Objectives of the guidelines	13
2.5 Target audience	13
2.6 Guiding principles	14
2.7 Methods for developing the guidelines	14
2.8 Reviews of the evidence	16
2.9 Modelling outcomes	17
2.10 Presentation of the evidence	18
2.11 Making recommendations	18
2.12 Managing conflicts of interest	19
<b>3. Case management for people with STIs</b>	<b>20</b>
3.1 Objectives of STI case management	20
3.2 Requirements to achieve the objectives of STI case management	20

<b>4. Diagnostic tests for asymptomatic and symptomatic people with STIs</b>	<b>33</b>
4.1 Role of microscopy in diagnosing STIs and other reproductive tract infections	34
4.2 Quality-assured laboratory testing with a fully operational management system	35
<b>5. Rationale for standardized treatment recommendations</b>	<b>36</b>
<b>6. Implementing the syndromic approach for the management of STIs</b>	<b>37</b>
<b>7. Urethral discharge syndrome</b>	<b>38</b>
7.1 Clinical presentation – symptoms	38
7.2 Examination findings – signs	38
7.3 Laboratory diagnosis	38
7.4 Recommendations for the management of urethral discharge	40
7.5 Treatment recommendations for urethral discharge	43
<b>8. Vaginal discharge syndrome</b>	<b>45</b>
8.1 <i>T. vaginalis</i>	45
8.2 Candidiasis	46
8.3 Bacterial vaginosis	47
8.4 Cervical infection – gonococcal and/or chlamydial cervicitis	48
8.5 Recommendations for the management of vaginal discharge	50
8.6 Treatment options for vaginal discharge	55
<b>9. Lower abdominal pain</b>	<b>58</b>
9.1 Recommendations for the management of lower abdominal pain among women	58
9.2 Treatment for people presenting with lower abdominal pain	61
<b>10. Genital ulcer disease syndrome</b>	<b>63</b>
10.1 Herpes simplex virus	63
10.2 Syphilis	64
10.3 <i>H. ducreyi</i> (chancroid)	69
10.4 Recommendations for the management of genital ulcer disease, including anorectal ulcers	70
10.5 Treatment of genital ulcer disease, including anorectal ulcers	74

<b>11. Anorectal discharge</b>	<b>76</b>
11.1 Anatomical sites of infection	76
11.2 Sexual practices that may be associated with anorectal infections	76
11.3 Examination	76
11.4 Recommendations for the management of anorectal discharge	77
11.5 Treatment recommendations for anorectal infections	80
<b>12. Dissemination and implementation of the guidelines</b>	<b>82</b>
12.1 Dissemination	82
12.2 Updating the STI guidelines and user feedback	82
12.3 Implementation considerations	83
<b>13. Surveillance and research needs</b>	<b>84</b>
13.1 Challenges in STI surveillance and anticipated responses	84
13.2 Research needs in STI case management	85
<b>References</b>	<b>86</b>
<b>Annex 1. STI Guideline Development Group</b>	<b>91</b>
<b>Annex 2. Declarations of conflicts of interest</b>	<b>97</b>
<b>Annex 3. Evidence-to-decision table: urethral discharge</b>	<b>102</b>
<b>Annex 4. Evidence-to-decision table: vaginal discharge</b>	<b>116</b>
<b>Annex 5. Evidence-to-decision table: lower abdominal pain</b>	<b>143</b>
<b>Annex 6. Evidence-to-decision table: genital ulcer disease</b>	<b>161</b>
<b>Annex 7. Evidence-to-decision table: anorectal discharge</b>	<b>186</b>
<b>Annex 8. Supplemental materials</b>	<b>201</b>

# ACKNOWLEDGEMENTS

The WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes is grateful and thanks all the individuals and organizations that contributed to developing these guidelines to make them relevant and responsive to the needs in the field.

We appreciate the overall support of the Secretariat of the WHO Guidelines Review Committee during the guideline development process.

## Methodologist, systematic reviewers and modellers

Special thanks to **Nancy Santesso** (McMaster University, Canada), the guideline methodologist, for her hard work and firm commitment to the guideline development process.

Sincere gratitude to **Eric Chow** and **Jason Ong** and the research team at Monash University, Australia and the systematic review team **Angela Barbara**, **Tejan Baldeh**, **Meha Bhatt**, **Stephanie Duda**, **Laura Fullerton**, **Anila Qasim**, **Rosa Stalteri**, **Matthew Ventresca** and **Holger Schünemann** of McMaster University, Michael G. DeGroot Cochrane Canada Centre for conducting the systematic reviews.

We thank **Samantha Berman**, **Jennifer Owen** and **Katy Turner**, University of Bristol, for modelling the cost and effectiveness of approaches for managing women with vaginal discharge.

## STI Guideline Development Group

The members of the STI Guideline Development Group (Annex 1) provided invaluable guidance and comments during the development of these guidelines through virtual meetings and comments by correspondence. Their meticulous attention to detail, expert comments and feedback ensured the consistency and relevance of these guidelines.

## Guideline Development Group members

**Ilya Abellanosa-Tacan** (Cebu City, Philippines), **Laith Abu-Raddad** (Weill Cornell Medical College, Qatar), **Yaw Adu-Sarkodie** (Kwame Nkrumah University of Science and Technology, Ghana), **Chris Akolo** (FHI 360, Washington, DC, USA), **Andrew Amato** (European Centre for Disease Prevention and Control, Sweden), **Mircea Betiu** (Nicolae Testemițanu State University of Medicine and Pharmacy, Republic of Moldova), **John Chagalucha** (National Institute for Medical Research, United Republic of Tanzania), **Rizwana Chaudhri** (Islamabad Specialists Clinic, Islamabad, Pakistan), **Xiang-Sheng Chen** (National Center for STD Control of Chinese CDC and Chinese Academy of Medical Sciences Institute of Dermatology, Nanjing, China), **Amina El Kettani** (Ministry of Health, Morocco), **Patricia Garcia** (Ministry of Health, Lima, Peru), **William M. Geisler** (University of Alabama at Birmingham, USA), **Edward W. Hook III** (University of Alabama at Birmingham, USA), **Rossaphorn Kittyaowamarn** (Ministry of Public Health, Thailand), **Jeffrey D. Klausner** (UCLA David Geffen School of Medicine and Fielding School of Public Health, Los Angeles, USA), **Ranmini Kularatne** (National Institute for Communicable Diseases, Johannesburg, South Africa), **David Lewis** (University of Sydney, Australia), **Nicola Low** (Institute of Social and Preventive Medicine, Berne, Switzerland), **Philippe Mayaud** (London School of Hygiene and Tropical Medicine, United Kingdom), **Daniel McCartney** (International Planned Parenthood Federation, United Kingdom), **Nelly Mugo** (Kenya Medical Research Institute, Kenya), **Saiqa Mullick** (Wits Reproductive Health and HIV Institute, South Africa), **Francis Ndowa** (Harare, Zimbabwe), **Kees Rietmeijer** (Denver Public Health Department, USA), **Pachara Sirivongrangson** (Ministry of Public Health, Thailand), **Katayoun Tayeri** (Ministry of Health, Tehran, Islamic Republic of Iran), **Ann Natalia Umar** (Ministry of Health, Jakarta, Indonesia), **Magnus Unemo** (Örebro University Hospital, Sweden), **Noor Mohamed Usman** (Chennai, India), **Bea Vuylsteke** (Institute of Tropical Medicine, Antwerp, Belgium) and **Judith Wasserheit** (University of Washington, USA).



## Observers

**Laura Bachmann** (United States Centers for Disease Control and Prevention, USA), **Cecilia Ferreyra** (FIND, Switzerland), **Fernando Pascual Martinez** (GARDP, Switzerland) and **Tim Sladden** (UNFPA, New York, USA).

## External Review Group

**Anupong Chitwarakorn** (Silom Clinic, Thailand), **H.J.C. de Vries** (Amsterdam, Netherlands), **Hans Benjamin Hampel** (University of Zurich, Switzerland), **Kausar Jabeen** (Aga Khan Foundation, Pakistan), **Monica Lahra** (New South Wales, Australia), **Ahmed Latif** (Public Health Consultant, National Territory, Australia), **Ioannis Mameletzis** (consultant, Ukraine), **Angelica Espinosa Miranda** (Ministry of Health, Brazil), **Koleka Mlisana** (University of KwaZulu Natal, South Africa), **Lori Newman** (National Institutes of Health, Washington, DC, USA), **Catherine Ngugui** (Ministry of Health, Kenya), **Lilani Rajapaksa** (National STD AIDS Control Programme, Sri Lanka), **Reshmie Ramautarsing** (Bangkok, Thailand), **Danvic Rosadiño** (Love Your Self Clinic, Mandaluyong City, Philippines) and **Janet Wilson** (International Union of STI, Leeds, United Kingdom).

## WHO Secretariat and consultants

### Overall coordination

**Teodora Elvira Wi** led the guideline development and coordinated the overall development process. The guideline would not have been developed without the unwavering support of **Meg Doherty**, Director, Global HIV, Hepatitis and Sexually Transmitted Infections Programmes.

### WHO headquarters

The following individuals contributed to developing these guidelines: Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes: **Rachel Baggaley**, **Theresa Babovic**, **Meg Doherty**, **Nathan Ford**, **Cadi Irvine**, **Yamuna Mundade**, **Annette Vester**, **Marco Vitorio**, **Lara Vojnov** and **Mayada Youssef-Fox**; Department of Sexual and Reproductive Health: **Ian Askew**, **Nathalie Broutet**, **Venkatraman Chandra-Mouli**, **Sami Gottlieb**, **James Kiarie**, **Melanie Taylor** and **Igor Toskin**; Department of Maternal, Newborn, Child and Adolescent Health: **Francis McConville**; and Department of Antimicrobial Resistance, Surveillance, Evidence and Laboratory Strengthening: **Carmen Pessoa**.

**Jasmin Leuterio**, **Laurent Poulain** and **Danilo Salvador** provided administrative support. **Adriana De Putter** and **Jerome Peron** managed the budget and commissioning processes. **Yann Seigenthaler** (consultant, WHO Communications) provided communication and product development support.

### WHO regional offices

**Hugues Lago** (WHO Regional Office for Africa); **Massimo Ghidinelli** (WHO Regional Office for the Americas); **Joumana Hermez** (WHO Regional Office for the Eastern Mediterranean); **Nicole Seguy** (WHO Regional Office for Europe); **Bharat Rewari** (WHO Regional Office for South-East Asia); **Naoko Ishikawa** (WHO Regional Office for the Western Pacific).

Special acknowledgement to **Francis Ndowa**, who assisted in collating and analysing all the comments from the Guideline Development Group and the External Review Group and compiling the various inputs. **David Breuer** edited the text.

### Funding

The Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, Ministry of Development Cooperation and Humanitarian Office, Luxembourg and UNDP/ UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction provided funding for this guideline.

# ABBREVIATIONS AND ACRONYMS

<b>AIDS</b>	acquired immune deficiency syndrome
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation
<b>HIV</b>	human immunodeficiency virus
<b>HPV</b>	human papillomavirus
<b>HSV</b>	herpes simplex virus
<b>HSV-2</b>	herpes simplex virus type 2
<b>NAAT</b>	nucleic acid amplification test
<b>PCR</b>	polymerase chain reaction
<b>PICO</b>	population, intervention, comparator, outcome
<b>PrEP</b>	pre-exposure prophylaxis
<b>RPR</b>	rapid plasma reagin
<b>STI</b>	sexually transmitted infection
<b>TPHA</b>	<i>Treponema pallidum</i> haemagglutination assay
<b>TPPA</b>	<i>Treponema pallidum</i> particle agglutination assay
<b>UNAIDS</b>	United Nations Programme on HIV/AIDS
<b>UNFPA</b>	United Nations Population Fund
<b>UNICEF</b>	United Nations Children's Fund
<b>VDRL</b>	Venereal Diseases Research Laboratory

# EXECUTIVE SUMMARY

Worldwide, people acquire more than 1 million curable sexually transmitted infections (STIs) every day. Based on prevalence data from 2009 to 2016, in 2019, WHO published estimates of new cases of chlamydia, gonorrhoea, syphilis and trichomoniasis, showing total estimated incident cases of 376.4 million among people 15–49 years old in 2016, with 127.2 million new cases of chlamydia, 86.9 million new cases of gonorrhoea, 156 million new cases of trichomoniasis and 6.3 million new cases of syphilis. The prevalence of some viral STIs is similarly high, with an estimated 417 million people infected with herpes simplex virus type 2 (HSV-2) and about 291 million women harbouring human papillomavirus (HPV) at any point in time.

The WHO global health sector strategy on sexually transmitted infections, 2016–2021, endorsed by the World Health Assembly in 2016, aims to eliminate STIs as a public health threat by 2030. The key pillars to eliminate STIs are to prevent people from being infected and to provide treatment and care for infected people to avoid further transmitting STIs to other people. The strategy makes a strong case for expanding the provision of high-quality STI prevention and care more widely into the areas of primary health care, sexual and reproductive health and HIV prevention and care services. Efforts should therefore be made to strengthen STI case management that ensures the widest possible access to high-quality services at the population level based on simplified and standardized interventions and services that can readily be taken to scale, especially in resource-limited settings.

Since the WHO guidelines for the management of sexually transmitted infections were published in 2003, changes in the epidemiology of STIs and progress in prevention, diagnosis and treatment of STIs and HIV have necessitated changes in approaches to STI prevention and management.

Syndromic management is widely used to manage people with symptoms of STIs. In most resource-limited settings, the syndromic management flow charts are still the standard of care where laboratory diagnosis is not available or, where it is available, getting results take several days. Although the STI syndromic approach has some shortcomings, it remains an essential component of managing people with symptoms of STIs. These guidelines aim to raise the quality of managing symptomatic STIs by providing evidence-informed recommendations. In addition, given the existence of rapid diagnostic tests that have recently become available, these guidelines also provide guidance on how to use them in settings in which they are accessible.

The objectives of these guidelines are:

- to provide updated, evidence-informed clinical and practical recommendations on the case management of people with symptoms of STIs; and
- to support countries in updating their national guidelines for the case management of people with symptoms of STIs.

These guidelines include the management of symptomatic infections related to:

- urethral discharge syndrome, including persistent urethral discharge syndrome;
- vaginal discharge syndrome, including persistent vaginal discharge;
- anorectal infection;
- genital ulcer disease syndrome; and
- lower abdominal pain syndrome.

These guidelines are intended for programme managers for STI prevention and control at the national level and the health-care providers at the frontline – primary, secondary and tertiary health care. For programme managers, the guidelines will assist in deciding how to organize the services for providing STI care and how to determine the distribution of equipment and commodities that ensures high-quality access to STI care for people.

The guidelines can also be used as an advocacy tool for the financial and human resources required to deliver adequate, acceptable and equitable STI care for everyone who needs STI services.

Similarly, these guidelines can offer guidance to policy-makers and other stakeholders, including finance ministries at the country level, partners in providing services for STI prevention and care, such as local and international donor agencies, nongovernmental organizations, including community-based organizations, patient representatives and other stakeholders.

These guidelines were developed following the methods outlined in the 2014 *WHO handbook for guideline development*. Multiple systematic reviews and modelling of health outcomes were carried out. The STI Guideline Development Group assessed the evidence and made the recommendations. The recommendations in the guidelines were based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach in reviewing evidence and formulating recommendations. The External Review Group reviewed the guidelines.

# 1. SUMMARY OF RECOMMENDATIONS

## 1.1 Recommendations for the management of urethral discharge

For people with symptom of urethral discharge from the penis, management is recommended to be based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit.

*(Strong recommendation; moderate-certainty evidence)*

Good practice includes:

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination of the genital and anal areas; and
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines.

Good practice statement

**Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit**

*(Strong recommendation; moderate-certainty evidence)*

WHO recommends the following.

1. Perform molecular assays such as nucleic-acid amplification testing (NAAT) to confirm or exclude *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.
2. Treat according to the test results on the same day. If urethral discharge is present but tests are negative, treat for non-gonococcal and non-chlamydial urethritis (such as *Mycoplasma genitalium* or *Trichomonas vaginalis*).
3. When treatment based on molecular assays is not feasible on the same day of the visit, WHO recommends syndromic treatment of infection with *N. gonorrhoeae* and *C. trachomatis* and using the test results to support managing the partner when tests are available.
4. Treat people with recurrent or persistent urethral discharge based on a repeat molecular assay (such as NAAT) after 21 days, testing for *N. gonorrhoeae*, *C. trachomatis* as well as *M. genitalium* and *T. vaginalis* and testing for antimicrobial-resistant *N. gonorrhoeae*.

### Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing

WHO suggests the following.

1. Treat people who have urethral discharge confirmed on examination for *N. gonorrhoeae* and *C. trachomatis* to ensure same-day treatment.
2. Treat people with recurrent or persistent urethral discharge for treatment failure based on WHO guidelines and review.

Good practice includes:

- if symptoms persist at review, checking partner notification and treatment history; and
- for people with recurrent or persistent urethral discharge, referring people to a centre with laboratory capacity to diagnose *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium*.

*(Conditional recommendation; low-certainty evidence)*

Good practice statement

## 1.2 Recommendations for the management of vaginal discharge

For people with symptom of vaginal discharge, WHO recommends treatment for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis* on the same visit. WHO suggests treatment based on the results of quality-assured molecular assays for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis*. In settings in which treatment based on the results of molecular assay in the same visit is not feasible or that have limited or no molecular testing, WHO suggests treatment based on testing with quality-assured rapid point-of-care tests or on syndromic treatment.

*(Strong recommendation; moderate-certainty evidence)*

For people with symptom of vaginal discharge, good practice includes:

Good practice statement

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination, including abdominal and pelvic examination, to assess for pelvic inflammatory disease, surgical conditions or pregnancy and external vulvovaginal examination to visualize any lesions, overt genital discharge or vulval erythema and excoriations;
- bimanual digital examination of the vagina (1) to assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) to assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove; and

- offering HIV and syphilis testing and other preventive services as recommended in other guidelines.

**Settings in which treatment is based on quality-assured molecular assays in a laboratory with a fully operational quality management system and results available on the same day of the visit**

*(Strong recommendation; moderate-certainty evidence)*

1. WHO recommends treating *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis* based on the results of quality-assured molecular assays on a self-collected, or clinician-collected, vaginal swab or on a urine specimen (Algorithm ①).
2. WHO suggests treating for bacterial vaginosis if vaginal discharge is present (for example, tenacious or thin) or based on the results of microscopy, if available.
3. WHO suggests treating for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available.

**Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing**

*(Conditional recommendation; low-certainty evidence)*

1. WHO suggests treating based on a quality-assured rapid test with a minimum sensitivity of 80% and specificity of 90%, if available, to confirm or exclude infection with *N. gonorrhoeae* and *C. trachomatis* (Algorithm ②).
2. If the availability of a low-cost rapid test or molecular assay is limited, WHO suggests performing a speculum examination and treating for *N. gonorrhoeae* and *C. trachomatis* if there is evidence of cervicitis and performing a low-cost rapid test or molecular assay for people with a negative speculum examination who are at high risk of infection with *N. gonorrhoeae* and *C. trachomatis* and treating based on the test results (Algorithm ③<sup>a</sup>).
3. If a rapid test is not available, WHO suggests treating people who have signs of cervicitis on speculum examination for infection with *N. gonorrhoeae* and *C. trachomatis* (Algorithm ③).
4. If a rapid test is not available and a speculum examination is not feasible or acceptable, WHO suggests treating people for *N. gonorrhoeae* and *C. trachomatis*, all people at high risk of STIs and all people who have vaginal discharge on genital examination (Algorithm ④).
5. WHO suggests treating people for bacterial vaginosis and *T. vaginalis* if vaginal discharge is present or based on the results of microscopy, if available.
6. WHO suggests treating people for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available.

Good practice includes the following.

- For people with recurrent or persistent vaginal discharge, good practice includes referring to a centre with laboratory capacity to diagnose infection with *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and bacterial vaginosis and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium* (if there is a test) or for a specialist's assessment (STI expert and physician or a gynaecologist), when no such testing is available in primary health care centres.

Good practice statement

### 1.3 Recommendations for the management of lower abdominal pain among women

**For sexually active women with symptom of lower abdominal pain, WHO suggests assessing for pelvic inflammatory disease and treating syndromically.**

*(Conditional recommendation; low-certainty evidence)*

Good practice includes:

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination, including abdominal and pelvic examination, to assess for pelvic inflammatory disease, surgical conditions or pregnancy and vulvovaginal examination to visualize any lesions, overt genital discharge, vulval erythema and excoriations;
- performing a bimanual digital examination of the vagina (1) to assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) to assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove; and
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines.

Good practice statement



For sexually active women with lower abdominal pain with either of the following features on clinical examination (bimanual palpation):

- cervical motion tenderness; or
- lower abdominal tenderness:

*(Conditional recommendation; moderate-certainty evidence)*

WHO suggests the following.

1. Treat for pelvic inflammatory disease on the same visit.
2. Test for infection with *N. gonorrhoeae* and *C. trachomatis* and, if available, *M. genitalium*, to support partner management when tests are available.
3. Schedule follow-up assessment three days later to assess for clinical improvement, and if the woman has not improved, refer for further assessment.

For women with lower abdominal pain with any of the following conditions, good practice includes referral to surgical or gynaecological assessment:

- missed or overdue period;
- recent delivery, abortion or miscarriage;
- abdominal guarding and/or rebound tenderness;
- abnormal vaginal bleeding in excess of spotting;
- abdominal mass; and
- detection of a suspected cervical lesion.

Good practice statement

## 1.4 Recommendations for the management of genital ulcer disease, including anorectal ulcers

**For people who present with genital ulcers (including anorectal ulcers), WHO recommends treatment based on quality-assured molecular assays of the ulcer. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit.**

*(Strong recommendation; moderate-certainty evidence)*

Good practice includes:

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination of the genital and anal areas;
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and
- providing analgesics for pain.

Good practice statement

### **Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit**

*(Strong recommendation; moderate-certainty evidence)*

For people with confirmed anogenital ulcers, WHO recommends the following.

1. Perform molecular assays (NAAT) from anogenital lesions to confirm or exclude herpes simplex virus and *Treponema pallidum* (syphilis).
2. Perform molecular assays from anogenital lesions to confirm lymphogranuloma venereum in geographical settings and/or populations in which cases are reported or emerging.
3. Perform serological tests for syphilis, with appropriate interpretation for management depending on the test or tests used.
4. Treat for syphilis and/or herpes simplex virus according to the results available on the same day of the visit or treat syndromically and revise management according to the results when available.
5. Treat for lymphogranuloma venereum when the results are positive.
6. Treat for chancroid only in geographical settings where cases are reported or emerging.

### Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing

For people with confirmed anogenital ulcers, WHO suggests the following.

1. Treat syndromically for syphilis and herpes simplex virus on the same day.
2. Treat for herpes simplex virus if the ulcer is recurrent or vesicular, and treat for syphilis if the person has no history of recent treatment for syphilis (in the past three months).
3. Treat for chancroid only in geographical settings where cases are reported or emerging.

Good practice includes:

- performing serological tests for syphilis, including an RPR-equivalent test, if available, to attempt to identify active syphilis and for monitoring the response to treatment; and
- referring men with persistent anogenital ulcers to a centre with laboratory capacity and expertise to diagnose herpes or less common pathogens (lymphogranuloma venereum, donovanosis and chancroid) and other genital or gastrointestinal conditions.

### Remarks

Genital ulcer disease refers to breaks in the skin or mucosa and may present as ulcers, sores or vesicles. Anogenital ulcers refer to those located on the genital or anal areas and may be painful or painless.

A negative serological test for syphilis when anogenital ulcers have been present for less than three weeks does not definitively exclude syphilis, since antibodies may not yet be present to be detected by a serological test for syphilis. See WHO guidance on interpreting syphilis tests (see subsection 10.2).

*(Conditional recommendation; moderate-certainty evidence)*

Good practice statement

## 1.5 Recommendations for the management of anorectal discharge

**For people with symptom of anorectal discharge and report receptive anal sex, WHO recommends management based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit.** *(Strong recommendation; moderate-certainty evidence)*

Good practice includes:

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination of the genital and perianal areas and a digital rectal examination, if acceptable (and anoscopy, if available and acceptable);
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and
- referring for other investigations when anorectal discharge is unrelated to a sexually transmitted infection, such as other gastrointestinal conditions.

Good practice statement

**Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit**  
WHO recommends the following. *(Strong recommendation; moderate-certainty evidence)*

1. Perform molecular assays (NAAT) using a self-collected or clinician-collected anorectal swab to confirm or exclude infection with *N. gonorrhoeae* and/or *C. trachomatis* and treat the individual infections detected.
2. Treat, additionally, for herpes simplex virus if there is anorectal pain.
3. Follow the genital ulcer guidelines if ulceration is present.

**Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing**  
WHO suggests the following. *(Conditional recommendation; moderate-certainty evidence)*

1. Treat for *N. gonorrhoeae* and *C. trachomatis* if discharge is present.
2. Treat, additionally, for herpes simplex virus if there is anorectal pain.

Good practice includes:

- following the genital ulcer guidelines if ulceration is present; and
- referring people with persistent anorectal discharge to a centre with laboratory capacity to diagnose *N. gonorrhoeae*, *C. trachomatis* (including lymphogranuloma venereum serovars) and *M. genitalium* and determine antimicrobial resistance for *N. gonorrhoeae* and *M. genitalium*.

Good practice statement

## 2. INTRODUCTION AND OVERVIEW OF THE DEVELOPMENT OF WHO GUIDELINES FOR THE MANAGEMENT OF SYMPTOMATIC SEXUALLY TRANSMITTED INFECTIONS

### 2.1 Epidemiology and global burden of sexually transmitted infections

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting the quality of life and causing serious illness and death. The illness caused by STIs profoundly affects the physical, mental and social well-being of children, adolescents and adults worldwide. Some STIs directly affect reproductive and child health by causing infertility, anogenital cancer, adverse outcomes of pregnancy, fetal deaths and abnormalities and general ill health. In addition, they have indirect effects through their role in facilitating the sexual transmission and acquisition of HIV, resulting in more suffering among people living with HIV; mental health comorbidities, including depression, anxiety, dementia and other cognitive disorders; and other comorbidities experienced by people living with HIV.

Worldwide, people acquire more than 1 million curable STIs every day. Based on prevalence data from 2009 to 2016, in 2019, WHO published estimates of new cases of chlamydia, gonorrhoea, syphilis and trichomoniasis, showing total estimated incident cases of 376.4 million among people 15–49 years old in 2016, with 127.2 million new cases of chlamydia, 86.9 million new cases of gonorrhoea, 156 million new cases of trichomoniasis and 6.3 million new cases of syphilis (1).

The burden of STIs varies by region and sex, and the burden is greatest in resource-limited countries. The global incidence rates in 2016 were estimated to be 34 new cases of chlamydia per 1000 women and 33 per 1000 men; 20 new cases of gonorrhoea per 1000 women and 26 per 1000 men; 40 new cases of trichomoniasis per 1000 women and 42 per 1000 men; and 1.7 new cases of syphilis per 1000 women and 1.6 per 1000 men. The WHO African Region had the highest numbers of new cases of gonorrhoea and trichomoniasis among women and men, and the WHO Region of the Americas had the highest numbers of new cases of chlamydia and syphilis among both men and women (1).

Although progress has been made in preventing the mother-to-child transmission of syphilis since 2012, the decline has not been substantial, since an estimated 661 000 cases of congenital syphilis occurred in 2016. The number of cases of congenital syphilis per 100 000 live births fell from 539 in 2012 to 473 in 2016, indicating that more efforts are needed to accelerate the interventions for sustainable and greater impact. Of the 661 000 cases of congenital syphilis in 2016, more than 350 000 occurred as adverse birth outcomes, including stillbirths and neonatal deaths (2,3).

The prevalence of some viral STIs is similarly high, with an estimated 417 million people infected with herpes simplex virus type 2 (HSV-2), and about 291 million women harbour human papillomavirus (HPV) at any time (4).

When left undiagnosed and untreated, STIs can result in serious complications and sequelae, such as pelvic inflammatory disease, infertility, ectopic pregnancy, miscarriage, fetal loss and congenital infections and cancer. Curable STIs accounted for the loss of nearly 11 million disability-adjusted life years (DALYs) in 2010 (5). The mental effects of STIs include stigma, shame and loss of self-worth. STIs have also been associated with fears of relationship disruption and gender-based violence, thus undermining effective partner notification (6).

Both ulcerative and non-ulcerative STIs are associated with a several-fold increased risk of transmitting or acquiring HIV (7,8). Infections causing genital ulcers are associated with the highest risk of HIV transmission. In addition to curable ulcer-causing STIs (such as syphilis and chancroid), highly prevalent HSV-2 infections substantially increase vulnerability to transmitting and acquiring HIV (9). Non-ulcerative STIs, such as gonorrhoea, chlamydia and trichomoniasis, have been shown to increase HIV transmission through genital shedding of HIV (10,11).

Preventing and controlling STIs are integral components of comprehensive sexual and reproductive health services that are needed to attain the related targets under Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages), including: target 3.2 – to end preventable deaths of neonates and children under 5 years of age; target 3.3 – to end the epidemics of AIDS and other communicable diseases; target 3.4 – to reduce premature mortality from noncommunicable diseases and promote mental health and well-being; target 3.7 – to ensure universal access to sexual and reproductive health-care services; and target 3.8 – to achieve universal health coverage.

## 2.2 STIs and HIV

Although HIV, which causes AIDS, is most commonly spread through sexual intercourse, the HIV epidemic has usually been addressed differently and separately from the other STIs. Initially, this was because AIDS emerged as a fatal, untreatable and rapidly spreading disease. Because of that, the focus was centred more around HIV and AIDS research and, in addition, palliative patient care programmes and community activism evolved to deal with the mounting HIV-related morbidity and mortality and acceleration of the development of antiretroviral therapy. In contrast, the care and research related to the other STIs were already embedded in other programmes. Consequently, since the 1980s, HIV and the other bacterial and viral STIs have often been addressed through separate programmes and through separate funding mechanisms, with many HIV programmes not funding STI-related interventions or costs.

### 2.2.1 The syndemics of HIV and other STIs

The syndemics model of health highlights the biosocial complex, which consists of interacting, co-present or sequential diseases and the social and environmental factors that amplify the negative effects of disease interactions. HIV and the other STIs have high co-prevalence, and sociobehavioural elements, especially in vulnerable populations, function as syndemics. This interaction requires integrated and multifaceted approaches to engage those at greatest risk of HIV and other STIs in interventions and programmes. This is especially essential from a public health perspective, in increasing access to appropriate testing, linkage to treatment and further strengthening preventive services.

Integrating the prevention and control of HIV and other STIs requires some understanding of the salient cultural and behavioural factors potentiating HIV susceptibility and transmission. Individuals at greatest risk of HIV and other STIs are often members of socially marginalized populations, whose life experiences and internalized stigma may result in high rates of concomitant depression, substance abuse and decreased self-worth, often resulting in avoiding health-care settings, in which discrimination may be anticipated and/or experienced.

Stigma and societal rejection frequently result in avoidant health-seeking behaviour, delaying diagnosis, interfering with effective partner notification and, consequently, impeding public health control of STI and HIV epidemics. Health-care providers need to be taught about providing culturally competent and sensitive STI and HIV care, so that vulnerable populations seek clinical services more readily, leading to earlier diagnosis and preventing the further spread of STIs, including HIV.

The increasing ability to control the HIV epidemic by using antiretroviral therapy can guarantee people living with HIV long and healthy lives, and pre-exposure prophylaxis (PrEP) of HIV means that people at higher risk do not need to acquire HIV. Although these advances are welcome developments, the resulting unprotective sex behaviour when HIV is more controllable has been noted to increase the burden of STIs in some populations on PrEP, which could be averted by incorporating regular screening for other STIs into PrEP projects (12,13).

The challenge for researchers, clinicians and public health officials is to understand how best to promote sexual health (see below) in this new age. The desirable benefits of improvements in HIV treatment, diagnostic capabilities for HIV and other STIs, and educational digital media create new challenges and opportunities for key stakeholders, including civil society, to limit the spread of STIs while respecting individual decisions about sexual expression.

According to WHO's current working definition (14), sexual health is:

"... a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled."

Guidelines alone will not achieve this shift in programming health-care services. There needs to be a strategic shift in implementing interventions and in the collaboration between programmes addressing different vulnerable population groups to address the common goals and outcomes of preventing people from acquiring both HIV and new cases of the other STIs.

## 2.3 Objectives and rationale for developing the guidelines

The WHO global health sector strategy on sexually transmitted infections, 2016–2021, endorsed by the World Health Assembly in 2016, aims to eliminate STIs as a public health threat by 2030 (15). The key pillars to eliminate STIs are to prevent people from becoming infected and to provide treatment and care for infected people to avoid further transmission of STIs to other people. The strategy makes a strong case for expanding the provision of high-quality STI prevention and care more widely into primary health care, sexual and reproductive health and HIV prevention and care services. Efforts should therefore be made to strengthen STI case management, which ensures the widest possible access to high-quality services at the population level, based on simplified and standardized interventions and services that can readily be taken to scale, especially in resource-limited settings.

Since WHO published the guidelines for the management of sexually transmitted infections in 2003, changes in the epidemiology of STIs and progress in prevention, diagnosis and treatment of STIs and HIV have necessitated changes in approaches to managing STI prevention (16).

There has also been an upsurge of antimicrobial resistance, and there is an urgent need to update global treatment recommendations to effectively respond to the changing antimicrobial resistance patterns of STIs, especially in *Neisseria gonorrhoeae*. Effective treatment protocols that consider global and local antimicrobial resistance patterns are essential to curb the further spread and escalation of antimicrobial resistance globally. High-level gonococcal resistance to quinolones, a previously recommended first-line treatment, is widespread, and decreased susceptibility to the extended-spectrum (third-generation) cephalosporins, current first-line treatment for gonorrhoea, is rising (17–20). Resistance to azithromycin and treatment failures have been reported in strains of *Treponema pallidum*, *N. gonorrhoeae* and *Mycoplasma genitalium*. In addition, instances of *Chlamydia trachomatis* treatment failure have been reported for tetracyclines and macrolides (21,22).

Etiological diagnosis of STIs, although ideal, remains unfeasible for health-care providers in resource-limited settings. It constrains their time and resources, increases costs and reduces access to treatment. Near point-of-care tests based on molecular technology can be performed during the clinic visit for the same-visit test results for gonorrhoea and chlamydial infections. These tests can be strategically used when available to reduce the above challenges and ensure treatment at the first point of contact with people with STIs.

To overcome issues related to etiological diagnosis and treatment, WHO introduced syndromic case management in 1984. Syndromic management for urethral discharge among men and genital ulcers among men and women has proved to be both valid and feasible. It has resulted in adequate treatment of large numbers of infected people and is relatively inexpensive, simple and very cost-effective (16). However, given the recent data on the changing causes of genital ulcer disease, HSV-2 infections being the commonest and predominant cause of genital ulcer disease, evidence-informed flow charts need to be updated.

WHO's simplified generic tool for syndromic management of STIs includes flow charts for women with symptoms of vaginal discharge and/or lower abdominal pain. The flow charts for abdominal pain are quite satisfactory, but those for vaginal discharge have limitations, especially in managing cervical (gonococcal and chlamydial) infections. In general, but especially in settings with low STI prevalence and among adolescent females, vaginitis rather than an STI is the main cause of vaginal discharge. Moreover, overtreatment is becoming



increasingly undesirable because of the worsening antimicrobial resistance and limited treatment options. Updating these guidelines has considered mechanisms to mitigate the escalation and further development of antimicrobial resistance, especially when near-patient point-of-care tests are rapidly becoming more available.

Syndromic management is widely used. In most resource-limited settings, these flow charts are still the standard of care when laboratory diagnosis is not available or when results take several days. The STI Guideline Development Group members have reiterated that the STI syndromic approach is still an essential component of STI prevention and control but that WHO should improve the various STI syndromic case management flow charts and that these guidelines should raise the quality of STI case management for people with STI symptoms and not promote suboptimal care. Member States, nongovernmental organizations (NGOs) and partners have requested WHO to give priority to updating these guidelines.

## 2.4 Objectives of the guidelines

The objectives of these guidelines are as follows:

- to provide updated, evidence-informed clinical and practical recommendations on case management of people with symptoms of STIs; and
- to support countries in updating their national guidelines for the case management of people with symptoms of STIs.

These guidelines include the management of people with symptoms related to:

- urethral discharge syndrome, including persistent urethral discharge syndrome;
- vaginal discharge syndrome, including persistent vaginal discharge;
- anorectal infection;
- genital ulcer disease syndrome; and
- lower abdominal pain syndrome.

## 2.5 Target audience

These guidelines will be part of a consolidated set of guidelines for the prevention of STIs and management of people with STIs that are intended for programme managers for STI prevention and control at the national level and the health-care providers at the frontline in primary, secondary and tertiary health-care facilities. For the programme managers, the guidelines will assist in deciding how to organize the services for providing STI care and to determine the distribution of equipment and commodities that ensure access to high-quality STI care for people.

The guidelines can also be used as an advocacy tool for the financial and human resources required to deliver adequate, acceptable and equitable STI care for everyone who needs STI services.

Similarly, these guidelines can offer guidance to policy-makers and other stakeholders, including finance ministries at the country level, partners in providing services for STI prevention and care, such as local and international donor agencies and nongovernmental organizations, including community-based organizations, patient representatives and other stakeholders.

## 2.6 Guiding principles

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

- The guidelines contribute to and expedite the achievement of key global and national goals to contribute to achieving the Sustainable Development Goals.
- The guidelines are based on a public health approach to scaling up the provision of care for people with STIs to reach everyone who needs such services, including vulnerable populations and key populations, with interventions, such as targeted screening (in accordance with WHO guidance) for *N. gonorrhoeae* and *C. trachomatis* and antimicrobial resistance monitoring in men who have sex with men who are receiving PrEP, especially in settings in which STI molecular testing is limited or not available as well as more targeted testing (in accordance with WHO guidance) around hepatitis C testing.
- Adaptation and implementation of the guidelines need to be accompanied by efforts to promote and protect the human rights of people who need services for STI care, including ensuring preventing stigma and discrimination in providing such services and promoting gender equity.
- 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 diagnosing STIs and providing STI treatment and care in the context of the capacity of the health system and anticipated cost–effectiveness.
- The guidelines allow adaptability that aims at promoting accessibility, acceptability and effectiveness in the case management of people with STIs through public and private health-care systems, including at the primary health-care level and other first-level health-care facilities providing services for STIs, such as maternal and child health, antenatal, family planning and other sexual and reproductive health-care facilities.
- The guidelines provide guidance for acceptable and effective STI care services to populations identified as being especially vulnerable to or at higher risk of STIs, including HIV infection.
- The guidelines are constructed based on evidence of effectiveness and feasibility, providing a comprehensive approach that is easy to follow, addressing issues of diagnosis, treatment protocols, partner notification, health education and disease prevention, including condoms and vaccines.

## 2.7 Methods for developing the guidelines

In 2014, WHO formulated a roadmap for updating guidelines in the *WHO handbook for guideline development* (23). These guidelines were developed in accordance with the handbook, especially in the processes summarized below.

The WHO STI Secretariat proposed four phases of STI guideline development, and the STI Guideline Development Group members agreed, with the goal of producing a comprehensive and consolidated set of guidelines for preventing STIs and managing the people who have STIs. The phased approach for developing the guidelines was established as follows (Table 1).

- Phase 1 was to include guidelines for managing people with specific STIs and for other important and urgent STI issues and the guidelines for the syndromic management of people with STIs (managing people with STIs using a syndromic approach). The recommendations for managing people infected with specific pathogens were published as independent modules and disseminated in 2016, comprising treatment recommendation for *C. trachomatis* (chlamydia), *N. gonorrhoeae* (gonorrhoea), HSV-2 (genital herpes), *T. pallidum* (syphilis) and syphilis screening and treatment of pregnant women (24–28). These guidelines update the guidelines for the syndromic management of STIs to managing people with symptoms of STIs.
- Phase 2 will focus on guidelines for STI prevention.
- Phase 3 will address the treatment of additional infections, including *Trichomonas vaginalis* (trichomoniasis), bacterial vaginosis, *Candida albicans* (candidiasis), *Haemophilus ducreyi* (chancroid), HPV (genital warts and cervical cancer) and *M. genitalium*.
- Phase 4 will provide guidance on laboratory diagnosis and screening of STIs.

**Table 1. Sensitivity and Specificity for different steps in the flowcharts**

Phases	Topics
Phase 1	<ol style="list-style-type: none"> <li>1. Treatment of people with specific STIs: <i>C. trachomatis</i> (chlamydia), <i>N. gonorrhoeae</i> (gonorrhoea), HSV (genital herpes) and <i>T. pallidum</i> (syphilis)</li> <li>2. Syphilis screening and treatment for pregnant women</li> <li>3. STI syndromic approach (managing people with symptoms of STIs)</li> <li>4. Clinical management package</li> </ol>
Phase 2	5. STI prevention: condoms, behaviour change communication, biomedical interventions and vaccines
Phase 3	6. Treatment of people with specific STIs and reproductive tract infections not addressed in phase 1: <i>T. vaginalis</i> (trichomoniasis), bacterial vaginosis, <i>C. albicans</i> (candidiasis), <i>H. ducreyi</i> (chancroid), <i>Klebsiella granulomatis</i> (donovanosis), human papillomavirus (HPV; genital warts or cervical cancer), <i>Sarcoptes scabiei</i> (scabies) and <i>Phthirus pubis</i> (pubic lice)
Phase 4	7. STI laboratory diagnosis and screening (managing people with STIs that are asymptomatic)

These STI guidelines focus on the management of people with symptomatic STIs, which includes the etiological approach (laboratory diagnosis) and the syndromic approach (based on symptoms and signs) to diagnose symptomatic STIs. To embark on the recommendations for managing people with symptoms of STIs, systematic reviews on various syndromes and modelling work on vaginal discharge were carried out by experts from McMaster University, the Michael G. DeGroote Cochrane Canada Centre, Monash University and the University of Bristol.

### 2.7.1 Guideline Development Group

WHO consulted with a group of experts, which included international STI experts, clinicians, researchers and programme managers and other key stakeholders in the domain of STIs and established the WHO STI Guideline Development Group (Annex 1).

The STI Guideline Development Group participated in meetings in person and virtually to set priorities for questions to address in the guidelines (including outcomes), review the evidence and make recommendations. The STI Guideline Development Group reviewed and approved the final version of the guidelines. In addition, an External Review Group was established, also of experts, implementers and community members, who reviewed the recommendations, provided feedback and approved the guidelines (Annex 2).

## 2.7.2 Meeting of the STI Guideline Development Group

### 2.7.2.1 Questions and outcomes

In August 2017, the STI Guideline Development Group met to define the scope of the guidelines. An analytical framework flow diagram for the syndromic approach was approved, which formed the basis for the population, intervention, comparator and outcome (PICO) questions and which evidence may be needed. During the meeting, the key PICO questions were identified that formed the basis for the systematic reviews and the recommendations. The STI Guideline Development Group set priorities for the syndromes for the specific STIs and the components of management, including history taking, risk assessment, microscopy and molecular tests. Based on the discussions, the Guideline Development Group identified the following syndromes as important to review:

- urethral discharge syndrome, including persistent urethral discharge syndrome;
- vaginal discharge syndrome, including persistent vaginal discharge;
- anorectal infection;
- genital ulcer disease syndrome; and
- lower abdominal pain syndrome.

Following this meeting, a survey was conducted among Guideline Development Group members to set priorities for the outcomes according to clinical relevance and importance. Outcomes varied by syndrome (Annexes 3–7).

### 2.7.2.2 Reviewing evidence and draft recommendations

Because of the complexity of developing flow chart–based recommendations, several subgroup virtual meetings were initiated in June 2019 to review the evidence. The STI Guideline Development Group subgroup proposed collecting additional evidence, including risk factors for *N. gonorrhoeae* and *C. trachomatis* infections and asymptomatic and symptomatic gonococcal and chlamydial infections and to model the cost and effectiveness of different strategies of diagnosing *N. gonorrhoeae* and *C. trachomatis* among women with vaginal discharge and the outcomes of the various syndromes. A series of virtual meetings followed to discuss the evidence and propose draft recommendations for the syndromes.

### 2.7.2.3 Recommendations

A virtual STI Guideline Development Group meeting was organized from 28 September to 2 October 2020 to present the main discussions and decisions made during the subgroup meetings, finalize the evidence-to-decision tables and finalize recommendations.

## 2.8 Reviews of the evidence

Multiple systematic reviews were conducted by a team at McMaster University, Michael G. DeGroote Cochrane Canada Centre and a team led by Monash University, Australia. For each syndrome, systematic reviews of studies were conducted to find studies comparing approaches to each other that reported the effects on important outcomes (Annexes 3–7). When these studies were not available, additional reviews were conducted that reported the

prevalence of the suspected STI and the accuracy of various syndromic approaches (including risk assessment, history taking, presence of signs and tests) (supplemental material for unpublished systematic reviews, Annex 8). Comprehensive searches for previously conducted systematic reviews, randomized controlled trials and non-randomized studies were performed up to September 2019. Additional searches were conducted to identify studies for patient values and preferences (such as qualitative research designs), acceptability, feasibility, equity and resources (such as cost–effectiveness studies). The steps of the systematic reviews were conducted in duplicate, and statistical pooling of the results from studies was performed when possible. Systematic reviews of the treatment of people with the suspected STIs (such as chlamydia, gonorrhoea, syphilis and herpes) were previously conducted for the WHO treatment guidelines (24–28) and were used to provide data for treatment outcomes.

## 2.9 Modelling outcomes

Because the effects on important outcomes for the people with STIs were not available from the studies, the effects were calculated using the diagnostic test accuracy from the studies. The numbers of true positives and negatives and false positives and negatives were calculated using the sensitivity and specificity of the approach and the prevalence of the STI in a population presenting with symptoms and then discussed with the Guideline Development Group the consequences of and weight of the consequences of, for example, a false negative (missing the diagnosis of a STI) on a patient or health system.

For the syndromic management of vaginal discharge, a static model using Excel was developed. The model simulates a range of management strategies to identify and treat vaginal and cervical infections. The model builds on previous work of WHO to provide a comprehensive, flexible model that can simulate a range of patient management flow charts based on syndromic management plus existing diagnostic procedures and tests (such as speculum examination and Gram stain) in different various prevalence, country or clinic settings. The strategies in the model include different combinations of risk assessment, speculum examination, microscopy and/or available and prospective rapid point-of-care diagnostic tests and the previously recommended WHO syndromic management approaches. The cost and effects were calculated based on the prevalence of the STIs.

In the cost analysis, the direct costs of managing women with vaginal discharge were incorporated: test cost, treatment cost, according to infection (chlamydia, gonorrhoea and combined bacterial vaginitis or *T. vaginalis* treatment) plus optionally the costs of long-term consequences (pelvic inflammatory disease, ectopic pregnancy and infertility) and/or partner management.

Because of the scarcity of evidence on the direct cost of overtreatment on antimicrobial resistance, the cost of antimicrobial resistance was incorporated in the form of an antimicrobial resistance externality tax, which can be applied to either all antibiotic treatments or to only those that are unnecessary. The antimicrobial resistance externality tax represents the current and future burden of antimicrobial resistance, including costs associated with treating resistant infections, increased morbidity and mortality and the cost of developing new drug therapies. We calculate this hypothetical antimicrobial resistance tax to be a tax associated with each single treatment of ceftriaxone and azithromycin, whether appropriate (the person has *N. gonorrhoeae* or *C. trachomatis*) or inappropriate (overtreatment – treated in the absence of infection).

The supplementary material (Annex 8) includes the Excel tool and describes the modelling of cost and effectiveness of different approaches to vaginal discharge.

## 2.10 Presentation of the evidence

Tables to facilitate decision-making for recommendations (evidence-to-decision frameworks) were produced for each recommendation and presented to the STI Guideline Development Group using the GRADEpro online software. These tables include a summary of the problem – test (diagnostic) accuracy, summary of the evidence for benefits and harm; certainty of the evidence; relevant patient values and preferences; and other issues, such as cost, resources, feasibility, equity and acceptability. The certainty of the body of evidence was assessed using the GRADE system, based on risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose-response and opposing confounding. Based on the above criteria, the overall certainty of evidence was defined as follows.

- very low: very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect;
- low: limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect;
- moderate: 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; and
- high: very confident that the true effect lies close to that of the estimate of the effect.

## 2.11 Making recommendations

The STI Guideline Development Group reviewed the evidence-to decision tables and the summaries of the evidence and made judgements about the effects of the syndromic management approaches during virtual meetings (28 September to 2 October 2020). Based on the discussions, the Guideline Development Group made decisions on whether to make strong or conditional recommendations for or against an approach. The Guideline Development Group agreed by consensus. There were no disagreements in which voting was necessary. The recommendations and evidence-to decision tables were finalized electronically via email.

According to the GRADE approach, the strength of each recommendation was rated as either strong or conditional. Strong recommendations are presented as recommendations and conditional recommendations are presented as suggestions. Table 2 explains the implications of the differing strengths of recommendations for patients, clinicians and policy-makers in detail. Good practice statements were made when the Guideline Development Group agreed that the guidance was necessary to provide 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 need to be considered. The External Review Group approved the methods and agreed with the recommendations made by the Guideline Development Group.

**Table 2. Implications of differing strengths of GRADE recommendations**

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

## 2.12 Managing conflicts of interest

Managing conflicts of interest was a key priority throughout the process of guideline development. WHO guidelines for declaration of interests for WHO experts were implemented. Declaration of interests statements were obtained from all members of the Guideline Development Group and the External Review Group before they assumed their role. At the beginning of the STI Guideline Development Group meetings, including subgroup meetings, the members disclosed their declared interests. The declaration of interests statements were summarized in a table as suggested by the WHO Guidelines Review Committee (Annex 2).

Five STI Guideline Development Group members declared interests. After analysing each declaration of interests, the WHO STI Secretariat found that one member (JK) had a huge noncommercial research grant from the United States National Institutes of Health that is not related to the current guidelines and a minor commercial interest related to STI diagnostics and thus concluded that this STI Guideline Development Group member would be allowed partial participation. Two members declared interests as consultants with global antimicrobial resistance and research development partnership (WHO–Drugs for Neglected Diseases Initiative partnership) not related to the current guidelines and no commercial interest and thus were allowed full participation. Two members declared support from a pharmaceutical company; one was provided minimal support for attending a meeting and the other received previous consultation fees and travel expenses but currently does not have any support from any pharmaceutical companies. Both were allowed full participation.

## 3. CASE MANAGEMENT FOR PEOPLE WITH STIs

### 3.1 Objectives of STI case management

The objectives of comprehensive STI case management are to provide treatment, obtain cure, reduce infectiveness, reduce the risk of developing complications of STIs and reduce or prevent future risk-taking behaviour, including in other biobehavioural interventions, such as PrEP and voluntary medical male circumcision, and ensure that sex partners are appropriately treated. This requires that the person with an STI receive the following services (15,29):

- have a medical and sexual history taken and noted;
- be given a correct diagnosis (whether syndromic or based on diagnostic tests);
- be given effective treatment;
- receive health education and counselling about the infection and risk reduction;
- receive advice on compliance with treatment;
- promotion and/or provision of condoms (male or female);
- promotion and/or provision of PrEP;
- promotion and/or provision of other preventive interventions, such as vaccines against hepatitis A and B, vaccines against HPV, where appropriate, and voluntary medical male circumcision;
- encouragement to notify sex partners; and
- clinical follow-up where appropriate.

Thus, effective case management consists not only of antimicrobial therapy to obtain cure and reduce infectiousness but also comprehensive assessment and care of the person's reproductive health and that of their sex partners. For adolescents, the approach must be appropriate and user-friendly so that the provision of STI services at primary health-care outlets can be regarded as accessible and non-judgemental by these vulnerable people at a critical stage in their development – a view they may carry with them into adulthood.

### 3.2 Requirements to achieve the objectives of STI case management

To achieve the objectives of STI case management, high-quality care and treatment for STIs must be available to people who need such services at their first point of contact with the health-care system. Regardless of the choice an individual makes for obtaining advice and treatment, whether



in the public or private sector, STI programmes should ensure that appropriate and effective comprehensive case management is available. Integrated care for STIs must be offered at as many primary health-care facilities as possible to ensure readily accessible services, reduction of stigma and promotion of the use of such facilities. This will be achieved more effectively if appropriate training in providing STI care is given to all health-care providers posted to work at primary health care facilities. Further, primary health care facilities should be appropriately equipped with relevant commodities and equipment to enable the staff to deliver high-quality care for people who need such services.

The rest of this section briefly describes the elements of case management.

### **3.2.1 Consultation with the person with an STI to establish the problem**

To establish a correct diagnosis, the health-care provider needs to ensure that there is a conducive environment to enable people with STI symptoms to discuss them freely. This requires the following as basic minimum items:

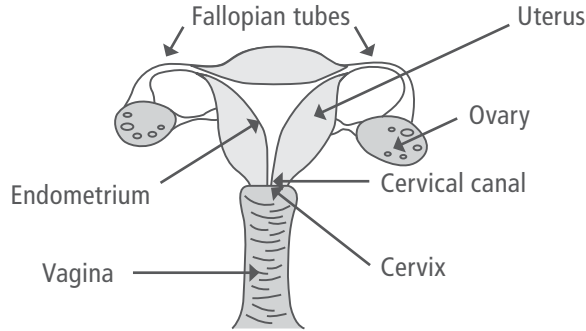
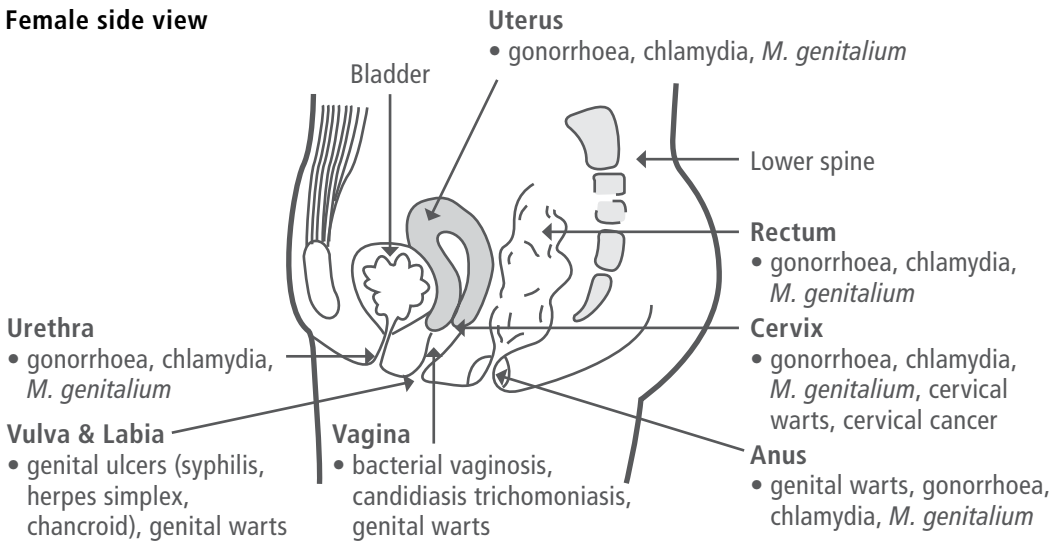
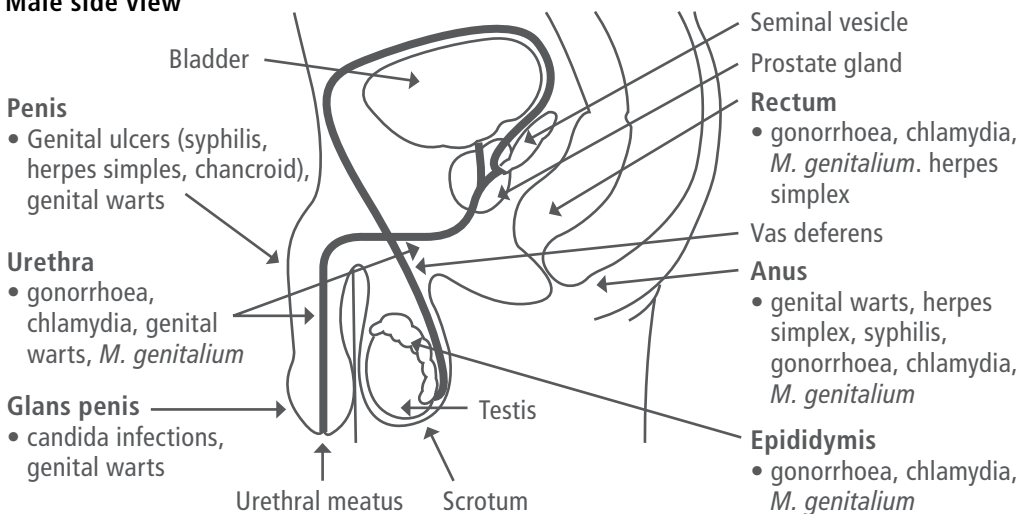
- adequate privacy for people to feel comfortable to discuss personal sexual matters;
- provision of private facilities for a good clinical examination, ideally with good lighting;
- an examination couch and a modesty blanket or draw sheet to cover the person in preparation for a physical examination; and
- examination gloves for the health-care provider.

#### **3.2.1.1 History-taking and risk assessment**

History-taking, with emphasis on sexual history, is important in establishing an understanding of the person's likelihood of being infected with an STI. During history-taking, the patient should be asked about the last unprotected sexual contact and whether with a regular or casual sex partner.

The importance of taking a sexual history cannot be emphasized enough in preventing STIs and managing a person suspected of having an STI, including HIV. Health-care providers should be non-judgemental in their approach to history-taking and make their patients feel comfortable to discuss personal and intimate issues about their sex life. Health-care providers need to integrate history-taking of common health risk factors together with sexual history risk factors. For example, as health-care providers ask about alcohol consumption and smoking, they should proceed at the same time to questions about sexual behaviour. Once this is done, it will all become part of general history-taking and will reduce the stigma and embarrassment associated with "talking about sex".

A sexual history involves talking about the genitalia. Discussing using illustrated diagrams can be helpful to health-care providers and patients alike in talking about risks of STIs in the genital area or the anorectal area (Fig. 1).

**Fig. 1. Common sites of infections in the female and male genital tract****Female front view****Female side view****Male side view**

History-taking, especially personal sexual history, is important in understanding the likelihood that the person has an STI. During history-taking, the person should be asked about the last sexual contact and sexual contacts before that and their sexual practices, including penile-vaginal, penile-anal, oral sex, use of sex toys and others and whether any protection, such as a condom, was used consistently. Documenting the type of sex partner(s), whether regular, casual or sex in exchange of money or favours, is also important.

One area in which risk assessment can be useful for a man is when he presents with dysuria without urethral discharge. The risk assessment may be considered to be positive for an STI if he has had unprotected sex within the last 7–21 days, to allow for the incubation period of both *N. gonorrhoeae* and *C. trachomatis*.

Verifying whether there has been any recent self-treatment is also important as well as when he last passed urine since urination within the past hour or two may temporarily wash away the discharge.

Usually, women who present to a health-care facility with a vaginal discharge do so when they perceive it as being unusual for them (such as the quantity, thickness or smell being abnormal for them), and usually their perception is correct (30–33). The majority will have either bacterial vaginosis or *T. vaginalis* infections as well as candidiasis.

Thus, during history-taking, risk assessment of a woman with abnormal vaginal discharge requires a good sexual history to estimate her risk of cervical infection with *N. gonorrhoeae* and/or *C. trachomatis*. In the published literature, clinical observations that have consistently been found to be associated with cervical infection are:

- the presence of cervical muco-purulent discharge;
- cervical erosions or cervical friability; and
- bleeding between menses or during sexual intercourse.

The risk assessment needs to consider these parameters together with some demographic and behavioural risk factors frequently associated with cervical infection, and the risk may be considered positive for STIs if the following criteria are met:

- if the client's sex partner has an STI, for example, a urethral discharge or genital ulcers; or
- if the answer is yes to two or more of the following, and she is sexually active:
  - younger than 25 years of age (some studies have found 21 years as significant);
  - she has had a new sexual partner in the three months preceding the current visit; or
  - she has had more than one sex partner in the three months preceding the current visit.

Positive responses to the risk assessment increase the likelihood that the client has an STI. In that situation, encouraging and discussing about partner treatment with the same regimen as the index client, even if it is not certain that the client has an STI, is therefore prudent, while recognizing that the commonest cause of vaginal discharge, bacterial vaginosis, is not considered to be sexually transmitted and neither is *Candida albicans*.

Thus, all women presenting with abnormal vaginal discharge should have a thorough medical and sexual history taken and be physically examined, ideally with a speculum, to view the cervix. However, external examination of the genitalia is better than no examination at all.

### 3.2.1.2 Clinical examination of people with STI-related symptoms

Once the medical and sexual history has been taken and assessment of risk of STIs duly noted, the person must be physically examined.

The person should be informed what the examination will entail and consent obtained. Any examination of the anogenital area should preferably be conducted in the presence of a chaperone. A male health-care provider must have a female chaperone in attendance, and vice versa, at all times, unless this is not feasible because of staff capacity. In that case, the person's consent to be examined without a chaperone should be obtained.

The examination must particularly focus on the anogenital area, but a general examination must also look for other manifestations of STIs, such as lymphadenopathy, cutaneous manifestations of some STIs, such as syphilis and HIV, and abdominal abnormalities, especially for women with pelvic inflammatory disease.

#### Steps to follow when examining men

- Wash hands before the examination and put on clean gloves with each patient.
- Inform the patient what is going to take place at each step of the examination.
- Ask the patient to lie down on a couch and expose the genital area from umbilicus to knee level. Where a couch is not available, the patient may be examined in a standing position, but this should be avoided as much possible. To avoid embarrassment and to show respect, the patient must be covered with a modesty blanket or a draw sheet and expose the part of the body to be examined when ready.

The examination of a man must include inspection in good light to look for rashes, sores, swellings, warts and urethral or anal discharge and general inspection including the following:

- looking inside the mouth for signs of oral thrush, oral sores or other lesions;
- looking at the skin over the abdomen for rashes and obvious swelling;
- checking the pubic area for evidence of other STIs, such as pubic lice and nits, scabies, sores and inguinal lymph nodes;
- checking for any skin rashes on the palms of the hands, soles of the feet, thighs and buttocks;
- checking the external genitals – penis and scrotum – and noting any discharge and other lesions, such as ulcers and warts;
- checking the area around the anus for a discharge, rashes (such as condylomata lata) and warts; and
- checking the groin for swellings and sores.

Palpation must be done gently to ensure that, if there are any tender areas, they are not pressed in a way that hurts unintentionally. This will enable the health-care provider to identify the following:

- palpating the inguinal region (groin), axillae, submandibular areas and neck looking for enlarged lymph nodes and buboes;
- palpating the scrotum, feeling for the testis, epididymis and spermatic cord on each side, and note any signs of discomfort suggestive of tenderness;
- examining the penis, noting any rashes, warts or sores;
- asking the person to pull back the foreskin, if present, and looking at the glans penis and urethral meatus for discharge or any other lesions;

- palpating any genital ulcers for tenderness and induration and looking for phimosis and paraphimosis; and
- examining the glans penis and urethral meatus for discharge or any other lesions.

If no obvious discharge is present, the patient may be asked to milk the urethra gently from the base towards the urethral meatus to determine any discharge. The patient may then be asked to bend the knees towards the chest to expose the perineum, buttocks and anal region. If the patient is examined in the standing position, he may be asked to turn his back to you and bend over, spreading his buttocks slightly, and the anus is then examined for ulcers, warts, rashes or discharge.

At the end of the examination, the gloves are removed, and both the health-care provider and the patient must wash their hands.

All the findings must be recorded, to complement the history, including the risk assessment and the clinical findings, such as the presence or absence of ulcers, buboes, genital warts and urethral discharge. Once the syndrome is determined, the appropriate flow chart should be followed for managing the patient.

### Steps to follow when examining women

A woman must be examined in good light and in privacy. It is important to inform the patient what the examination will entail. A male health-care provider must have a female chaperone in attendance at all times, unless this is not feasible because of staff capacity. In that case, the patient's consent to be examined without a chaperone should be obtained.

Examination of a woman during menstruation is not contraindicated, and testing for STIs, such as *N. gonorrhoeae* and *C. trachomatis* can be performed if the woman gives consent. Urine samples, vaginal swabs and blood tests can all be collected for STI tests during menstruation.

Before proceeding with examination, ensure the following:

- washing hands before the examination and putting on clean gloves with each patient;
- asking the patient to undress to enable examination from the chest down; and
- getting the patient to lie down on an examination couch in good light; a woman should not be examined standing up and should be covered with a draw sheet or a modesty blanket, exposing only the part of the body to be examined when ready.

The inspection must be general to ensure that other conditions are captured. The examination must include the following steps:

- looking inside the mouth for signs of oral thrush, oral sores or other lesions;
- looking at the skin over the abdomen for rashes and any obvious swellings;
- checking the pubic area for evidence of other STIs, such as pubic lice and nits, scabies, sores and inguinal lymph nodes;
- checking for any skin rashes on the palms of the hands and soles of the feet;
- checking the thighs and buttocks for rashes;
- checking the area around the anus for rashes and warts;
- checking the groin for swellings and sores; and
- checking the external genitalia and taking note of any discharge, or other lesions, such as warts, condylomata lata and excoriations on the vulva.

Palpation must be done gently to avoid hurting unintentionally. The abdomen must be palpated gently, watching the face for any indication of areas of tenderness and feeling for any masses and swellings, including pregnancy. In women with lower abdominal pain or vaginal discharge, the examination must focus on the pelvis to assess for signs of pelvic inflammatory disease (see section on pelvic inflammatory disease).

The general palpation by the health-care provider should include the groin, axillae, submandibular areas and neck for enlarged lymph nodes, noting whether they are painful.

Then the patient should be asked to bend her knees towards the chest and then separate them and the following should continue to be observed:

- inspection of the vulva, perineum (between the vagina in front, the buttocks behind and the medial sides of the thighs on both sides), and the perianal skin for rashes, sores, warts and swelling;
- inspect between the labia of the vagina and the urethral opening for any obvious lesions or discharge and any vaginal discharge;
- note: the colour of the discharge, whether it is yellow, white and/or blood stained; the smell, whether a “fishy smell” can be discerned; and the type of vaginal discharge: whether it is frothy, thick or sticky;
- two fingers should be inserted into the vagina and a bimanual examination carried out with one hand on the pelvic area of the abdomen and the other inside the vagina, feeling for masses and tenderness and checking for cervical motion tenderness by moving the cervix gently from side to side to elicit uterine and/or adnexal tenderness (see pelvic inflammatory disease); and
- a speculum examination should be performed next to visualize the cervix and vaginal mucosa.

### 3.2.1.3 How to perform a speculum examination

A speculum is a medical device used to examine inside the vagina. A speculum examination is often performed alongside a bimanual examination as part of a good practice gynaecological workup, especially for women with anogenital symptoms. Metal specula must be sterilized before use, and plastic specula must not be reused.

Before a speculum examination, the patient should be informed about the device, what the health-care provider is going to do and the patient reassured that the procedure should not be painful but if the patient is uncomfortable or experiences pain, the procedure will be discontinued.

Explain that the patient needs to remove the underwear and lie on the examination couch, covering herself with the sheet provided. The patient must be provided with privacy to undress.

In preparation for performing a speculum examination, the following steps should be taken.

- The patient should have an empty bladder to make the examination more comfortable;
- The speculum should be properly sterilized before use.
- All the secondary equipment needed should be laid out ready on a trolley, such as warm water, gloves, swabs and a waste disposal bin.
- The light source should be prepared and tested before beginning the procedure;
- The privacy screen, curtain or door should be closed for the examination.

The procedure should be done as follows.

- Wet the speculum with clean warm water before inserting it;
- Insert the first finger of the gloved hand in the opening of the woman's vagina (some clinicians use the tip of the speculum instead of a finger for this step). As the finger is put in, it is gently pushed downward on the muscle surrounding the vagina, and then the speculum is inserted slowly while asking the woman to relax her muscles;
- With the other hand, the speculum is held with the speculum blades together between the index and middle fingers and turned sideways as the speculum is slipped into the vagina, while taking care not to press on the urethra or clitoris because these areas are very sensitive.
- When the speculum is halfway in, it is turned so the handle is facing downward. (Note: some examination couches do not have enough room to insert the speculum with the handle down – in this case, it is turned up)
- The blades of the speculum are then gently opened a little while searching for the cervix.
- The speculum is then moved around slowly and gently until the cervix can be seen between the blades – at this point the screw (or otherwise lock on the speculum) can be tightened so it will stay in place.
- Now the cervix can be examined, in good light, and it should look pink, round and smooth. There may be small yellowish cysts, areas of redness around the opening of the cervix (cervical os) or a clear mucoid discharge – these are normal findings.
- Look for signs of cervical infection by checking for yellowish discharge or easy bleeding when the cervix is touched with a swab and any abnormal growths or sores.
- Note whether the cervical os is open or closed and whether there is any discharge or bleeding.
- If there was blood in the vagina, the clinician should look for any biological tissue coming from the cervix, which could be signs of induced abortion or miscarriage.
- If any specimens are to be taken, this would be the stage to perform endocervical swabs, swabs from the posterior fourchette of the vagina – as well as biopsy, if applicable.
- To remove the speculum, it should first be gently pulled out until the blades are clear of the cervix. Then the blades are brought together but not completely closed to avoid pinching the vaginal wall and gently pulled out, turning the speculum gently to look at the walls of the vagina.
- The patient can then be thanked and informed that the procedure has been completed and to get dressed while the patient's privacy is observed. After that, the patient can wash her hands and be asked to sit down to receive feedback on the findings of the examination.
- The health-care provider should remove the gloves before touching anything, wash hands and sit with the patient to give feedback on the examination findings.

As noted above, the next step is either to establish the diagnosis at this stage after the history-taking and examination and manage the patient syndromically using the appropriate flow chart(s) based on the examination findings or proceed to perform any additional diagnostic tests.

### 3.2.1.4 How to perform an anoscopy examination

An anoscope is an instrument used for visualizing the anus and lowest portion of the rectum. It is tubular and can be inserted with a lubricant into the anal canal. Once inserted, the examiner visualizes the walls of the anus and lower rectum using an appropriate light source. It can be used to identify abnormalities, such as haemorrhoids, inflammation and tumours in this part of the gastrointestinal tract.

Anoscopy can be performed within a health-care facility if sufficient training has been undertaken and equipment such as an examination couch, gloves, a light source and lubricants are available. No special preparations are needed, such as emptying the bowels or topical anaesthetic. However, some health facilities apply a topical anaesthetic 30 minutes before the procedure. Caution is needed among patients who have undergone recent anal surgery or are known to have anal fissures.

Before performing the procedure, the patient should be informed about the device, what the health-care provider is going to do and the patient informed that the procedure is painless, but pressure similar to that of a bowel movement may be felt.

In preparation for performing anoscopy, the following steps should be taken.

- The anoscope should have been properly sterilized before use.
- All the secondary equipment needed should be laid out ready on a trolley, such as lubricant, gloves, light source and cotton swabs, preferably with large tips.
- Privacy should be assured – a privacy screen, curtain or door that can be closed for the examination.

The procedure should be carried out as follows.

- Lie the patient down in the left lateral position.
- Separate the buttocks or ask the patient or an assistant to help and examine the perianal area for warts, haemorrhoids or polyp prolapses.
- Perform a digital rectal examination with a lubricated, gloved index finger, taking note of sphincter tone and any prostate abnormalities.
- Remove the finger and change glove to a new one.
- Lubricate the anoscope and insert it into the anus gently and, pointing the anoscope towards the umbilicus, advance it completely into the anus or as far as the patient can tolerate;
- Remove the obturator of the anoscope to examine the anal mucosa, removing any faecal matter with a swab.
- Check for blood, mucus, pus or haemorrhoidal tissue.
- Gently remove the anoscope, when done, and observe the sides of the anal canal in the process.
- The health-care provider should remove the gloves before touching anything, and both the provider and the patient must wash their hands before the provider sits with the patient to give feedback on the examination findings.

Any observation of suspicious growths or bleeding lesions should be referred for gynaecological assessment.



### 3.2.1.5 Establishing a diagnosis

Traditionally, laboratory tests have been used to address STI prevention and control to achieve the following.

- to provide a definitive diagnosis, thus, allowing for cause-guided treatment;
- to provide screening services for asymptomatic individuals at risk of infection;
- to provide statistical information on the prevalence of various infections;
- to determine the antimicrobial susceptibility of causative organisms; and
- to assist in managing sex partners.

Thus, ideally, everyone presenting with a condition assumed to be an STI should be diagnosed through a process of obtaining the medical and sexual history, physical examination and laboratory testing of relevant specimens from either the lesion, blood or urine. The diagnosis could then be made through a combination of direct microscopy in syndromes with genital discharges, culture of the organisms, such as *N. gonorrhoeae*, serological testing as in syphilis and HIV infection and molecular detection. The health-care level at which these tests can be done varies with availability of resources, both financial and human, as well as the skills required to conduct the tests. Regardless of which system is set up for diagnosing STIs, there should be a mechanism to refer to a level at which more tests can be done, especially for patients with recurrent or persistent infections and those with unusual clinical presentations.

However, in many parts of the world, such a process is constrained by a lack of inexpensive diagnostic tests, and especially in the regions where the burden of STIs is highest and laboratories and laboratory technicians have insufficient capacity. In many instances, the appropriate reagents necessary to detect STI pathogens are not locally available and would be expensive to procure. Further, even if laboratory-based tests were available, substantial financial resources would be required for such an approach and probably unaffordable for the programme and for the patients. A further disadvantage of laboratory-based etiological diagnosis is the delay in access to treatment if treatment is withheld until the results are available.

Affordable, rapid point-of-care diagnostic tests for STIs provide a means to strengthen the diagnosis of STIs more readily. This would be such a welcome advance in the diagnosis of STIs, especially for women with vaginal discharge, a syndrome commonly labelled as an STI syndrome but that neither indicates nor predicts gonococcal or chlamydial cervical infections among women. Genital ulcers would also benefit enormously from a rapid point-of-care test, since recent studies indicate that most genital ulcers are caused by viral infections, especially HSV-2. The rapid diagnostic tests for gonococcal and chlamydial infections currently commercially in circulation are of poor sensitivity and specificity and expensive. Their use would negatively affect the reliability of laboratory testing for STI diagnosis. However, rapid diagnostic tests for syphilis (treponemal test) are available and cheap and allow for a same-day “screen and treat” approach. Dual HIV and syphilis rapid tests are also available and provide an opportunity for increasing access to HIV and syphilis testing.

In the absence of diagnostic tests, a syndrome-based approach to managing people with STIs has been developed and adopted in many countries. The approach is more rational and scientific than a clinical approach in which a health-care provider reaches a diagnosis based on the clinical appearance of the lesion or the nature of a genital discharge. Several studies have shown that clinical judgement based on the experience and appearance of an ulcer, for example, has poor sensitivity in the diagnosis (34–36).

The syndromic management approach is based on identifying consistent groups of symptoms and easily recognized signs (syndromes) and providing treatment that will take care of most of or the most serious organisms responsible for producing the syndrome. By giving treatment for the most common causative pathogens for a particular syndrome, the syndromic approach, generally, has high sensitivity at the expense of specificity, thus resulting in overtreatment. WHO developed simplified flow charts to guide health-care workers in implementing the syndromic management of STIs. These WHO flow charts have been designed to be adapted at the local level, using locally available data and information.

### 3.2.1.6 Health education and counselling

People seeking care for STIs are especially worried about the condition and are more receptive to education messages than at other times. This is probably because they are aware of their vulnerability when they face an infection. Health-care providers should take advantage of this time to educate their patients about STIs, including HIV, and how they are transmitted and acquired. Further, the counselling can help them to assess their own risk and take responsibility to reduce the risk, if feasible, or change sexual behaviour and start using preventive interventions, such as the male and female condoms.

Health education is the provision of accurate and evidence-informed information about STIs so that a person becomes knowledgeable about the subject and can make informed choice.

Counselling is a two-way interaction between patients and provider intended to help the patients to understand themselves better in their feelings, attitudes, values and beliefs and to empower them to execute changes for healthy living in their life.

The key messages to give during an encounter with a person seeking care for STIs is how the infection may have been contracted, how to prevent future infections and the importance of completing a course of treatment and abstaining from further sexual intercourse until treatment has been completed and the infection has been controlled or cured. This should be emphasized to patients. However, patients should also be strongly advised to use condoms if abstinence from sex is not possible.

During the encounter with the patients, screening for other infections should be offered, especially for HIV infection and syphilis, both of which have rapid diagnostic tests currently available.

Health education and counselling are covered in other relevant WHO publications, such as *Brief sexuality-related communication: recommendations for a public health approach* (37).

### 3.2.1.7 Partner notification and treatment

A person with STIs has contracted the infection from a sex partner who also had the infection. Equally, from the time that the attending (index) patient was infected, he or she has also been infectious – able to transmit the STI to other sex partners or the same partner (the source of the infection) who, in the meantime, may have been treated. Thus, the chain of transmission of the STI can be broken only if all the mutual sex partners are treated for the infections before they have further sex with each other.

Many STIs, such as gonococcal infection, chlamydial infections, syphilis and HIV, are asymptomatic, and people may not be aware that they are infected. Thus, partner notification can be one way to detect and treat asymptomatic individuals.

Some reproductive tract infections are not sexually transmitted, such as the bacteria responsible for bacterial vaginosis among women with vaginal discharge. Although *C. albicans*

can be sexually transmitted, it is not classified as an STI. The sex partners of people with candidiasis do not need treatment unless they exhibit symptoms. Partner notification therefore needs to be approached with caution for women with vaginal discharge since they may not have a sexually transmitted pathogen. This is one reason affordable, rapid diagnostic tests to screen for STIs in such situations and guide appropriate partner notification and treatment are so urgently needed.

There are several approaches to partner notification for STIs. The patient can be issued with a contact-tracing card to give to the sex partner(s) to invite them to attend for an assessment for STIs and be treated accordingly (patient referral partner notification). The other method is for the health-care provider to obtain contact details from the index patient and then to attempt to contact the sex partners (provider referral partner notification).

Other methods of partner notification and treatment are variations of these two in which the index case may be given a prescription or medicines to give to their sex partners without the health-care provider having the opportunity to examine the sex partner (expedited partner therapy). Another method, sometimes referred to as contractual partner referral, is agreement between the service provider and the index patient that the latter will reach the sex partner(s) within an agreed time frame, after which the health-care provider will then try to contact the sex partner if the agreement period has elapsed without the sex partners presenting for examination and treatment.

Regardless of which method of partner notification and treatment is followed, confidentiality, non-judgemental attitudes and absence of coercion must be observed. Health education and counselling are important to equip people with STIs to embark on informing their sex partners about their STI.

### **3.2.1.8 Follow-up and referral for people with STIs**

WHO encourages that people diagnosed with STIs be provided immediate treatment and, if any diagnostic tests are to be carried out, that they do not delay the provision of treatment. This would ensure an immediate break in the chain of transmission and prevent STI-related complications and long-term sequelae of STIs.

Giving treatment during the same visit reduces infectiousness and onward transmission, even more so if single-dose therapies are available.

If effective medicines are given and any test results are available on the same visit, then follow-up may be restricted only to those with persistent symptoms after a stipulated period. This will reduce costs for both the patient and the health-care system. Treatment given on the same visit is especially relevant in settings in which patient return rates are inconsistent for several reasons, such as distances to the clinic, user fees, transport fees, user-friendliness of health services and attitudes of health-care providers.

Follow-up may be specifically requested in certain conditions, such as a woman being treated for acute pelvic inflammatory disease as an outpatient or a neonate with ophthalmia neonatorum to ensure that the treatment has been effective, since delays in cure may result in severe consequences such as loss of eyesight.

The patient may return for further assessment either because the condition has not resolved when treatment ends or it has recurred. The health-care provider will need to determine whether this resulted from poor compliance, which is unlikely if single-dose therapy was given and taken on the same day as the patient attended the clinic or the patient has a persistent infection because of antimicrobial resistance or has been reinfected.

Depending on the assessment, health-care providers have the following options for treatment:

- poor compliance – such as a patient taking a 7-day or 21-day course of doxycycline for chlamydial infections, including for lymphogranuloma venereum;
- reinfection – perhaps because sex took place, without a condom, with an untreated sex partner or a new partner;
- antimicrobial resistance – this is of particular importance in gonococcal and *M. genitalium* infections since antimicrobial resistance in *N. gonorrhoeae* and *M. genitalium* are being experienced with recommended treatments for these infections; and
- the presence of an untreated infection – such as *T. vaginalis* and/or *M. genitalium* among men with urethral discharge treated only for *N. gonorrhoeae* and *C. trachomatis* at the first visit.

The health-care provider should assess the most likely scenario for the individual and treat appropriately.

Sometimes the patient needs to be referred to another level of care. The health-care provider at the first point of care should then determine whether the referral should be made to clinicians who have extensive specialized training or experience in diagnosing, treating and following up complex STI cases or to a facility with laboratory-based tests to exclude antimicrobial resistance or to any other specialist centre. For example, someone with an abnormality in the anorectal area may need to be referred to a colorectal surgeon or oncologist and someone with a testicular problem to a urologist.

In any specific country or setting, providers of care for people with STIs need to have information on referral channels at their disposal for complex genitourinary symptoms they feel unable to handle.

## 4. DIAGNOSTIC TESTS FOR ASYMPTOMATIC AND SYMPTOMATIC PEOPLE WITH STIs

The accurate identification of asymptomatic and symptomatic STIs, as well as improvements in the sensitivity and specificity of the syndromic approach, all depend on the availability of diagnostic tests and a screening strategy. High-quality diagnostic tests for STIs are available but are often expensive, frequently labour intensive and, at this stage, not suitable for use as rapid point-of-care tests. This situation is further complicated by a lack of interest from pharmaceutical companies in developing low-cost, high-quality diagnostic tests for diseases that are more prevalent in low- and middle-income countries, since they perceive that the market is not sufficient to recover research and development costs and make a profit.

Gold-standard tests with high levels of sensitivity and specificity are generally used to develop management flow charts and to subsequently evaluate and improve them, but these tests are typically not available for the day-to-day management of people with STIs.

For purposes of equity, diagnostic tests should be affordable, sensitive, specific, user friendly, rapid and robust, equipment-free and deliverable – thus making them accessible. Equally, the tests should be acceptable – which is usually achieved by making the testing procedure minimally invasive.

Currently, however, there are often trade-offs. Nucleic acid amplification testing (NAAT) is very sensitive and specific and can usually be done on non-invasive samples such as urine but often takes 3–4 hours to complete, is expensive and is usually based in a laboratory rather than at a health facility where people present with STI symptoms. Other rapid immunochromatographic strip tests may be less sensitive, but results may be available in 30 minutes or less (38).

Two rapid immunochromatographic strip tests for *N. gonorrhoeae* were evaluated in Brazil and Benin and had sensitivity of 60% and 70%, respectively, specificity of 91% and 97%, respectively, and a positive predictive value of 56% in Brazil (prevalence of *N. gonorrhoeae* 15%) and 55% in Benin, where the prevalence of *N. gonorrhoeae* was 5% (39,40). However, it has been suggested that these rapid tests, despite their lower sensitivity, may be as efficient as or more efficient than the more sensitive gold-standard tests in treating gonococcal infections, given the proportion of people who do not return for the results of the more sensitive test. Thus, in day-to-day practice, if longer waiting times or having to return for test results leads to loss to follow-up, the less sensitive tests may well result in more people with STIs receiving treatment (41). Several platforms and assays are being developed to be more portable and easier to operate and to be used at the primary point of care and give rapid turnaround times for results, with accuracy similar to that of laboratory-based NAAT (42–44). Such considerations were deliberated in the STI Guideline Development Group meeting to propose acceptable performance characteristics of prospective point-of-care tests that may improve the treatment flow charts and minimize the undesirable consequences of untreated STIs.

There are several rapid diagnostic tests for screening for syphilis. Most use whole blood, plasma or serum and can be performed within 5–30 minutes. Based on a meta-analysis, sensitivity ranges from 75% to 99% and specificity from 92% to 99% compared with *Treponema pallidum* haemagglutination assay (TPHA) and *Treponema pallidum* particle agglutination (TPPA) tests (45). A combination of rapid diagnostic tests for HIV and syphilis (dual HIV and syphilis test) provides potential for increasing syphilis testing. These tests have high sensitivity and specificity, are more cost-effective than a single rapid diagnostic test and are acceptable in terms of turnaround time, cost and a single finger prick (46).

Additionally, already in existence are traditional rapid tests, including microscopy (Gram stain, wet mount and dark field), pH strip tests, the Whiff test using potassium hydroxide solution and the rapid plasma reagin (RPR) test for syphilis. The role of these tests was discussed intensively at the STI Guideline Development Group meeting and assessed in the modelling exercise to explore their utility.

Some of these traditional rapid tests are briefly discussed below.

## 4.1 Role of microscopy in diagnosing STIs and other reproductive tract infections

The light microscope is used in studying microorganisms, especially for identification purposes. The light microscope uses visible light to directly illuminate specimens, which appear dark against a bright background. In most light microscopes, the image is viewed directly through binocular eyepieces with a magnifying glass and the objective lens located in the revolving nosepiece to give a total magnification ranging from  $\times 10$  to  $\times 1000$ .

The light microscope has been used with Gram staining to detect intracellular gram-negative diplococci within polymorphonuclear leukocytes for the presumptive diagnosis of gonorrhoea. The light microscope is also used to diagnose bacterial vaginosis when Gram-stained vaginal smears show an abundance of gram-positive and gram-negative cocci with reduced gram-positive lactobacilli in the vaginal flora. Another area the light microscope has a role is in wet-mount examination of samples collected from the posterior fornix of the vagina when motile trichomonads can establish a diagnosis of trichomoniasis.

A fluorescence microscope is a type of light microscope that works on the principle of fluorescence. Fluorescence can be used to visualize some bacteria and viruses that are not easily visible by light microscopy following staining by a specific antibody attached to a fluorochrome. In STI detection, the immunofluorescence can be used to detect *T. pallidum*, *C. trachomatis* and HSV.

Dark-field microscopy uses a special type of light microscope in which the light beam is split such that the edges of objects in the samples are illuminated so that they appear as silhouettes against a dark background, thus enabling the sample to be seen without stains. In STIs, dark-field microscopes have been used for detecting *T. pallidum*. However, this has to be performed by well-trained and experienced personnel who can adjust the microscope correctly and can differentiate *T. pallidum* from other non-pathogenic treponemes and spiral organisms commonly present on genital and anal mucous membranes. Further, since spirochaetes other than treponemes colonize the oral cavity, dark-field microscopy is not recommended for samples from the mouth.

The microscope should be available in any laboratory licensed to perform moderately complex tasks, but it is not usually available as a point-of-care test.

Microscopy for STIs provides a simple, rapid and relatively inexpensive test that can be used near the patient – for example, it can be placed in a procedure room within a primary health care facility. The skills needed for preparing smears for microscopic examination and interpretation of the microscopic image require training and a good working knowledge of the microscope. Further, the microscope should be serviced regularly and should be kept clean and covered when not in use.

## 4.2 Quality-assured laboratory testing with a fully operational management system

Diagnosing a person with an STI has serious health implications at the individual and public health levels, and the best available diagnostic tests should therefore be used. All laboratory tests performed and the reports produced for patient management must be of high quality. WHO has developed an implementation tool to assist laboratories in implementing a quality management system (47). To maintain a high-quality service, laboratories should be accredited to a suitable national or international body, such as the International Organization of Standardization. The goal is to achieve compliance with international standard ISO 15189. Such accreditation involves an external audit of the ability to provide a service of high quality by declaring a defined standard of practice, which is confirmed by peer review.

Although this does not include assessment of the appropriateness of the molecular tests chosen for diagnosing STIs, the laboratory is expected to be able to provide evidence of the assessment of the performance capabilities of the tests before they are incorporated into the STI services offered.

Such a laboratory will be considered to have quality-assured molecular testing with a fully operational management system.

In addition, for STI prevention and control, WHO recommends that laboratories aim to offer tests that minimize the time between the sample is taken and the patient receives the results – ideally on the same day as the visit. It is further suggested that laboratories set indicators that reflect the quality of their results with targets for rapid turnaround times.

## 5. RATIONALE FOR STANDARDIZED TREATMENT RECOMMENDATIONS

Correct and effective treatment of STIs, ideally given and taken on the same day, at the first contact between patients and health-care providers, 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.

Countries should establish and use national standardized treatment protocols for STIs. Standardization ensures that all patients receive appropriate and adequate treatment at all levels of the health-care service. The protocols can also facilitate the training and supervision of health-care providers and can help reduce the risk of development of resistance to antimicrobials. Finally, having a standardized list of antimicrobial agents can also facilitate procurement of the medicines.

It is anticipated that the recommendations contained in this document will assist countries to develop standardized flow charts adapted to the local epidemiological situation and antimicrobial susceptibility data. It is recommended that national guidelines for the effective management of STIs be developed in close consultation between local STI and public health experts and laboratorians.



## 6. IMPLEMENTING THE SYNDROMIC APPROACH FOR THE MANAGEMENT OF STIs

A flow chart is a diagrammatic map that guides through a series of actions and decisions needed to solve a problem. All flow charts have the same general features: an entry point, action, decision and treatment boxes. Each action or decision is enclosed in a box, with one or two routes leading out of it to another box with another decision or action.

Thus, a health-care provider learning of a problem would turn to the relevant flow chart and work through the decisions and actions it suggests. Each flow chart would then follow the following three basic steps:

- the clinical problem (the presenting symptom) at the top: the entry point;
- a decision to make, usually by answering “yes” or “no” to a question; and
- an action to take, with various boxes suggesting treatment, counselling, health education and condom promotion or patient referral, if necessary.

Although using boxes, circles, diamonds or other such symbols to construct a flow chart is not strictly necessary, most flow charts are constructed from standard symbols to help communicate the processes to everyone who uses them. When people see a specific symbol in a chart, they would therefore understand a specific meaning. Thus, knowing the meaning of the standard symbols can be helpful in reading, using and creating flow charts. ISO 5807 specifies the standard flow chart symbols for information processing. The commonly used flow chart symbols are as follows.



A rounded rectangle identifies the beginning or end of a process or origin and destination of data. This would normally be the patient’s symptoms.



The process symbol: this is a rectangle that designates an activity. Typically, this would be a step or action that needs to be taken. Within the rectangle would be a short description of the activity: for example, “examine the patient”.



The decision symbol is represented as a diamond (rhombus) from which the process branches into two or more paths. The path taken depends on the answer to the question appearing within the diamond. Each path is labelled to correspond to an answer to the question, usually from the bottom point and right point, one corresponding to yes or true and the other to no or false. The arrows should always be clearly labelled.



An arrow coming from one symbol and ending at another symbol indicates that the process passes to the symbol the arrow points to. The line for the arrow can be solid or dashed. The meaning of the arrow with dashed lines may differ from one flow chart to another and can be defined in the legend.

To use a flow chart, one simply starts at the clinical problem box and works through step by step until one arrives at an exit box at the end of a branch. Along the way there may be branching arrows from the decision box to action boxes, which should be followed in the direction of the arrows until the exit box or boxes.

## 7. URETHRAL DISCHARGE SYNDROME

Urethral discharge among men is commonly caused by *N. gonorrhoeae* and/or *C. trachomatis* and/or non-gonococcal and non-chlamydial pathogens, such as *M. genitalium* and *T. vaginalis*. The prevalence of each of these pathogens varies geographically and by population group. Countries must conduct studies periodically in their settings to determine the most prevalent and important causes of urethral discharge or urethritis in that setting.

### 7.1 Clinical presentation – symptoms

Characteristically, men with urethritis (inflammation of the urethra) present with urethral discharge with or without dysuria (pain on urination). Occasionally, dysuria or itching at the tip of the urethra may be the only symptoms.

### 7.2 Examination findings – signs

Most men with urethritis have urethral discharge, which may range in quantity from being scanty to copious and in character from being clear to purulent. Distinguishing between discharge caused by gonorrhoea, chlamydia or any other cause of urethritis is not clinically possible.

### 7.3 Laboratory diagnosis

#### 7.3.1 Molecular detection

NAAT is the current gold standard for detecting *C. trachomatis* and *N. gonorrhoeae* among men and women. NAAT also performs well for pharyngeal and anorectal samples for *C. trachomatis* and *N. gonorrhoeae*. For anorectal samples among men who have sex with men, chlamydia genovar testing for lymphogranuloma venereum should be done to guide the appropriate treatment regimen for lymphogranuloma venereum (48).

##### 7.3.1.1 Specimens for *N. gonorrhoeae* and *C. trachomatis* for molecular assays

A first-catch urine or a urethral swab can be used for *C. trachomatis* and *N. gonorrhoeae*. NAAT for *N. gonorrhoeae* from anorectal and pharyngeal samples is also good, but there is potential for cross-reactivity with commensal *Neisseria* spp., especially in the throat.

##### 7.3.1.2 Specimens for *M. genitalium*

*M. genitalium* causes urethritis. NAAT offers the best method for detecting *M. genitalium* from a first-catch urine in men. *M. genitalium* testing is not yet widely available.

### 7.3.1.3 Specimens for *T. vaginalis*

NAAT has the highest sensitivity of all diagnostic methods for detecting *T. vaginalis*. Urine can be used for some assays, but residual genital swab samples used for diagnosing chlamydia and gonorrhoea using NAAT are also good enough for detecting *T. vaginalis* nucleic acids.

### 7.3.2 Culture methods

Culture of *N. gonorrhoeae* is still the standard method for performing antimicrobial susceptibility testing. However, this organism is not that easy to grow in the laboratory, requiring special training and a special culture medium. For this reason, culture of *N. gonorrhoeae* is not routinely performed as part of managing people with gonococcal infection in resource-limited settings.

Culture of *T. vaginalis* was the cornerstone for detecting *T. vaginalis* before the advent of point-of-care antigen tests and NAAT. Although a culture medium is commercially available, once inoculated into the medium, cultures from men have to be incubated for a full five days while being examined daily using a microscope before being determined to be negative. Further, multiple sites, including semen, urine and urethral swabs, need to be examined before a definitive negative result can be certain. Routine culture methods for detecting *T. vaginalis* are no longer widely performed.

### 7.3.3 Microscopy

*N. gonorrhoeae* can be identified by light microscopy of Gram-stained samples and a presumptive diagnosis of gonorrhoea made if gram-negative diplococci are observed intracellularly in polymorphonuclear leukocytes, best seen when there is a urethral discharge. If carried out by an experienced person, a negative gram stain for intracellular diplococci, in the context of urethral discharge in a man, can be presumed to suggest non-gonococcal urethritis. Microscopy of methylene blue stain of a male urethral sample is an acceptable method for the presumptive diagnosis of gonorrhoea, but it does not allow for the differentiation of gram-negative cocci.

## 7.4 Recommendations for the management of urethral discharge

**For people with symptom of urethral discharge from the penis, management is recommended to be based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit.**

*(Strong recommendation; moderate-certainty evidence)*

Good practice includes:

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination of the genital and anal areas; and
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines.

Good practice statement

*Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit*

*(Strong recommendation; moderate-certainty evidence)*

WHO recommends the following.

1. Perform molecular assays such as nucleic-acid amplification testing (NAAT) to confirm or exclude *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.
2. Treat according to the test results on the same day. If urethral discharge is present but tests are negative, treat for non-gonococcal and non-chlamydial urethritis (such as *Mycoplasma genitalium* or *Trichomonas vaginalis*).
3. When treatment based on molecular assays is not feasible on the same day of the visit, WHO recommends syndromic treatment of infection with *N. gonorrhoeae* and *C. trachomatis* and using the test results to support managing the partner when tests are available.
4. Treat people with recurrent or persistent urethral discharge based on a repeat molecular assay (such as NAAT) after 21 days, testing for *N. gonorrhoeae*, *C. trachomatis* as well as *M. genitalium* and *T. vaginalis* and testing for antimicrobial-resistant *N. gonorrhoeae*.

Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing

(Conditional recommendation; low-certainty evidence)

WHO suggests the following.

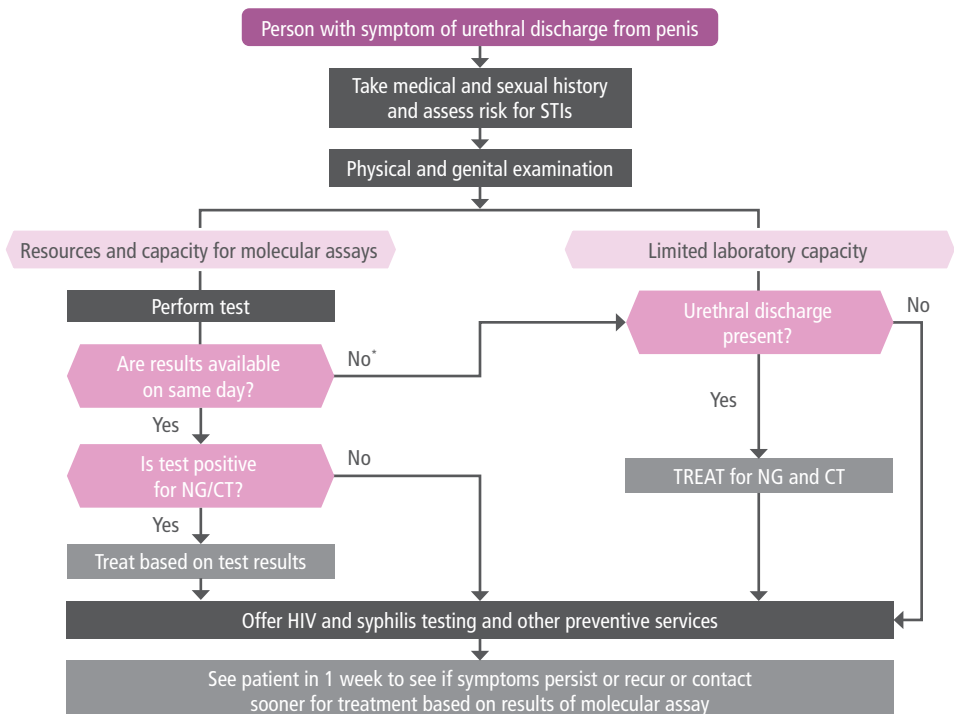
1. Treat people who have urethral discharge confirmed on examination for *N. gonorrhoeae* and *C. trachomatis* to ensure same-day treatment.
2. Treat people with recurrent or persistent urethral discharge for treatment failure based on WHO guidelines and review.

Good practice includes:

- if symptoms persist at review, checking partner notification and treatment history; and
- for people with recurrent or persistent urethral discharge, referring people to a centre with laboratory capacity to diagnose *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium*.

Good practice statement

**Fig. 2. Flow chart for the management of urethral discharge from the penis**



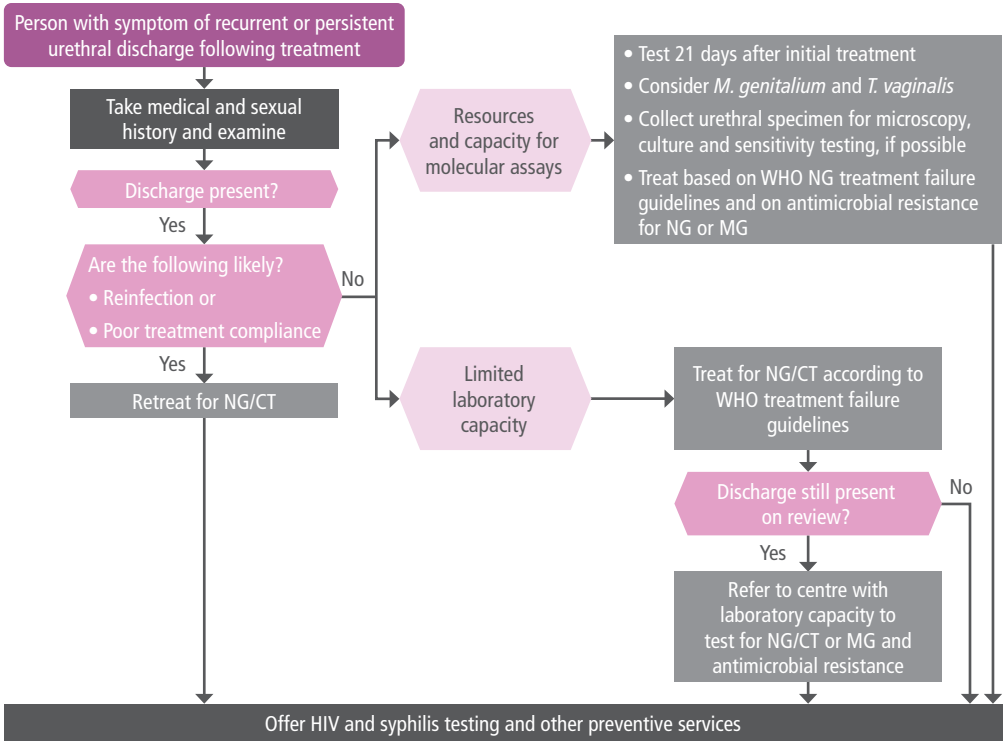
NG, *N. gonorrhoeae*; CT, *C. trachomatis*.

\* If molecular assay was performed and results were not available on same day, revise the syndromic treatment initially provided according to the test results when available

# If test is negative but urethral discharge is present, treat for non-gonococcal/non-chlamydial urethritis (such as *M. genitalium*, *T. vaginalis* or herpes simplex virus)

### Fig. 3. Flow chart for men with persistent or recurrent urethral discharge

This flow chart assumes that the patient has received and taken effective therapy for gonorrhoea and chlamydia before this consultation.



NG, *N.gonorrhoeae*; CT, *C. trachomatis*; MG, *M. genitalium*.

### 7.4.1 Evidence summary (Annex 3)

A systematic review of the accuracy of syndromic approaches for urethral discharge was conducted, including history, risk assessment, examination and microscopy (supplementary material: systematic review urethral discharge). Six studies were found for assessing the accuracy of syndromic management to detect *N. gonorrhoeae* and *C. trachomatis*, but the pooled sensitivity and specificity of the approaches did not improve as expected when adding microscopy (low-certainty evidence). In addition, studies show that there is variability in the implementation of the syndromic approaches based on symptoms or laboratory testing (49). Instead, the WHO Guideline Development Group considered that, when available, performing molecular assay tests for *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* and/or *M. genitalium* and basing treatment on these results leads to treating the most people correctly. In the systematic review, the median prevalence of *N. gonorrhoeae* and/or *C. trachomatis* was 69% in men with urethral discharge. In a population with 60% prevalence of *N. gonorrhoeae* and *C. trachomatis* among those with urethral discharge, if molecular assays are not available, treating everyone for *N. gonorrhoeae* and *C. trachomatis* would mean 40% of them would be unnecessarily treated. The Guideline Development Group agreed that this proportion is acceptable and even higher proportions in settings with lower prevalence, because treating everyone would ensure that people infected with *N. gonorrhoeae* and *C. trachomatis* are treated, thereby reducing the chance of complications and further transmission. The Guideline Development Group also agreed that simple syndromic treatment based on the presence of urethral discharge would likely improve adherence to the approach and costs a minimal amount more than using history and/or risk assessment with or without examination (but with no missed cases).

## 7.5 Treatment recommendations for urethral discharge

Based on the recommendations in subsection 7.4, syndromic treatment for urethral discharge combines treatment for gonococcal and chlamydial infections. Other modifications can be made based on the availability of molecular diagnostic tests. Table 3 gives first-line and effective substitutes for treating people with urethral discharge syndrome.

Managing people with recurrent or persistent urethral discharge will require excluding reinfection by taking a thorough sexual history. When that has been done, additional treatment for *M. genitalium* and *T. vaginalis* may be considered. WHO guidelines on *Neisseria gonorrhoeae* (24) give guidance on how to approach apparent treatment failures among people with gonococcal infections.

**Table 3. Recommended treatment options for urethral discharge syndrome<sup>a</sup>**

<ul style="list-style-type: none"> <li>• Therapy for uncomplicated <i>Neisseria gonorrhoeae</i> (24)</li> </ul> <i>Plus</i> <ul style="list-style-type: none"> <li>• Therapy for <i>Chlamydia trachomatis</i> (25)</li> </ul>		
Infections covered	First-line options	Effective substitutes
In settings in which local antimicrobial resistance data are not available, the WHO STI guideline suggests dual therapy for gonorrhoea.		
<i>N. gonorrhoeae</i> <sup>a</sup>	<b>Ceftriaxone 250 mg</b> , intramuscularly, single dose <i>Plus</i> <b>Azithromycin 1 gram</b> , orally, single dose	<b>Cefixime 400 mg</b> , orally, single dose <i>Plus</i> <b>Azithromycin 1 gram</b> , orally, single dose
<i>C. trachomatis</i>	<b>Doxycycline 100 mg</b> , orally, twice daily for seven days (to be given only if gonorrhoea therapy did not include azithromycin)	<b>Azithromycin 1 gram</b> , orally, single dose <i>or</i> <b>Erythromycin 500 mg</b> , orally, 4 times a day for 7 days <i>or</i> <b>Ofloxacin 200–400 mg</b> , orally, twice a day for 7 days. (to be given only if gonorrhoea therapy did not include azithromycin)
In settings in which local antimicrobial resistance data reliably confirm the susceptibility of <i>N. gonorrhoeae</i> to the antimicrobial agent, single therapy may be given.		
<i>N. gonorrhoeae</i>	<b>Ceftriaxone 250 mg</b> , intramuscularly, single dose	<b>Cefixime 400 mg</b> , orally, single dose <i>or</i> <b>Spectinomycin 2 grams</b> , intramuscularly, single dose (availability makes this antibiotic impractical)
Additional therapeutic options for recurrent or persistent infections		
<i>T. vaginalis</i>	<b>Metronidazole 2 grams</b> , orally, single doses	<b>Metronidazole 400 or 500 mg</b> , twice daily for 7 days
<i>M. genitalium</i>	<b>Azithromycin 500 mg</b> , orally on day 1, 250 mg daily on days 2–5	

<sup>a</sup>Because of increasing antimicrobial resistance to azithromycin in *N. gonorrhoeae* and *M. genitalium* and reduced susceptibility of *N. gonorrhoeae* to cephalosporins, WHO is in the process of revising current treatment recommendations and dosages.



## 8. VAGINAL DISCHARGE SYNDROME

Vulvovaginal symptoms are one of the commonest reasons for women attending a health facility. The symptoms include a vaginal discharge perceived by the woman to be abnormal, vulval irritation or itching. Other conditions may include vulvovaginal growths, such as warts and cancer, especially of the cervix – these are not discussed in these guidelines.

The three most common causes of vaginal discharge are bacterial vaginosis and infection with *T. vaginalis* and *C. albicans*. Among postpubertal women, *N. gonorrhoeae* and *C. trachomatis* infect the endocervix rather than the vagina, and they therefore may not present with vaginal discharge. These infections may be present without any clinically evident abnormality of the cervical os. If an abnormality is present at the cervical os because of infection with *C. trachomatis* or *N. gonorrhoeae*, it would be a mucus discharge or a purulent discharge (mucopus) or inflammation and friability of the cervical os. In the context of STIs, it should therefore be emphasized that vaginal discharge more reliably indicates vaginal infections but poorly predicts cervical infection caused by *N. gonorrhoeae* and/or *C. trachomatis*. The challenge for a health-care provider consulting a woman with vaginal discharge is to determine the cause of the discharge when a variety of infectious and non-infectious causes may be at play.

The summary of the systemic review and the recommendations given in this section offer guidance on how to manage people presenting with symptoms of abnormal vaginal discharge. The commonest causes of vaginal discharge are briefly discussed below.

### 8.1 *T. vaginalis*

*T. vaginalis* is a sexually transmitted protozoan that specifically infects women's vagina, urethra and paraurethral glands. Although many women are asymptomatic, more than 50% of women with *T. vaginalis* infection have vaginal discharge.

#### 8.1.1 Clinical presentation – symptoms

Among symptomatic women, infection with *T. vaginalis* presents with an abnormal vaginal discharge as perceived by the woman. About 50% of symptomatic women report vulval itching. The discharge may be described as yellow and may appear purulent.

#### 8.1.2 Examination findings – signs

On examination, vulval erythema and oedema may be noted.

On speculum examination, a discharge of variable colour can be seen in the vagina – classically described as yellow or greenish and may be frothy. The vaginal walls may be erythematous. The cervix may have punctate haemorrhages, giving rise to what has been referred to as “strawberry cervix”. Although this finding is uncommon, it is highly indicative of trichomoniasis.

### 8.1.3 Molecular testing

NAAT has the highest sensitivity of all diagnostic methods to detect *T. vaginalis*. Vaginal swabs are the samples of choice, but endocervical samples and urine can be used for some assays. Additionally, residual genital samples used for diagnosing chlamydia and gonorrhoea using NAAT are also good enough for detecting *T. vaginalis* nucleic acids. NAAT is, however, not currently widely available as rapid point-of-care tests. However, when resources permit, such tests can be incorporated strategically to use as near-patient rapid point-of-care testing in managing people with STIs.

### 8.1.4 Microscopy

*T. vaginalis* has historically been diagnosed by performing wet mount microscopy. Although it is not the gold standard technique for diagnosing trichomoniasis, a wet mount is frequently used because it is quick, inexpensive and easy to perform. However, to have a good chance of successfully identifying the motile trichomonads, the slide should be read within 10 minutes of collection since trichomonads quickly lose their motility (50). Non-motile cells cannot be diagnosed as trichomonads.

### 8.1.5 Culture methods

Culture of *T. vaginalis*, which has a higher sensitivity than the wet mount microscopic examination, was the cornerstone for detecting *T. vaginalis* before the advent of point-of-care antigen tests and NAAT. Although a culture medium is commercially available, cultures from women with trichomoniasis are usually positive in the first three days of inoculation, but they have to be incubated for up to seven days to rule out infection. Routine culture methods detecting *T. vaginalis* are no longer widely performed.

## 8.2 Candidiasis

Vulvovaginal candidiasis is caused by *C. albicans* in about 90% of cases. The non-albicans species cause the rest of vulvovaginal candidiasis – *C. glabrata* in about 8% of cases, and the other non-albicans species, such as *C. tropicalis*, *C. krusei* and *C. parapsilosis* cause most of the remainder (51). Although men can be colonized with *Candida* species and the male sex partners of women with candidiasis are transiently colonized, candida balanitis and balanoposthitis among men are not recognized as STIs (52). *Candida* yeasts may be detected in 20–30% of asymptomatic nonpregnant women of childbearing age (53). The detection of candida yeasts among asymptomatic women therefore does not necessarily require treatment.

### 8.2.1 Clinical presentation – symptoms

Candidiasis presents with pruritus (itching) or a burning sensation of the vulva and vaginal soreness or irritation. Other clinical manifestations include pain during sexual intercourse (dyspareunia) and dysuria. If there is discharge, it characteristically is curdy, white or creamy and thick. The discharge is not always curd-like (sometimes described as cottage-cheese-like in character) but can vary from watery to homogeneously thick.

## 8.2.2 Examination findings – signs

On examination, the vulva may be erythematous and excoriated. The vulva and the labia may be swollen. Some pimples with pus (pustulopapular) lesions peripheral to the erythematous area of the vulva may be present.

Speculum examination shows the vaginal wall to be erythematous, and an adherent discharge may be seen, either curd-like or homogeneously white. The cervix looks normal.

## 8.2.3 Microscopy

Vaginal pH is normally between 4 and 4.5 among most women with candidiasis. A Gram stain of vaginal secretions from the walls of the vagina demonstrates gram-positive *Candida* species. A 10% potassium hydroxide preparation is also useful in identifying germinated yeasts.

## 8.2.4 Culture methods

*Candida* culture on solid media is the most sensitive diagnostic test for candidiasis but does not offer same-day treatment. The results may take up to three days to confirm the growth of fungal colonies.

## 8.3 Bacterial vaginosis

Bacterial vaginosis is the most common cause of vaginal discharge among women of childbearing age. It is a polymicrobial disorder of the vaginal microbiome. The condition is characterized by low concentrations or an absence of lactobacilli and a florid presence of anaerobic flora (54).

Bacterial vaginosis is not a sexually transmitted condition, but it has been linked to several adverse outcomes, including adverse outcomes of pregnancy and an increased risk of STIs, including HIV, pelvic inflammatory disease and tubal factor infertility (55,56).

### 8.3.1 Clinical presentation – symptoms

About 90% of symptomatic women have a white vaginal discharge, which can be seen on the vulva, and an abnormal vaginal odour (52).

### 8.3.2 Examination findings – signs

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

### 8.3.3 Laboratory diagnosis

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 or Whiff test).

However, examining the woman during menses, within a day of sexual intercourse, after recent douching and when taking antimicrobial agents can affect the clinical and laboratory assessments of a woman with bacterial vaginosis. The pH paper may give a wrong reading if it samples the water used to lubricate the speculum or if it samples cervical secretions, which are relatively alkaline. The amine smell, described as smelling like “dead fish”, can be subjective, since some people cannot discern the smell.

### 8.3.3.1 Microscopy

If the microscope is available at the point of care, a wet-mount microscopic test for clue cells can be done. Clue cells are vaginal epithelial squamous cells coated with coccobacilli with absence of rods of lactobacilli. When visualized, clue cells predict bacterial vaginosis. Identifying clue cells requires adequate training and good skills and good knowledge of the microscope.

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).

## 8.4 Cervical infection – gonococcal and/or chlamydial cervicitis

*N. gonorrhoeae* and *C. trachomatis* infections among postpubertal women infect the endocervix rather than the vagina and can thus cause a cervical discharge, which may manifest as vaginal discharge. However, these two pathogens are less commonly associated with vaginal discharge.

### 8.4.1 Risk factors for STI-related cervical infections

Several demographic and behavioural factors have also been frequently associated with cervical infections and have been established as risk factors for STIs. Some of those that have been found to predict cervical infection in the presence of abnormal vaginal discharge in some settings are: being younger than 21 years (25 years in some places); having more than one sex partner in the previous three months; having a new partner in the previous three months; and having a current partner with an STI (57). Such risk factors are, however, usually specific to the population group for which they have been identified and validated and cannot be extrapolated to other populations or to other locations. Most researchers have suggested that obtaining more than one demographic risk factor from any particular person is important but that clinical signs such as cervical erosion can be valid as a single factor.

### 8.4.2 Clinical presentation – symptoms

At least 50% of women with gonococcal infection of the cervix are asymptomatic. Women with symptoms may have vaginal discharge, abnormal vaginal bleeding or dysuria. Most women with chlamydial cervical infection are asymptomatic. The ones who may be symptomatic have vaginal discharge, dyspareunia and dysuria. Several women may have lower abdominal pain because of ascending infection, causing pelvic inflammatory disease.

### 8.4.3 Examination findings – signs

Speculum examination may reveal a normal-looking cervix in the presence of endocervical infection. For those with abnormalities, the cervix may be erythematous or severely eroded and associated with a muco-purulent cervical discharge. The cervix may be friable and bleed easily on contact.

### 8.4.4 Microscopy

Gram-stained smears from the cervix are considered positive for the presumptive diagnosis of gonorrhoea in women if intracellular gram-negative diplococci are observed in polymorphonuclear leukocytes. Gram stain of urethral samples among women has low yield and may not be cost-effective (58).

### 8.4.5 Molecular detection

Molecular testing has greatly improved the detection of *C. trachomatis* and *N. gonorrhoeae* among both symptomatic and asymptomatic women and has become the recommended gold standard technology to diagnose and screen populations for *C. trachomatis* and *N. gonorrhoeae*. Among women, a vulvovaginal specimen, which may be self-collected, can be used for testing for these infections. An endocervical swab can also be an alternative but requires a speculum. First-catch urine is another option, but the sensitivity and specificity tend to be lower in women.

### 8.4.6 Culture methods

Processing *C. trachomatis* for culture requires highly experienced laboratories and technicians and is complex, laborious and time-consuming to be of economic value. It is rarely performed in middle- or high-income countries nowadays except for special purposes (59).

Culture for *N. gonorrhoeae* requires a special culture medium with nutrient supplementation for the organism to grow. Cervical and anorectal specimens can be used. The process is still necessary to undertake antimicrobial susceptibility testing to guide therapy, especially in cases of infection with *N. gonorrhoeae* isolates resistant to standard recommended therapies.

## 8.5 Recommendations for the management of vaginal discharge

For people with symptom of vaginal discharge, WHO recommends treatment for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis* on the same visit. WHO suggests treatment based on the results of quality-assured molecular assays for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis*. In settings in which treatment based on the results of molecular assay in the same visit is not feasible or that have limited or no molecular testing, WHO suggests treatment based on testing with quality-assured rapid point-of-care tests or on syndromic treatment.

*(Strong recommendation; moderate-certainty evidence)*

For people with symptom of vaginal discharge, good practice includes:

Good practice statement

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination, including abdominal and pelvic examination, to assess for pelvic inflammatory disease, surgical conditions or pregnancy and external vulvovaginal examination to visualize any lesions, overt genital discharge or vulval erythema and excoriations;
- bimanual digital examination of the vagina (1) to assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) to assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove; and
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines.

*Settings in which treatment is based on quality-assured molecular assays in a laboratory with a fully operational quality management system and results available on the same day of the visit*

*(Strong recommendation; moderate-certainty evidence)*

1. WHO recommends treating *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis* based on the results of quality-assured molecular assays on a self-collected, or clinician-collected, vaginal swab or on a urine specimen (Algorithm ①).
2. WHO suggests treating for bacterial vaginosis if vaginal discharge is present (for example, tenacious or thin) or based on the results of microscopy, if available.
3. WHO suggests treating for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available.

*Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing* (Conditional recommendation; low-certainty evidence)

1. WHO suggests treating based on a quality-assured rapid test with a minimum sensitivity of 80% and specificity of 90%, if available, to confirm or exclude infection with *N. gonorrhoeae* and *C. trachomatis* (Algorithm ②).
2. If the availability of a low-cost rapid test or molecular assay is limited, WHO suggests performing a speculum examination and treating for *N. gonorrhoeae* and *C. trachomatis* if there is evidence of cervicitis and performing a low-cost rapid test or molecular assay for people with a negative speculum examination who are at high risk of infection with *N. gonorrhoeae* and *C. trachomatis* and treating based on the test results (Algorithm ③<sup>a</sup>).
3. If a rapid test is not available, WHO suggests treating people who have signs of cervicitis on speculum examination for infection with *N. gonorrhoeae* and *C. trachomatis* (Algorithm ③).
4. If a rapid test is not available and a speculum examination is not feasible or acceptable, WHO suggests treating people for *N. gonorrhoeae* and *C. trachomatis*, all people at high risk of STIs and all people who have vaginal discharge on genital examination (Algorithm ④).
5. WHO suggests treating people for bacterial vaginosis and *T. vaginalis* if vaginal discharge is present or based on the results of microscopy, if available.
6. WHO suggests treating people for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available.

Good practice includes the following.

- For people with recurrent or persistent vaginal discharge, good practice includes referring to a centre with laboratory capacity to diagnose infection with *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and bacterial vaginosis and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium* (if there is a test) or for a specialist's assessment (STI expert and physician or a gynaecologist), when no such testing is available in primary health care centres.

*Good practice statement*

Fig. 4 offers programme managers guidance on the most applicable approaches to manage people presenting with vaginal discharge. It can be used to select sites or health facilities that can implement an option that has the appropriate diagnostic capacity and expertise. For example, a rural health centre with only basic commodities could follow one option, whereas a referral centre could implement a different option.

**Fig. 4. Flow chart for programme managers to determine which management options to implement for vaginal discharge**

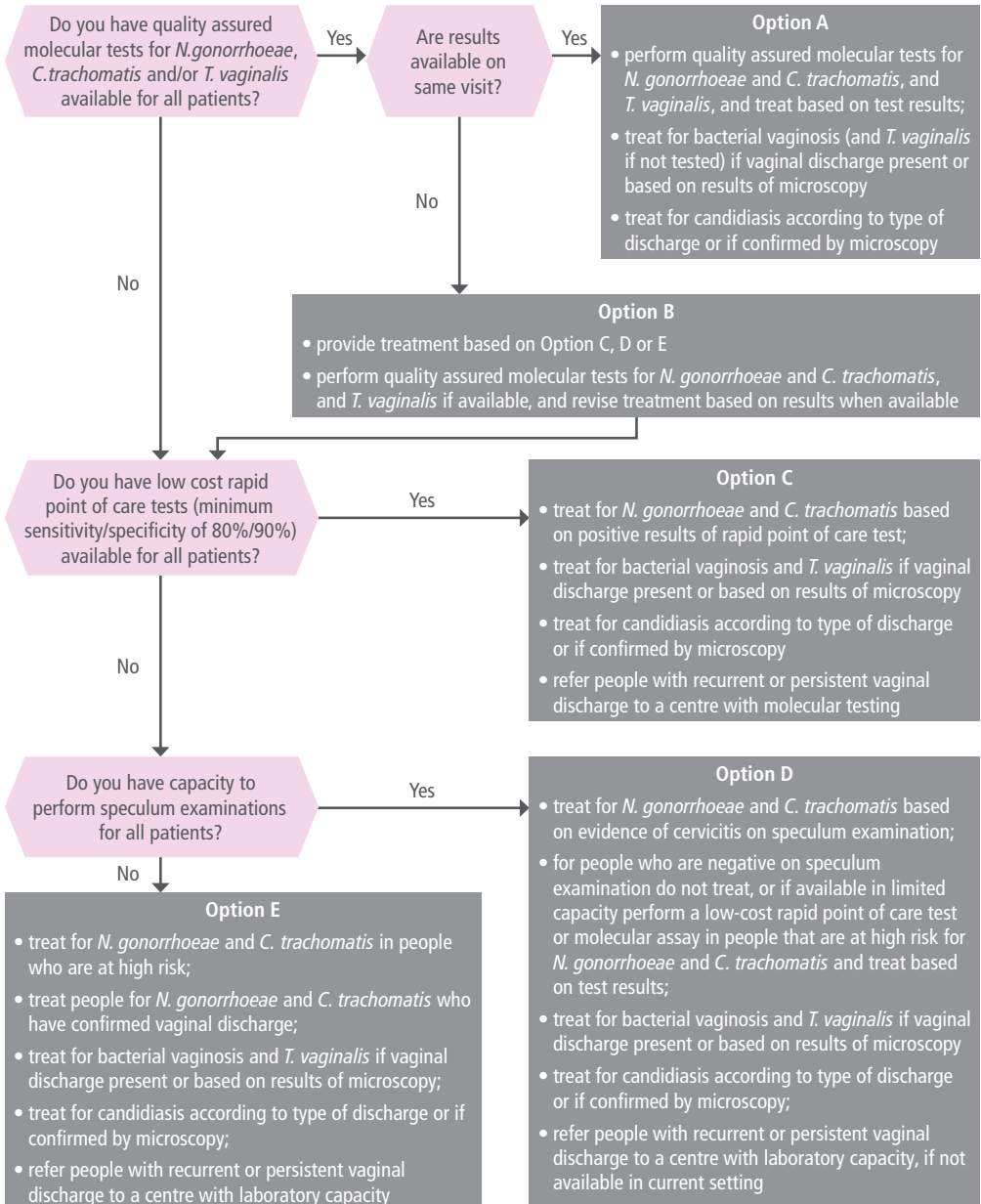
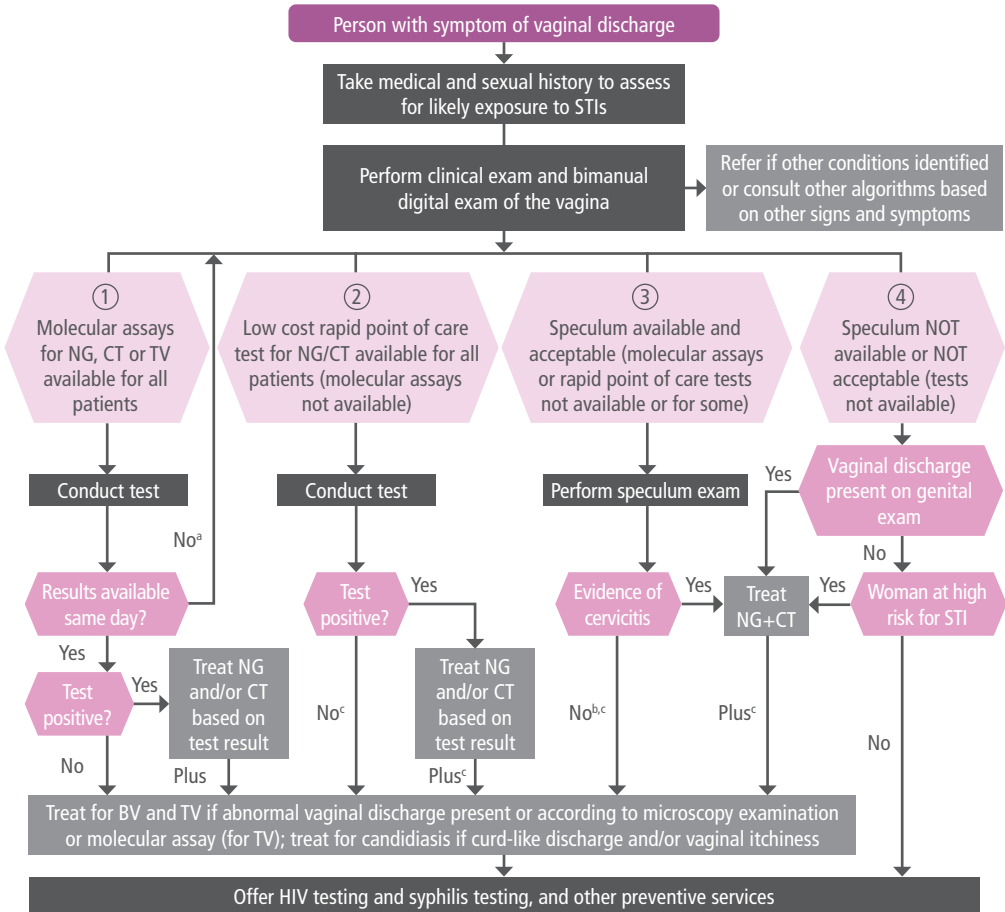




Fig. 5 is a proposed flow chart for health-care providers to follow in the process of managing people presenting with vaginal discharge. This flow chart can be adopted as it is or adapted to respond to the situation at the country level.

**Fig. 5. Flow chart for health-care providers to manage vaginal discharge according to local availability of resources and preferences**



NG, *N. gonorrhoeae*; CT, *Chlamydia trachomatis*; TV, *Trichomonas vaginalis*; BV, bacterial vaginosis.

<sup>a</sup>If molecular assay was performed and results were not available on same day, revise the syndromic treatment initially provided according to the test results when available

<sup>b</sup>perform rapid point of care test or molecular assay if available to confirm NG/CT and treat if positive; if negative do not treat and ask woman to return if symptoms recur

<sup>c</sup>if woman complains of recurrent or persistent discharge refer to a centre with laboratory capacity

### 8.6.1 Evidence summary (Annex 4)

Using a model, we compared the benefits, harm and costs of different combinations of using a risk assessment, speculum examination, microscopy, rapid point-of-care test and/or molecular assay test or treating none or all people who have vaginal discharge (supplementary materials – description of the modelling of vaginal discharge). We modelled two scenarios in which the prevalence of *N. gonorrhoeae* and/or *C. trachomatis* among people with vaginal discharge is low (5%) and high (20%) and applied different levels of antimicrobial resistance. We assumed same-day treatment for the different combinations of assessment and calculated the number of people with pelvic inflammatory disease as a critical harm and accounted for loss to follow-up and transmission. The evidence for the effects of the different strategies is moderate-certainty evidence because of the risk of bias of the included studies for calculating sensitivity and specificity.

In the model, we assumed that the costs of treatment for bacterial vaginosis or *T. vaginalis* is about US\$ 0.10, and we assumed that everyone with confirmed vaginal discharge would be treated for bacterial vaginosis and *T. vaginalis*. These figures are based on a review of the accuracy of risk assessment, speculum examination and/or laboratory testing for bacterial vaginosis and *T. vaginalis* (supplemental materials – systematic review vaginal discharge).

Although microscopy was accurate, with no false-positive treatments and less than 1% of cases missed, the costs of implementing microscopy in settings that currently do not have facilities outweighs the costs of treating everyone with confirmed vaginal discharge for bacterial vaginosis and *T. vaginalis* and the harm to people unnecessarily treated (about 40% of the people). We considered the effects of screening for bacterial vaginosis and *T. vaginalis* using pH testing compared with confirmed vaginal discharge and found that the differences in people missed and people treated unnecessarily were negligible and the costs and harm of treatment or missing treatment are relatively low.

When available, performing molecular tests for *N. gonorrhoeae*, *C. trachomatis* or *T. vaginalis* and treating on the same day based on the results leads to the most people treated correctly. However, when the results of the tests are not available on the same day of the visit, delay in treatment may lead to complications, transmission of infections and loss to treatment. Therefore, treatment could be determined based on signs and/or symptoms or on rapid diagnostic tests.

- Using a low-cost rapid point-of-care test with 80% sensitivity and 90% specificity will lead to fewer missed and falsely treated people compared with other syndromic approaches or with no treatment. Since there is a reduction in missed cases, the number of people who progress to pelvic inflammatory disease (and consequently to poor fertility and other negative reproductive health outcomes for some people) may be reduced by 70%, resulting in 4 per 1000 people experiencing pelvic inflammatory disease in settings in which the prevalence of *N. gonorrhoeae* and *C. trachomatis* is low versus 15 people per 1000 in settings in which it is high compared with no treatment. Since the accuracy of the test increases towards 95% sensitivity and 98% specificity, there are even greater reductions in missed cases and unnecessary treatments, but costs will increase. Using diagnostic tests with higher sensitivity and specificity may also lead to greater understanding of the prevalence of STIs in the community, enhanced sex partner tracing and improved overall quality of care.

We also modelled strategies in which molecular assays or rapid point-of-care tests are not widely available. The following observations were made.

- Performing a speculum examination and treating people with cervicitis and then microscopy for people who were negative on speculum examination may also lead to fewer missed cases and falsely treated people than using a rapid point-of-care test (at a minimum of 80% sensitivity and 90% specificity) for everyone. Alternatively, if a rapid point-of-care test is used for the people with a negative speculum examination, there would be even fewer missed cases and falsely treated people.
- Treating based only on the results of a speculum examination will still result in pelvic inflammatory disease cases and costs similar to a rapid point-of-care test, although the number of people treated unnecessarily would be slightly higher when using the speculum.

However, performing a speculum examination on everyone with vaginal discharge may not be feasible in some settings.

- Thus, when speculum examination is not feasible, the costs of an approach in which everyone at high risk (including with risk factors in high-prevalence settings) and/or people with confirmed vaginal discharge are treated may be higher than strategies with rapid point-of-care tests or speculum examination, but there are large beneficial reductions in the number of pelvic inflammatory disease cases. Compared with treating everyone, fewer people are unnecessarily treated.

## 8.6 Treatment options for vaginal discharge

Table 4 lists the options for the respective medicines to cover vaginal infections. If a decision was reached to include treatment for *N. gonorrhoeae* and/or *C. trachomatis*, Table 5 lists the options for the recommended medicines.

Bacterial vaginosis and *T. vaginalis* may be treated simultaneously with the same medicine, metronidazole. Similarly, in the treatment of cervicitis, some medicines, such as doxycycline and azithromycin, can simultaneously treat *C. trachomatis* and *M. genitalium*.

**Table 4. Treatment options for vaginal infections**

<ul style="list-style-type: none"> <li>• Therapy for bacterial vaginosis and trichomoniasis</li> </ul> <i>Plus</i> <ul style="list-style-type: none"> <li>• Therapy for yeast infection if curd-like white discharge, vulvovaginal redness and itching are present</li> </ul>			
Infections covered	First-line options	Effective substitutes	Note: In pregnancy, metronidazole should, ideally, be avoided in the first trimester
Bacterial vaginosis	<b>Metronidazole 400 mg or 500 mg</b> , orally, twice daily for 7 days	<b>Clindamycin 300 mg</b> , orally, twice daily for 7 days <i>or</i> <b>Metronidazole 2 grams</b> , orally, single dose	<b>Metronidazole 200 mg or 250 mg</b> , orally, 3 times a day for 7 days <i>or</i> <b>Metronidazole gel 0.75%</b> , one full applicator (5 grams) intravaginally, twice a day for 7 days <i>or</i> <b>Clindamycin 300 mg</b> , orally, twice daily for 7 days
<i>T. vaginalis</i>	<b>Metronidazole 2 grams</b> , orally, in a single dose <i>or</i> <b>Metronidazole 400 mg or 500 mg</b> , orally, twice daily for 7 days	<b>Tinidazole 2 grams</b> orally, single dose <i>or</i> <b>Tinidazole 500 mg</b> orally, twice daily for 5 days	<b>Metronidazole 200 mg or 250 mg</b> , orally, 3 times a day for 7 days <i>or</i> <b>Metronidazole gel 0.75%</b> , one full applicator (5 grams) intravaginally, twice a day for 7 days
<i>C. albicans</i> (yeast infection)	<b>Miconazole vaginal pessaries, 200 mg</b> inserted at night for 3 nights <i>or</i> <b>Clotrimazole vaginal tablet, 100 mg</b> , inserted at night for 7 nights	<b>Fluconazole 150 mg (or 200mg)</b> , orally, single dose <i>OR</i> <b>Nystatin, 200,000-unit vaginal tablet</b> , inserted at night for 7 nights	<b>Miconazole 200 mg vaginal pessaries</b> inserted once daily for 3 days <i>or</i> <b>Clotrimazole vaginal tablet 100 mg</b> inserted at night for 7 days <i>or</i> <b>Nystatin pessaries 200,000 units</b> , inserted at night for 7 nights

People taking metronidazole should be cautioned to avoid alcohol. Use of metronidazole in the first trimester of pregnancy is not recommended unless the benefits outweigh the potential hazards.

**Table 5. Treatment options for cervical infection<sup>a</sup>**

<ul style="list-style-type: none"> <li>• Therapy for uncomplicated <i>N. gonorrhoeae</i> (24)</li> </ul> <i>Plus</i> <ul style="list-style-type: none"> <li>• Therapy for <i>C. trachomatis</i> (25)</li> </ul>			
Infections covered	First-line options	Effective substitutes	Options for pregnant women or during breastfeeding
In settings in which local antimicrobial resistance data are not available, the WHO STI guidelines suggest dual therapy for gonorrhoea.			
<i>N. gonorrhoeae</i> <sup>a</sup>	<b>Ceftriaxone 250 mg</b> , intramuscularly, single dose <i>plus</i> <b>Azithromycin 1 gram</b> , orally, single dose	Cefixime 400 mg, orally, single dose <i>plus</i> Azithromycin 1 gram, orally, single dose	<b>Ceftriaxone 250 mg</b> , intramuscularly, single dose <i>plus</i> <b>Azithromycin 1 gram</b> , orally, single dose <i>or</i> <b>Cefixime 400 mg</b> , orally, single dose <i>plus</i> <b>Azithromycin 1 gram</b> , orally, single dose
<i>C. trachomatis</i>	<b>Doxycycline 100 mg</b> , orally, twice daily for 7 days (to be given only if gonorrhoea therapy did not include azithromycin)	<b>Azithromycin 1 gram</b> , orally, single dose <i>or</i> <b>Erythromycin 500 mg</b> , orally, 4 times a day for 7 days <i>or</i> <b>Ofloxacin 200–400 mg</b> , orally, twice daily for 7 days (to be given only if gonorrhoea therapy did not include azithromycin)	<b>Erythromycin 500 mg</b> , orally, 4 times a day for 7 days <i>or</i> <b>Azithromycin 1 gram</b> , orally, single dose (to be given only if gonorrhoea therapy did not include azithromycin)
<i>M. genitalium</i>	<b>Azithromycin 500 gram</b> , orally day 1, 250 mg daily, days 2–5 (absence of macrolide resistance)		<b>Azithromycin 500 gram</b> , orally, day 1, 250 mg daily, days 2–5 (absence of macrolide resistance)

<sup>a</sup>Because of increasing antimicrobial resistance to azithromycin in *N. gonorrhoeae* and *M. genitalium* and reduced susceptibility of *N. gonorrhoeae* to cephalosporins, WHO is in the process of revising current treatment recommendations and dosages.

## 9. LOWER ABDOMINAL PAIN

Causative agents of pelvic inflammatory disease include *N. gonorrhoeae*, *C. trachomatis* and bacteria associated with bacterial vaginosis. Facultative gram-negative rods and mycoplasmas have also been implicated. Since differentiating between these clinically is impossible and precise microbiological diagnosis is difficult, the treatment regimens must be effective against this broad range of pathogens. The regimens recommended below are based on this principle.

### 9.1 Recommendations for the management of lower abdominal pain among women

For sexually active women with symptom of lower abdominal pain, WHO suggests assessing for pelvic inflammatory disease and treating syndromically.

*(Conditional recommendation; low-certainty evidence)*

Good practice includes:

Good practice statement

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination, including abdominal and pelvic examination, to assess for pelvic inflammatory disease, surgical conditions or pregnancy and vulvovaginal examination to visualize any lesions, overt genital discharge, vulval erythema and excoriations;
- performing a bimanual digital examination of the vagina (1) to assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) to assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove; and
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines.

For sexually active women with lower abdominal pain with either of the following features on clinical examination (bimanual palpation):

- cervical motion tenderness; or
- lower abdominal tenderness:

*(Conditional recommendation; moderate-certainty evidence)*

WHO suggests the following.

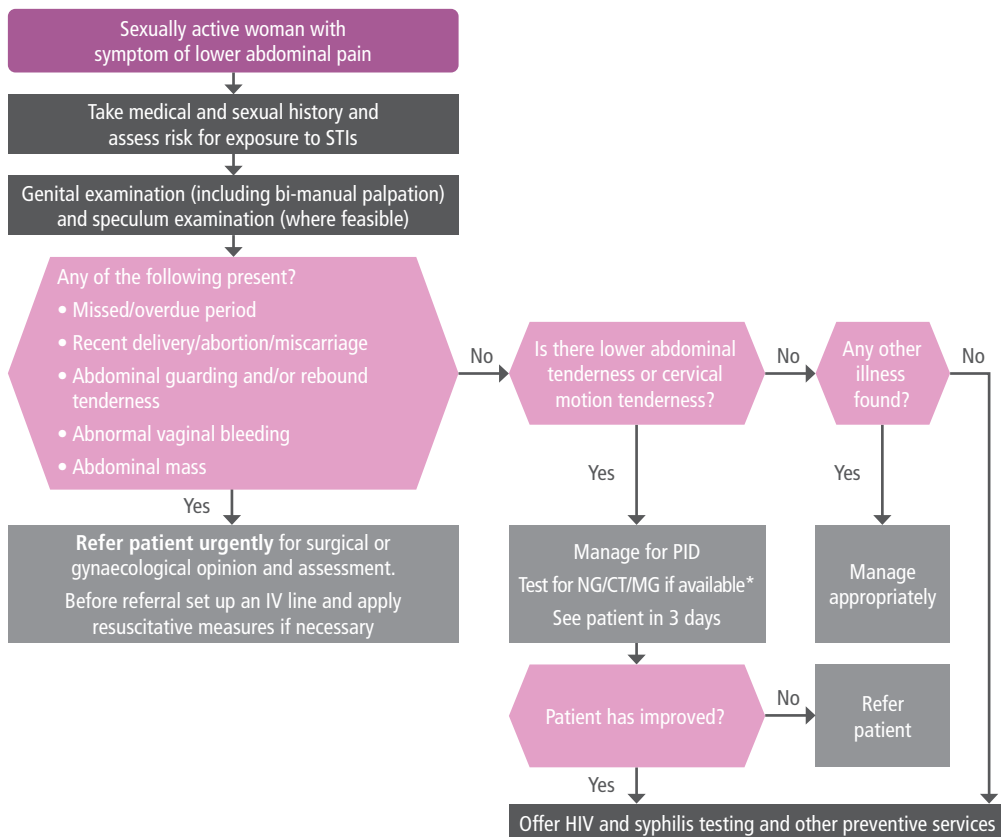
- Treat for pelvic inflammatory disease on the same visit.
- Test for infection with *N. gonorrhoeae* and *C. trachomatis* and, if available, *M. genitalium*, to support partner management when tests are available.
- Schedule follow-up assessment three days later to assess for clinical improvement, and if the woman has not improved, refer for further assessment.

For women with lower abdominal pain with any of the following conditions, good practice includes referral to surgical or gynaecological assessment:

- missed or overdue period;
- recent delivery, abortion or miscarriage;
- abdominal guarding and/or rebound tenderness;
- abnormal vaginal bleeding in excess of spotting;
- abdominal mass; and
- detection of a suspected cervical lesion.

Good practice statement



**Fig. 6. Flow chart for the management of lower abdominal pain**

\*to support partner notification.

NG, *N.gonorrhoeae*; CT, *C. trachomatis*; MG, *M. genitalium*.



### 9.1.1 Evidence summary (Annex 5)

We conducted systematic reviews of the diagnostic accuracy of syndromic management strategies to detect STIs (supplementary materials – systematic review lower abdominal pain). To detect *N. gonorrhoeae* and *C. trachomatis*, the syndromic management approach based on lower abdominal pain has 30% sensitivity and 73% specificity (moderate-certainty evidence). The accuracy of various signs and symptoms has also been calculated in individual studies. In a study of 623 women suspected of pelvic inflammatory disease, the sensitivity and specificity of fever was 47% and 64%, vaginal discharge 7% and 24% and tenderness of pelvic organs on bimanual examination 99% and 0.007%, respectively. In addition, a large study of 651 women in the United States of America (PEACH study) using criteria similar to the previous WHO syndromic management flow chart showed 83% sensitivity and 22% specificity. This accuracy means that, in a population with 5% prevalence of pelvic inflammatory disease among women with lower abdominal pain, 74% of the women would be unnecessarily treated but only 1% would have pelvic inflammatory disease and be missed. Immediate treatment of an acute pelvic inflammatory disease can avert adverse serious consequences such as chronic pelvic pain, ectopic pregnancy and infertility (moderate-certainty evidence). Therefore, higher value was placed on missing no woman with pelvic inflammatory disease and moderate value (although less) was placed on reducing the risk of transmitting STIs to partners.

Managing people presenting with lower abdominal pain based on a syndromic approach results in moderate benefits and minor harm compared with treating everyone or no treatment. The syndromic approach is already in place in most countries and would therefore be feasible and acceptable. The Guideline Development Group agreed that it would likely not negatively affect equity (in some settings it may increase equity) and would incur negligible costs because of the low costs of assessment and treatment.

## 9.2 Treatment for people presenting with lower abdominal pain

If pelvic inflammatory disease is confirmed or suspected, the treatment options for managing the person as an outpatient are shown in Table 6.

**Table 6. Treatment options for pelvic inflammatory disease<sup>a</sup>**

<ul style="list-style-type: none"> <li>• Therapy for uncomplicated <i>N. gonorrhoeae</i> (24) <i>plus</i></li> <li>• Therapy for <i>C. trachomatis</i> (25) <i>plus</i></li> <li>• Therapy for anaerobic infections</li> </ul>		
Infections covered	First-line options	Effective substitutes
In settings in which local antimicrobial resistance data are not available, the WHO STI guidelines suggest dual therapy for gonorrhoea.		
<i>N. gonorrhoeae</i>	<b>Ceftriaxone 250 mg</b> , intramuscularly, single dose <i>plus</i> <b>Azithromycin 1 gram</b> , orally, single dose	<b>Cefixime 400 mg</b> , orally, single dose <i>plus</i> <b>Azithromycin 1 gram</b> , orally, single dose
<i>C. trachomatis</i>	<b>Doxycycline 100 mg</b> , orally, twice daily for 14 days	<b>Erythromycin 500 mg</b> , four times daily for 14 days (to be given only if gonorrhoea therapy did not include azithromycin)
In settings in which local antimicrobial resistance data reliably confirm the susceptibility of <i>N. gonorrhoeae</i> to the antimicrobial agent, single therapy may be given as below.		
<i>N. gonorrhoeae</i>	<b>Ceftriaxone 250 mg</b> , intramuscularly, single dose	<b>Cefixime 400 mg</b> , orally, single dose
The treatment for anaerobes must be included in either treatment option above.		
<b>Anaerobes</b>	<b>Metronidazole 400 mg or 500 mg</b> , orally, twice daily for 14 days	

<sup>a</sup>Because of increasing antimicrobial resistance to azithromycin in *N. gonorrhoeae* and reduced susceptibility to cephalosporins, WHO is in the process of revising current treatment recommendations and dosages.

Hospitalization of people with acute pelvic inflammatory disease should be seriously considered under the following circumstances.

- the diagnosis is uncertain;
- surgical emergencies, such as appendicitis and ectopic pregnancy cannot be ruled out;
- a pelvic abscess is suspected;
- severe illness precludes management on an outpatient basis;
- the person is pregnant;
- the person is unable to follow or tolerate an outpatient regimen; or
- the person has failed to respond to outpatient therapy.

## 10. GENITAL ULCER DISEASE SYNDROME

The relative prevalence of causative organisms for genital ulcer disease varies considerably in different parts of the world and may change dramatically over time. Currently, however, HSV-2 and HSV-1 have become the commonest causative agents of genital ulcer disease in many parts of the world. The other causes frequently identified among people presenting with genital ulcer disease are *T. pallidum* (syphilis) and *C. trachomatis* serovars L1–L3, causing lymphogranuloma venereum and, less so, *H. ducreyi* (chancroid) (49,60,61).

Genital ulceration among people with primary syphilis occurs before serological laboratory tests become positive; thus, laboratory findings are rarely helpful at the initial visit and may even be misleading by being negative in the presence of syphilis infection. Further, in settings with a high prevalence of syphilis, a person with a genital ulcer may have a reactive serological test for syphilis from a previously treated infection, even if HSV-2 is the cause of the current ulcer.

In addition, since the differential diagnosis of genital ulcers using clinical judgement has been shown to be inaccurate in over 50% of cases, even by experienced clinicians, the management of people with genital ulcer disease must be based either on laboratory-based etiological studies or a syndromic approach, guided by periodic evaluation of the causative agents at the local setting.

### 10.1 Herpes simplex virus

#### 10.1.1 Clinical presentation – symptoms

Although the observation of a cluster of vesicular lesions on the genital area or perianal area is usually used as clinically indicative of genital herpes, other causes of genital ulcers, such as syphilis and chancroid, may have a similar clinical appearance. Clinical manifestations and patterns of genital ulcer disease may also be further altered in the presence of HIV infection.

First-episode genital herpes infections are those in which the person does not have a previous history of genital herpes, and they are often associated with systemic and local symptoms of fever, headache, malaise and myalgia, usually in the first 3–4 days. Locally, there may be pain, itching, dysuria, vaginal or urethral discharge and tender inguinal lymphadenopathy. Among both men and women with primary genital HSV infection, the presentation is with blistering or ulcerative lesions on the external genitalia. The lesions may start as papules (pimples) or vesicles (blisters), which spread rapidly over the genital area. The lesions may last up to 15–20 days until crusting and/or healing. Crusting does not occur on mucosal surfaces.

The first episode can be primary genital herpes in which the person is seronegative for HSV antibodies, occurring after an incubation period of within 5–14 days of sexual contact. Initial episodes of genital herpes refer to individuals who have the lesions for the first time but already have antibodies to HSV-2, indicating past asymptomatic acquisition of HSV-2. Although this would be the person's first recognized episode, it would not indicate recent acquisition.

Recurrent genital herpes tends to have more localized symptoms of itching, recurrent ulcers and mild pain, and the duration of the episode averages between four and five days but may be as long as up to 12–15 days.

### 10.1.2 Examination findings – signs

Among both men and women, a cluster of vesicopustular or ulcerative lesions is observed on the external genitalia (penis, urethral meatus, scrotum, pubic area and vulva) or on the anal and perianal areas (anus and buttocks). The patients may describe them as having started as papules or vesicles that spread rapidly. Multiple small vesicular lesions may coalesce into large ulcers. Most people with HSV-2 infection present at later stages of ulceration and hardly show the typical vesicles of early HSV-2 manifestation. However, when a person has a typical appearance of a crop of vesicles or gives a history of recurrent ulcers, a presumptive diagnosis of genital herpes can be made and treatment tailored appropriately.

Among immunosuppressed individuals, these ulcers may persist and continue to expand laterally and superficially for a considerable period of time if not treated. Since the ulceration of herpes is shallow (intraepidermal), residual scarring from these lesions is uncommon.

### 10.1.3 Molecular testing

Amplified molecular detection by PCR of HSV DNA from swabs of genital lesions is the most sensitive and specific test. Using a combined HSV and *T. pallidum* PCR, when available, would be of added benefit to implicate or exclude syphilis at the same time. PCR assays have also been developed for HSV-1 and HSV-2.

### 10.1.4 Culture methods

Culture enables replication of the virus for determining resistance to antiviral therapy and for confirming diagnosis, but results take about 2–4 days, and culture requires appropriate viral transport medium and special expertise to be a viable procedure. In expert hands, culture from vesicles has the highest yield of about 94% rather than from pustules or ulcer base. Crusted lesions give the lowest yield of about 27%.

### 10.1.5 Serology

Type-specific antibody tests can distinguish between HSV-1 and HSV-2. However, even immunoglobulin G (IgG)-based type-specific testing for HSV-1 and HSV-2 antibodies has limited value in diagnosis. The usefulness of testing is only by demonstrating seroconversion from a negative result at the time of the lesions to a positive result 6–12 weeks later. Although IgM detection can be used in diagnosing a new herpes infection, as many as 35% of the people with recurrent herpes episodes have IgM responses. IgM is therefore a poor marker of new infection and has limited diagnostic value (62).

## 10.2 Syphilis

Syphilis is a systemic disease caused by the spirochaete *T. pallidum*. The infection can be classified as congenital or acquired. Congenital syphilis is transmitted from mother to child in utero.

Acquired syphilis is divided into early and late syphilis. Early syphilis comprises the primary, secondary and early latent stages – syphilis of less than two years from acquisition of infection. Late syphilis refers to late latent syphilis, gummatous, nervous system and cardiovascular syphilis.

## 10.2.1 Clinical presentation – symptoms

Primary syphilis is characterized by an ulcer (syphilitic chancre) at the site of infection that develops after an incubation period of about three weeks from sexual contact but can range from nine to 90 days. The ulcers are usually single lesions and painless. The person with syphilis may miss them if they occur on concealed areas, such as the rectum, the cervix or the pharynx. If not treated, the ulcer will heal without scarring after some 2–10 weeks. The infection may then progress to the secondary stage.

Secondary syphilis sets in about six weeks to six months after infection. In some instances of secondary syphilis, especially among immunosuppressed individuals, the chancre may still be visible at the time secondary manifestation of syphilis occur. At this stage, the spirochaetes enter the blood stream and may cause systemic symptoms of fever, malaise, arthralgia and anorexia. If not treated at this stage, syphilis enters latency which might be followed by the tertiary stage of syphilis. A more detailed account of the natural history of syphilis is available (26).

Below follows a summary of clinical presentations of the different stages of syphilis and some guidance for diagnosis, followed by recommendations for a syndromic approach for managing people with syphilis and a summary of commonly used tests for diagnosing syphilis.

## 10.2.2 Examination findings – signs and laboratory diagnosis

### 10.2.2.1 Primary syphilis

Primary syphilis comprises one or more ulcerated lesions called the chancre of syphilis at the site of initial infection. The lesions are minimally tender or nontender and may have characteristic indurated edges with a clean base. Regional lymph nodes may be felt within the first week. The mouth and anus must also be examined for ulcers. Ulcers heal even without treatment in 2–10 weeks.

The following diagnostic tests are used:

- darkfield microscopy – syphilitic treponemes from lesions of primary syphilis observed (see section on microscopy); a negative dark-field result does not exclude syphilis;
- molecular detection – PCR testing can directly detect *T. pallidum* from lesion samples; and
- serology – both nontreponemal (such as RPR) and treponemal tests (such as TPHA and rapid syphilis strip test) are negative in the early phase of primary syphilis, taking 1–4 weeks after the chancre appears to become reactive (Fig. 7).

A negative RPR or rapid syphilis test therefore does not exclude syphilis at the primary syphilis stage. Tests should be repeated at four and 12 weeks from the initial testing to be certain if the person does not receive treatment.

### 10.2.2.2 Secondary syphilis

Secondary syphilis presents with signs of disseminated syphilis, about 3–6 weeks after infection, but this can be as long as six months. The manifestations may include any of the following:

- a generalized maculo-papular rash that is usually asymptomatic or mildly itchy and may also be seen on the palms and plantar surfaces of feet;
- patchy alopecia;
- generalized lymphadenopathy;
- condylomata lata – hypertrophic lesions resembling flat warts in the moist areas, such as the labia and perineum, the folds of the foreskin and around the anus that are teeming with spirochaetes and are therefore highly contagious; and
- painless shallow ulcers of the oral or genital mucous membranes (mucous patches) that are highly contagious.

The following diagnostic tests are used:

- dark-field microscopy – syphilitic treponemes can be observed from lesions of secondary syphilis, such as condylomata lata and mucous patches;
- molecular detection – *T. pallidum* can be detected by molecular methods from lesions of secondary syphilis; and
- serology – both nontreponemal (such as RPR) and treponemal tests (such as TPHA and a rapid syphilis test) are almost always reactive (positive) in secondary syphilis, and usually in high titre (Fig. 7).

A negative treponemal test at this stage of syphilis can reasonably be used to rule out syphilis. Rarely, some people may have such high levels of antibody that give a false-negative result with nontreponemal tests – a prozone phenomenon. Nontreponemal tests usually have high titres of 1:16 or greater at this stage of infection. Titres decline with adequate treatment and can be used to monitor response to treatment at three-monthly intervals for at least 1 year.

### 10.2.2.3 Early latent syphilis

As its name implies, latent syphilis has no clinical manifestations. The lesions of primary syphilis and those of secondary syphilis have resolved spontaneously and the infection goes into latency. Early latent syphilis is infection of less than two years in duration, as designated by WHO, based on the infectiousness of syphilis and its response to therapy during this stage of infection.

During the first two years (primary, secondary and early latent) of syphilis infection, the individual is infectious to the sex partner and there is a high risk of transmission to the fetus during pregnancy. In addition, nearly 25% of those with syphilis in the first year of infection will relapse and develop manifestations of secondary syphilis, termed mucocutaneous relapse (63).

#### 10.2.2.4 Late latent syphilis

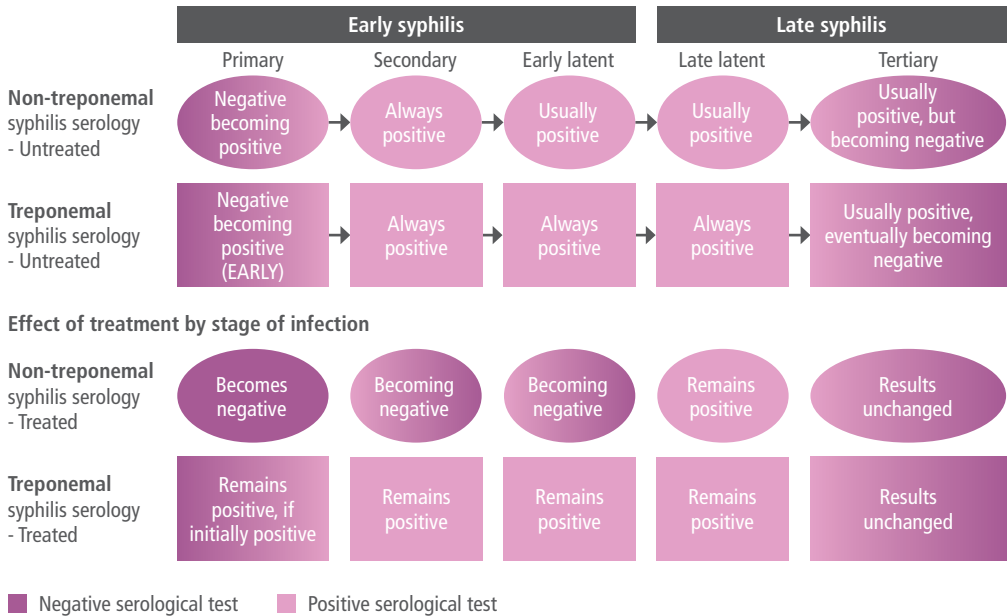
An infection of more than two years in duration without clinical evidence of treponemal infection is referred to as late latent syphilis. In late latency, the individual with untreated syphilis is less and less likely to transmit the infection to a sex partner and to the fetus during pregnancy as the latency progresses.

Late latent syphilis is diagnosed with serological tests. Nontreponemal and treponemal tests are mostly reactive (positive) in early latent and late latent syphilis, but nontreponemal tests, such as the VDRL, may become negative in late latent syphilis (Fig. 7). A negative treponemal test at this stage of infection can be taken as sufficient to rule out the diagnosis of syphilis. Once the specific treponemal tests are positive, they remain reactive for the person's lifetime. Therefore, these tests cannot be used for monitoring the response to treatment.

Fig. 7 shows an overview of the reactivity of non-treponemal and treponemal serological tests for syphilis and the effect of successful treatment. Serological tests for syphilis give only a presumptive diagnosis of syphilis, and they must be interpreted together with a good sexual history of the individual, a physical examination and information about any recent treatments with antibiotics, especially for syphilis. A good medical history must also be obtained, since some underlying conditions may cause a false-positive reaction with non-treponemal tests, such as acute febrile illnesses, immunizations, pregnancy and autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus. Such false positives are usually at low titres of less than in 1:8 (64). If possible, positive non-treponemal tests (RPR or VDRL) should be quantified (the titres should be determined).

Non-treponemal tests may be negative in primary syphilis for 1–4 weeks after the appearance of the chancre (4–6 weeks after infection). The tests are reactive almost without exception in secondary syphilis. As the duration of the early and late latent stages of syphilis increases, the antibody titre decreases and may eventually give a negative result in late syphilis (late latent and tertiary stages), even without treatment. With treatment, syphilis serology tests may revert to negative depending on the stage of syphilis when treatment is instituted. This is more likely to happen if the individual is treated during the primary or secondary stage of syphilis. If early syphilis is treated, the non-treponemal test titres will decline and become negative and may thus be used to monitor response to treatment. If the disease is diagnosed at the late syphilis stage, low titres of non-treponemal tests may remain positive for life.

**Fig. 7. Reactivity of serological tests by stage of syphilis and effect of treatment**



Source: Unemo et al. (48).

The specific treponemal tests, including TPHA, TPPA and fluorescent treponemal antibody absorption, may become positive earlier than the non-treponemal tests. Once an individual tests positive on a treponemal test, most (85%) remain positive on subsequent treponemal tests even when the infection is successfully treated.

The more recent rapid syphilis tests in circulation are immunochromatographic strips with treponemal antigens. These rapid syphilis tests are therefore equivalent to specific treponemal tests, such as the TPHA and TPPA, and the results produced by such tests should be interpreted as indicated in Fig. 7. A positive rapid syphilis test measures lifetime exposure to treponemal infection and not necessarily active disease that requires treatment. If an RPR-equivalent test is available, it should be performed following a positive rapid syphilis test to determine whether there may be active syphilis infection or not. More detailed guidelines on the use and interpretation of rapid syphilis tests are available (28). For details about the procedures for performing rapid syphilis tests and RPR tests, see the WHO manual (48).

Further, in areas of high syphilis prevalence, a reactive serological test for syphilis may reflect a previous infection and give a misleading picture of the person's present condition. This is especially important in populations at higher risk of STIs, who may end up being unnecessarily treated repeatedly for syphilis. When available, an RPR test with titration may indicate which people need treatment since false-positive or sero-fast reactions usually have titres of less than 1:8.



## 10.3 *H. ducreyi* (chancroid)

### 10.3.1 Clinical presentation – symptoms

Lesions of chancroid begin as an erythematous papule within hours to days of sexual exposure. Over the following 1–2 days, the papule evolves into a pustule that breaks down and becomes a painful ulcer. People usually seek health care at the stage of the painful ulcer. Among men, the ulcers are usually on the penis (foreskin, shaft and sometimes on the glans), and as many as 50% develop unilateral or bilateral painful inguinal lymph nodes. Large, painful, fluctuant lymph nodes (buboes) may also occur. If not treated, buboes may suppurate and form fistulae or ulcers.

In women, ulcers of chancroid are on the vulva, and anal ulcers from autoinoculation may also occur. Ulcers among women may be asymptomatic, especially when they are internal. Women do not frequently present with inguinal adenopathy because of the different lymphatic drainage.

### 10.3.2 Examination findings

There are generally single or multiple ulcers on the penile shaft, the foreskin or the glans penis, usually deep with an irregular edge and a red margin. There is usually no induration, and the base is granular or purulent. The ulcers are normally tender when being examined or when walking. Men may have unilateral or bilateral inguinal buboes.

However, chancroid ulcers often have atypical clinical appearances and may dispel suspicion of chancroid, with some small ulcers mimicking infected genital herpes. In HIV infection, the ulcers may be less purulent and resemble syphilitic chancres. Also, people with immunosuppression may have rapidly aggressive and erosive ulcers of chancroid to the point of anatomically destroying the genital organs.

### 10.3.3 Laboratory diagnosis

*H. ducreyi* has been characteristically diagnosed by culture methods but only in limited specialized centres because of the fastidious nature of the organism with a sensitivity of 75% compared with M-PCR from genital ulcer swabs. Although multiplex PCR for genital ulcer disease, including *H. ducreyi*, has been developed, it is found only in research settings and reference centres (65,66). Since *H. ducreyi* has almost disappeared globally as a cause of genital ulcer disease (67,68), further advances in diagnostic tests for this pathogen are unlikely.

Clinicians must have a high index of suspicion when they see an unusually painful, suppurative ulcer among men or women. If there are also painful inguinal lymph nodes with the ulcer, especially among men, chancroid must be high in the differential diagnosis. If in any particular setting more and more such lesions are being seen, then the national authorities should be alerted to the fact so that the treatment regimen can be adapted accordingly.

## 10.4 Recommendations for the management of genital ulcer disease, including anorectal ulcers

For people who present with genital ulcers (including anorectal ulcers), WHO recommends treatment based on quality-assured molecular assays of the ulcer. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit.

*(Strong recommendation; moderate-certainty evidence)*

Good practice includes:

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination of the genital and anal areas;
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and
- providing analgesics for pain.

Good practice statement

*Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit*

*(Strong recommendation; moderate-certainty evidence)*

For people with confirmed anogenital ulcers, WHO recommends the following.

1. Perform molecular assays (NAAT) from anogenital lesions to confirm or exclude herpes simplex virus and *Treponema pallidum* (syphilis).
2. Perform molecular assays from anogenital lesions to confirm lymphogranuloma venereum in geographical settings and/or populations in which cases are reported or emerging.
3. Perform serological tests for syphilis, with appropriate interpretation for management depending on the test or tests used.
4. Treat for syphilis and/or herpes simplex virus according to the results available on the same day of the visit or treat syndromically and revise management according to the results when available.
5. Treat for lymphogranuloma venereum when the results are positive.
6. Treat for chancroid only in geographical settings where cases are reported or emerging.

*Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing*

*(Conditional recommendation; moderate-certainty evidence)*

For people with confirmed anogenital ulcers, WHO suggests the following.

1. Treat syndromically for syphilis and herpes simplex virus on the same day.
2. Treat for herpes simplex virus if the ulcer is recurrent or vesicular, and treat for syphilis if the person has no history of recent treatment for syphilis (in the past three months).
3. Treat for chancroid only in geographical settings where cases are reported or emerging.

Good practice includes.

Good practice statement

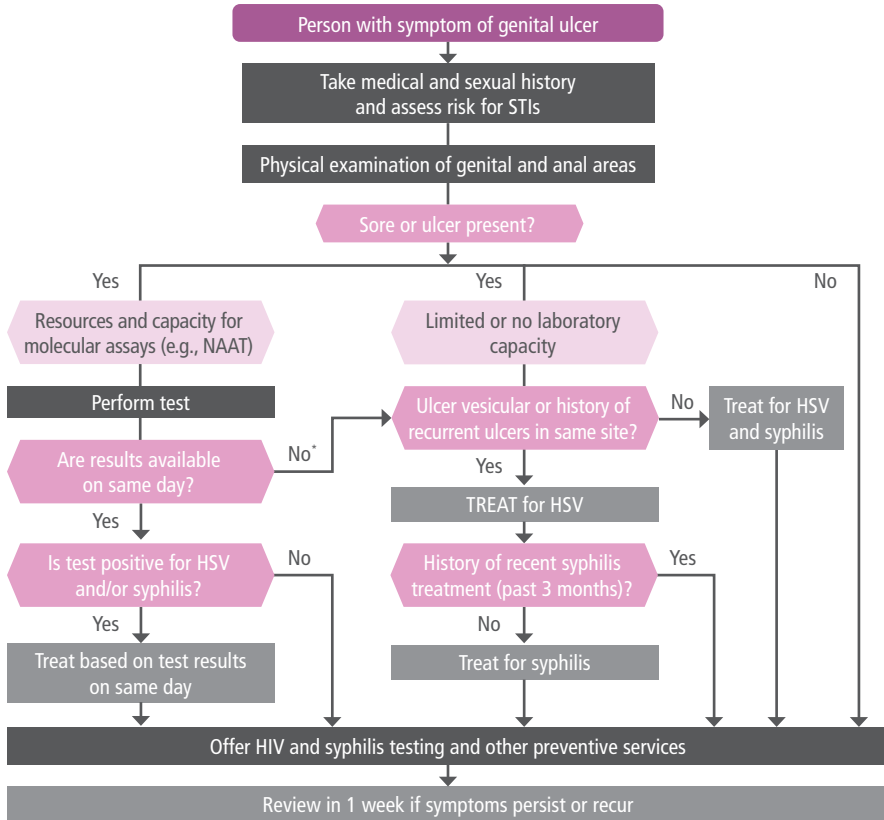
- performing serological tests for syphilis, including an RPR-equivalent test, if available, to attempt to identify active syphilis and for monitoring the response to treatment; and
- referring men with persistent anogenital ulcers to a centre with laboratory capacity and expertise to diagnose herpes or less common pathogens (lymphogranuloma venereum, donovanosis and chancroid) and other genital or gastrointestinal conditions.

### Remarks

Genital ulcer disease refers to breaks in the skin or mucosa and may present as ulcers, sores or vesicles. Anogenital ulcers refer to those located on the genital or anal areas and may be painful or painless.

A negative serological test for syphilis when anogenital ulcers have been present for less than three weeks does not definitively exclude syphilis, since antibodies may not yet be present to be detected by a serological test for syphilis. See WHO guidance on interpreting syphilis tests (see subsection 10.2).

**Fig. 8. Flow chart for the management of genital ulcer disease including anorectal ulcers**



HSV, herpes simplex virus

\* If molecular assay was performed and results were not available on same day, revise the syndromic treatment initially provided according to the test results when available

### 10.4.1 Evidence summary (Annex 6)

These recommendations were informed by evidence that was of high and moderate certainty from a systematic review of the sensitivity and specificity of using a clinical diagnosis of an STI pathogen based on the presence of an anogenital ulcer. No studies were found for clinical diagnosis of lymphogranuloma venereum (supplementary material – systematic review genital ulcer disease).

For detecting syphilis, which typically ranges from 5% to 10% as a cause of anogenital ulcers, if clinical diagnosis was used for 100 people with ulcers (sensitivity 64% and specificity 84%), about 2–4 cases would be missed, and 14–15 people would be falsely identified as having syphilis and unnecessarily treated. Alternatively, if all 100 people with an anogenital ulcer were treated for syphilis, 90–95 would be unnecessarily treated but no cases would be missed. Molecular assays could reduce the number of people unnecessarily treated or missed cases (since they are highly sensitive and specific), but the costs of diagnostics may be high and inaccessible. The WHO Guideline Development Group assessed the long-term consequences of a missed case of syphilis as more important than the number of people unnecessarily treated (false positives) and the cost of unnecessary treatment and therefore suggests treating all ulcers for syphilis when there is limited testing capacity. Other challenges of managing people with syphilis, such as with medications, are likely not linked to cost but to logistical support for procuring and distributing medications.

For detecting herpes, which typically ranges from 30% to 70% as a cause of anogenital ulcers, using a clinical diagnosis for 100 people with ulcers (sensitivity 40% and specificity 88%), about 18–42 cases of herpes would be missed and about 4–8 people with an ulcer would be identified falsely and be unnecessarily treated. Treating all 100 people with an anogenital ulcer for herpes would mean that 30–70 people would be unnecessarily treated, but the cost of treatment may be relatively inexpensive. The WHO Guideline Development Group agreed that it is uncertain that missing a case would lead to serious long-term harm. It likely contributes to increased HIV acquisition or HSV transmission and means discomfort for the people with symptoms (69). Treating everyone with a genital ulcer for herpes was therefore suggested for improving the quality of life when there is limited capacity for laboratory testing. The Guideline Development Group agreed that treating everyone is likely feasible, the costs of treatment would be negligible and be acceptable to all and would likely not have negatively affect equity (in some settings it may increase equitable access to treatment).

The systematic review of the literature found that the prevalence of chancroid has been decreasing in high-income and low- and middle-income countries alike and using a clinical diagnosis to determine treatment of chancroid therefore results in only a trivial number of missed cases and greater unnecessary treatment. Based on the current prevalence of chancroid, the Guideline Development Group therefore agreed to suggest no treatment for chancroid for people with anogenital ulcers, unless surveillance shows reported or emerging cases. Although no evidence was found for lymphogranuloma venereum and the cost-benefit and harm of clinical diagnosis, the Guideline Development Group agreed that performing tests for lymphogranuloma venereum would also depend on the number of emerging cases and suggested no treatment for lymphogranuloma venereum unless a test was positive.

## 10.5 Treatment of genital ulcer disease, including anorectal ulcers

Table 7 outlines treatment options for the syndromic management of people with genital ulcer disease. Syndromic management should include treatment for syphilis, unless the person has been treated for syphilis within the past three months, and treatment for herpes.

For persons with recurrent ulcers that are too frequent (such as 4–6 episodes or more a year) or with severe symptoms or causing distress, suppressive therapy may be proposed and preferred to episodic treatment (27). People receiving suppressive therapy may be assessed after one year and asked whether they want to continue or to change to episodic therapy. Note that recurrence rates may revert to the period before suppressive therapy started, and patients need to be aware of that.

For people living with HIV and immunosuppressed individuals, dose adjustments are recommended for valaciclovir and famciclovir but not for acyclovir.

- For recurrent episodes, valaciclovir 500 mg is recommended for five days instead of three days, and famciclovir is recommended at a dose of 500 mg twice daily for five days instead of 250 mg.
- For suppressive therapy, valaciclovir is recommended at 500 mg twice daily instead of once daily and famciclovir at 500 mg twice daily instead of 250 mg twice daily.

People who report allergies to penicillin should be treated with the effective alternatives for syphilis, which include doxycycline and erythromycin.

**Table 7. Recommended treatment options for genital ulcer disease**

<ul style="list-style-type: none"> <li>Multiple-dose therapy for herpes simplex virus infection (27)</li> </ul> <i>Plus</i> <ul style="list-style-type: none"> <li>Single-dose long-acting penicillin therapy or multi-dose therapy of alternatives (26)</li> </ul>			
Infections covered	First-line options	Effective substitutes	For pregnant and breastfeeding women and people younger than 16 years
Genital herpes	<b>Primary infection</b> Acyclovir 400 mg, orally, 3 times a day for 10 days <i>or</i> Acyclovir 200 mg, orally, 5 times a day for 10 days	<b>Primary infection</b> Valaciclovir 500 mg, twice a day for 10 days <i>or</i> Famciclovir 250 mg, orally, 3 times a day for 10 days	<b>Primary infection</b> Use acyclovir only when the benefit outweighs the risk. The dosage is the same as for primary infection in non-pregnancy.
	<b>Recurrent infection – episodic therapy</b> Acyclovir 400 mg, orally, 3 times a day for 5 days <i>or</i> Acyclovir 800 mg, orally, twice daily for 5 days <i>or</i> Acyclovir 800 mg, 3 times a day for 2 days	<b>Recurrent infection – episodic</b> Valaciclovir 500 mg, twice daily for 5 days <i>or</i> Famciclovir 250 mg, orally, twice daily for 5 days	<b>Recurrent infection – episodic therapy</b> Acyclovir 400 mg, orally, 3 times a day for 5 days <i>or</i> Acyclovir 800 mg, orally, twice daily for 5 days <i>or</i> Acyclovir 800 mg, 3 times a day, for 2 days
	<b>Suppressive therapy for recurrent herpes<sup>a</sup></b> Acyclovir 400 mg, orally, twice daily <i>or</i> Valaciclovir 500 mg, once daily	<b>Suppressive therapy for recurrences<sup>a</sup></b> Famciclovir 250 mg, orally, twice daily	<b>Suppressive therapy for recurrent herpes</b> Acyclovir 400 mg, orally, twice daily <i>or</i> Valaciclovir 500 mg, once daily
<b>Syphilis (early)</b> (treatment for primary, secondary and early latent [less than two years since infection] syphilis)	<b>Benzathine penicillin 2.4 million units</b> , intramuscularly in a single dose	Doxycycline 100 mg, orally, twice a day for 14 days <i>or</i> Erythromycin 500 mg, 4 times a day for 14 days	<b>Benzathine penicillin 2.4 million units</b> , intramuscularly in a single dose <i>or</i> Erythromycin 500 mg, orally, 4 times a day for 14 days <sup>b</sup>
<b>Syphilis (late)</b> (treatment for late latent and tertiary syphilis)	<b>Benzathine penicillin 2.4 million units</b> by intramuscular injection, once weekly for 3 consecutive weeks	<b>Procaine penicillin 1.2 million units</b> by intramuscular injection, once daily for 20 consecutive days <i>or</i> Doxycycline 100 mg, orally, twice daily for 30 days	Erythromycin 500mg orally, 4 times a day for 30 days <sup>b</sup>

<sup>a</sup>Suppressive therapy for recurrent herpes is recommended for individuals with 4–6 or more recurrent episodes per year, severe symptoms or episodes that cause distress. Increased dosages or duration of treatment are required for people living with HIV (27).

<sup>b</sup>Although erythromycin is used to treat pregnant women, it does not cross the placental barrier completely and the fetus is not treated. The newborn infant therefore needs treatment soon after delivery.

# 11. ANORECTAL DISCHARGE

Anorectal symptoms and anorectal STIs are prevalent among men who have sex with men, female sex workers, transgender people and heterosexual women who engage in anal sexual intercourse.

## 11.1 Anatomical sites of infection

Infections of the anorectal region can be divided into the following anatomical sites:

- anal infections: infections of the anus and perianal area involving the stratified squamous epithelium – a common site for pathogens such as HPV, HSV and syphilis;
- proctitis: infections from the dentate line to the rectosigmoid junction – a common site for gonococcal and chlamydial infections and HSV (the dentate line is the line between the simple columnar epithelium of the rectum and the stratified epithelium of the anal canal, usually defined as being at the level of the anal valves; and
- proctocolitis: infections of the rectum and colon – a common site for infections with *Shigella*, *Campylobacter*, *Salmonella* and cytomegalovirus and amoebiasis.

For syndromic diagnosis and management, these infections have been grouped under anorectal infections. Anorectal infections may be associated with anorectal pain, itching, discharge, bleeding, sensation of rectal fullness, tenesmus, constipation and mucus streaking of stools.

Asymptomatic anorectal infections are not uncommon, although precise data are scarce. The people at highest risk of asymptomatic anorectal infections are men who have sex with men, male and female sex workers, transgender people and women who have had receptive anal intercourse with men with STIs.

## 11.2 Sexual practices that may be associated with anorectal infections

Specific high-risk sexual behaviour associated with anorectal infections include receptive anal sex, oro-anal contact (anilingus or rimming), fisting (inserting a hand into the rectum or vagina), fingering (touching another's genitals or anus using fingers or digital-vaginal penetration), nudging (unprotected penile-anal external contact without penetration), dipping (partly inserting or briefly inserting the penis into the anus without a condom, followed by immediate withdrawal) and sharing sex toys.

## 11.3 Examination

An examination for anal infections includes an external examination of the anus and, where available, an anoscopy. In asymptomatic infections, anoscopy can be performed, possibly with Gram-stained smear and a count of the number of polymorphonucleated leukocytes to screen for STIs. However, an anoscope is not available in most primary point-of-care settings, and an external examination may be the only practical procedure to observe a discharge, ulcers or external warts.



Although an anoscopic examination can be used to take samples for Gram-stained smear for *N. gonorrhoeae* and for leukocytes, as well as for culture of *N. gonorrhoeae*, samples for nucleic acid amplification tests for *Chlamydia* and dark-field microscopy for *T. pallidum*, the performance of such tests on rectal specimens is not well established. However, some test kits have been licensed for use on rectal specimens. Little or no data exist to validate using microscopy in diagnosing anorectal infections.

In many low- and middle-income countries, male and females sex workers have similar rates of anorectal infection (70–72). A more practical approach in such a situation might be periodic presumptive treatment for high-risk men or presumptive treatment at the first visit, but there is limited experience with the outcomes of such an approach in anorectal infections for both men and women.

Given the limited data and information on both symptomatic and asymptomatic anorectal infections, the providing care for people with STIs associated with anorectal infections requires close supervision and research, especially in populations at high risk of infection. Research is also needed to validate laboratory tests on rectal specimens and to validate the treatment choices for anorectal infections.

Knowledge of the prevalence of asymptomatic, seroreactive syphilis infection among men who have sex with men can be helpful in adapting the flow chart to include syphilis treatment for those at high risk of infection and for those with ulcerative disease.

## 11.4 Recommendations for the management of anorectal discharge

For people with symptom of anorectal discharge and report receptive anal sex, WHO recommends management based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit.

*(Strong recommendation; moderate-certainty evidence)*

Good practice includes:

- taking a medical and sexual history and assessing the risk of STIs;
- performing a physical examination of the genital and perianal areas and a digital rectal examination, if acceptable (and anoscopy, if available and acceptable);
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and
- referring for other investigations when anorectal discharge is unrelated to a sexually transmitted infection, such as other gastrointestinal conditions.

Good practice statement

*Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit*

*(Strong recommendation; moderate-certainty evidence)*

WHO recommends the following.

1. Perform molecular assays (NAAT) using a self-collected or clinician-collected anorectal swab to confirm or exclude infection with *N. gonorrhoeae* and/or *C. trachomatis* and treat the individual infections detected.
2. Treat, additionally, for herpes simplex virus if there is anorectal pain.
3. Follow the genital ulcer guidelines if ulceration is present.

Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing

*(Conditional recommendation; moderate-certainty evidence)*

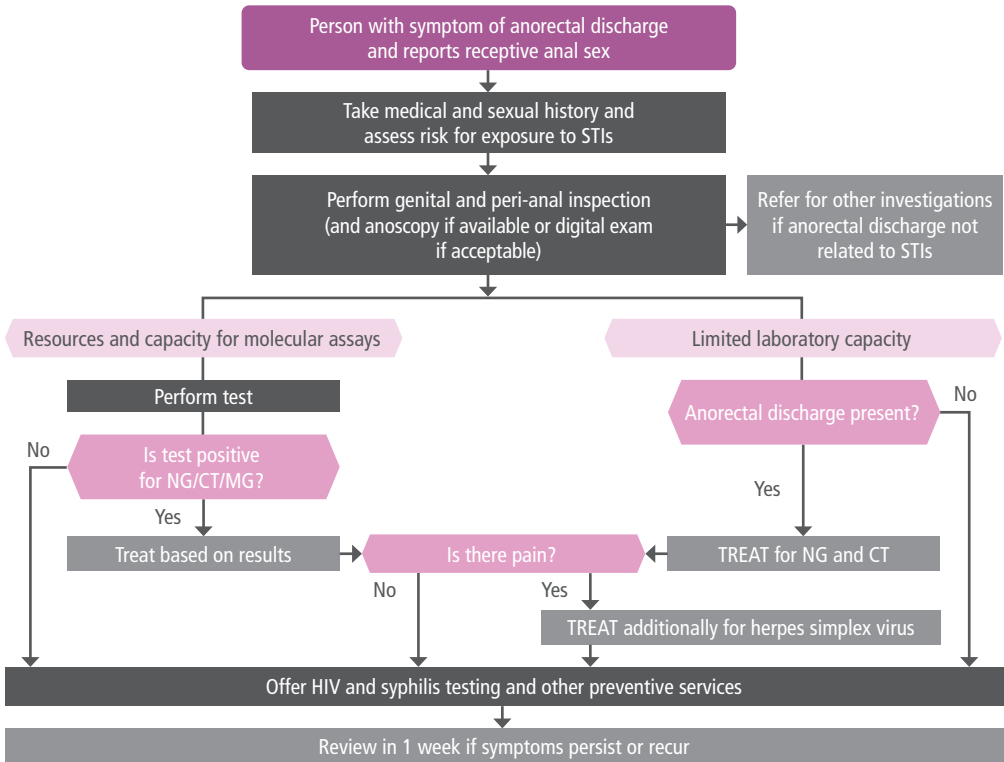
WHO suggests the following.

1. Treat for *N. gonorrhoeae* and *C. trachomatis* if discharge is present.
2. Treat, additionally, for herpes simplex virus if there is anorectal pain.

Good practice includes:

*Good practice statement*

- following the genital ulcer guidelines if ulceration is present; and
- referring people with persistent anorectal discharge to a centre with laboratory capacity to diagnose *N. gonorrhoeae*, *C. trachomatis* (including lymphogranuloma venereum serovars) and *M. genitalium* and determine antimicrobial resistance for *N. gonorrhoeae* and *M. genitalium*.

**Fig. 9.** Flow chart for the management of anorectal discharge

NG, *N.gonorrhoeae*; CT, *C. trachomatis*; MG, *M. genitalium*.

### 11.4.1 Evidence summary (Annex 7)

These recommendations were informed by evidence that was of moderate certainty from a systematic review of the sensitivity and specificity of using syndromic management based on anorectal discharge to diagnose *N. gonorrhoeae* and/or *C. trachomatis* (supplementary materials – systematic review anorectal discharge). When available, performing molecular assay tests for *N. gonorrhoeae* and *C. trachomatis* as well as *C. trachomatis* (serovars L1, L2 and L3) causing lymphogranuloma venereum and *M. genitalium* and basing treatment on these results leads to the most people treated correctly. If the previously recommended syndromic management algorithm was used for 100 people with anorectal discharge in which 20–50% would typically have *N. gonorrhoeae* or *C. trachomatis* (with 32% sensitivity and 82% specificity), then 9–15 would be falsely identified with *N. gonorrhoeae* or *C. trachomatis* and unnecessarily treated and 14–34 would be missed. The previously recommended algorithm is based on assessment of risk, anorectal pain and discharge. The Guideline Development Group agreed that the numbers of cases missed using syndromic management means many people would continue to harbour the infections, which would increase the risk of transmission to others and the risk of acquiring and transmitting HIV. Instead, when molecular assay tests are not available, although the number of people treated unnecessarily would be high, if everyone with anorectal discharge were treated for *N. gonorrhoeae* or *C. trachomatis*, no cases would be missed.

Managing people presenting with anorectal discharge based on a syndromic approach results in minor benefits and moderate harm compared with molecular testing or treating everyone. Molecular testing may not be feasible in all settings and, alternatively, treating everyone would be feasible and the costs would be negligible.

## 11.5 Treatment recommendations for anorectal infections

In implementing a flow chart for managing people with anorectal infections, the following should be considered:

- establishing that the person engages in anal sex;
- differentiating between anorectal infection and other disease; and
- thresholds for adding treatment for HSV, lymphogranuloma venereum or syphilis.

The choice of medicines, dosage and duration of treatment do not generally differ from those for infections at other anatomical sites. Table 8 summarizes treatment options for anorectal infections.

Generally, the following syndromic treatment of symptomatic people is recommended: for chlamydia, doxycycline 100 mg twice daily for seven days (extended to 21 days to cover lymphogranuloma venereum if NAAT is positive for *C. trachomatis*) or azithromycin 1 g at once (25) plus ceftriaxone 250 mg intramuscularly or cefixime 400 mg orally as single doses for gonorrhoea, and with acyclovir, valaciclovir or famciclovir for HSV infection (27), if indicated.

If ulcerations are seen, treatment should follow the flow chart for genital ulcers as well and consider managing the person for syphilis and/or lymphogranuloma venereum.

**Table 8. Treatment options for people with anorectal discharge<sup>a</sup>**

Recommended treatment regimens for anorectal infections		
Infections covered	First-line options	Effective substitutes
<b>N. gonorrhoeae</b> (24)	<b>Ceftriaxone 250 mg</b> , intramuscularly, single dose <i>plus</i> <b>Azithromycin 1 gram</b> , orally, single dose	<b>Cefixime 400 mg</b> , orally, single dose <i>plus</i> <b>Azithromycin 1 gram</b> , orally, single dose
<b>C. trachomatis</b> (25)	<b>Doxycycline 100 mg</b> orally, twice daily, for 7 days <i>or</i> <b>Doxycycline for 21 days</b> (to cover rectal lymphogranuloma venereum) if suspected or confirmed on NAAT (to be given only if dual therapy did not include azithromycin)	<b>Erythromycin 500 mg</b> , orally, 4 times a day for 14 days (to be given only if dual therapy did not include azithromycin)
<b>Syphilis</b> (26) (if ulcer present)	<b>Benazathine penicillin 2.4 million units</b> intramuscularly, single dose  People with a positive syphilis test and no ulcer: administer the same dose at weekly intervals for a total of three doses	<b>Doxycycline 100 mg</b> orally, twice daily for 14 days <b>Erythromycin 500 mg</b> 4 times a day, orally, for 14 days Extend treatment to 30 days if syphilis serology is positive
<b>Genital herpes</b> (27)	<b>Recurrent infection:</b> <b>Acyclovir 400 mg</b> , orally, 3 times a day for 5 days <i>or</i> <b>Acyclovir 800 mg</b> , orally, 3 times a day for 2 days <i>or</i> <b>Acyclovir 800 mg</b> , orally, 2 times a day for 5 days	<b>Recurrent infection:</b> <b>Valaciclovir 500 mg</b> , twice daily for 3 days
	Primary genital herpes: <b>Acyclovir 400 mg</b> , orally, 3 times a day for 10 days <i>or</i> <b>Acyclovir 200 mg</b> , 5 times a day for 10 days	<b>Primary genital herpes:</b> <b>Valaciclovir 500 mg</b> , orally, twice daily for 10 days
	<b>Suppressive therapy for recurrent herpes</b> <b>Acyclovir 400 mg</b> , orally, twice daily <i>or</i> <b>Valaciclovir 500 mg</b> , once daily  For duration, see the genital ulcer disease section	Suppressive therapy for recurrences Famciclovir 250 mg, orally, twice daily (Famciclovir 500 mg, twice daily for people living with HIV or immunocompromised)

<sup>a</sup>Because of increasing antimicrobial resistance to azithromycin in *N. gonorrhoeae* and reduced susceptibility to cephalosporins, WHO is in the process of revising current treatment recommendations and dosages.

# 12. DISSEMINATION AND IMPLEMENTATION OF THE GUIDELINES

## 12.1 Dissemination

The syndromic guidelines will be made available as a printed publication and as downloadable documents on the WHO website under sexually transmitted infections – guidelines. There will be links to other supporting documentation at [https://www.who.int/health-topics/sexually-transmitted-infections#tab=tab\\_1](https://www.who.int/health-topics/sexually-transmitted-infections#tab=tab_1).

WHO headquarters will work with WHO regional offices and country offices to ensure that countries receive support in adapting, implementing and monitoring these guidelines. All levels of WHO (headquarters, regional offices and country offices) will work with regional and national partners – including the United Nations Population Fund (UNFPA), the United Nations Children’s Fund (UNICEF), the Joint United Nations Programme on HIV/AIDS (UNAIDS), NGOs and other agencies implementing HIV, STI and sexual and reproductive health services to ensure an integrated approach to preventing and controlling STIs. WHO will ensure that these external partners are fully engaged in supporting the dissemination and implementation of these guidelines.

These guidelines will also be disseminated at conferences related to STIs and HIV and conferences linked with HIV and STIs and sexual and reproductive health. Efforts will be made to disseminate the information recommended in these guidelines through electronic media, especially during restrictions on meetings because of the COVID-19 pandemic.

The approved guidelines will be officially launched and followed by regional webinars to disseminate the guidelines. WHO will also work with Project ECHO (Extension for Community Healthcare Outcomes), which has been previously partnered with in the WHO African Region in disseminating WHO HIV guidelines using the amplified Internet connectivity and wide network of health-care providers. WHO will also work with the Integrated Best Practice Platform to disseminate the guidelines to health-care providers providing sexual and reproductive health services.

## 12.2 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. Some of the mechanisms will be by electronic communication. An electronic follow-up survey of key end-users of these guidelines will be conducted after one year of their dissemination. The results of the survey will be used to identify challenges and barriers to the uptake of the guidelines, to evaluate their usefulness in improving service delivery for STIs and to identify topics or gaps in managing people with STIs that need to be addressed in future editions.

## 12.3 Implementation considerations

### 12.3.1 Adaptation, implementation and monitoring

These guidelines provide recommendations for providing STI services, mainly using the syndromic approach to enable countries and settings with limited resources to provide evidence-informed interventions for managing people with symptomatic STIs. These guidelines address the syndromes of urethral discharge among men, vaginal discharge and pelvic inflammatory disease among women, genital ulcers among men and women and anorectal infections among men and women.

However, the epidemiology of the specific pathogens causing the syndromes needs to be established in each setting since there is wide geographical variation. Further, the patterns of antimicrobial resistance need to be monitored and may necessitate adapting the choice of medicines used in each syndrome. In areas lacking local data as a basis for adaptation, the recommendations in these guidelines can be adopted as presented since there has been global assessment before inclusion in these guidelines.

#### 12.3.1.1 Opportunities for integrated approaches

- **Testing opportunities using rapid point-of-care tests**

Existing services should be used for making the etiological diagnosis of STIs. Many countries have facilities for implementing point-of-care testing for diagnosing HIV infection. Already, many countries have adopted the dual or triple elimination projects to test for HIV, syphilis and/or viral hepatitis at the same time. This should be scaled up for people seeking care for STIs, people receiving PrEP for HIV infection, young people undergoing voluntary medical male circumcision and others.

- **Testing opportunities using molecular testing technologies**

The molecular platform (such as for tuberculosis antimicrobial resistance diagnosis or viral load detection) is available in many countries. Molecular testing can be expanded at specific sentinel sites or designated laboratories to include detecting STIs, determining the causes of STI syndromes and possibly incorporating the detection of antimicrobial resistance genetic markers in pathogens such as *N. gonorrhoeae* and *M. genitalium* as technologies advance and become affordable and more accessible.

- **Integrated training of health-care providers**

Health-care providers should be trained jointly in implementing the guidelines to enhance services for HIV and the other STIs, antenatal care and family planning care.

#### 12.3.1.2 Establishing referral centres and sentinel site laboratories

Countries should establish or strengthen sentinel sites that can provide support to primary health-care services that need specialist services, such as an STI expert or physician or gynaecologist or genitourinary referral centres for or places to refer people with persistent or recurrent STIs. At the same time, these centres or nearby laboratories can be equipped and strengthened to provide support for STI programmes in areas such as etiological studies and antimicrobial resistance monitoring.

## 13. SURVEILLANCE AND RESEARCH NEEDS

In June 2020, the Department of Global HIV, Hepatitis & STI Programmes convened a think-tank meeting of experts to propose strategic areas of focus for preventing and controlling STIs. One area that got input from the meeting was STI surveillance and its importance in putting STIs on the global agenda. It was highlighted that surveillance is the backbone of public health, and poor surveillance and lack of data on STIs undermine the importance of STIs and their burden on populations. Some of the key areas that need to be implemented are as follows.

### 13.1 Challenges in STI surveillance and anticipated responses

The challenges in STI surveillance include:

- difficulty in conducting robust surveillance when laboratory testing is not available to detect STIs and understand the causes of STI syndromes;
- the asymptomatic nature of many STIs, resulting in a significant burden of infections being missed for lack of diagnostic testing; and
- limited linking of laboratory data to epidemiological data in many settings.

Ongoing STI surveillance at the country level therefore needs to be strengthened. The few data that are available should be used as stepping stones to improve surveillance by using the gaps for planning and programming to obtain more robust data. This should be done on continuously and not only periodically.

- Since the syndromic approach is widely used in STI country programmes, countries should keep on top of the causes of the STI syndromes emerging by regularly conducting etiological studies from sentinel sites using molecular assays, linked to other programmes, if necessary.
- STI surveillance should be an integral part of the syndromic approach, linked with periodic assessment of the antimicrobial resistance of key pathogens.
- The complications of STIs are another component that adds to the disease burden, and routine STI surveillance should incorporate monitoring of STI complications within STI management reporting systems.
- STI surveillance in key populations remains fundamental, since the STI prevalence in these populations remains a significant contributor to the STI epidemic. For this, the collaboration of NGOs should be sought and strengthened to harness these stakeholders as sources of data. Regular systematic STI surveillance and screening for STIs among key populations would be more relevant than occasional surveillance in providing information for effective interventions.
- Capacity-building is required for STI surveillance and monitoring. This requires strengthening laboratories by investing in human resources for laboratories and fostering the availability of and access to affordable STI diagnostic tests.
- Advocating for funding is essential for developing alternative approaches for managing people with STIs by using rapid point-of-care diagnostic tests.



- For syphilis, since there is routine maternal screening and trend estimation at the country level, modelling should be used more systematically and frequently to establish maternal syphilis trend estimates, together with the WHO congenital syphilis estimation tool to estimate the incidence of congenital syphilis as a basis for validating the elimination of mother-to-child transmission. These elements can be strengthened and scaled up, linked with STI workshops that are often conducted by UNAIDS for regional HIV estimation.

## 13.2 Research needs in STI case management

There are outstanding questions regarding the role of some organisms and their relevance and need for strategic control that require more research. Some of the key ones are the following.

- The role of overtreatment in developing or accelerating antimicrobial resistance, especially for *N. gonorrhoeae* and *M. genitalium*.
- *M. genitalium*: how important is this organism in pathogenicity and the need for control?
  - The role and impact on sexual and reproductive health, and need for effective control, of *M. genitalium* in urethritis among men, pelvic inflammatory disease among women and proctitis among women and men.
  - Research on best treatments for people with *M. genitalium*?
- *H. ducreyi*: this pathogen seems to have been controlled, but it is occasionally detected in some settings through infrequent etiological studies.
  - What mechanisms should be put in place to keep vigilance to ensure that the infection does not re-emerge, and if it does, how to detect it and prevent its spread?
  - What is the most feasible way of determining whether *H. ducreyi* has been eliminated?
- *C. trachomatis* genovar L1–L3: there seems to be a resurgence of lymphogranuloma venereum, especially among men who have sex with men, causing rectal infections.
  - Are there specific clinical manifestations that should alert the health-care provider to this infection?
  - What is the burden of this infection among men who have sex with men and people engaging in anal sex?
  - What are the long-term consequences of lymphogranuloma venereum if not treated?
  - How can the diagnosis of lymphogranuloma venereum be made more affordable and improved?
- Validation studies and cost–effectiveness studies of the various recommended flow charts, considering important outcomes, such as pelvic inflammatory disease and the development of antimicrobial resistance.
- Studies on the prevalence and effective treatment of people with anorectal and pharyngeal infections and the role of pooled sampling.

Overall, real rapid low-cost point-of-care tests for diagnosing *N. gonorrhoeae* and *C. trachomatis* need to be developed.

# REFERENCES

1. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ*, 2019;97:548–562.
2. Korenromp EL, Rowley J, Alonso M, Mello MB, Wijesooriya NS, Mahiané SG et al. Global burden of maternal and congenital syphilis and associated adverse birth outcomes – estimates for 2016 and progress since 2012. *PLoS One*. 2019;14:e0211720.
3. Wijesooriya NS, Rochat RW, Kamb ML, Turlapati P, Temmerman M, Broutet N et al. Global burden of maternal and congenital syphilis in 2008 and 2012: a health systems modelling study. *Lancet Global Health*. 2016;4:e525–33.
4. De Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Muñoz N et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis*. 2007;7:453–9.
5. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2197–223.
6. Decker M, Miller E, McCauley H, Tancredi D, Levenson R, Waldman J et al. Intimate partner violence and partner notification of sexually transmitted infections among adolescent and young adult family planning clinic patients. *Int J STD AIDS*. 2011;22:345–7.
7. Wasserheit JN. Epidemiological synergy: interrelationships between human immunodeficiency virus infections and other sexually transmitted diseases. *Sex Transm Dis*. 1992;19:61–77.
8. Sexton J, Garnett G, Røttingen J-A. Metaanalysis and metaregression in interpreting study variability in the impact of sexually transmitted diseases on susceptibility to HIV infection. *Sex Transm Dis*. 2005;32:351–7.
9. Glynn JR, Biraro S, Weiss HA. Herpes simplex virus type 2: a key role in HIV incidence. *AIDS*. 2009;23:1595–8.
10. Johnson LF, Lewis DA. The effect of genital tract infections on HIV-1 shedding in the genital tract: a systematic review and meta-analysis. *Sex Trans Dis*. 2008;35:946–59.
11. Cohen MS. Classical sexually transmitted diseases drive the spread of HIV-1: back to the future. *J Infect Dis*. 2012;206:1–2.
12. Jenness SM, Weiss KM, Goodreau SM, Gift T, Chesson H, Hoover KW et al. Incidence of gonorrhea and chlamydia following human immunodeficiency virus preexposure prophylaxis among men who have sex with men: a modeling study. *Clin Infect Dis*. 2017;65:712–8.
13. Prevention and control of sexually transmitted infections (STIs) in the era of oral pre-exposure prophylaxis (PrEP) for HIV: technical brief. Geneva; World Health Organization; 2018 (<https://www.who.int/hiv/pub/prep/prevention-sti-prep/en>, accessed 22 March 2021).
14. Defining sexual health. Report of a technical consultation on sexual health, 28–31 January 2002, Geneva. Geneva: World Health Organization; 2006 ([https://www.who.int/reproductivehealth/publications/sexual\\_health/defining\\_sh/en](https://www.who.int/reproductivehealth/publications/sexual_health/defining_sh/en), accessed 22 March 2021).

15. Global health sector strategy on sexually transmitted infections, 2016–2021. Geneva: World Health Organization; 2016 (<https://www.who.int/publications/i/item/WHO-RHR-16.09>, accessed 22 March 2021).
16. Wi TE, Ndowa FJ, Ferreyra C, Kelly-Cirino C, Taylor MM, Toskin I et al. Diagnosing sexually transmitted infections in resource-constrained settings: challenges and ways forward. *J Int AIDS Soc.* 2019;22 (Suppl. 6):e25343.
17. Wi T, Lahra MM, Ndowa F, Bala M, Dillon J-AR, Ramon-Pardo P, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: global surveillance and a call for international collaborative action. *PLoS Med.* 2017;14:e1002344.
18. Unemo M, Golparian D, Eyre DW. Antimicrobial resistance in *Neisseria gonorrhoeae* and treatment of gonorrhea. *Methods Mol Biol.* 2019;1997:37–58.
19. Unemo M, Lahra MM, Cole M, Galarza P, Ndowa F, Martin I et al. World Health Organization Global Gonococcal Antimicrobial Surveillance Program (WHO GASP): review of new data and evidence to inform international collaborative actions and research efforts. *Sex Health.* 2019;16:412–25.
20. Ndowa FJ, Ison CA, Lusti-Narasimhan M. Gonococcal antimicrobial resistance: the implications for public health control. *Sex Transm Infect.* 2013;89(Suppl. 4):iv1–2.
21. Horner PJ. Azithromycin antimicrobial resistance and genital *Chlamydia trachomatis* infection: duration of therapy may be the key to improving efficacy. *Sex Transm Infect.* 2012;88:154–6.
22. Wang S, John Papp , Stamm W, Peeling R, Martin D, Holmes K. Evaluation of antimicrobial resistance and treatment failures for *Chlamydia trachomatis*: a meeting report. *Journal of Infectious Diseases*, 2005, 191:917–23.
23. WHO handbook for guideline development, 2nd ed. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>, accessed 22 March 2021).
24. WHO guidelines for the treatment of *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2016 (<https://www.who.int/publications/i/item/who-guidelines-for-the-treatment-of-neisseria-gonorrhoeae>, accessed 22 March 2021).
25. WHO guidelines for the treatment of *Chlamydia trachomatis*. Geneva: World Health Organization; 2016 (<https://www.who.int/publications/i/item/who-guidelines-for-the-treatment-of-chlamydia-trachomatis>, accessed 22 March 2021).
26. WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016 ([https://www.who.int/publications/i/item/who-guidelines-for-the-treatment-of-treponema-pallidum-\(syphilis\)](https://www.who.int/publications/i/item/who-guidelines-for-the-treatment-of-treponema-pallidum-(syphilis)), accessed 22 March 2021).
27. WHO guidelines for the treatment of genital herpes simplex virus. Geneva: World Health Organization; 2016 (<https://www.who.int/publications/i/item/978924154987>, accessed 22 March 2021).
28. WHO guidelines on syphilis screening and treatment for pregnant women. Geneva: World Health Organization; 2016 (<https://www.who.int/publications/i/item/9789241550093>, accessed 22 March 2021).
29. UNAIDS, WHO. Sexually transmitted diseases: policies and principles for prevention and care. Geneva: UNAIDS; 1999 ([https://data.unaids.org/publications/irc-pub04/una97-6\\_en.pdf](https://data.unaids.org/publications/irc-pub04/una97-6_en.pdf), accessed 22 March 2021).

30. Hawkes S, Morison L, Foster S, Gausia K, Chakraborty J, Peeling RW et al. Reproductive tract infections in women in low-income, low-prevalence situations: assessment of syndromic management in Matlab, Bangladesh. *Lancet*. 1999;354:1776–81.
31. Wasserheit JN, Harris JR, Chakraborty J, Kay BA, Mason KJ. Reproductive tract infections in a family planning population in rural Bangladesh. *Stud Fam Planning*. 1989;20:69–80.
32. Balamurugan SS, Bendigeri N D. Community-based study of reproductive tract infections among women of the reproductive age group in the urban health training centre area in Hubli, Karnataka. *Indian J Community Med*. 2012;37:34–8.
33. Nandan D, Gupta YP, Krishnan V, Sharma A, Misra SK. Reproductive tract infection in women of reproductive age group in Sitapur/Shahjahanpur District of Uttar Pradesh. *Indian J Public Health*. 2001;45:8–13.
34. Htun Y, Morse SA, Dangor Y, Fehler G, Radebe F, Trees DL et al. Comparison of clinically directed disease specific, and syndromic protocols for the management of genital ulcer disease in Lesotho. *Sex Transm Infect*. 1998;74(Suppl. 1):S23–8.
35. Dangor Y, Ballard RC, Exposto L, Filomena DA, Fehler G, Miller SD et al. Accuracy of clinical diagnosis of genital ulcer disease. *Sex Trans Dis*. 1990;17:184–9.
36. Richard P. DiCarlo, & Martin, D. The clinical diagnosis of genital ulcer disease in men. *Clin Infect Dis*. 1997;25:292–8.
37. Brief sexuality-related communication: recommendations for a public health approach. Geneva: World Health Organization; 2015 (<https://www.who.int/publications/item/9789241549004>, accessed 22 March 2021).
38. Peeling RW. Applying new technologies for diagnosing sexually transmitted infections in resource-poor settings. *Sex Transm Infect*. 2011;87:ii28–30.
39. Benzaken AS, Galban EG, Antunes W, Dutra JC, Peeling RW, Mabey D, Salama A. Diagnosis of gonococcal infection in high risk women using a rapid test. *Sex Transm Infect*. 2006;82(Suppl. 5):v26–8.
40. Alary M, Gbenafa-Agossa C, Aïna G, Ndour M, Labbé AC, Fortin D et al. Evaluation of a rapid point-of-care test for the detection of gonococcal infection among female sex workers in Benin. *Sex Transm Infect*. 2006;82(Suppl. 5):v29–32.
41. Gift TL, Pate MS, Hook EW 3rd, Kassler WJ. The rapid test paradox: when fewer cases detected lead to more cases treated: a decision analysis of tests for *Chlamydia trachomatis*. *Sex Transm Dis*. 1999;26:232–40.
42. Gaydos C, Hardick J. Point of care diagnostics for sexually transmitted infections: perspectives and advances. *Expert Rev Antiinfect Ther*. 2014;12:657–72.
43. Cristillo AD, Bristow CC, Peeling R, Van Der Pol B, de Cortina SH, Dimov IK, et.al. Point-of-care sexually transmitted infection diagnostics: proceedings of the STAR sexually transmitted Infection – clinical trial group programmatic meeting. *Sex Transm Dis*. 2017;44:211–8.
44. Herbst de Cortina S, Bristow CC, Davey JD, Klausner JD. A systematic review of point of care testing for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis*. *Infect Dis Obstet Gynecol*. 2016;2016:4386127-17.
45. Jafari Y, Peeling R, Shivkumar S, Claessens C, Joseph L, Pai N. Are *Treponema pallidum* specific rapid and point-of-care tests for syphilis accurate enough for screening in resource limited settings? Evidence from a meta-analysis. *PLoS One*. 2013;8:e54695.

46. Gliddon H, Peeling R, Kamb M, Toskin I, Wi T, Taylor M. A systematic review and meta-analysis of studies evaluating the performance and operational characteristics of dual point-of-care tests for HIV and syphilis. *Sex Transm Infect.* 2017;93(Suppl. 4):S3–15.
47. Laboratory Quality Stepwise Implementation Tool. Lyon. World Health Organization; 2005 ([https://www.who.int/ihr/lyon/hls\\_lqsi/en](https://www.who.int/ihr/lyon/hls_lqsi/en), accessed 22 March 2021).
48. Unemo M, Ballard R, Ison C, Lewis D, Ndowa F, Peeling R, editors. Laboratory diagnosis of sexually transmitted infections including human immunodeficiency virus. Geneva: World Health Organization; 2016 ([https://apps.who.int/iris/bitstream/handle/10665/85343/9789241505840\\_eng.pdf;jsessionid=9CC5FDF5142E1760B4E9306CD7490102?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/85343/9789241505840_eng.pdf;jsessionid=9CC5FDF5142E1760B4E9306CD7490102?sequence=1), accessed 22 March 2021).
49. Mindel A, Dallabetta G, Gerbase A, Holmes K, ed. Syndromic approach to STD management. *Sex Transm Infect.* 1998;74(4):Suppl. 1.
50. Kingston MA, Bansal D, Carlin EM. “Shelf life” of *Trichomonas vaginalis*. *Int J STD AIDS.* 2003;14:28–9.
51. Willems H, Ahmed SS, Liu J, Xu Z, Peters BM. Vulvovaginal candidiasis: a current understanding and burning questions. *J Fungi.* 2020;6:27.
52. Marrazzo J, Sobel J, Hillier S. Vaginal infections. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, eds. Atlas of sexually transmitted diseases and AIDS. 4th ed. Philadelphia: Saunders, 2010:76–93.
53. Achkar JM, Fries BC. Candida infections of the genitourinary tract. *Clin Microbiol Rev.* 2010;23:253–73.
54. Paavonen J and Brunham RC. Bacterial vaginosis and desquamative inflammatory vaginitis. *N Engl J Med.* 2018;379:2246–54.
55. Cohen CR, Lingappa JR, Baeten JM, Ngayo MO, Spiegel CA, Hong T et al. Bacterial vaginosis associated with increased risk of female-to-male HIV-1 transmission: a prospective cohort analysis among African couples. *PLoS Med.* 2012;9:e1001251.
56. Haahr T, Zacho J, Brauner M, Shathmigha K, Skov Jensen J, Humaidan P. Reproductive outcome of patients undergoing in vitro fertilisation treatment and diagnosed with bacterial vaginosis or abnormal vaginal microbiota: systematic PRISMA review and meta-analysis. *Int J Obstet Gynaecol.* 2019;126:200–7.
57. Kapiga S, Kelly C, Weiss S, Daley T, Peterson L, Leburg C, Ramjee G. Risk factors for incidence of sexually transmitted infections among women in South Africa, Tanzania, and Zambia: results from HPTN 055 study. *Sex Transm Dis.* 2009;36:199–206.
58. Ghanem M, Radcliffe K, Allan P. The role of urethral samples in the diagnosis of gonorrhoea in women. *Int J STD AIDS.* 2004;15:45–7.
59. Unemo M, Papp JR. Infections caused by *Chlamydia trachomatis*. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, eds. Atlas of sexually transmitted diseases and AIDS. 4th ed. Philadelphia: Saunders; 2010:40–63.
60. Muralidhar S, Talwar R, Anil Kumar D, Kumar J, Bala M, Khan N, Ramesh V. Genital ulcer disease: how worrisome is it today? A status report from New Delhi, India. *J Sex Transm Dis.* 2013;2013:203636.
61. Magdaleno-Tapiál J, Hernández-Bel P, Valenzuela-Oñate C, Ortiz-Salvador JM, García-Legaz-Martínez M, Martínez-Domenech Á et al. Genital infection with herpes simplex virus type 1 and type 2 in Valencia, Spain: a retrospective observational study. *Actas Dermosifiliogr.* 2020;111:53–8.

62. Johnston C, Ashley Morrow R, Moreland A, Wald A. Genital herpes. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, eds. Atlas of sexually transmitted diseases and AIDS. 4th ed. Philadelphia: Saunders, 2010:169–85.
63. Gjestland T. The Oslo study of untreated syphilis; an epidemiologic investigation of the natural course of the syphilitic infection based upon a re-study of the Boeck-Bruusgaard material. *Acta Derm Venereol Suppl (Stockh)*. 1955;35(Suppl. 34):3–368.
64. Cox D, Ballard RC. Syphilis. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, eds. Atlas of sexually transmitted diseases and AIDS. 4th ed. Philadelphia: Saunders; 2010:111–40.
65. Lewis DA. Diagnostic tests for chancroid. *Sex Transm Infect*. 2000;76:137–41.
66. Raffe S, Soni S. Diagnostic tests for sexually transmitted infections. *Medicine*. 2018;46:277–82.
67. Mungati M, Machiha A, Mugurungi O, Tshimanga M, Kilmarx PH, Nyakura J et al. The etiology of genital ulcer disease and coinfections with *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in Zimbabwe: results from the Zimbabwe STI etiology study. *Sex Transm Dis*. 2018;45:61–8.
68. Prabhakar P, Narayanan P, Deshpande GR, Das A, Neilsen G, Mehendale S et al. Genital ulcer disease in India: etiologies and performance of current syndrome guidelines. *Sex Transm Dis*. 2012;39:906–10.
69. Looker KJ, Elmes JAR, Gottlieb SL, Schiffer JT, Vickerman P, Turner KME et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17:1303–16.
70. Minichiello V, Scott J, Callander D. A new public health context to understand male sex work. *BMC Public Health*. 2015;15:282.
71. Muraguri N, Tun W, Okal J, Broz D, Raymond HF, Kellogg T et al. HIV and STI prevalence and risk factors among male sex workers and other men who have sex with men in Nairobi, Kenya. *J Acquir Immune Defic Syndr*. 2015;68:91–6.
72. Van Gerwen OT, Jani A, Long DM, Austin EL, Musgrove K, Muzny CA. Prevalence of sexually transmitted infections and human immunodeficiency virus in transgender persons: a systematic review. *Transgender Health*. 2020;5:90–103.
73. Yared N, Horvath K, Fashanu O, Zhao R, Baker J, Kulasingam S. Optimizing screening for sexually transmitted infections in men using self-collected swabs – a systematic review. *Sex Transm Dis*. 2018;45:294–300.

# ANNEX 1. STI GUIDELINE DEVELOPMENT GROUP

## STI Guideline Development Group

### Ilya Abellanosa-Tacan

STI Physician  
Social Hygiene Clinic  
Cebu City  
Philippines

### Laith Abu-Raddad

Professor of Biostatistics, Epidemiology and Biomathematics Research Core  
Department of Public Health  
Weill Cornell Medical College – Qatar  
Cornell University Education City  
Doha  
Qatar

### Yaw Adu-Sarkodie

School of Medical Sciences  
Kwame Nkrumah University of Science and Technology  
Bantama Kumasi  
Ghana

### Chris Akolo

Deputy Director  
Technical, Linkages Project  
FHI 360  
Washington, DC  
USA

### Andrew Amato

European Centre for Disease Prevention and Control  
Stockholm  
Sweden

### Mircea Betiu

Nicolae Testemițanu State University of Medicine and Pharmacy  
Chișinău  
Republic of Moldova

### John Chungalucha

National Institute for Medical Research  
Mwanza Medical Research Centre  
Mwanza  
United Republic of Tanzania

### Rizwana Chaudhri

Obstetrics and Gynecology Department  
Islamabad Specialists Clinic  
Islamabad  
Pakistan

### Xiang-Sheng Chen

Deputy Director  
National Center for STD Control  
Chinese CDC and Chinese Academy of Medical Sciences  
Institute of Dermatology  
Nanjing  
China

### Amina El Kettani

Direction de l'Épidémiologie  
Service des MST-sida  
Ministry of Health  
Rabat  
Morocco

### Patricia Garcia

Dean, School of Public Health and Administration  
Universidad Peruana Cayetano Heredia  
Lima  
Peru

### William M. Geisler

Clinical Associate Director and Medical Scientist  
Training Program  
Professor of Medicine, Division of Infectious Diseases  
University of Alabama at Birmingham  
Birmingham, AL  
USA

**Edward W. Hook III**

Director, UAB Division of Infectious Diseases  
University of Alabama at Birmingham  
Birmingham, AL  
USA

**Rossaphorn Kittyaowamarn**

Department of Diseases Control  
Bureau of AIDS, TB and STIs, Thailand  
Ministry of Public Health  
Nonthaburi  
Thailand

**Jeffrey D. Klausner**

Professor of Medicine and Public Health  
UCLA David Geffen School of Medicine and  
Fielding School of Public Health  
Los Angeles, CA  
USA

**Ranmini Kularatne**

Head, STI Section  
Centre for HIV & STIs  
National Institute for Communicable Diseases  
Johannesburg, South Africa

**David Lewis**

Western Sydney Sexual Health Centre  
Marie Bashir Institute for Infectious Diseases  
and Biosecurity  
Sydney Medical School  
University of Sydney  
Sydney, Australia

**Nicola Low**

Epidemiology and Public Health  
Institute of Social and Preventive Medicine  
University of Berne  
Berne  
Switzerland

**Philippe Mayaud**

Clinical Research Department  
Faculty of Infectious and Tropical Diseases  
London School of Hygiene and Tropical  
Medicine  
London  
United Kingdom

**Daniel McCartney**

Research and Technical Support  
International Planned Parenthood Federation  
London  
United Kingdom

**Nelly Mugo**

Kenya Medical Research Institute  
Nairobi  
Kenya

**Saiqa Mullick**

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

**Francis Ndowa**

Harare  
Zimbabwe

**Kees Rietmeijer**

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

**Pachara Sirivongrangson**

Senior Advisor and Programme Manager  
Department of Diseases Control  
Bureau of AIDS, TB and STIs, Thailand  
Ministry of Public Health  
Nonthaburi  
Thailand

**Katayoun Tayeri**

HIV&AIDS specialist  
Iranian Research Center of HIV&AIDS  
Iranian Institute for Reduction of High Risk  
Behaviors  
Tehran University of Medical Sciences  
National HIV/AIDS Care & Treatment Adviser  
Ministry of Health  
Tehran  
Islamic Republic of Iran

**Ann Natalia Umar**

National STI Program Manager  
HIV AIDS and STI, Subdirectorates  
Ministry of Health  
Indonesia

**Magnus Unemo**

Department of Laboratory Medicine  
Microbiology  
Örebro University Hospital  
Örebro  
Sweden



**Noor Mohamed Usman**

STI Physician  
Chennai  
India

**Bea Vuylsteke**

Institute of Tropical Medicine  
Antwerp  
Belgium

Judith Wasserheit

Professor of Global Health and Medicine  
Department of Global Health  
Adjunct Professor of Epidemiology  
University of Washington  
Seattle, WA  
USA

**Observers****Laura Bachmann**

Division of Sexually Transmitted Diseases  
Prevention  
Centers for Disease Control and Prevention  
Atlanta, GA  
USA

**Cecilia Ferreyra**

Medical Officer  
Antimicrobial Resistance  
FIND  
Geneva  
Switzerland

**Fernando Pascual Martinez**

Senior Access Manager  
Global AMR Research and Development  
Partnership Foundation  
Geneva  
Switzerland

**Tim Sladden**

Senior Adviser  
Sexual & Reproductive Health Branch  
UNFPA  
New York, NY  
USA

**External Review Group****Anupong Chitwarakorn**

NGO clinic physician  
Silom Clinic  
Thailand

**H.J.C. de Vries**

Amsterdam Sexual Health Clinics  
Amsterdam  
Netherlands

**Hans Benjamin Hampel**

University Hospital Zurich  
Department of Infectious Diseases and  
Hospital Epidemiology  
University of Zurich  
Epidemiology, Biostatistics and Prevention  
Institute  
Zurich  
Switzerland

**Kausar Jabeen**

Aga Khan Foundation  
Pakistan

**Monica Lahra**

Division of Bacteriology  
WHO Collaborating Centre for Sexually  
Transmitted Infections and Antimicrobial  
Resistance  
Department of Microbiology  
Prince of Wales Hospital  
New South Wales  
Australia

**Ahmed Latif**

Public Health Consultant  
Northern Territory  
Australia

**Ioannis Mameletzis**

Consultant, Key Populations  
Ukraine and Sri Lanka

**Angelica Espinosa Miranda**

Ministry of Health  
STI, AIDS and Viral Hepatitis Department  
Brazil

**Koleka Mlisana**

Head of Medical Microbiology  
University of KwaZulu-Natal  
Durban  
South Africa

**Lori Newman**

National Institute of Allergy and Infectious  
Diseases  
Department of Health and Human Services  
National Institutes of Health  
Washington, DC  
USA

**Catherine Nguni**

Head, National AIDS and STI Control  
Programme  
Ministry of Health  
Kenya

**Lilani Rajapaksa**

Consultant Venereologist  
Coordinator, HIV Care Services, Elimination  
of Mother-to-child Transmission of HIV and  
Syphilis Programme  
National STD AIDS Control Programme  
Sri Lanka

**Reshmie Ramautarsing**

Physician  
Thai Red Cross AIDS Research Centre  
Bangkok  
Thailand

**Danvic Rosadiño**

Senior Operations Manager and Data  
Protection Officer  
LoveYourself, Inc.  
Mandaluyong City  
Philippines

**Janet Wilson**

President  
International Union of STIs  
Consultant in Genitourinary Medicine and  
HIV  
Leeds Teaching Hospitals NHS Trust  
Leeds General Infirmary  
Leeds  
United Kingdom

**WHO Steering Committee  
(headquarters)****Ian Askew**

Director  
Department of Sexual and Reproductive  
Health and Research

**Theresa Babovic**

Technical Officer  
Department of Global HIV, Hepatitis and  
Sexually Transmitted Infections Programmes

**Rachel Baggaley**

Coordinator, Testing, Prevention and  
Populations  
Department of Global HIV, Hepatitis and  
Sexually Transmitted Infections Programmes

**Nathalie Broutet**

Medical Officer  
Department of Sexual and Reproductive  
Health and Research

**Venkatraman Chandra-Mouli**

Scientist  
Department of Sexual and Reproductive  
Health and Research

**Meg Doherty**

Director  
Department of Global HIV, Hepatitis and  
Sexually Transmitted Infections Programmes

**Nathan Ford**

Medical Officer  
Department of Global HIV, Hepatitis and  
Sexually Transmitted Infections Programmes

**Sami Gottlieb**

Medical Officer  
Department of Sexual and Reproductive  
Health and Research

**Cadi Irvine**

Consultant  
Department of Global HIV, Hepatitis and  
Sexually Transmitted Infections Programmes

**James Kiarie**

Department of Sexual and Reproductive  
Health and Research

**Niklas Luhmann**

Technical Officer  
Department of Global HIV, Hepatitis and  
Sexually Transmitted Infections Programmes

**Virginia MacDonald**

Technical Officer  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Francis McConville**

Technical Officer  
Department for Maternal, Newborn, Child and Adolescent Health and Ageing

**Yamuna Mundade**

Programme Manager  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Carmem Pessoa-Silva**

Unit Head  
Surveillance, Evidence & Laboratory Strengthening

**Ajay Rangaraj**

Technical Officer  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Melanie Taylor**

Medical Officer  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Igor Toskin**

Scientist  
Department of Sexual and Reproductive Health and Research

**Annette Vester**

Technical Officer  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Marco Vitoria**

Medical Officer  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Lara Vojnov**

Technical Officer  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Teodora Wi<sup>a</sup>**

Medical Officer STI  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**Mayada Youseff-Fox**

Technical Officer  
Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

**WHO Steering Committee (regional offices)****Massimo Ghidinelli**

Unit Chief  
HIV, Hepatitis, TB and Sexually Transmitted Diseases  
WHO Regional Office for the Americas

**Joumana Hermez**

Regional Adviser  
Hepatitis, AIDS & STDs Sexually Transmitted Diseases  
WHO Regional Office for the Eastern Mediterranean

**Naoko Ishikawa**

Coordinator  
HIV, Hepatitis and STI  
WHO Regional Office for the Western Pacific

**Hugues Lago**

Coordinator  
HIV/TB/Hepatitis/STI Programmes  
Integrated Communicable and Noncommunicable Diseases Cluster  
WHO Regional Office for Africa

**Bharat Rewari**

Medical Officer, HIV/STI/Hepatitis  
WHO Regional Office for South-East Asia

**Nicole Seguy**

Joint Tuberculosis, HIV/AIDS & Hepatitis Programme  
WHO Regional Office for Europe

**Methodologist**

**Nancy Santesso**, Department of Clinical Epidemiology and Biostatistics  
McMaster University  
Hamilton, Ontario  
Canada

<sup>a</sup>Overall coordinator of the STI guidelines.

## Systematic Review Team

**Angela Barbara, Tejan Baldeh, Meha Bhatt, Stephanie Duda, Laura Fullerton, Anila Qasim, Rosa Stalteri, Matthew Ventresca and Holger Schünemann:** McMaster University, Michael G. DeGroot Cochrane, Centre, Hamilton, Ontario, Canada  
**Eric Chow and Jason Ong:** Monash University, Melbourne, Australia

### Modeller

**Katy Turner,** University of Bristol, United Kingdom



## STI Guideline Development Group members

# ANNEX 2. DECLARATIONS OF CONFLICTS OF INTEREST

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 <sup>a</sup>
<b>Ilya Abellanosa-Tacan</b> (Cebu City, Philippines)	0	0	0	0	0	0	Full participation
<b>Laith Abu-Raddad</b> (Weill Cornell Medical College, Qatar)	0	0	0	0	0	0	Full participation
<b>Yaw Adu-Sarkodie (Sax)</b> (Kwame Nkrumah University of Science and Technology, Ghana)	0	0	0	0	0	0	Full participation
<b>Chris Akolo</b> (FHI 360, Washington, DC, USA)	0	0	0	0	0	0	Full participation
<b>Andrew Amato</b> (European Centre for Disease Prevention and Control)	0	0	0	0	0	0	Full participation
<b>Mircea Betiu</b> (Nicolae Testemitanu State University of Medicine and Pharmacy, Republic of Moldova)	0	0	0	0	0	0	Full participation
<b>John Changalucha</b> (National Institute for Medical Research, United Republic of Tanzania)	0	0	0	0	0	0	Full participation
<b>Xiang-Sheng Chen</b> (National Center for STD Control of Chinese CDC and Chinese Academy of Medical Sciences Institute of Dermatology, Nanjing, China)	0	0	0	0	0	0	Full participation
<b>Amina El Kettani</b> (Ministry of Health, Morocco)	0	0	0	0	0	0	Full participation
<b>Patricia Garcia</b> (Ministry of Health, Peru)	0	0	0	0	0	0	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 <sup>a</sup>
<b>William M. Geisler</b> (University of Alabama, Birmingham, USA)	Ceased in 2018: consulting and travel from Hologic Inc. = US\$ 9000; from Roche = US\$ 10,000	0	0	0	0	0	Declare. None are active. Full participation
<b>Edward W. Hook III</b> (University of Alabama, Birmingham, USA)	Adviser to GARDP (Global AMR Research and Development Partnership, not for profit organization established by WHO and DNDI) = US\$ 12 000	0	0	0	0	0	Full participation
<b>Rossaphorn Kittyoowamarn</b> (Ministry of Public Health, Thailand)	0	0	0	0	0	0	Full participation
<b>Jeffrey D. Klausner</b> (UCLA David Geffen School of Medicine and Fielding School of Public Health, Los Angeles, CA, USA)	Scientific advisory board participant, Danaher Diagnostics, parent company of Cepheid = US\$ 6000	United States National Institutes of Health R01 and R21 research awards related to syphilis, gonorrhoea, STIs in pregnant women (US\$ 5 million over multiple years)	0	0	0	0	Declare and allowed partial participation
<b>Ranmini Kularatne</b> (National Institute for Communicable Diseases, Johannesburg, South Africa)	0	0	0	0	0	0	Full participation
<b>David Lewis</b> (University of Sydney, Australia)	AUD 780 from GSK (attending a meeting)	0	0	0	0	0	Finance not significant, full participation.
<b>Nicola Low</b> (Institute of Social and Preventive Medicine, Berne, Switzerland)	0	0	0	0	0	0	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 <sup>a</sup>
<b>Philippe Mayaud</b> (London School of Hygiene and Tropical Medicine, United Kingdom)	0	0	0	0	0	0	Full participation
<b>Daniel McCartney</b> (International Planned Parenthood Federation, United Kingdom)	0	0	0	0	0	0	Full participation
<b>Nelly Mugo</b> (Kenya Medical Research Institute, Kenya)	0	0	0	0	0	0	Full participation
<b>Saiqa Mullick</b> (Population Council, South Africa)	0	0	0	0	0	0	Full participation
<b>Francis Ndowa</b> (Harare, Zimbabwe)	0	0	0	0	0	0	Full participation
<b>Kees Rietmeijer</b> (Denver Public Health Department, CO, USA)	0	0	0	0	0	0	Full participation
<b>Pachara Sirivongrangson</b> (Ministry of Public Health, Thailand)	Consulting work for GARDP = US\$ 10 000	0	0	0	0	0	Full participation
<b>Katayoun Tayeri</b> (Ministry of Health, Tehran, Islamic Republic of Iran)	0	0	0	0	0	0	Full participation
<b>Magnus Unemo</b> (Örebro University Hospital, Sweden)	0	0	0	0	0	0	Full participation
<b>Noor Mohamed Usman</b> (Chennai, India)	0	0	0	0	0	0	Full participation
<b>Ann Natalia Umar</b> (Ministry of Health, Indonesia)	0	0	0	0	0	0	Full participation
<b>Bea Vuylsteke</b> (Institute of Tropical Medicine, Antwerp, Belgium)	0	0	0	0	0	0	Full participation
<b>Judith Wasserheit</b> (University of Washington, USA)	0	0	0	0	0	0	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 <sup>a</sup>
<b>Observers</b>							
<b>Laura Bachmann</b> (United States Centres for Disease Control and Prevention)	0	0	0	0	United States Government employee	0	Nil
<b>Cecilia Ferreyra</b> (FIND)	0	0	0	0	0	0	Nil
<b>Tim Sladden</b> (UNFPA)	0	0	0	0	0	0	Nil

<sup>a</sup>Of the financial declarations made, none was considered to be related to the subject matter of these guidelines since formulating recommendations related to the use of antiretroviral drugs was not within the scope of these guidelines.

## 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 <sup>a</sup>
<b>Anupong Chitwarakorn</b> (Silom Clinic, Thailand)	0	0	0	0	0	0	Full participation
<b>H.J.C. de Vries</b> (Amsterdam, Netherlands)	0	0	0	0	0	0	Full participation
<b>Hans Benjamin Hampel</b> (University of Zurich, Switzerland)	0	0	0	0	0	0	Full participation
<b>Monica Lahra</b> (New South Wales, Australia)	0	0	0	0	0	0	Full participation
<b>Ahmed Latif</b> (Public Health Consultant, Australia)	0	0	0	0	0	0	Full participation
<b>Ioannis Mameletzis</b> (Consultant, Ukraine)	0	0	0	0	0	0	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 <sup>a</sup>
<b>Angelica Espinosa Miranda</b> (Ministry of Health, Brazil)	0	0	0	0	0	0	Full participation
<b>Koleka Mlisana</b> (University of KwaZulu Natal, South Africa)	0	0	0	0	0	0	Full participation
<b>Lori Newman</b> (National Institutes of Health, Washington DC, USA)	0	0	0	0	United States Government employee.	0	Full participation
<b>Catherine Ngugui</b> (Ministry of Health, Kenya)	0	0	0	0	0	0	Full participation
<b>Lilani Rajapaksa</b> (National STD/AIDS Control Programme, Sri Lanka)	0	0	0	0	0	0	Full participation
<b>Reshmie Ramautarsing</b> (Bangkok, Thailand)	0	0	0	0	0	0	Full participation
<b>Danvic Rosadiño</b> (Mandaluyong City, Philippines)	0	0	0	0	0	0	Full participation
<b>Janet Wilson</b> (UUSTI, Leeds, United Kingdom)	0	0	0	0	0	0	Full participation

## ANNEX 3. EVIDENCE-TO-DECISION TABLE: URETHRAL DISCHARGE

Should current WHO syndromic management be recommended versus laboratory diagnosis, no treatment or treat all to identify STIs among men with urethral discharge or persistent or recurrent urethral discharge?

**Population:**

Men with urethral discharge

**Intervention and comparator:**

Current WHO syndromic approach versus laboratory diagnosis (or no treatment or treat all)

**Purpose of the approach:**

To identify men for treatment of STIs

**Linked treatments:**

Treatments for infections caused by *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* and *M. genitalium*

**Anticipated outcomes:**

Number of people identified correctly as having or not having STI; number of people identified incorrectly as having or not having STI; consequences of appropriate or inappropriate treatment; patient and provider acceptability, feasibility, equity and resource use

**Setting:**

Outpatient

**Perspective:**

Population level

**Subgroups:**

High- or low-prevalence settings; settings with limited versus established laboratory capacity

**Background:**

Syndromic management refers to a strategy for identifying and treating STIs based on specific syndromes (symptoms identified by a patient) and signs (clinically observed signs of infection) associated with clearly defined causes. Although etiological diagnosis is preferred, it is not always accessible or affordable.

Fig. A3.1 provides clinical guidelines for the syndromic management of urethral discharge and persistent or recurrent urethral discharge in the 2003 WHO publication *Guidelines for the management of sexually transmitted infections*.

## Assessment

	Judgement	Research evidence																								
Problem	<p><b>Is the problem a priority?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>STIs are important because of their magnitude, potential complications and increased risk of HIV. STIs have health, social and economic consequences.</p> <p><b>High cost of molecular STI testing</b></p> <p>Molecular-based tests enable etiological diagnosis to guide appropriate treatment if available but are expensive and not available in many settings.</p>																								
Test accuracy	<p><b>How accurate is the test?</b></p> <p><input type="radio"/> Very inaccurate</p> <p><input checked="" type="radio"/> Inaccurate</p> <p><input type="radio"/> Accurate</p> <p><input type="radio"/> Very accurate</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>We conducted a systematic review for the following.</p> <p>Diagnostic accuracy of syndromic management for <i>M. genitalium</i> – no studies found</p> <p>Diagnostic accuracy of syndromic management for recurrent or persistent urethral discharge – no studies found</p> <p>Diagnostic accuracy of syndromic management for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i></p> <ul style="list-style-type: none"> <li>• Flow chart 1 (WHO algorithm 1) = history and risk assessment</li> <li>• Flow chart 2 (WHO algorithm 2) = history, risk assessment and genital examination (for example, milking urethra)</li> <li>• Flow chart 3 (WHO algorithm 3) = history, risk assessment, genital examination (for example, milking urethra), and urethral discharge samples for Gram staining and microscopy</li> </ul> <p>We found six studies (1570 participants) in the general population of men (1–6). See Table A3.1.</p> <p>Following are the sensitivity and specificity of the flow charts and a hypothetical point-of-care test, and the molecular assay (GeneXpert) test. The pooled accuracy data are of low certainty because of few events.</p> <p><b>Table A3.1. GRADE summary of findings table (see absolute effects for true and false positives and negatives in Table A3.3)</b></p> <table border="1"> <thead> <tr> <th>Flow chart</th> <th>Sensitivity (%; 95% confidence interval)</th> <th>Specificity (%; 95% confidence interval)</th> <th>Certainty of evidence</th> </tr> </thead> <tbody> <tr> <td>1. History, risk</td> <td>94.6 (91–97)</td> <td>41.1 (32–51)</td> <td>Low</td> </tr> <tr> <td>2. History, risk, examination</td> <td>85.2 (80–89)</td> <td>66.5 (62–71)</td> <td>Low</td> </tr> <tr> <td>3. History, risk, examination, microscopy</td> <td>91.7 (88–94)</td> <td>4.5</td> <td>Low</td> </tr> <tr> <td>4. Hypothetical point-of-care testing</td> <td>80</td> <td>90</td> <td>–</td> </tr> <tr> <td>5. GeneXpert®</td> <td>95</td> <td>98</td> <td>High</td> </tr> </tbody> </table>	Flow chart	Sensitivity (%; 95% confidence interval)	Specificity (%; 95% confidence interval)	Certainty of evidence	1. History, risk	94.6 (91–97)	41.1 (32–51)	Low	2. History, risk, examination	85.2 (80–89)	66.5 (62–71)	Low	3. History, risk, examination, microscopy	91.7 (88–94)	4.5	Low	4. Hypothetical point-of-care testing	80	90	–	5. GeneXpert®	95	98	High
Flow chart	Sensitivity (%; 95% confidence interval)	Specificity (%; 95% confidence interval)	Certainty of evidence																							
1. History, risk	94.6 (91–97)	41.1 (32–51)	Low																							
2. History, risk, examination	85.2 (80–89)	66.5 (62–71)	Low																							
3. History, risk, examination, microscopy	91.7 (88–94)	4.5	Low																							
4. Hypothetical point-of-care testing	80	90	–																							
5. GeneXpert®	95	98	High																							

	Judgement	Research evidence																		
Desirable effects	<p><b>How substantial are the desirable anticipated effects of syndromic approach?</b></p> <p> <input checked="" type="radio"/> Trivial  <input type="radio"/> Small  <input type="radio"/> Moderate  <input type="radio"/> Large  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	<p>We conducted a systematic review of risk factors for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> in men with urethral discharge. We found 62 studies that showed that the odds of <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> infection among men with urethral discharge is 10 times the odds among men with no urethral discharge.</p> <p><b>Table A3.2. Pooled risk of <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> by risk factor</b></p> <table border="1"> <thead> <tr> <th>Risk factor</th> <th>Pooled adjusted odds ratio (95% confidence interval)</th> <th>Pooled unadjusted odds ratio (95% confidence interval)</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>6.58 (1.76–24.51)</td> <td>10.79 (4.40–26.43)</td> </tr> <tr> <td>Any urethritis symptoms</td> <td>–</td> <td>9.40 (4.40–20.08)</td> </tr> <tr> <td>Dysuria and/or urethral discharge</td> <td>–</td> <td>12.99 (2.68–62.93)</td> </tr> <tr> <td>Dysuria only</td> <td>2.10 (1.40–3.15)</td> <td>2.02 (1.34–3.05)</td> </tr> <tr> <td>Urethral discharge only</td> <td>9.73 (1.94–48.74)</td> <td>15.00 (4.67–48.17)</td> </tr> </tbody> </table>	Risk factor	Pooled adjusted odds ratio (95% confidence interval)	Pooled unadjusted odds ratio (95% confidence interval)	Overall	6.58 (1.76–24.51)	10.79 (4.40–26.43)	Any urethritis symptoms	–	9.40 (4.40–20.08)	Dysuria and/or urethral discharge	–	12.99 (2.68–62.93)	Dysuria only	2.10 (1.40–3.15)	2.02 (1.34–3.05)	Urethral discharge only	9.73 (1.94–48.74)	15.00 (4.67–48.17)
Risk factor	Pooled adjusted odds ratio (95% confidence interval)	Pooled unadjusted odds ratio (95% confidence interval)																		
Overall	6.58 (1.76–24.51)	10.79 (4.40–26.43)																		
Any urethritis symptoms	–	9.40 (4.40–20.08)																		
Dysuria and/or urethral discharge	–	12.99 (2.68–62.93)																		
Dysuria only	2.10 (1.40–3.15)	2.02 (1.34–3.05)																		
Urethral discharge only	9.73 (1.94–48.74)	15.00 (4.67–48.17)																		
Undesirable effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <p> <input type="radio"/> Large  <input type="radio"/> Moderate  <input checked="" type="radio"/> Small  <input type="radio"/> Trivial  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	<p>Another systematic review analysed the association of <i>M. genitalium</i> among men with persistent or recurrent urethral discharge and showed that the odds of <i>M. genitalium</i> infection among men with persistent or recurrent urethritis is 20 times the odds among men without persistent or recurrent urethral discharge (Jensen, supplementary material).</p> <p>Based on the sensitivity and specificity of the algorithms and tests, we calculated true positive, false negative, true negative and false positive.</p> <p>The following were identified as desirable effects and undesirable effects:</p> <ul style="list-style-type: none"> <li>• potential consequences of true positive could include appropriate treatment, cure, side-effects, partner notification, reduced transmission of STI and HIV, resistance, couple difficulties, costs;</li> <li>• potential consequences of true negative could include alternative diagnoses possible, psychological benefit;</li> <li>• potential consequences of false negative could include cure still possible, persistent symptoms, complications, STI and/or HIV transmission, no counselling, no partner notification; and</li> <li>• potential consequences of false positive could include inappropriate treatment, side-effects, antimicrobial resistance, couple difficulties, costs.</li> </ul>																		

	Judgement	Research evidence									
Certainty of the evidence of test accuracy	<p>What is the overall certainty of the evidence of test accuracy?</p> <p><input type="radio"/> Very low</p> <p><input checked="" type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p><b>Table A3.3. Absolute effects by true and false positives and negatives based on the sensitivity and specificity of syndromic approaches</b></p>									
	<table border="1"> <thead> <tr> <th data-bbox="450 311 787 402"></th> <th colspan="3" data-bbox="787 311 1087 402">Prevalence of <i>Neisseria gonorrhoeae</i> or <i>Chlamydia trachomatis</i></th> </tr> <tr> <th data-bbox="450 402 787 438"></th> <th data-bbox="787 402 888 438">10%</th> <th data-bbox="888 402 989 438">40%</th> <th data-bbox="989 402 1087 438">60%</th> </tr> </thead> </table>				Prevalence of <i>Neisseria gonorrhoeae</i> or <i>Chlamydia trachomatis</i>				10%	40%	60%
		Prevalence of <i>Neisseria gonorrhoeae</i> or <i>Chlamydia trachomatis</i>									
		10%	40%	60%							
	<b>History and risk</b>										
	True positive	10	38	57							
	False negative – missed treatment	0	2	3							
	True negative	37	25	16							
	False positive – unnecessary treatment	53	35	24							
	<b>History, risk and examination</b>										
	True positive	9	34	51							
	False negative – missed treatment	1	6	9							
	True negative	60	40	27							
	False positive – unnecessary treatment	30	20	13							
	<b>History, risk, examination and microscopy</b>										
	True positive	9	37	55							
	False negative – missed treatment	1	3	5							
	True negative	4	3	2							
	False positive – unnecessary treatment	86	57	38							
	<b>Point-of-care testing (80% or 90%)</b>										
	True positive	8	32	48							
	False negative – missed treatment	2	8	12							
True negative	81	54	36								
False positive – unnecessary treatment	9	6	4								
<b>GeneXpert® (95%, 98%)</b>											
True positive	10	38	57								
False negative – missed treatment	0	2	3								
True negative	88	59	39								
False positive – unnecessary treatment	2	1	1								

	Judgement	Research evidence
Certainty of the evidence of the effects of management	<p><b>What is the overall certainty of the evidence of effects of the management that is guided by the test results?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	
Certainty of effects	<p><b>What is the overall certainty of the evidence of effects of the test?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	
Values	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <p><input type="radio"/> Important uncertainty or variability</p> <p><input type="radio"/> Possibly important uncertainty or variability</p> <p><input checked="" type="radio"/> Probably no important uncertainty or variability</p> <p><input type="radio"/> No important uncertainty or variability</p>	The Guideline Development Group placed greater value on avoiding missed cases despite possible unnecessary treatment for some cases.
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favour the intervention or the comparison?</b></p> <p><input checked="" type="radio"/> Favours the comparison</p> <p><input type="radio"/> Probably favours the comparison</p> <p><input type="radio"/> Does not favour either the intervention or the comparison</p> <p><input type="radio"/> Probably favours the intervention</p> <p><input type="radio"/> Favours the intervention</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>The undesirable effects of a syndromic approach (such as missed cases) were greater than treating all or treating according to molecular testing; and the desirable effects (such as correct treatment) of a syndromic approach were none to trivial compared with treating all or molecular testing.</p> <p>Therefore, the balance of benefits and harm favoured using molecular testing or treating all.</p>

	Judgement	Research evidence
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Large costs</li> <li><input type="radio"/> Moderate costs</li> <li><input checked="" type="radio"/> Negligible costs and savings</li> <li><input type="radio"/> Moderate savings</li> <li><input type="radio"/> Large savings</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>Therapy for all positives (<i>N. gonorrhoeae</i> or <i>C. trachomatis</i>) was 1000 mg azithromycin + ceftriaxone 250 mg intramuscularly = US\$ 1.66</p> <p>Therapy for negatives was 1000 mg azithromycin = US\$ 0.95</p> <p>Costs of flow chart 1, 2 = US\$ 0</p> <p>Costs of flow chart 3 = US\$ 1</p> <p>Costs of point-of-care test = US\$ 3</p> <p>GeneXpert costs: US\$ 16</p> <p>Estimated costs of treatment for <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> with antimicrobial resistance: US\$ 25</p>
Certainty of evidence of required resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	
Cost-effectiveness	<p><b>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li><input checked="" type="radio"/> Favours the comparison</li> <li><input type="radio"/> Probably favours the comparison</li> <li><input type="radio"/> Does not favour either the intervention or the comparison</li> <li><input type="radio"/> Probably favours the intervention</li> <li><input type="radio"/> Favours the intervention</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> No included studies</li> </ul>	<p>Basic modelling was conducted using the costs (of tests and treatments) and accuracy of the management strategies.</p> <p>History, risk assessment and examination (with or without microscopy) appear to be lower (~US\$ 2500 for 1000 men with urethral discharge) than the use of low-cost point-of-care tests (~US\$ 4000) or GenXpert (~US\$ 17 000) at any prevalence. Treating all with urethral discharge costs ~ US\$ 1660, slightly more than using history and risk assessment.</p> <p>Therefore, with little difference in costs between treating all and syndromic management, but no missed cases when treating all, cost-effectiveness favoured treating all (the comparison).</p> <p>Average cost for a correct treatment was US\$ 3.86 for a syndromic approach compared with US\$ 32.83 for an etiological approach (4).</p> <p>Average cost for a correct treatment was US\$ 3.15 for a syndromic approach compared with US\$ 323.48 for an etiological approach (3).</p>
Equity	<p><b>What would be the impact on health equity?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Reduced</li> <li><input type="radio"/> Probably reduced</li> <li><input checked="" type="radio"/> Probably no impact</li> <li><input type="radio"/> Probably increased</li> <li><input type="radio"/> Increased</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	

	Judgement	Research evidence
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <p><input type="radio"/> No</p> <p><input checked="" type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>By men (8,9):</p> <p>The syndromic approach is acceptable by men with urethral discharge; staff were competent; better care than by healers; felt treated with respect. 83% of patients in the United Republic of Tanzania reporting satisfaction with STI services that use syndromic management (9).</p> <p>The STI Guideline Development Group also commented that patients would prefer immediate relief of symptoms rather than waiting for the results.</p> <p>By clinicians (8,10–12):</p> <p>Variability in implementation of syndromic approach from 20% to 70% receiving correct treatment; may not apply the approach as they are uncertain about efficacy.</p>
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input checked="" type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>A review found nine studies addressing feasibility (7,12–19):</p> <p>Men may delay seeking care for urethral discharge due to unawareness, knowledge or beliefs, disappointment in health care or when female practitioners provide care.</p> <p>About half of the clinicians in some countries do not know how to treat urethral discharge according to the guidelines.</p> <p>Training was found to increase awareness and knowledge about treatment.</p>



## Summary of judgements

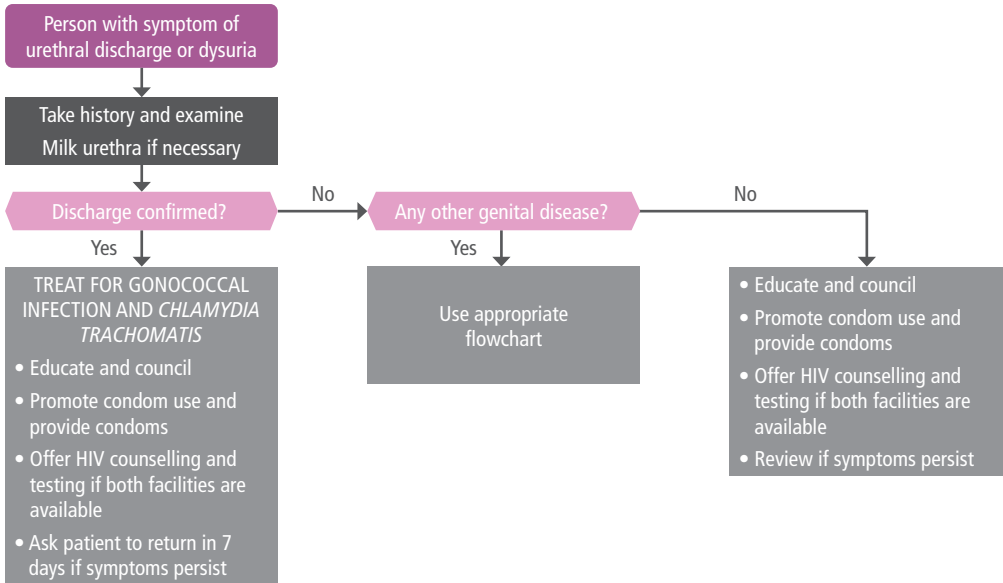
	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of the effects of management	Very low	Low	Moderate	High			No included studies
Certainty of effects	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

## Conclusions

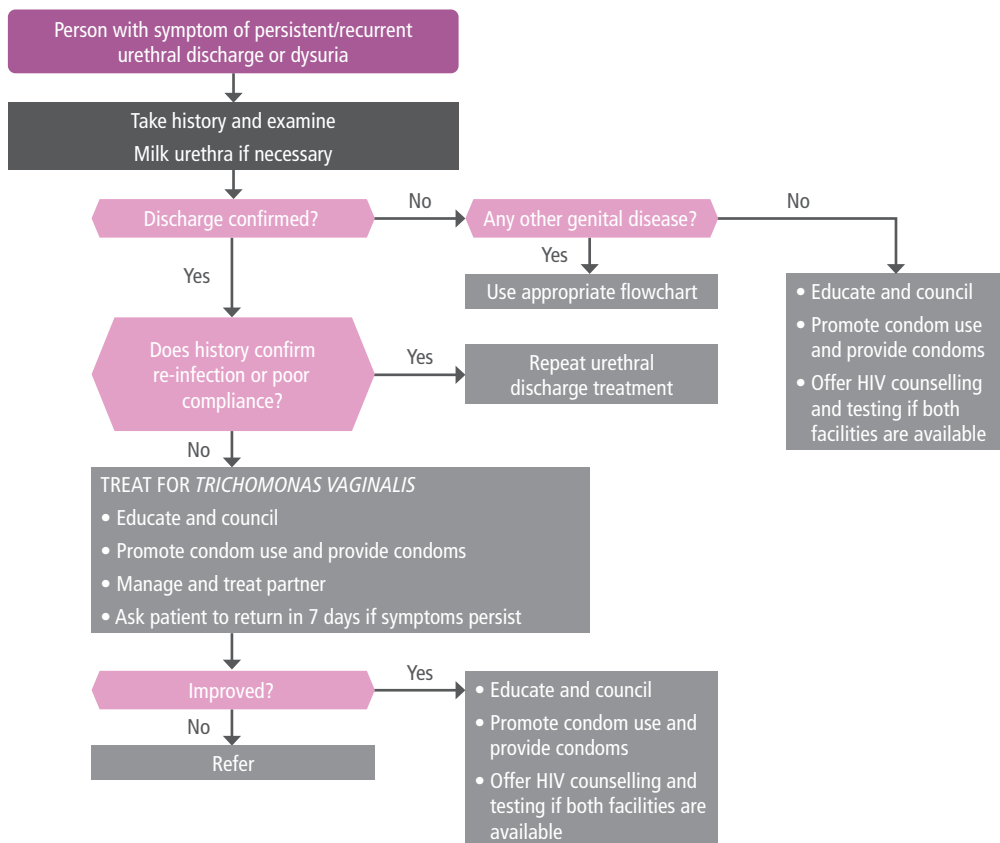
### Should current WHO syndromic management be recommended versus laboratory diagnosis, no treatment or treat all to identify STIs among men with urethral discharge or persistent or recurrent urethral discharge?

Type of recommendation	○ Strong recommendation against the intervention	○ Conditional recommendation against the intervention	○ Conditional recommendation for either the intervention or the comparison	○ Conditional recommendation for the intervention	● Strong recommendation for the intervention
Recommendation	<p><b>Recommendations for the management of urethral discharge</b></p> <p>For people with symptom of urethral discharge from the penis, management is recommended to be based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, we recommend syndromic treatment to ensure treatment on the same day of visit. Good practice includes:</p> <ul style="list-style-type: none"> <li>• taking a medical and sexual history and assessing the risk of STIs;</li> <li>• performing a physical examination of the genital and anal areas; and</li> <li>• offering HIV and syphilis testing and other preventive services as recommended in other guidelines.</li> </ul> <p><i>Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit.</i></p> <p>We recommend the following.</p> <ol style="list-style-type: none"> <li>1. Perform molecular assays such as nucleic-acid amplification test (NAAT) to confirm or exclude <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i>.</li> <li>2. Treat according to the test results on the same day. If urethral discharge is present but tests are negative, treat for non-gonococcal and non-chlamydial urethritis (such as <i>Mycoplasma genitalium</i> or <i>Trichomonas vaginalis</i>).</li> <li>3. When treatment based on molecular assays is not feasible on the same day of the visit, we recommend syndromic treatment of infection with <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> and use the test results to support managing the partner when tests are available.</li> <li>4. Treat people with recurrent or persistent urethral discharge based on a repeat molecular assay (such as NAAT) after 21 days, testing for <i>N. gonorrhoeae</i>, <i>C. trachomatis</i> as well as <i>M. genitalium</i> and <i>T. vaginalis</i> and test for antimicrobial-resistant <i>N. gonorrhoeae</i>.</li> </ol> <p><i>Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing.</i></p> <p>We suggest the following.</p> <ol style="list-style-type: none"> <li>1. Treat people who have urethral discharge confirmed on examination for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> to ensure same-day treatment.</li> <li>2. Treat people with recurrent or persistent urethral discharge for treatment failure based on WHO guidelines and review.</li> </ol> <p>Good practice includes:</p> <ul style="list-style-type: none"> <li>• if symptoms persist at review, checking partner notification and treatment history; and</li> <li>• for people with recurrent or persistent urethral discharge, referring people to a centre with laboratory capacity to diagnose <i>N. gonorrhoeae</i>, <i>C. trachomatis</i>, <i>M. genitalium</i> and <i>T. vaginalis</i> and to test for antimicrobial-resistant <i>N. gonorrhoeae</i> and <i>M. genitalium</i>.</li> </ul>				
Justification	<ul style="list-style-type: none"> <li>• Adding microscopy did not improve the sensitivity and specificity of the flow chart.</li> <li>• Studies show variability in the implementation of syndromic approaches based on symptoms or laboratory testing, and a simple management approach could lead to better implementation.</li> <li>• Performing molecular assay tests for <i>N. gonorrhoeae</i>, <i>C. trachomatis</i> and <i>T. vaginalis</i> and/or <i>M. genitalium</i> and basing treatment on these results leads to the most people treated correctly.</li> <li>• In a population with 60% prevalence of <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> among those with urethral discharge, treating all for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> would mean that 40% of people would be unnecessarily treated. The Guideline Development Group agreed that this proportion is acceptable, as are higher proportions in lower-prevalence settings, because treating all would ensure that people with <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> are treated, thereby reducing the chance of complications and further transmission.</li> </ul>				

**Fig. A3.1. Current WHO syndromic approach to the management of urethral discharge**



**Fig. A3.2. Current WHO syndromic approach to the management of persistent or recurrent urethral discharge**



## References

1. Bhavsar C, Patel RM, Marfatia Y. A study of 113 cases of genital ulcerative disease and urethral discharge syndrome with validation of syndromic management of sexually transmitted diseases. *Indian J Sex Transm Dis AIDS*. 2014;35:35–9.
2. Chandeying V, Skov S, Tabrizi SN, Kemapunmanus M, Garland S. Can a two-glass urine test or leucocyte esterase test of first-void urine improve syndromic management of male urethritis in southern Thailand? *Int J STD AIDS*. 2000;11:235–40.
3. Liu H, Jamison D, Li X, Ma E, Yin Y, Detels R. Is syndromic management better than the current approach for treatment of STDs in China? Evaluation of the cost–effectiveness of syndromic management for male STD patients. *Sex Transm Dis*. 2003;30:327–30.
4. Tsai CH, Lee TC, Chang HL, Tang LH, Chiang CC, Chen KT. The cost–effectiveness of syndromic management for male sexually transmitted disease patients with urethral discharge symptoms and genital ulcer disease in Taiwan. *Sex Transm Infect*. 2008;84:400–4.
5. Wang Q, Yang P, Zhong M, Wang G. Validation of diagnostic algorithms for syndromic management of sexually transmitted diseases. *Chin Med J (Engl)*. 2003;116:181–6.
6. Yu MC, Li LH, Lu TH, Tang LH, Tsai CH, Chen KT. Aetiology of sexually transmitted disease (STD) and comparison of STD syndromes and aetiological diagnosis in Taipei, Taiwan. *Clin Microbiol Infect*. 2005;11:914–8.
7. Leichter JS, Paz-Bailey G, Friedman AL, Habel MA, Zezi A, Sello M et al. “Clinics aren’t meant for men”: sexual health care access and seeking behaviours among men in Gauteng province, South Africa. *Sahara J*. 2011;8:82–8.
8. Kohler PK, Marumo E, Jed SL, Mema G, Galagan S, Tapia K et al. A national evaluation using standardised patient actors to assess STI services in public sector clinical sentinel surveillance facilities in South Africa. *Sex Transm Infect*. 2017;93:247–52.
9. Grosskurth H, Mwijarubi E, Todd J, Rwakatare M, Orroth K, Mayaud P, et al. Operational performance of an STD control programme in Mwanza Region, Tanzania. *Sexually Transmitted Infections*. 2000;76(6):426–36.
10. Khan AA, Khan A. Sexually transmitted infection care in Pakistan: the providers’ perspective. *J Pak Med Assoc*. 2012;62:941–5.

11. Iipinge SN, Pretorius L. The delivery and quality of sexually transmitted infections treatment by private general practitioners in Windhoek Namibia. *Glob J Health Sci.* 2012;4:156–71.
12. Weaver MR, Pillay E, Jed SL, De Kadt J, Galagan S, Gilydydis J et al. Three methods of delivering clinic-based training on syndromic management of sexually transmitted diseases in South Africa: a pilot study. *Sex Transm Infect.* 2016;92:135–41.
13. Hoffman CM, Fritz L, Matlakala N, Mbambazela N, Railton JP, McIntyre JA et al. Community-based strategies to identify the unmet need for care of individuals with sexually transmitted infection-associated symptoms in rural South Africa. *Trop Med Int Health.* 2019;24:987–93.
14. Aaron K, Jordan S, Schwebke J, Van Der Pol B, Hook E. Continued sexual activity following onset of urethritis symptoms in men. *Sex Transm Dis.* 2018;45(Suppl. 2):S38.
15. Ham DC, Hariri S, Kamb M, Mark J, Ilunga R, Forhan S et al. Quality of sexually transmitted infection case management services in Gauteng Province, South Africa: an evaluation of health providers' knowledge, attitudes, and practices. *Sex Transm Dis.* 2016;43:23–9.
16. Alemayehu A, Godana W. Knowledge and practice of clinicians regarding syndromic management of sexually transmitted infections in public health facilities of Gamo Gofa Zone, South Ethiopia. *J Sex Transm Dis.* 2015;2015:310409.
17. Hussain MF, Khanani MR, Siddiqui SE, Manzar N, Raza S, Qamar S. Knowledge, attitudes & practices (KAP) of general practitioners (GPs) regarding sexually transmitted diseases (STDs) and HIV/AIDS in Karachi, Pakistan. *J Pak Med Assoc.* 2011;61:202–5.
18. Adhikari LM, Thapa SB, Sherchan L, Adhikari C. Effectiveness of syndromic STI case management/RH training in knowledge and practice of auxiliary health workers. *J Universal Coll Med Sci.* 2014;2:34–7.
19. Garcia PJ, Carcamo CP, Garnett GP, Campos PE, Holmes KK. Improved STD syndrome management by a network of clinicians and pharmacy workers in Peru: the PREVEN Network. *PLoS One.* 2012;7.

**Table A3.4. Studies included in the diagnostic accuracy of syndromic approaches to urethral discharge**

Study	Country	Design	n	STI prevalence	Setting	Population (age group)	Flow chart description(s)	Reference test(s)
Bhavsar et al. (1)	India	Cross-sectional	17	<i>N. gonorrhoeae</i> : 88.2	Hospital skin and venereal disease outpatient department	General population men (15–70 years)	History, risk assessment and genital examination	<i>N. gonorrhoeae</i> : Gram stain
Chandeying et al. (2)	Thailand	Cross-sectional	129	<i>N. gonorrhoeae</i> : 32.6; <i>C. trachomatis</i> : 23.3;	STI units	General population men (mean and median age = 30 years)	History, risk assessment and genital examination plus microscopy	<i>N. gonorrhoeae</i> : culture and/or PCR <i>C. trachomatis</i> : PCR
Liu et al. (3)	China	Cross-sectional	347	<i>N. gonorrhoeae</i> : 61.1 <i>C. trachomatis</i> : 23.6 <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> : 69.2	STD clinics	General population men (18–83 years)	History and risk assessment	<i>N. gonorrhoeae</i> or <i>C. trachomatis</i> : PCR
Tsai et al. (4)	Taiwan	Cross-sectional	335	<i>N. gonorrhoeae</i> or <i>C. trachomatis</i> : 40.6	STD clinic, genitourinary outpatient clinic	General population men (17–50 years)	History, risk assessment and genital examination	<i>N. gonorrhoeae</i> or <i>C. trachomatis</i> : PCR
Wang et al. (5)	China	Cross-sectional	325	<i>N. gonorrhoeae</i> : 64.3 <i>C. trachomatis</i> : 16.3 <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> : 72.6	Urban STD clinics	General population men (16–63 years)	History, risk assessment and genital examination plus microscopy for Gram staining	<i>N. gonorrhoeae</i> : Gram stain + culture <i>C. trachomatis</i> : PCR
Yu et al. (6)	Taiwan	Cross-sectional	307	<i>N. gonorrhoeae</i> : 10.1 <i>C. trachomatis</i> : 14.3	STD Control Center clinic	General population men (16–50 years)	History, risk assessment and genital examination	<i>N. gonorrhoeae</i> / <i>C. trachomatis</i> : PCR microscopy plus culture

## ANNEX 4. EVIDENCE-TO-DECISION TABLE: VAGINAL DISCHARGE

Should other syndromic management algorithms be used to identify and treat women for common sexually transmitted infections rather than the current WHO algorithms based on risk or speculum examination?

### Population:

Women presenting to clinics with vaginal discharge symptoms

### Intervention and comparator:

Other syndromic management algorithms versus current WHO algorithms

### Purpose of the test:

To identify and treat cervical infections caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and vaginal infections caused by *Trichomonas vaginalis* and bacterial vaginosis

### Role of the test:

Syndromic management may consist of different components: history and risk assessment, speculum examination, vaginal samples for Gram staining and microscopy and/or point-of-care testing

### Linked treatments:

Treatments for vaginal infections caused by *T. vaginalis*, bacterial vaginosis and/or *Candida albicans* and/or treatment for cervical infections caused by *N. gonorrhoeae* and/or *C. trachomatis* with combination of ceftriaxone and azithromycin dual treatment

### Anticipated outcomes:

Critical: treatment rate (true positive), over- and undertreatment (false positive and false negative), true negatives, treatment side-effects, antimicrobial resistance, identification of other reproductive diseases

Important: reproductive health outcomes, maternal outcomes, infant and child outcomes

Other: coverage, patient and provider acceptability, partner notification and treatment

### Setting:

Outpatient; community

### Perspective:

Population level

### Subgroups:

To consider pregnant women and key populations: transgender persons, female sex workers, people living with HIV (immunocompromised)

### Background:

Syndromic management refers to a strategy for identifying and treating STIs based on specific syndromes (symptoms identified by a patient) and signs (clinically-observed signs of infection) associated with clearly defined causes.

Cervical infections include *N. gonorrhoeae* and *C. trachomatis* and vaginal infections include *Trichomonas vaginalis*, bacterial vaginosis and also with candidiasis, which is part of the resident flora.

When tests are not available or costly, different clinical flow charts or algorithms to aid clinicians in the syndromic management of people with symptoms of STI have been recommended.

The last clinical guidelines for the syndromic management of vaginal discharge from WHO were published in the 2003 WHO guidelines for the management of sexually transmitted infections (see Fig. A4.1 and A4.2 for current algorithms)



## Assessment

	Judgement	Research evidence																																							
Problem	<p><b>Is the problem a priority?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>Cervical infections</b></p> <p>Untreated <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> infection can lead to pelvic inflammatory disease, which could lead to complications such as tubo-ovarian abscess, perihepatitis, ectopic pregnancy, infertility and chronic pain and/or permanent damage to reproductive organs causing infertility. Untreated <i>N. gonorrhoeae</i> infection could also lead to premature delivery or spontaneous abortion and cause ophthalmia neonatorum.</p> <p><b>Vaginal infections</b></p> <p><i>T. vaginalis</i> and bacterial vaginosis are curable infections of the reproductive tract. If untreated, <i>T. vaginalis</i> infection could lead to endometriosis, cervical cancer, infertility and placental membrane rupture, leading to preterm delivery, and bacterial vaginosis infection could lead to miscarriage, preterm delivery and increased susceptibility to and ability to transmit other STIs such as HIV.</p> <p><b>Antimicrobial resistance</b></p> <p>Increasing concern about <i>N. gonorrhoeae</i> treatment has been documented globally, with high rates of resistance to penicillin, tetracyclines and quinolones. Resistance to newer medications (azithromycin) and reports of treatment failures and reduced susceptibility of cephalosporins (a last-line treatment for <i>N. gonorrhoeae</i>) raise concern that <i>N. gonorrhoeae</i> could become untreatable.</p>																																							
Test accuracy	<p><b>How accurate is the test?</b></p> <p><input type="radio"/> Very inaccurate</p> <p><input type="radio"/> Inaccurate</p> <p><input type="radio"/> Accurate</p> <p><input type="radio"/> Very accurate</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>We updated one review (1) up to September 2019 that assessed the diagnostic accuracy of different algorithms to identify women who have cervical infections <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> and also for vaginal infections bacterial vaginosis and/or <i>T. vaginalis</i>.</p> <p><b>Cervical infections</b></p> <p>The sensitivity and specificity of different steps in the algorithms were synthesized when appropriate and calculated by adding sensitivity and specificity together for some algorithms (such as WHO algorithms).</p> <p><b>Table A4.1. Sensitivity and specificity of tests for cervical infections</b></p> <table border="1"> <thead> <tr> <th colspan="3">To identify <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i></th> </tr> <tr> <th></th> <th>Sensitivity</th> <th>Specificity</th> </tr> </thead> <tbody> <tr> <td>Treat all</td> <td>100%</td> <td>0%</td> </tr> <tr> <td>Risk assessment (2)</td> <td>63</td> <td>60</td> </tr> <tr> <td>Risk assessment or genital exam (3)</td> <td>92</td> <td>12</td> </tr> <tr> <td>Genital exam (3)</td> <td>78</td> <td>20</td> </tr> <tr> <td>Speculum (4)</td> <td>73</td> <td>56</td> </tr> <tr> <td>Gram stain and microscopy (5)</td> <td>52</td> <td>73</td> </tr> <tr> <td>Speculum or microscopy</td> <td>87</td> <td>41</td> </tr> <tr> <td>WHO algorithm by risk (low prevalence)</td> <td>90</td> <td>34</td> </tr> <tr> <td>WHO algorithm by risk (high prevalence)</td> <td>100</td> <td>0</td> </tr> <tr> <td>WHO algorithm by speculum (low prevalence)</td> <td>49</td> <td>68</td> </tr> <tr> <td>WHO algorithm by speculum (high prevalence)</td> <td>78</td> <td>20</td> </tr> </tbody> </table>	To identify <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i>				Sensitivity	Specificity	Treat all	100%	0%	Risk assessment (2)	63	60	Risk assessment or genital exam (3)	92	12	Genital exam (3)	78	20	Speculum (4)	73	56	Gram stain and microscopy (5)	52	73	Speculum or microscopy	87	41	WHO algorithm by risk (low prevalence)	90	34	WHO algorithm by risk (high prevalence)	100	0	WHO algorithm by speculum (low prevalence)	49	68	WHO algorithm by speculum (high prevalence)	78	20
To identify <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i>																																									
	Sensitivity	Specificity																																							
Treat all	100%	0%																																							
Risk assessment (2)	63	60																																							
Risk assessment or genital exam (3)	92	12																																							
Genital exam (3)	78	20																																							
Speculum (4)	73	56																																							
Gram stain and microscopy (5)	52	73																																							
Speculum or microscopy	87	41																																							
WHO algorithm by risk (low prevalence)	90	34																																							
WHO algorithm by risk (high prevalence)	100	0																																							
WHO algorithm by speculum (low prevalence)	49	68																																							
WHO algorithm by speculum (high prevalence)	78	20																																							

	Judgement	Research evidence					
Test accuracy		Hypothetical sensitivity and specificity of point-of-care tests for <i>N. gonorrhoeae</i>					
		Parameter	Point-of-care test a	Point-of-care test c			
		Sensitivity	0.80	0.95			
		Specificity	0.90	0.98			
		<b>Vaginal infections</b>					
		Table A4.2 shows the sensitivity and specificity of testing and syndromic approaches to detect bacterial vaginosis and/or <i>T. vaginalis</i> from the update of the review (see Table A4.4 for a summary of the included studies).					
		<b>Table A4.2. GRADE summary of findings table for bacterial vaginosis and <i>T. vaginalis</i> flow charts</b>					
		Approach	Number of studies	Sensitivity (%)	Specificity (%)	Certainty of the evidence	
		Treat all with conditions	–	100	0	–	
		History, risk assessment	9	56.2 (54.5–57.9)	71.0 (69.4–72.6)	Moderate	
Plus speculum exam	8	74.8 (74.0–75.6)	53.2 (52.5–54.0)	Moderate			
Lab (wet mount, gram stain)	2	91.7 (89.2–94.2)	100 (99.9–100)	Moderate			
Local adaptation	5	53.1 (50.5–55.6)	85.8 (84.7–86.9)	Moderate			
Moderate certainty of evidence due to some concern with risk of bias of the included studies; the results were precise with no inconsistency.							
The review by Zemouri et al. (1) also reported prevalence: <i>T. vaginalis</i> ranged from 0.9% in Colombia to 17.3% in Uganda; bacterial vaginosis ranged from 39% in Colombia to 47.7% in Uganda.							
The Guideline Development Group agreed that the sensitivity and specificity should have increased when adding additional steps in order to not miss women with infection; however, the increases did not occur and could not be explained by the different populations in the studies, setting or other factors.							
The use of pH was also compared with treating all women with discharge and treating women with confirmed excess discharge (6). The sensitivity was greater, and specificity was reduced slightly ( <i>T. vaginalis</i> ) and translated into small differences in the numbers of people missed or treated unnecessarily.							

Test accuracy		Judgement	Research evidence									
Variable	Bacterial vaginosis					<i>T. vaginalis</i> infection						
	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)		
Abnormal vaginal discharge	76.4	25.6	17.2	84.3	73.3	24.7	9.9	89.2				
Vulval itching	43.1	64.2	19.6	84.8	57.8	64.5	15.5	93.1				
Burning sensation	23.6	66.5	12.5	81.1	37.8	68.7	11.9	90.8				
Discharge and/or itching	95.8	12.7	18.2	93.7	91.1	11.5	10.4	92.0				
Signs of excess vaginal discharge <sup>a</sup>	37.5	61.1	16.4	82.8	55.6	63.3	14.5	92.7				
Signs of vaginal erythema	20.8	83.6	20.5	83.9	42.2	85.7	25.0	93.0				
pH >4.5	79.2	50.1	24.4	92.2	77.8	46.5	14.1	94.5				
Positive Whiff test (amine test)	23.6	89.9	32.1	93.3	35.6	90.3	29.1	92.6				
Wet mount examination <sup>b</sup>	13.9	97.2	47.4	84.6	53.3	100.0	100.0	94.9				
Symptoms and signs	40.3	70.1	21.4	85.7	51.1	70.7	16.4	92.8				
Positive Whiff test and/or pH >4.5	83.3	47.0	24.2	93.3	82.9	43.5	14.1	95.6				

All variables are compared to *T. vaginalis* culture as the gold standard for *T. vaginalis* and to Nugent score of  $\geq 7$  on Gram stain for bacterial vaginosis.

<sup>a</sup>Vaginal discharge defined as yellow or green discharge for *T. vaginalis* and milky white discharge for bacterial vaginosis.

<sup>b</sup>Wet mount examination shows trichomonads for *T. vaginalis* and Clue cells.

Source: Madhivanan et al. (6).

**Table A4.3. Sensitivity, specificity and predictive value of clinical diagnosis for *T. vaginalis* infection and bacterial vaginosis among 445 young women of reproductive age presenting with symptoms in Mysore, India**

	Judgement	Research evidence																								
Certainty of the evidence of test accuracy	<p><b>What is the overall certainty of the evidence of test accuracy?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>																									
Certainty of the evidence of the effects of management	<p><b>What is the evidence of effects of the management that is guided by the test results?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p><b>Effects of treatment interventions</b></p> <p>We modelled different flow charts to identify and manage women coming to the clinic with vaginal discharge (see the supplementary materials for a description of modelling of the cost and effectiveness of different approaches to diagnose <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> among women with vaginal discharge).</p> <p>We modelled the effects of treatment based on the following:</p> <p>Dual treatment <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>: azithromycin and ceftriaxone</p> <p>Treatment for <i>T. vaginalis</i> and bacterial vaginosis: metronidazole</p> <p>All symptomatic women (with vaginal discharge, itching, etc.) are treated for <i>T. vaginalis</i> and bacterial vaginosis</p> <p><b>Table A4.4. Assumptions in the model</b></p> <table border="1"> <thead> <tr> <th>Treatment effects</th> <th>%</th> </tr> </thead> <tbody> <tr> <td>Proportion completing treatment when indicated</td> <td>100</td> </tr> <tr> <td colspan="2"><b>Pelvic inflammatory disease</b></td> </tr> <tr> <td>Proportion of women with untreated gonorrhoea or chlamydia developing (pelvic inflammatory disease)</td> <td>0.3</td> </tr> <tr> <td>Proportion of women with pelvic inflammatory disease requiring and accessing outpatient services</td> <td>0.15</td> </tr> <tr> <td>Proportion of women with pelvic inflammatory disease requiring and accessing hospital services</td> <td>0.02</td> </tr> <tr> <td>Proportion of women with untreated pelvic inflammatory disease becoming infertile or having an ectopic pregnancy</td> <td>0.25</td> </tr> <tr> <td colspan="2"><b>Partner management and reinfection</b></td> </tr> <tr> <td>Proportion of treated women receiving partner treatment</td> <td>0.8</td> </tr> <tr> <td>Number of partners receiving treatment per woman</td> <td>0.2</td> </tr> <tr> <td>Proportion of women reinfected among those whose partner is treated</td> <td>0.3</td> </tr> <tr> <td>Proportion of women reinfected among those whose partner is not treated</td> <td>0.6</td> </tr> </tbody> </table> <p><b>Antimicrobial resistance</b></p> <p>In the base case, we assume no additional treatment costs due to antimicrobial resistance infections directly. We investigate the case in which all antibiotic prescriptions incur a cost – “antimicrobial resistance tax” – based on wider costs of antibiotic resistance (future treatment costs of resistant infection, increased morbidity and mortality associated with antimicrobial resistance in general and costs of developing new treatments). The tax was added to individuals treated, whether appropriately or inappropriately.</p>	Treatment effects	%	Proportion completing treatment when indicated	100	<b>Pelvic inflammatory disease</b>		Proportion of women with untreated gonorrhoea or chlamydia developing (pelvic inflammatory disease)	0.3	Proportion of women with pelvic inflammatory disease requiring and accessing outpatient services	0.15	Proportion of women with pelvic inflammatory disease requiring and accessing hospital services	0.02	Proportion of women with untreated pelvic inflammatory disease becoming infertile or having an ectopic pregnancy	0.25	<b>Partner management and reinfection</b>		Proportion of treated women receiving partner treatment	0.8	Number of partners receiving treatment per woman	0.2	Proportion of women reinfected among those whose partner is treated	0.3	Proportion of women reinfected among those whose partner is not treated	0.6
Treatment effects	%																									
Proportion completing treatment when indicated	100																									
<b>Pelvic inflammatory disease</b>																										
Proportion of women with untreated gonorrhoea or chlamydia developing (pelvic inflammatory disease)	0.3																									
Proportion of women with pelvic inflammatory disease requiring and accessing outpatient services	0.15																									
Proportion of women with pelvic inflammatory disease requiring and accessing hospital services	0.02																									
Proportion of women with untreated pelvic inflammatory disease becoming infertile or having an ectopic pregnancy	0.25																									
<b>Partner management and reinfection</b>																										
Proportion of treated women receiving partner treatment	0.8																									
Number of partners receiving treatment per woman	0.2																									
Proportion of women reinfected among those whose partner is treated	0.3																									
Proportion of women reinfected among those whose partner is not treated	0.6																									

	Judgement	Research evidence						
Certainty of the evidence of the effects of management	<p><b>What is the overall certainty of the evidence of effects of the management that is guided by the test results?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>							
Desirable effects	<p><b>How substantial are the desirable anticipated effects of syndromic approach?</b></p> <p><input type="radio"/> Trivial</p> <p><input type="radio"/> Small</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> Large</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>The diagnostic test accuracy and treatment data were used to model the effects on important outcomes.</p> <p>We modelled the effects among women with different prevalence of <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> infections based on a systematic review of the literature:</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>Scenario 1</th> <th>Scenario 3</th> </tr> </thead> <tbody> <tr> <td>Prevalence of gonorrhoea or chlamydia among women with vaginal discharge</td> <td>5%</td> <td>20%</td> </tr> </tbody> </table>	Parameter	Scenario 1	Scenario 3	Prevalence of gonorrhoea or chlamydia among women with vaginal discharge	5%	20%
Parameter	Scenario 1	Scenario 3						
Prevalence of gonorrhoea or chlamydia among women with vaginal discharge	5%	20%						
Undesirable effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <p><input type="radio"/> Large</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> Small</p> <p><input type="radio"/> Trivial</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>See Table A4.5 for the different approaches that were modelled and Table A4.6 for the assessment of the magnitude of the effects for each syndromic approach.</b></p> <p>The benefits and harm have been assessed as best (dark green) or least benefit (light green), and harm (yellow) or most harm (red).</p>						
Values	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <p><input type="radio"/> Important uncertainty or variability</p> <p><input type="radio"/> Possibly important uncertainty or variability</p> <p><input checked="" type="radio"/> Probably no important uncertainty or variability</p> <p><input type="radio"/> No important uncertainty or variability</p>	<p>The Guideline Development Group identified the following outcomes as critical: treatment rate (true positive), overtreatment (false positive) and undertreatment (false negative), true negatives, treatment side-effects, antimicrobial resistance, identification of other reproductive diseases</p> <p>The Guideline Development Group placed highest value on the incidence of pelvic inflammatory disease due to missed cases but also considered overtreatment, which can lead to an increase in antimicrobial resistance.</p> <p>Reproductive health outcomes, maternal outcomes and infant and child outcomes are important.</p> <p>Other considerations: coverage, patient and provider acceptability and partner notification and treatment.</p>						

	Judgement	Research evidence																																
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <p><input type="radio"/> Large costs</p> <p><input type="radio"/> Moderate costs</p> <p><input type="radio"/> Negligible costs and savings</p> <p><input type="radio"/> Moderate savings</p> <p><input type="radio"/> Large savings</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>Table A4.7. Costs used in the cost–effectiveness model</b></p> <table border="1" data-bbox="451 256 1089 955"> <thead> <tr> <th data-bbox="451 256 898 293">Costs of flow charts</th> <th data-bbox="898 256 1089 293">Cost in US dollars</th> </tr> </thead> <tbody> <tr> <td data-bbox="451 293 898 329">Risk assessment</td> <td data-bbox="898 293 1089 329">0.00</td> </tr> <tr> <td data-bbox="451 329 898 365">Speculum exam</td> <td data-bbox="898 329 1089 365">1.00</td> </tr> <tr> <td data-bbox="451 365 898 402">Speculum and Gram stain</td> <td data-bbox="898 365 1089 402">1.50</td> </tr> <tr> <td data-bbox="451 402 898 475">Point-of-care test: lower sensitivity of 80% and specificity of 90%</td> <td data-bbox="898 402 1089 475">3.00</td> </tr> <tr> <td data-bbox="451 475 898 538">Flow chart 4, 5, 6: point-of-care test (best sensitivity of 95% and specificity of 98%)</td> <td data-bbox="898 475 1089 538">16.00</td> </tr> <tr> <td colspan="2" data-bbox="451 538 1089 575"><b>Treatment and outcome costs</b></td> </tr> <tr> <td data-bbox="451 575 898 611">Dual treatment (chlamydia and gonorrhoea)</td> <td data-bbox="898 575 1089 611">1.66</td> </tr> <tr> <td data-bbox="451 611 898 647">Treatment for <i>T. vaginalis</i> and bacterial vaginitis</td> <td data-bbox="898 611 1089 647">0.10</td> </tr> <tr> <td data-bbox="451 647 898 684">Partner treatment</td> <td data-bbox="898 647 1089 684">0.12</td> </tr> <tr> <td data-bbox="451 684 898 748">Average outpatient costs per case of pelvic inflammatory disease</td> <td data-bbox="898 684 1089 748">4.00</td> </tr> <tr> <td data-bbox="451 748 898 784">Average cost of hospitalization</td> <td data-bbox="898 748 1089 784">45.00</td> </tr> <tr> <td data-bbox="451 784 898 820">Average costs to woman to access health services</td> <td data-bbox="898 784 1089 820">1.00</td> </tr> <tr> <td data-bbox="451 820 898 857">Social costs of infertility and ectopic pregnancy</td> <td data-bbox="898 820 1089 857">500.00</td> </tr> <tr> <td colspan="2" data-bbox="451 857 1089 893"><b>Cost of antimicrobial resistance</b></td> </tr> <tr> <td data-bbox="451 893 898 955">Tax</td> <td data-bbox="898 893 1089 955">5.00</td> </tr> </tbody> </table> <p data-bbox="451 966 864 993"><b>Costs of flow charts from literature since 2010</b></p> <p data-bbox="451 1002 1089 1075">Staffing costs are the largest component of providing mobile health services to South African rural communities; screening and treatment of STI had marginal cost (8).</p> <p data-bbox="451 1084 1089 1188">The cost of a syndromic approach to treat symptoms of vaginal discharge at a nongovernmental sexual health clinic in Bulgaria was €24.08 per person treated (assessment of risk factors, speculum examination and microscopy were used) (2).</p>	Costs of flow charts	Cost in US dollars	Risk assessment	0.00	Speculum exam	1.00	Speculum and Gram stain	1.50	Point-of-care test: lower sensitivity of 80% and specificity of 90%	3.00	Flow chart 4, 5, 6: point-of-care test (best sensitivity of 95% and specificity of 98%)	16.00	<b>Treatment and outcome costs</b>		Dual treatment (chlamydia and gonorrhoea)	1.66	Treatment for <i>T. vaginalis</i> and bacterial vaginitis	0.10	Partner treatment	0.12	Average outpatient costs per case of pelvic inflammatory disease	4.00	Average cost of hospitalization	45.00	Average costs to woman to access health services	1.00	Social costs of infertility and ectopic pregnancy	500.00	<b>Cost of antimicrobial resistance</b>		Tax	5.00
	Costs of flow charts	Cost in US dollars																																
	Risk assessment	0.00																																
	Speculum exam	1.00																																
	Speculum and Gram stain	1.50																																
	Point-of-care test: lower sensitivity of 80% and specificity of 90%	3.00																																
	Flow chart 4, 5, 6: point-of-care test (best sensitivity of 95% and specificity of 98%)	16.00																																
	<b>Treatment and outcome costs</b>																																	
	Dual treatment (chlamydia and gonorrhoea)	1.66																																
	Treatment for <i>T. vaginalis</i> and bacterial vaginitis	0.10																																
	Partner treatment	0.12																																
	Average outpatient costs per case of pelvic inflammatory disease	4.00																																
	Average cost of hospitalization	45.00																																
	Average costs to woman to access health services	1.00																																
	Social costs of infertility and ectopic pregnancy	500.00																																
<b>Cost of antimicrobial resistance</b>																																		
Tax	5.00																																	

	Judgement	Research evidence																																										
Resources required		<p><b>Table A4.8. Costs used in the cost–effectiveness model</b></p> <table border="1"> <thead> <tr> <th>STI</th> <th>Treatment</th> <th>Dose per day</th> <th>Treatment duration</th> <th>Drugs, per dose (US dollars)</th> <th>Drugs and service delivery (US dollars)</th> </tr> </thead> <tbody> <tr> <td>Gonorrhoea</td> <td>Ceftriaxone 250 mg</td> <td>1</td> <td>1 day</td> <td>0.57</td> <td>10.71</td> </tr> <tr> <td>Chlamydia and mycoplasma</td> <td>Azithromycin 500 mg</td> <td>2</td> <td>1 day</td> <td>0.38</td> <td>10.95</td> </tr> <tr> <td>Trichomoniasis</td> <td>Metronidazole 500 mg</td> <td>4</td> <td>1 day</td> <td>0.01</td> <td>10.05</td> </tr> <tr> <td colspan="6"><b>Diagnostic test</b></td> </tr> <tr> <td>Gonorrhoea and chlamydia</td> <td colspan="4">NAAT: assuming a price reduction starting 2016, from US\$ 20 as of 2016 (specimen collection at primary level; testing in secondary and tertiary care facilities)</td> <td>12.00</td> </tr> <tr> <td>Trichomoniasis</td> <td colspan="4">Wet mount (point of care)</td> <td>4.00</td> </tr> </tbody> </table>	STI	Treatment	Dose per day	Treatment duration	Drugs, per dose (US dollars)	Drugs and service delivery (US dollars)	Gonorrhoea	Ceftriaxone 250 mg	1	1 day	0.57	10.71	Chlamydia and mycoplasma	Azithromycin 500 mg	2	1 day	0.38	10.95	Trichomoniasis	Metronidazole 500 mg	4	1 day	0.01	10.05	<b>Diagnostic test</b>						Gonorrhoea and chlamydia	NAAT: assuming a price reduction starting 2016, from US\$ 20 as of 2016 (specimen collection at primary level; testing in secondary and tertiary care facilities)				12.00	Trichomoniasis	Wet mount (point of care)				4.00
STI	Treatment	Dose per day	Treatment duration	Drugs, per dose (US dollars)	Drugs and service delivery (US dollars)																																							
Gonorrhoea	Ceftriaxone 250 mg	1	1 day	0.57	10.71																																							
Chlamydia and mycoplasma	Azithromycin 500 mg	2	1 day	0.38	10.95																																							
Trichomoniasis	Metronidazole 500 mg	4	1 day	0.01	10.05																																							
<b>Diagnostic test</b>																																												
Gonorrhoea and chlamydia	NAAT: assuming a price reduction starting 2016, from US\$ 20 as of 2016 (specimen collection at primary level; testing in secondary and tertiary care facilities)				12.00																																							
Trichomoniasis	Wet mount (point of care)				4.00																																							
Certainty of evidence of required resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <p><input type="radio"/> Very low</p> <p><input checked="" type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>The estimated average tool cost per episode for women treated with acute NG was US \$205. This estimate does not include intangible (e.g. pain) and indirect costs (e.g., lost productivity). Uwusu-Edusei 2010).</p>																																										
Cost–effectiveness	<p><b>Does the cost–effectiveness of the intervention favour the intervention or the comparison?</b></p> <p><input checked="" type="radio"/> Favours the comparison</p> <p><input type="radio"/> Probably favours the comparison</p> <p><input type="radio"/> Does not favour either the intervention or the comparison</p> <p><input type="radio"/> Probably favours the intervention</p> <p><input type="radio"/> Favours the intervention</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> No included studies</p>	<p>The Guideline Development Group favoured the following algorithms rather than the WHO algorithms based on balance of benefits and harm and costs.</p> <p><b>Low prevalence (5% <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>)</b></p> <p>Favourable choices:</p> <ul style="list-style-type: none"> <li>• treat all women who are positive using lower sensitivity (80%) and specificity (90%) rapid point-of-care tests; and</li> <li>• treat based on point-of-care tests among women who have positive risk assessment or confirmed vaginal discharge by genital examination.</li> </ul> <p>Further favourable choices:</p> <ul style="list-style-type: none"> <li>• treat based on positive speculum among women who have positive risk assessment or confirmed vaginal discharge by genital examination; and</li> <li>• treat based on positive speculum among all women</li> </ul> <p>The WHO algorithm using speculum is cheapest but results in the highest missed cases and therefore most pelvic inflammatory disease and moderate overtreatment, and the WHO algorithm by risk has trivial pelvic inflammatory disease and missed cases but moderate to high overtreatment, which results in higher cost.</p>																																										

	Judgement	Research evidence
Cost-effectiveness		<p><b>Higher prevalence (20% <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>)</b></p> <p>Favourable choices:</p> <ul style="list-style-type: none"> <li>• treat based on positive speculum or microscopy among women who have positive risk assessment or confirmed vaginal discharge by genital examination;</li> <li>• treat based on positive speculum or microscopy among all women; and</li> <li>• treat based on positive risk assessment or confirmed vaginal discharge by genital examination.</li> </ul> <p>Favourable but slightly costly:</p> <ul style="list-style-type: none"> <li>• treat based on confirmed vaginal discharge by genital examination.</li> </ul> <p>Favourable but slightly high pelvic inflammatory disease (but not costly):</p> <ul style="list-style-type: none"> <li>• treat all women who are positive on a low-sensitivity and -specificity point-of-care test; and</li> <li>• treat all women who are positive on a speculum exam.</li> </ul> <p>The Guideline Development Group agreed that the approach should be similar across prevalence settings – and therefore a common approach was chosen that balanced the benefits, harm and costs in both settings.</p>
Equity	<p><b>What would be the impact on health equity?</b></p> <p><input type="radio"/> Reduced</p> <p><input type="radio"/> Probably reduced</p> <p><input type="radio"/> Probably no impact</p> <p><input type="radio"/> Probably increased</p> <p><input type="radio"/> Increased</p> <p><input checked="" type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>From a systematic review of literature up to February 2020</b></p> <p><b>Issues of who is seeking care by symptoms and tested</b></p> <p>Providers were significantly more likely to test symptomatic African-American women for STI than symptomatic white women (10).</p> <p>Treatment seeking for vaginal discharge was disproportionately high among poor women in Mumbai, India and associated with problematic husbands, spousal abuse, tension and stress and higher perceived empowerment (11).</p> <p>A remote area of South Africa with poor access to health-care services has a large burden of untreated symptomatic and asymptomatic STIs, demonstrating the importance of out-of-facility STI services through a mobile clinic (12).</p> <p>Studies indicate a relationship between socioeconomic status and STIs.</p> <ul style="list-style-type: none"> <li>• A higher prevalence of chlamydia was found in patients in the public health sector versus private in Brazil (13).</li> <li>• A higher prevalence of chlamydia was found among illiterate women versus women with higher education and in women living in rural areas versus urban areas (14).</li> <li>• An inverse association was found between education and chlamydia and gonorrhoea among young women in the United States of America. Black women who were enrolled in or had graduated from college had significantly higher predicted probabilities of having chlamydia or gonorrhoea than white females with less than a high school diploma (15).</li> <li>• The prevalence of bacterial vaginosis, <i>C. trachomatis</i> and <i>T. vaginalis</i> is significantly higher among non-Hispanic African-Americans versus white Americans (16–19).</li> <li>• Working women and spouses of unskilled workers had a higher risk of infection than homemakers and the spouses of semiskilled or skilled workers (20).</li> <li>• Female adolescents in juvenile detention facilities had high chlamydia test positivity (21–24).</li> </ul>



	Judgement	Research evidence
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input checked="" type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>Clinicians</b></p> <p>Half were willing to follow the syndromic approach (25); 80% always conduct examination, and no preference for watching and waiting, symptomatic therapy, empiric antibiotics or referral (26).</p> <p>Awareness of the consequences of no treatment increased the willingness to use the syndromic approach (25,26).</p> <p>A South African study in 50 public health facilities found that most facilities had STI guidelines available, and 64% had STI treatment flow charts posted. Assessment using standardized patient actors showed that the syndromic management according to the guidelines was provided in only 61% of cases. Only 19% received all predefined essential STI services, with significant gaps in treatment for women (27). Similar gaps in provider knowledge and practice have been identified in Gujarat (28) and Ethiopia (29).</p> <p><b>Patients</b></p> <p>Wide variability in seeking treatment – 15–87% (30–37).</p> <p>Reasons for not seeking health care:</p> <ul style="list-style-type: none"> <li>• formal advice not needed or rely on self-treatment (70% from Jiang et al. (38); Ilankoon et al. (39));</li> <li>• stigma (40,41);</li> <li>• Discomfort or fear (5–8% from Ekabua et al. (42); 33% from Rosenheck et al. (31));</li> <li>• lack of awareness of symptoms or considered natural phenomena (64% from Sharma et al. (35); 34% from Hoffman et al. (41); approximately 50% from Tayerih et al. (37));</li> <li>• disappointment in care due to persistent (23%) or recurrent (15%) symptoms after previous treatment (41);</li> <li>• disappointment with health services in general during previous visit(s) for any reason (10% in Hoffman (41));</li> <li>• costs (67% from Miller et al. (43); 89% from Jayapalan et al. (44); Tayerih et al. (37));</li> <li>• geographical access or transport (57% from Miller et al. (43); 86% from Jayapalan et al. (44));</li> <li>• lack of privacy (60% from Miller et al. (43); 67% from Jayapalan et al. (44));</li> <li>• lack of free medicine (71% from Jayapalan et al. (44)); and</li> <li>• lack of confidentiality (12% from Jayapalan et al. (44); 13% from Leichter et al. (45)).</li> </ul> <p>In a study in India, 11 of 42 (26%) reported that, although they went to the hospital, they could not disclose their symptoms (35).</p> <p>Vaginal discharge was reported by 49% of female sex workers in central Brazil; but 42% had not sought treatment at health-care facilities (46).</p> <p>Of 986 female sex workers in Hong Kong Special Administrative Region, China, 7.8% reported having at least one episode of STI in the past six months. About two thirds would either self-medicate or adopt a wait-and-see approach, and about one third attended a private doctor or a doctor across the border. Only 26% reported attending a public STI clinic and 25% an NGO testing centre in the past year (47).</p>

	Judgement	Research evidence
Acceptability		<p>In Utter Pradesh, India, 84 (88.4%) of women living in urban slums sought treatment for their STIs or reproductive tract infection problems from quacks. Very few women had treatment from a government health facility (6.3%) or from a private health facility (5.3%) (48).</p> <p>In a study of pregnant women attending antenatal care in Sudan, 14.3% of the participants declined gynaecological examinations; probably because most (13.8%) perceived speculum examinations as a painful procedure. A total of 11.6% of the patients were embarrassed by their vaginal discharge and thus refused to be examined. Others (7.1%) were in doubt and feared receiving a positive result. In general, the reason for rejecting any of the examinations is because most women thought being tested was an endeavour too great for diseases they know they do not have (49).</p> <p>College students in India had good knowledge about the prevention and transmission of STIs; however, not many were aware of the clinical features and complications of STIs. Only about 40% of students knew that vaginal discharge was a symptom of STIs (50).</p> <p>Among women seeking health care for the presence of symptoms, the length of delay varied greatly, with some people seeking health care immediately and others waiting for several months. Studies report that 39–45% of women waited longer than seven days to see a health-care provider (51,52).</p>
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input checked="" type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>A syndromic management programme in Kenya effectively reduced the incidence of STIs from its initiation (1990–1994) to 2000. The incidence increased in 2001 when the programme was terminated (53).</p> <p>A syndromic management programme applied in 25 rural primary health-care units in the United Republic of Tanzania treated 12 895 people with STI syndromes in 2 years. The programme was used by 50–75% of symptomatic people (54).</p> <p>An integrated network of physicians, midwives and pharmacy workers trained in STI syndromic management (the PREVEN Network) was developed and evaluated as part of a national urban community randomized trial of STI prevention in Peru. Training pharmacy workers linked to a referral network of clinicians proved feasible and acceptable. High turnover was challenging but was overcome. By the end of the intervention, the Network included 792 pharmacies and 597 clinicians. Pharmacies reported more cases of STIs than did clinicians. Evaluations by simulated patients showed significant and substantial improvements in the management of people with STI syndromes at pharmacies in the 10 intervention cities but not in the 10 control cities (55).</p> <p>The implementation of STI management guidelines was evaluated in Pakistan. Guideline adherence was associated with the sex of the patient, the type of health facility, the availability of male and female doctors, the age of the patient (dichotomized at 25 years) and diagnosis. Women attending the rural health facility for STI treatment had 0.87 times the chance of guidelines being followed compared with the urban health facility (56).</p> <p>A syndromic management approach for vaginal discharge was effectively used by nurses to diagnose vaginal infections within a primary care setting (57).</p> <p>A medical record review of reproductive health services in Karachi found that the health-care providers – doctors and midwives – had difficulties in using the syndromic management algorithm (58).</p>

## Summary of judgements

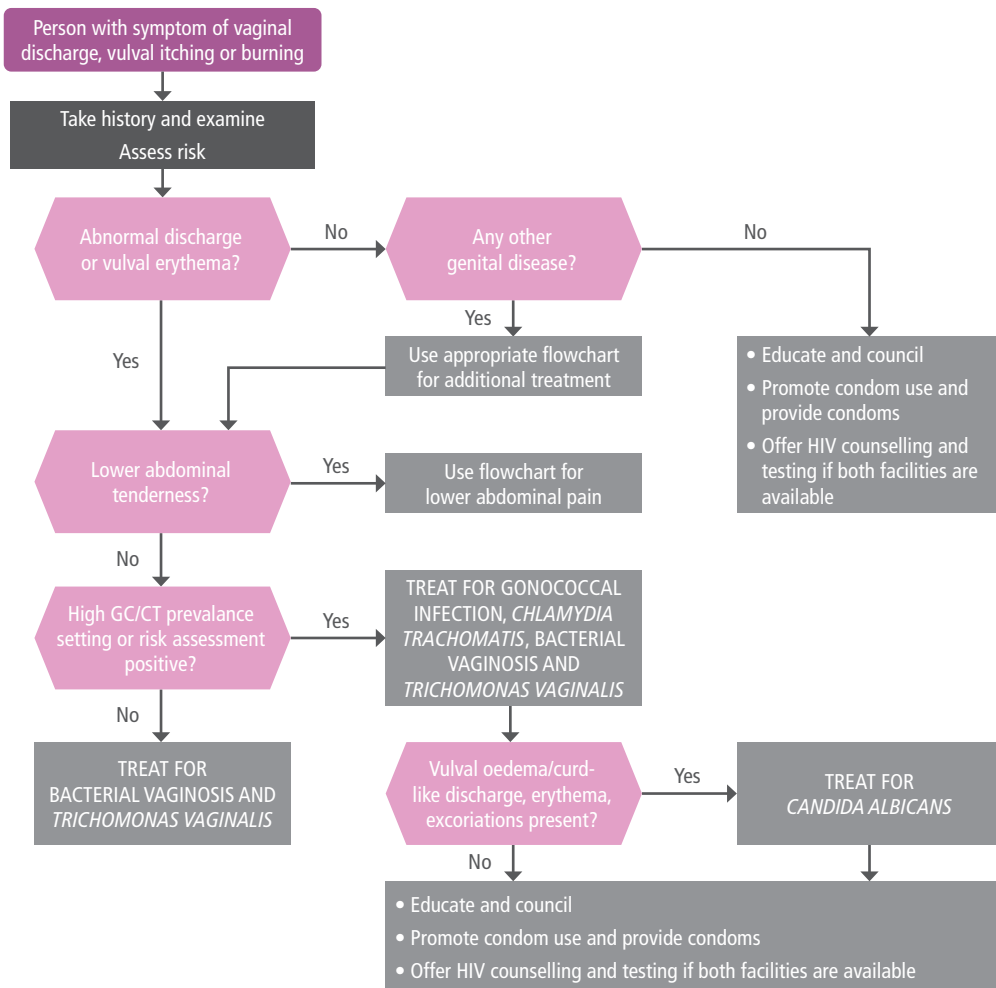
Problem	Judgement						
	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of the effects of management	Very low	Low	Moderate	High			No included studies
Certainty of effects	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

## Conclusions

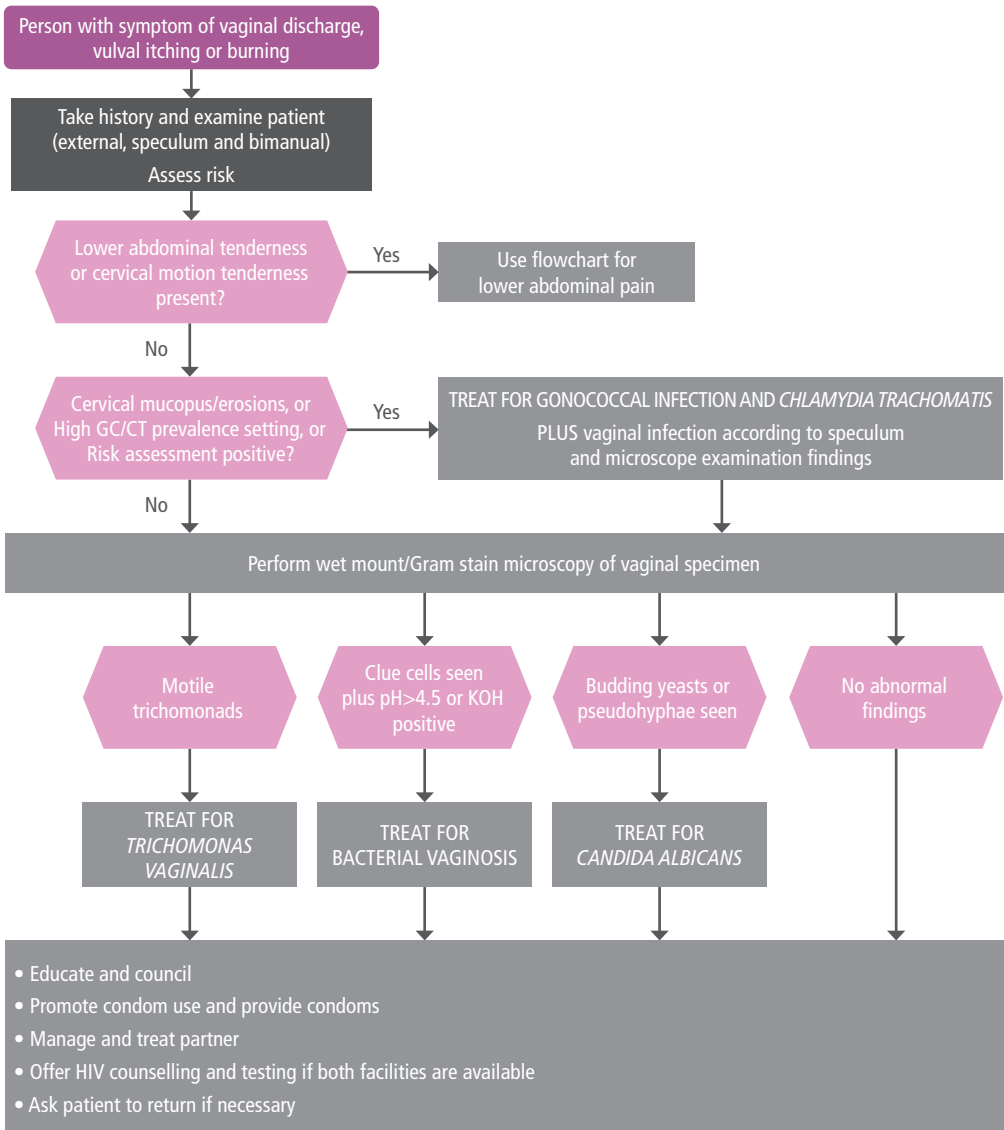
### Should other syndromic management algorithms be used to identify and treat women for common sexually transmitted infections rather than the current WHO algorithms based on risk or speculum examination?

Type of recommendation	○ Strong recommendation against the intervention	○ Conditional recommendation against the intervention	○ Conditional recommendation for either the intervention or the comparison	○ Conditional recommendation for the intervention	● Strong recommendation for the intervention
Recommendation	<p><b>Recommendations for the management of vaginal discharge</b></p> <p>For people with symptom of vaginal discharge, we recommend treatment for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> and/or <i>T. vaginalis</i> on the same visit. We suggest treatment based on the results of quality-assured molecular assays for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> and/or <i>T. vaginalis</i>. In settings in which treatment based on the results of molecular assay in the same visit is not feasible or that have limited or no molecular testing, we suggest treatment based on testing with quality-assured rapid point-of-care tests or on syndromic treatment.</p> <p>For people with symptom of vaginal discharge, good practice includes:</p> <ul style="list-style-type: none"> <li>• taking a medical and sexual history and assessing the risk of STIs;</li> <li>• performing a physical examination, including abdominal and pelvic examination, to assess for pelvic inflammatory disease, surgical conditions or pregnancy and external vulvovaginal examination to visualize any lesions, overt genital discharge or vulval erythema and excoriations;</li> <li>• bimanual digital examination of the vagina to (1) assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) to assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove; and</li> <li>• offering HIV and syphilis testing and other preventive services as recommended in other guidelines.</li> </ul> <p><i>Settings in which treatment is based on quality-assured molecular assays in a laboratory with a fully operational quality management system and results available on the same day of the visit</i></p> <ol style="list-style-type: none"> <li>1. We recommend treating <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> and/or <i>T. vaginalis</i> based on the results of quality-assured molecular assays on a self-collected, or clinician-collected, vaginal swab or on a urine specimen (Algorithm ①).</li> <li>2. We suggest treating for bacterial vaginosis if vaginal discharge is present (for example, tenacious or thin) or based on the results of microscopy, if available.</li> <li>3. We suggest treating for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available.</li> </ol> <p><i>Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing</i></p> <ol style="list-style-type: none"> <li>1. We suggest treating based on a quality-assured rapid test with a minimum sensitivity of 80% and specificity of 90%, if available, to confirm or exclude infection with <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> (Algorithm ②).</li> <li>2. If the availability of a low-cost rapid test or molecular assay is limited, we suggest performing a speculum examination and treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if there is evidence of cervicitis and perform a low-cost rapid test or molecular assay for people with a negative speculum examination who are at high risk of infection with <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> and treat based on the test results (Algorithm ③a).</li> </ol>				

<p><b>Recommendation</b></p>	<p>3. If a rapid test is not available, we suggest treating people who have signs of cervicitis on speculum examination for infection with <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> (Algorithm ③).</p> <p>4. If a rapid test is not available and a speculum examination is not feasible or acceptable, we suggest treating people for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> all persons at high risk of STIs and all persons who have vaginal discharge on genital examination (Algorithm ④).</p> <p>5. We suggest treating people for bacterial vaginosis and <i>T. vaginalis</i> if vaginal discharge is present or based on the results of microscopy, if available.</p> <p>6. We suggest treating people for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available.</p> <p>Good practice includes.</p> <ul style="list-style-type: none"> <li>For people with recurrent or persistent vaginal discharge, good practice includes referring to a centre with laboratory capacity to diagnose infection with <i>N. gonorrhoeae</i>, <i>C. trachomatis</i>, <i>M. genitalium</i> and <i>T. vaginalis</i> and bacterial vaginosis and to test for antimicrobial-resistant <i>N. gonorrhoeae</i> and <i>M. genitalium</i> (if there is a test) or for a specialist's assessment (STI expert and physician or a gynaecologist), when no such testing is available in primary health care centres.</li> </ul>
<p><b>Justification</b></p>	<p><b>Bacterial vaginosis and/or <i>T. vaginalis</i></b></p> <p>Although microscopy was the most accurate with no false treatments and less than 1% of cases missed, the costs of implementing microscopy in settings that currently do not have facilities outweighs the costs of treating everyone with confirmed vaginal discharge for bacterial vaginosis and <i>T. vaginalis</i> and the harm to people unnecessarily treated (about 40%). We considered the effects of screening for bacterial vaginosis or <i>T. vaginalis</i> using pH testing compared with confirmed vaginal discharge and found that the differences in people missed and people unnecessarily treated were negligible, since the costs of treatment are relatively low.</p> <p><b><i>N. gonorrhoeae</i> and <i>C. trachomatis</i></b></p> <ul style="list-style-type: none"> <li>Performing molecular assay tests for <i>N. gonorrhoeae</i>, <i>C. trachomatis</i> or <i>T. vaginalis</i> and basing treatment on these results leads to the most people treated correctly when treatment is provided on the same day.</li> <li>Using a low-cost rapid point-of-care test with 80% sensitivity and 90% specificity will lead to fewer missed and falsely treated people than other syndromic approaches and no treatment.</li> <li>Performing a speculum examination and treating people with cervicitis and then microscopy for people who were negative on speculum examination may also lead to fewer missed cases and falsely treated people than using a rapid point-of-care test (at a minimum of 80% sensitivity and 90% specificity) for everyone. Alternatively, if a rapid point-of-care test is used for the people with a negative speculum examination, there would be even fewer missed cases and falsely treated people.</li> <li>Treating based only on the results of a speculum examination will still result in similar pelvic inflammatory disease cases and similar costs to a rapid point-of-care test, although the number of people treated unnecessarily would be slightly higher when using speculum examination.</li> <li>If everyone at high risk (including with risk factors in high prevalence settings) and/or people with confirmed vaginal discharge are treated, the costs may be higher than strategies with rapid point-of-care tests or speculum examination, but there are large beneficial reductions in the number of pelvic inflammatory disease cases and, compared with treating everyone, there are fewer unnecessarily treated people.</li> </ul>

**Fig. A4.1. WHO algorithm based on risk**

**Fig. A4.2. WHO algorithm based on speculum (and microscopy for bacterial vaginosis and *T. vaginalis*)**



## References

1. Zemouri C, Wi TE, Kiarie J, Seuc A, Mogasale V, Latif A et al. The performance of the vaginal discharge syndromic management in treating vaginal and cervical infection: a systematic review and meta-analysis. *PLoS One*. 2016;11:e0163365.
2. Cornier N, Petrova E, Cavailler P, Dentcheva R, Terris-Prestholt F, Janin A et al. Optimising the management of vaginal discharge syndrome in Bulgaria: cost-effectiveness of four clinical algorithms with risk assessment. *Sex Transm Infect*. 2010;86:303–9.
3. Tolosa JE, Rodriguez A, Muller E, Ruiz-Parra A, Nunez-Forero L, Moyano L et al. Accuracy of syndromic diagnosis and management for vaginal discharge and cervicitis in women of reproductive age in Bogota, Colombia. *Int J Gynecol Obstet*. 2012;119(S3):729.
4. Haberland N, Winikoff B, Sloan N, Coggins C, Elias C. Case finding and case management of chlamydia and gonorrhoea infections among women: What we do and do not know. New York: Population Council; 1999 ([https://knowledgecommons.popcouncil.org/departments\\_sbsr-rh/496](https://knowledgecommons.popcouncil.org/departments_sbsr-rh/496), accessed 22 March 2021).
5. Sloan NL, Winikoff B, Haberland N, Coggins C, Elias C. Screening and syndromic approaches to identify gonorrhoea and chlamydial infection among women. *Stud Fam Plann*. 2000;31:55–68.
6. Madhivanan P, Krupp K, Hardin J, Karat C, Klausner JD, Reingold AL. Simple and inexpensive point-of-care tests improve diagnosis of vaginal infections in resource constrained settings. *Trop Med Int Health*. 2009;14:703–8.
7. Korenromp EL, Wi T, Resch S, Stover J, Broutet N. Costing of national STI program implementation for the global STI control strategy for the health sector, 2016–2021. *PLoS One*. 2017;12:e0170773.
8. Schnippel K, Lince-Deroche N, van den Handel T, Molefi S, Bruce S, Firnhaber C. Cost evaluation of reproductive and primary health care mobile service delivery for women in two rural districts in South Africa. *PLoS One* 2015;10:e0119236.
9. Owusu-Eduese Jr K, Gift TL, Chesson HW. Treatment cost of acute gonococcal infections: Estimates from employer-sponsored private insurance claims data in the United States, 2003–2007. *Sex Transm Dis*. 2010;37:316–8.
10. Goyal MK, Hayes KL, Mollen CJ. Racial disparities in testing for sexually transmitted infections in the emergency department. *Acad Emerg Med*. 2012;19:6047.
11. Kostick KM, Schensul SL, Jadhav K, Singh R, Bavadekar A, Saggurti N. Treatment seeking, vaginal discharge and psychosocial distress among women in urban Mumbai. *Cult Med Psychiatry*. 2010;34:529–47.
12. Hoffman CM, Fritz L, Matlakala N, Mbambazela N, Railton JP, McIntyre JA, et al. Community-based strategies to identify the unmet need for care of individuals with sexually transmitted infection-associated symptoms in rural South Africa. *Trop Med Int Health*. 2019;24:987–93.
13. Lobo CD, Quixabeira DC, Albuquerque GS, Tavares JR, Neto JS. Detection of *Chlamydia trachomatis* by real-time PCR of a sample of the female population of Maceió, Alagoas, Brazil referred to the private and public health services. *J Am Soc Cytopathol*. 2012;1:S50.
14. Ali MK, Shia JS. Detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in genitourinary specimens in Iraq women by real time PCR assay. *Res J Pharm Biol Chem Sci*. 2018;9:799–808.



15. Annang L, Walsemann KM, Maitra D, Kerr JC. Does education matter? Examining racial differences in the association between education and STI diagnosis among black and white young adult females in the U.S. *Public Health Reports*. 2010;125(Suppl. 4):110–21.
16. Centers for Disease Control and Prevention: CDC Grand Rounds: chlamydia prevention: challenges and strategies for reducing disease burden and sequelae. *MMWR Morb Mortal Wkly Rep*. 2011;60:370–3.
17. Gaydos CA, Hsieh YH, Barnes M, Quinn N, Agreda P, Jett-Goheen M et al. *Trichomonas vaginalis* infection in women who submit self-obtained vaginal samples after internet recruitment. *Sex Transm Dis*. 2011;38:828–32.
18. Lazenby GB, Soper DE, Nolte FS. Correlation of leukorrhea and *Trichomonas vaginalis* infection. *J Clin Microbiol*. 2013;51:2323–7.
19. Cartwright CP, Pherson AJ, Harris AB, Clancey MS, Nye MB. Multicenter study establishing the clinical validity of a nucleic-acid amplification-based assay for the diagnosis of bacterial vaginosis. *Diagn Microbiol Infect Dis*. 2018;92:173–8.
20. Durai V, Varadharajan S, Muthuthandavan AR. Reproductive tract infections in rural India – a population-based study. *J Family Med Prim Care*. 2019;8:3578–83.
21. Spaulding AC, Miller J, Trigg BG, Braverman P, Lincoln T, Reams PN et al. Screening for sexually transmitted diseases in short-term correctional institutions: summary of evidence reviewed for the 2010 Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines. *Sex Transm Dis*. 2013;40:679–83.
22. Satterwhite CL, Newman D, Collins D, Torrone E. Chlamydia screening and positivity in juvenile detention centers, United States, 2009–2011. *Women Health*. 2014;54:712–25.
23. Burghardt NO, Chow JM, Steiner A, Bauer HM. Trends in chlamydia screening, test positivity, and treatment among females in California juvenile detention facilities, 2003–2014. *Sex Transm Dis*. 2016;43:12–7.
24. Torrone E, Beeston T, Ochoa R, Richardson M, Gray T, Peterman T, Katz KA. Chlamydia screening in juvenile corrections: even females considered to be at low risk are at high risk. *J Correct Health Care*. 2016;22:21–7.
25. Ward K, Butler N, Mugabo P, Klausner J, McFarland W, Chen S et al. Provision of syndromic treatment of sexually transmitted infections by community pharmacists: a potentially underutilized HIV prevention strategy. *Sex Transm Dis*. 2003;30:609–13.
26. Anderson MR, Karasz A. How do clinicians manage vaginal complaints? An Internet survey. *MedGenMed*. 2005;7:61.
27. Kohler PK, Marumo E, Jed SL, Mema G, Galagan S, Tapia K et al. A national evaluation using standardised patient actors to assess STI services in public sector clinical sentinel surveillance facilities in South Africa. *Sex Transm Infect* 2017; 93:247–52.
28. Sharma R, Prajapati S, Patel B, Kumar P. Evaluation of skill-oriented training on enhanced syndromic case management (ESCM) of reproductive tract infections/sexually transmitted infections (RTI/STIs) of care providers from three-tier health-care system of Gujarat. *Indian J Community Med*. 2016;41:183–9.
29. Alemayehu A, Godana W. Knowledge and practice of clinicians regarding syndromic management of sexually transmitted infections in public health facilities of Gamo Gofa Zone, South Ethiopia. *J Sex Transm Dis*. 2015;2015:310409.
30. Jiang Z, Wang D, Hong Q, Cherry N, Cheng J, Chai J et al. Use of health services by women with gynecological symptoms in rural China. *World Health Popul*. 2010;11:23–37.

31. Rosenheck R, Ngilangwa D, Manongi R, Kapiga S. Treatment-seeking behavior for sexually transmitted infections in a high-risk population. *AIDS Care*. 2010;22:1350–8.
32. Samanta A, Ghosh S, Mukherjee S. Prevalence and health-seeking behavior of reproductive tract infection/sexually transmitted infections symptomatics: a cross-sectional study of a rural community in the Hooghly district of West Bengal. *Indian J Public Health*. 2011;55:38–41.
33. Hegde S, Agrawal T, Ramesh N, Sugara M, Joseph P, Singh S et al. Reproductive tract infections among women in a peri-urban under privileged area in Bangalore, India: knowledge, prevalence, and treatment seeking behavior. *Ann Trop Med Public Health*. 2013;6:215–20.
34. Girish HO, Kumar A, Balu PS. A study on STI morbidity pattern and STI treatment seeking behavior among female sex workers of Davangere city, Central Karnataka. *Int J Life Sci Biotechnol Pharma Res*. 2014;3:254–60.
35. Sharma D, Goel NK, Thakare MM. Prevalence of reproductive tract infection symptoms and treatment-seeking behavior among women: a community-based study. *Indian J Sex Transm Dis AIDS*. 2018;39:79–83.
36. Tanton C, Geary RS, Clifton S, Field N, Heap KL, Mapp F et al. Sexual health clinic attendance and non-attendance in Britain: findings from the third National Survey of Sexual Attitudes and Lifestyles (Natsal-3). *Sex Transm Infect*. 2018;94:268–76.
37. Tayerih K, Jozani ZB, Golchehregan H, Rostam-Afshar Z, Taj L, Nasab SA et al. Woman's sexual health knowledge and needs assessment in behavioral clinics and shelters in Tehran. *J Fam Reprod Health*. 2019;13:26–34.
38. Jiang Q, Qin Q, Zhang X. HIV, syphilis, and condom use among female drug users in Maanshan, China. *Int J Gynaecol Obstet*. 2010;110:158–9.
39. Ilankoon MPS, Goonewardena CSE, Fernandopulle RC, Rasika Perera PP. Women's knowledge and experience of abnormal vaginal discharge living in estates in Colombo District, Sri Lanka. *Int J Women Health Reprod Sci*. 2017;5:90–6.
40. Arrindell D, Barclay L, Boxt J. The forgotten STI: a survey of knowledge about trichomoniasis. *Sex Transm Infect*. 2013;89(Suppl. 1):A323.
41. Hoffman CM, Mbambazela N, Sithole P, Morre SA, Dubbink JH, Railton J et al. Provision of sexually transmitted infection services in a mobile clinic reveals high unmet need in remote areas of South Africa: a cross-sectional study. *Sex Transm Dis*. 2019;46:206–12.
42. Ekabua JE, Agan TU, Eklaki CU, Ekanew EI. Adjuncts to case assessment of vaginal discharge syndrome in pregnant women. *Asian Pac J Trop Med*. 2010;3:63–5.
43. Miller MK, Dowd MD, Harrison CJ, Mollen CJ, Selvarangan R, Humiston SG. Prevalence of 3 sexually transmitted infections in a pediatric emergency department. *Pediatr Emerg Care*. 2015;31:107–12.
44. Jayapalan S. Healthcare-seeking preferences of patients with sexually transmitted infection attending a tertiary care center in South Kerala. *Indian J Sex Transm Dis*. 2016;37:157–61.
45. Leichter JS, Copen C, Dittus PJ. Confidentiality issues and use of sexually transmitted disease services among sexually experienced persons aged 15–25 years – United States, 2013–2015. *MMWR Morb Mortal Wkly Rep*. 2017;66:237–41.
46. de Matos MA, Caetano KA, Franca DD, Pinheiro RS, de Moraes LC, Teles SA. Vulnerability to sexually transmitted infections in women who sell sex on the route of prostitution and sex tourism in central Brazil. *Rev Lat Am Enfermagem*. 2013;21:906–12.

47. Lee K Wong KH. What do female sex workers do if they have genital symptoms? *Sex Transm Infect.* 2011;87(Suppl. 1):A129.
48. Kumar A. A health seeking behavior of the women of urban slums of Puducherry regarding reproductive tract infections. *Indian J Public Health Res Devel.* 2017;8:152–6.
49. Abdelrahim NA, Ahmed HI, Fadl-Elmula IM, Bayoumi MA, Homeida MM. Sexually transmitted infections other than HIV/AIDS among women of low socio-economic class attending antenatal clinics in Khartoum, Sudan. *Int J STD AIDS.* 2017;28:781–7.
50. Subbarao NT, Akhilesh A. Knowledge and attitude about sexually transmitted infections other than HIV among college students. *Indian J Sex Transm Dis.* 2017;38:10–4.
51. Malek AM, Chang CC, Clark DB, Cook RL. Delay in seeking care for sexually transmitted diseases in young men and women attending a public STD clinic. *Open AIDS J.* 2013;7:7–13.
52. Denison HJ, Woods L, Bromhead C, Kennedy J, Grainger R, Jutel A et al. Healthcare-seeking behaviour of people with sexually transmitted infection symptoms attending a sexual health clinic in New Zealand. *N Z Med J.* 2018;131:40–9.
53. Cheluget B, Joesoef MR, Marum LH, Wandera C, Ryan CA, Decock KM et al. Changing patterns in sexually transmitted disease syndromes in Kenya after the introduction of a syndromic management program. *Sex Transm Dis.* 2004;31:522–5.
54. Grosskurth H, Mwijarubi E, Todd J, Rwakatare M, Orroth K, Mayaud P et al. Operational performance of an STD control programme in Mwanza Region, Tanzania. *Sex Transm Infect.* 2000;76:426–36.
55. Garcia PJ, Carcamo CP, Garnett GP, Campos PE, Holmes KK. Improved STD Syndrome Management by a Network of Clinicians and Pharmacy Workers in Peru: the PREVEN Network. *PLoS ONE.* 2012;7:e47750.
56. Khan MA, Javed W, Ahmed M, Walley J, Munir MA. Sexually transmitted disease syndromic case management through public sector facilities: development and assessment study in Punjab Pakistan. *Ann Glob Health.* 2014;80:486–92.
57. Kisa S, Taskin L. Validity of the symptomatic approach used by nurses in diagnosing vaginal infections. *J Clin Nurs.* 2009;18:1059–68.
58. Mahmood MA, Sanjotis A. Use of syndromic management algorithm for sexually transmitted infections and reproductive tract infections management in community settings in Karachi. *J Pak Med Assoc.* 2011;61:453–7.
59. Banneheke H, Fernandopulle R, Gunasekara U, Barua A, Fernando N, Wickremasinghe R. Can *Trichomonas* immunochromatographic test increase the validity and reliability of WHO syndromic algorithm for vaginal discharge as a screening tool for trichomoniasis? *Ann Trop Med Public Health.* 2016;9:43–7.
60. Barry MS, Ba Diallo A, Diadihou M, Mall I, Gassama O, Ndiaye Gueye MD et al. Accuracy of syndromic management in targeting vaginal and cervical infections among symptomatic women of reproductive age attending primary care clinics in Dakar, Senegal. *Trop Med Int Health.* 2018;23:541–8.
61. Das A, Prabhakar P, Narayanan P, Neilsen G, Wi T, Kumta S et al. Prevalence and assessment of clinical management of sexually transmitted infections among female sex workers in two cities of India. *Infect Dis Obstet Gynecol.* 2011;2011:494769.
62. Desai VK, Kosambiya JK, Thakor HG, Umrigar DD, Khandwala BR, Bhuyan KK. Prevalence of sexually transmitted infections and performance of STI syndromes against aetiological diagnosis, in female sex workers of red light area in Surat, India. *Sex Transm Infect.* 2003;79:111–5.

63. Francis SC, Ao TT, Vanobberghen FM, Chilongani J, Hashim R, Andreasen A et al. Epidemiology of curable sexually transmitted infections among women at increased risk for HIV in northwestern Tanzania: inadequacy of syndromic management. *PLoS One*. 2014;9:e101221.
64. Garcia PJ, Chavez S, Feringa B, Chiappe M, Li W, Jansen KU et al. Reproductive tract infections in rural women from the highlands, jungle, and coastal regions of Peru. *Bull World Health Organ*. 2004;82:483–92.
65. Lima TM, Teles LM, de Oliveira AS, Campos FC, Barbosa Rde C, Pinheiro AK et al. [Vaginal discharge in pregnant women: comparison between syndromic approach and examination of clinical nursing practice]. *Rev Esc Enferm USP*. 2013;47:1265–71.
66. Moherdau F, Urquia M, Castro de Midecne L, Morales G. Validation of STI flowcharts for the syndromic management of vaginal discharge and lower abdominal pain in Honduras. *Rev Med Hondur*. 2005;6:263.
67. Molaei B, Mohmmadian F, Tadayon P, Gholami H, Kiani M, Rashtchi V. Comparative evaluation of accuracy and compatibility level of different diagnostic methods for bacterial vaginosis. *Kuwait Med J*. 2018;50:205–12.
68. Msuya SE, Uriyo J, Stray-Pedersen B, Sam NE, Mbizvo EM. The effectiveness of a syndromic approach in managing vaginal infections among pregnant women in northern Tanzania. *East Afr J Public Health*. 2009;6:263–7.
69. Onyekonwu CL, Olumide YM, Oresanya FA, Onyekonwu GC. Vaginal discharge: aetiological agents and evaluation of syndromic management in Lagos. *Niger J Med*. 2011;20:155–62.
70. Romoren M, Velauthapillai M, Rahman M, Sundby J, Klouman E, Hjortdahl P. Trichomoniasis and bacterial vaginosis in pregnancy: inadequately managed with the syndromic approach. *Bull World Health Organ*. 2007;85:297–304.
71. Tann CJ, Mpairwe H, Morison L, Nassimu K, Hughes P, Omara M et al. Lack of effectiveness of syndromic management in targeting vaginal infections in pregnancy in Entebbe, Uganda. *Sex Transm Infect*. 2006;82:285–9.
72. Vallely LM, Toliman P, Ryan C, Rai G, Wapling J, Gabuzzi J et al. Performance of syndromic management for the detection and treatment of genital *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study. *BMJ Open*. 2017;7:e018630.

**Table A4.4. Studies included in the review of sensitivity and specificity of vaginal infections (bacterial vaginosis and/or *T. vaginalis*)**

Algorithm	Study	Country	Design	n	Prevalence (%)	Setting	Population	Flow chart	Reference test
+ speculum exam Local adaptation	Banneheke et al. (59)	Sri Lanka	Cross-sectional	100	<i>T. vaginalis</i> : 6.0	STI clinics, well-woman clinics, gynaecology clinics, institutional health clinics	General population women (15–45 years)	WHO syndromic algorithm flow chart 1 + clinical and speculum examination; WHO flow chart 1 + clinical and speculum examination + <i>Trichomonas</i> immunochromatographic test	<i>T. vaginalis</i> : culture
+ speculum exam	Barry et al. (60)	Senegal	Cross-sectional	276	<i>N. gonorrhoeae</i> : 1.1 <i>C. trachomatis</i> : 4.7 <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : 5.4 Bacterial vaginosis (GV): 39.5 <i>T. vaginalis</i> : 2.5 Bacterial vaginosis and <i>T. vaginalis</i> : 40.2	Hospitals, primary health facilities	General population women (18–49 years)	WHO syndromic algorithm: symptoms, history, risk assessment, bimanual and speculum examination	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : NAAT Bacterial vaginosis: Nugent scoring <i>T. vaginalis</i> : wet mount microscopy
+ speculum exam Lab (wet mount, Gram stain) Local adaptation	Cornier et al. (2)	Bulgaria	Cross-sectional	424	<i>N. gonorrhoeae</i> : 0.7 <i>C. trachomatis</i> : 9.2 <i>T. vaginalis</i> : 2.9 Either <i>C. trachomatis</i> or <i>N. gonorrhoeae</i> : 9.5	Sexual health clinic	Non-pregnant women	WHO 1, 2, 3, MSF 1	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : NAAT Bacterial vaginosis and <i>T. vaginalis</i> : microscopy

Algorithm	Study	Country	Design	n	Prevalence (%)	Setting	Population	Flow chart	Reference test
History, risk assessment	Tsai et al. (4)	Taiwan	Cross-sectional	335	<i>N. gonorrhoeae</i> : 14.1 <i>C. trachomatis</i> : 17.1 <i>T. vaginalis</i> : 31.1 Bacterial vaginosis: 71 Either <i>N. gonorrhoeae</i> or <i>C. trachomatis</i> : 26.1	STI clinic for sex workers	Sex workers	WHO 1, 2, NACO 3	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : NAAT <i>T. vaginalis</i> : PCR Bacterial vaginosis: Nugent's criteria
Local adaptation	Desai et al. (62)	India	Cross-sectional	118	<i>N. gonorrhoeae</i> : 15.3 <i>C. trachomatis</i> : 8.5 <i>T. vaginalis</i> : 14.4	Red-light district	Sex workers	NACO 2	<i>N. gonorrhoeae</i> : Culture and Gram staining <i>C. trachomatis</i> : Pace 2 <i>C. trachomatis</i> assay. <i>T. vaginalis</i> : wet mount
+ speculum exam	Francis et al. (63)	United Republic of Tanzania	Cross-sectional	966	<i>N. gonorrhoeae</i> : 4 <i>C. trachomatis</i> : 12 <i>T. vaginalis</i> : 19	Women working in bars, hotels.	HIV-negative women	WHO 2	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : PCR <i>T. vaginalis</i> : culture Bacterial vaginosis: Nugent's criteria
History, risk assessment + speculum exam	Garcia et al. (64)	Peru	Cross-sectional	754	<i>N. gonorrhoeae</i> : 1.2 <i>C. trachomatis</i> : 6.8	Mothers' Club	General population	Peruvian algorithm 1	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : PCR
History, risk assessment	Kisa et al. (57)	Turkey	Cross-sectional	300	<i>T. vaginalis</i> : 14	Maternal health clinic	Married women	WHO 2	<i>T. vaginalis</i> : Wet mount
History, risk assessment	Lima et al. (65)	Brazil	Cross-sectional	104	<i>T. vaginalis</i> : 3.8 Bacterial vaginosis: 27.9	Antenatal care	Pregnant women	WHO 1	<i>T. vaginalis</i> : wet mount Bacterial vaginosis: Amsel criteria.

Algorithm	Study	Country	Design	n	Prevalence (%)	Setting	Population	Flow chart	Reference test
+ speculum exam Lab (wet mount, gram stain)	Moherdai et al. (66)	Honduras	Cross-sectional	933	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : 5.9 <i>T. vaginalis</i> : 6.8 Bacterial vaginosis: 27.4	General health clinic	General population	WHO 1, 2, 3	<i>N. gonorrhoeae</i> : Gram <i>C. trachomatis</i> : immunofluorescence <i>T. vaginalis</i> : microscopy
History, risk assessment + speculum exam	Molaei et al. (67)	Islamic Republic of Iran	Prospective	100	Bacterial vaginosis (GV): 14.0 <i>T. vaginalis</i> : 10.0	Hospital gynaecological outpatient department	General population married women (18-49 years)	History; History + bimanual and speculum examination (clinical diagnosis)	Bacterial vaginosis: Amsel criteria + Nugent score <i>T. vaginalis</i> : wet mount microscopy
Local adaptation	Msiya et al. (68)	United Republic of Tanzania	Cross-sectional	2645	<i>T. vaginalis</i> : 5 Bacterial vaginosis: 20.9 Either: 23.9	Antenatal care	Pregnant women	Tanzanian STI case management 2	<i>T. vaginalis</i> : wet mount Bacterial vaginosis: Amsel Nugent.
Local adaptation	Onyekowu et al. (69)	Nigeria	Cross-sectional	195	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : 12.8 Bacterial vaginosis and <i>T. vaginalis</i> : 57.4	STI clinic	General population	Nigerian national algorithm (2b)	<i>N. gonorrhoeae</i> : Culture <i>C. trachomatis</i> : Elisa <i>T. vaginalis</i> : wet mount Bacterial vaginosis: Nugent's criteria
History, risk assessment	Romoren et al. (70)	Botswana	Cross-sectional	703	<i>N. gonorrhoeae</i> : 3 <i>C. trachomatis</i> : 8 <i>T. vaginalis</i> : 18.8 Bacterial vaginosis: 38.1	Antenatal care	Pregnant women	WHO 2	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : LCR <i>T. vaginalis</i> : wet-mount Bacterial vaginosis: Nugent's criteria

Algorithm	Study	Country	Design	n	Prevalence (%)	Setting	Population	Flow chart	Reference test
History, risk assessment	Tam et al. (71)	Uganda	Cross-sectional	250	<i>T. vaginalis</i> : 17.3 Bacterial vaginosis: 47.7	Antenatal care	Pregnant women	Nigerian national algorithm 2	<i>T. vaginalis</i> : inoculation culture media kit and wet mount Bacterial vaginosis: Nugent's criteria.
History, risk assessment	Tolosa et al. (3)	Colombia	Cross-sectional	1266	<i>N. gonorrhoeae</i> : 1.2 <i>C. trachomatis</i> : 9 <i>T. vaginalis</i> : 0.9 Bacterial vaginosis: 39	General health clinic	General population	WHO 1	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : PCR <i>T. vaginalis</i> : wet mount Bacterial vaginosis: Nugent's criteria
History, risk assessment + speculum exam	Vallely et al. (72)	Papua New Guinea	Cross-sectional	1764	<i>N. gonorrhoeae</i> : 12.5 <i>C. trachomatis</i> : 16.9 <i>T. vaginalis</i> : 18.0	Antenatal clinics, well-woman clinics, sexual health clinics	General population women (18–59 years)	WHO history + risk factors (antenatal clinic); WHO history + risk factors + genital examination (well-woman and sexual health clinics)	<i>N. gonorrhoeae</i> and <i>C. trachomatis</i> : real-time PCR <i>T. vaginalis</i> : real-time PCR



**Table A4.5. Different flow charts and approaches modelled to manage gonorrhoea and/or chlamydial infection among women with vaginal discharge**

No treatment
Treat all
1a: Risk assessment, then treat high-risk women for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>
2a: Speculum examination then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if positive (presence of signs of cervicitis – mucus)
3a: Speculum examination, treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if positive, and if negative perform microscopy (Gram stain) and if positive for presence of gram-negative diplococci or pus cell >20/hpf treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>
4: Speculum examination, treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if positive, and if negative perform point-of-care test and if positive test, treat for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i>
5: Microscopy (Gram stain) then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if positive
6: Risk assessment and/or genital examination then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if risk assessment positive (context specific such as age) and/or genital examination positive (presence of vaginal discharge)
7: Risk assessment and/or genital examination, if positive then perform speculum examination then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if speculum positive
8: Risk assessment and/or genital examination, if positive perform speculum examination then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if speculum positive, if negative speculum perform microscopy then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if positive
9: Risk assessment and/or genital examination, if positive then perform low-cost point-of-care test then treat for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> if positive point-of-care test
10a: Risk assessment then perform low-cost point-of-care test in women at high risk, then treat for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> if positive point-of-care test
11a: Perform low-cost point-of-care test then treat for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> if positive point-of-care test
12: Risk assessment and/or genital examination, if positive then perform high-cost point-of-care test then treat for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> if positive point-of-care test
13a: Risk assessment then perform high-cost point-of-care test among women at high risk, then treat for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> if positive point-of-care test
14a: Perform high-cost point-of-care test then treat for <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> if positive point-of-care test
15: WHO risk: low prevalence: risk assessment and/or speculum examination then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if positive risk assessment and/or speculum; high prevalence: treat all for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>
16: WHO spec: low prevalence: genital examination, if positive for discharge then risk assessment, if high risk then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> ; high prevalence: genital examination, if positive then treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i>

**Table A4.6. Management of 1000 symptomatic women (5% and 20% prevalence of *N. gonorrhoeae* and *C. trachomatis*) based on modelling**

		Certainty of the evidence (refer to the table above)																		
		No treatment	Treat all	1a	2a	3a	4	5a	6	7	8	9	10a	11a	12			13a	14a	15
Sensitivity/specificity		0/100	100/0	63/60	73/56	87/41	95/50	52/73	92/12	92/12	92/12	87/41	80/90	80/90	92/12	63/60	95/98	95/98	L:90/34 H:100/0	L:49/68 H:78/20
<b>5% prevalence</b>																				
Infected and treated correctly		0	50	32	37	44	48	26	46	34	43	35	24	38	43	30	46	45	25	25
Uninfected and treated unnecessarily		0	950	380	418	561	475	257	836	371	561	159	72	180	33	15	38	627	304	304
Infected and not treated		50	0	19	14	7	3	24	4	17	7	15	26	12	7	20	3	5	26	26
Uninfected and not treated		950	0	570	532	390	475	694	114	580	390	791	878	770	917	935	912	323	646	646
Cases of pelvic inflammatory disease		15	0	6	4	2	1	7	1	5	2	5	8	4	2	6	1	2	8	8
Cost per person for antimicrobial resistance US\$ 5		2.03	8.09	4.11	5.26	6.68	~5.38	4.79	7.30	~4.38	~5.79	4.82	3.09	5.25	15.08	7.83	16.89	6.67	3.72	3.72
<b>20% prevalence</b>																				
Infected and treated correctly		0	200	126	146	174	200	104	184	134	174	139	95	151	172	118	187	200	156	156
Uninfected and treated unnecessarily		0	800	320	352	472	800	216	704	312	472	134	61	152	28	13	32	800	640	640
Infected and not treated		200	0	74	54	26	0	96	16	66	26	61	105	49	28	82	13	0	44	44
Uninfected and not treated		800	0	480	448	328	0	584	96	488	328	666	739	648	772	787	768	0	160	160
Cases of pelvic inflammatory disease		60	0	22	16	8	0	29	5	20	8	18	31	15	8	25	4	0	13	13
Cost per person for antimicrobial resistance US\$ 5		7.75	8.09	6.50	7.15	7.76	~6.76	7.83	7.81	~7.07	~7.58	7.20	6.66	7.31	16.90	11.38	18.27	9.09	8.14	8.14

Dark green: best benefit; light green: less benefit; yellow: harm; red: most harm.

Estimates from modelling for *N. gonorrhoeae* or *C. trachomatis*

## ANNEX 5. EVIDENCE-TO-DECISION TABLE: LOWER ABDOMINAL PAIN

Should the current WHO syndromic management be recommended versus laboratory diagnosis, no treatment or treat all to identify pelvic inflammatory disease caused by STIs among women with lower abdominal pain?

### Population:

Women presenting with lower abdominal pain

### Intervention and comparator:

Intervention: current WHO syndromic approach versus comparison: laboratory diagnosis (or no treatment or treat all)

### Purpose of the test:

To identify women for treatment of STIs related to pelvic inflammatory disease

### Linked treatments:

Treatment for infections caused by *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis* and anaerobic infections

### Anticipated outcomes:

Number of people identified correctly as having or not having STI and/or pelvic inflammatory disease; number of people identified incorrectly as having or not having STI and/or pelvic inflammatory disease; consequences of appropriate or inappropriate treatment; patient and provider acceptability, feasibility, equity and resource use

### Setting:

Outpatient

### Perspective:

Population level

### Subgroups:

Pregnant women, sex workers and heterosexual women (general population).

### Background:

Syndromic management refers to a strategy for identifying and treating STIs based on specific syndromes (symptoms identified by a patient) and signs (clinically observed signs of infection) associated with clearly defined causes. Although etiological diagnosis is preferred, it is not always accessible or affordable.

Individuals presenting with lower abdominal pain syndrome could suggest the presence of acute pelvic inflammatory disease that requires immediate attention. Lower abdominal pain is a vague symptom and can be caused by myriad potential diseases, including pelvic inflammatory disease with consequent risk of chronic pelvic pain, tubal factor infertility and ectopic pregnancy. Pelvic inflammatory disease represents a spectrum of disease with a wide range of severity and results from an infection from the cervix or vagina entering into the endometrium, fallopian tubes and/or contiguous structures. Pelvic inflammatory disease is a polymicrobial infection and can be caused by an STI or by dysbiosis of the vaginal microbiome. The likely causes of lower abdominal pain could change depending on the age of the woman.

WHO published clinical guidelines for the syndromic management of lower abdominal pain syndrome in 2003 (Fig. A5.1).

## Assessment

	Judgement	Research evidence
Problem	<p><b>Is the problem a priority?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>There is currently no objective test for pelvic inflammatory disease, and symptoms can vary widely from severe to none. Clinical diagnosis involves bimanual examination of the cervix and uterus to detect tenderness among women presenting with acute lower pelvic pain, fever and vaginal or cervical discharge. The procedure is uncomfortable, invasive and subjective, thereby presenting a significant barrier to clinicians and women. Pelvic inflammatory disease cases could be missed and may increase women's risk of ectopic pregnancy and infertility. Laparoscopic examination is considered the gold standard for diagnosing pelvic inflammatory disease (or endometrial biopsy, transvaginal sonography, magnetic resonance imaging techniques or Doppler studies) but, because of their impracticality as a screening tool, until more accurate diagnostics are available, clinicians are advised to have a low threshold for syndromic management for suspected cases of pelvic inflammatory disease.</p> <p><b>High cost of molecular STI testing</b></p> <p>There is a need for cheaper platforms, near-patient or point-of-care tests for <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> and potentially for <i>M. genitalium</i>.</p> <p><b>Antimicrobial resistance</b></p> <p>There is increasing concern about the treatment of people with <i>N. gonorrhoeae</i>, since high rates of resistance to penicillin, tetracycline and quinolone have been documented globally. Resistance to commonly used first-line medications (azithromycin) and reports of treatment failure or reduced susceptibility in <i>N. gonorrhoeae</i> to cephalosporin (a last-line treatment for <i>N. gonorrhoeae</i>) raise concern that <i>N. gonorrhoeae</i> could become untreatable.</p>
Test accuracy	<p><b>How accurate is the test?</b></p> <p><input type="radio"/> Very inaccurate</p> <p><input checked="" type="radio"/> Inaccurate</p> <p><input type="radio"/> Accurate</p> <p><input type="radio"/> Very accurate</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>We systematically reviewed the literature, searching up to September 2019. In summary, we identified five studies that assessed the diagnostic accuracy of lower abdominal pain syndromic management to detect any STI (Table A5.1), five studies for genital chlamydia (Table A5.2) and four studies for genital gonorrhoea (Table A5.3) and three studies for genital trichomoniasis (Table A5.4).</p> <p>For detection of any STI (chlamydia, gonorrhoea or trichomoniasis), five studies provided eight estimates for pooling. The pooled sensitivity for detecting chlamydia, gonorrhoea or trichomonas using a syndromic management approach (lower abdominal pain) is 30.0% (95% CI: 17.7–46.0%), and pooled specificity is 73.3% (95% CI: 56.3–85.4%).</p>

	Judgement	Research evidence			
Test accuracy		<b>Table A5.5. GRADE summary of findings table for abdominal pain and any STI</b>			
	Test result	Number of results per 1000 people tested (95% confidence interval)	Number of participants (studies)	Certainty of the evidence (GRADE)	
		Prevalence of 5% typically seen in:			
	True positives	15 (9–23)	3908 (5)	⊕⊕⊕⊕	
	False negatives	35 (27–41)		High	
	True negatives	696 (535–811)	3908 (5)	⊕⊕⊕○	
	False positives	254 (139–415)		Moderate <sup>a,b</sup>	
		a Most studies showed consistent results.			
		b The threshold for unnecessary treatment was high (about 75%), and the confidence intervals cross that threshold and there is therefore some imprecision for false positives.			
		<b>Accuracy of criteria for pelvic inflammatory disease in the WHO syndromic management flow chart (also similar to the minimal criteria of the United States Centers for Disease Control and Prevention)</b>			
	The value of various clinical characteristics to identify pelvic inflammatory disease has been studied among 651 women in the United States of America (PEACH Study) (1).				
		<b>Table A5.6. Diagnostic test characteristics of clinical signs of pelvic inflammatory disease</b>			
Clinical characteristic	Sensitivity in % (95% confidence interval)	Specificity in % (95% confidence interval)			
Abdominal tenderness	93.9 (90.6–96.3)	7.4 (4.8–10.7)			
Cervical motion tenderness	91.6 (88.0–94.5)	12.6 (9.1–16.7)			
Uterine tenderness	94.2 (91.0–96.6)	5.3 (3.1–8.2)			
Adnexal tenderness	95.5 (92.6–97.5)	3.8 (2.1–6.5)			
Minimal criteria of the United States Centers for Disease Control and Prevention	83.3 (78.7–87.3)	21.8 (17.5–26.5)			
	Source: Peipert et al. (1).				

	Judgement	Research evidence																																																						
Test accuracy		<p><b>Table A5.7. Evaluation of supportive criteria for diagnosing endometritis</b></p> <table border="1"> <thead> <tr> <th data-bbox="446 252 558 451">Clinical characteristic</th> <th data-bbox="558 252 663 451">Sensitivity in % (95% confidence interval)</th> <th data-bbox="663 252 768 451">Specificity in % (95% confidence interval)</th> <th data-bbox="768 252 872 451">Positive likelihood ratio</th> <th data-bbox="872 252 977 451">Negative likelihood ratio</th> <th data-bbox="977 252 1087 451">Measure of separation (95% confidence interval)<sup>a</sup></th> </tr> </thead> <tbody> <tr> <td data-bbox="446 451 558 566">Abnormal cervical or vaginal discharge</td> <td data-bbox="558 451 663 566">79.7 (74.6–84.2)</td> <td data-bbox="663 451 768 566">29.8 (24.8–35.2)</td> <td data-bbox="768 451 872 566">1.14</td> <td data-bbox="872 451 977 566">0.681</td> <td data-bbox="977 451 1087 566">1.67 (1.15–2.43)</td> </tr> <tr> <td data-bbox="446 566 558 680">Elevated body temperature (&gt;38°C)</td> <td data-bbox="558 566 663 680">11.1 (7.8–15.2)</td> <td data-bbox="663 566 768 680">94.7 (91.7–96.9)</td> <td data-bbox="768 566 872 680">2.09</td> <td data-bbox="872 566 977 680">0.939</td> <td data-bbox="977 566 1087 680">2.25 (1.23–4.13)</td> </tr> <tr> <td data-bbox="446 680 558 820">Elevated leukocyte count (≥10 000 cells)</td> <td data-bbox="558 680 663 820">41.1 (35.1–47.3)</td> <td data-bbox="663 680 768 820">76.1 (70.6–81.0)</td> <td data-bbox="768 680 872 820">1.72</td> <td data-bbox="872 680 977 820">0.774</td> <td data-bbox="977 680 1087 820">2.22 (1.54–3.22)</td> </tr> <tr> <td data-bbox="446 820 558 911">Positive bacterial results<sup>b</sup></td> <td data-bbox="558 820 663 911">56.0 (50.2–61.6)</td> <td data-bbox="663 820 768 911">81.6 (77.0–85.6)</td> <td data-bbox="768 820 872 911">3.04</td> <td data-bbox="872 820 977 911">0.539</td> <td data-bbox="977 820 1087 911">5.64 (3.94–8.06)</td> </tr> </tbody> </table> <p data-bbox="446 924 837 948">a Positive likelihood ratio/negative likelihood ratio.</p> <p data-bbox="446 948 1008 971">b Polymerase chain reaction testing for <i>N. gonorrhoeae</i> or <i>C. trachomatis</i>.</p> <p><b>Table A5.8. GRADE summary of findings table for the minimal criteria of the United States Centers for Disease Control and Prevention (tenderness) and detection of pelvic inflammatory disease based on sensitivity 83.8% and specificity 21.8%</b></p> <table border="1"> <thead> <tr> <th data-bbox="446 1233 597 1352">Test result</th> <th data-bbox="597 1233 780 1352">Number of results per 1000 people tested (95% CI)</th> <th data-bbox="780 1233 955 1352">Number of participants (studies)</th> <th data-bbox="955 1233 1087 1352">Certainty of the evidence (GRADE)</th> </tr> </thead> <tbody> <tr> <td data-bbox="446 1352 597 1415"></td> <td data-bbox="597 1352 780 1415">Prevalence of 5% typically seen in:</td> <td data-bbox="780 1352 955 1415"></td> <td data-bbox="955 1352 1087 1415"></td> </tr> <tr> <td data-bbox="446 1415 597 1457">True positives</td> <td data-bbox="597 1415 780 1457">42 (39–44)</td> <td data-bbox="780 1415 955 1457">651</td> <td data-bbox="955 1415 1087 1457">⊕⊕⊕○</td> </tr> <tr> <td data-bbox="446 1457 597 1499">False negatives</td> <td data-bbox="597 1457 780 1499">8 (6–11)</td> <td data-bbox="780 1457 955 1499">(1)</td> <td data-bbox="955 1457 1087 1499">Moderate<sup>a</sup></td> </tr> <tr> <td data-bbox="446 1499 597 1541">True negatives</td> <td data-bbox="597 1499 780 1541">207 (166–252)</td> <td data-bbox="780 1499 955 1541">651</td> <td data-bbox="955 1499 1087 1541">⊕⊕⊕○</td> </tr> <tr> <td data-bbox="446 1541 597 1583">False positives</td> <td data-bbox="597 1541 780 1583">743 (698–784)</td> <td data-bbox="780 1541 955 1583">(1)</td> <td data-bbox="955 1541 1087 1583">Moderate<sup>a</sup></td> </tr> </tbody> </table> <p data-bbox="446 1588 627 1612">CI: confidence interval.</p> <p data-bbox="446 1612 765 1636">a Most studies showed consistent results.</p> <p data-bbox="446 1636 847 1659">Single study sensitivity: 0.84 (95% CI: 0.79–0.87)</p> <p data-bbox="446 1659 844 1683">Single study specificity: 0.22 (95% CI: 0.17–0.27)</p>	Clinical characteristic	Sensitivity in % (95% confidence interval)	Specificity in % (95% confidence interval)	Positive likelihood ratio	Negative likelihood ratio	Measure of separation (95% confidence interval) <sup>a</sup>	Abnormal cervical or vaginal discharge	79.7 (74.6–84.2)	29.8 (24.8–35.2)	1.14	0.681	1.67 (1.15–2.43)	Elevated body temperature (>38°C)	11.1 (7.8–15.2)	94.7 (91.7–96.9)	2.09	0.939	2.25 (1.23–4.13)	Elevated leukocyte count (≥10 000 cells)	41.1 (35.1–47.3)	76.1 (70.6–81.0)	1.72	0.774	2.22 (1.54–3.22)	Positive bacterial results <sup>b</sup>	56.0 (50.2–61.6)	81.6 (77.0–85.6)	3.04	0.539	5.64 (3.94–8.06)	Test result	Number of results per 1000 people tested (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)		Prevalence of 5% typically seen in:			True positives	42 (39–44)	651	⊕⊕⊕○	False negatives	8 (6–11)	(1)	Moderate <sup>a</sup>	True negatives	207 (166–252)	651	⊕⊕⊕○	False positives	743 (698–784)	(1)	Moderate <sup>a</sup>
	Clinical characteristic	Sensitivity in % (95% confidence interval)	Specificity in % (95% confidence interval)	Positive likelihood ratio	Negative likelihood ratio	Measure of separation (95% confidence interval) <sup>a</sup>																																																		
	Abnormal cervical or vaginal discharge	79.7 (74.6–84.2)	29.8 (24.8–35.2)	1.14	0.681	1.67 (1.15–2.43)																																																		
	Elevated body temperature (>38°C)	11.1 (7.8–15.2)	94.7 (91.7–96.9)	2.09	0.939	2.25 (1.23–4.13)																																																		
	Elevated leukocyte count (≥10 000 cells)	41.1 (35.1–47.3)	76.1 (70.6–81.0)	1.72	0.774	2.22 (1.54–3.22)																																																		
	Positive bacterial results <sup>b</sup>	56.0 (50.2–61.6)	81.6 (77.0–85.6)	3.04	0.539	5.64 (3.94–8.06)																																																		
	Test result	Number of results per 1000 people tested (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)																																																				
		Prevalence of 5% typically seen in:																																																						
	True positives	42 (39–44)	651	⊕⊕⊕○																																																				
	False negatives	8 (6–11)	(1)	Moderate <sup>a</sup>																																																				
True negatives	207 (166–252)	651	⊕⊕⊕○																																																					
False positives	743 (698–784)	(1)	Moderate <sup>a</sup>																																																					

	Judgement	Research evidence																																																																																							
Test accuracy		<p><b>Other criteria to identify pelvic inflammatory disease</b></p> <p>A study of 189 women clinically diagnosed with pelvic inflammatory disease from a hospital outpatient setting in Sweden reported the sensitivity of various symptoms and signs – tenderness of pelvic organs on bimanual exam. Laparoscopic confirmation of pelvic inflammatory disease was not conducted for these women (2).</p>																																																																																							
	<p><b>Table A5.9. Prediction of laparoscopically diagnosed PID: sensitivity and specificity of signs and symptoms, likelihood ratios and post-test probabilities (pretest probability = 79%)</b></p>																																																																																								
	<table border="1"> <thead> <tr> <th rowspan="3">Signs and symptoms</th> <th rowspan="2">Sensitivity (%)</th> <th rowspan="2">Specificity (%)</th> <th colspan="2">Laparoscopically diagnosed PID</th> <th rowspan="2">Likelihood ratio* (Positive)</th> <th rowspan="2">Post-test probability</th> </tr> <tr> <th>Present (n=494)</th> <th>Absent (n=129)</th> </tr> <tr> <th>(95% CI)</th> <th>(95% CI)</th> <th>No (%)</th> <th>No (%)</th> </tr> </thead> <tbody> <tr> <td>Vaginal discharge</td> <td>74 (69.99–77.90)</td> <td>24 (16.95–32.34)</td> <td>366 (74)</td> <td>98 (76)</td> <td>0.98</td> <td>0.79</td> </tr> <tr> <td>Fever</td> <td>47 (42.49–51.47)</td> <td>64 (55.43–72.58)</td> <td>234 (47)</td> <td>47 (36)</td> <td>1.30</td> <td>0.83</td> </tr> <tr> <td>Vomiting</td> <td>14 (11.03–17.34)</td> <td>88 (81.55–93.34)</td> <td>68 (14)</td> <td>16 (12)</td> <td>1.11</td> <td>0.81</td> </tr> <tr> <td>Menstrual irregularity</td> <td>45 (40.49–49.45)</td> <td>57 (48.36–66.03)</td> <td>223 (45)</td> <td>56 (43)</td> <td>1.04</td> <td>0.80</td> </tr> <tr> <td>Ongoing bleeding</td> <td>25 (21.24–29.17)</td> <td>77 (68.49–83.73)</td> <td>124 (25)</td> <td>29 (22)</td> <td>1.12</td> <td>0.81</td> </tr> <tr> <td>Urinary symptoms</td> <td>35 (30.81–39.41)</td> <td>64 (55.43–72.58)</td> <td>173 (35)</td> <td>46 (36)</td> <td>0.98</td> <td>0.79</td> </tr> <tr> <td>Proctitis symptoms</td> <td>10 (7.43–12.90)</td> <td>92 (86.21–96.22)</td> <td>50 (10)</td> <td>10 (8)</td> <td>1.31</td> <td>0.83</td> </tr> <tr> <td>Tenderness of pelvic organs on bimanual examination</td> <td>99 (97.65–99.67)</td> <td>0.007 (&lt;0.001–2.84)</td> <td>489 (99)</td> <td>128 (99)</td> <td>1.00</td> <td>0.79</td> </tr> <tr> <td>Palpable adnexal mass or swelling</td> <td>52 (47.52–56.51)</td> <td>70 (61.06–77.54)</td> <td>258 (52)</td> <td>39 (30)</td> <td>1.73</td> <td>0.84</td> </tr> <tr> <td>Erythrocyte sedimentation rate ≥15mm in 1<sup>st</sup> hour</td> <td>81 (77.23–84.34)</td> <td>33 (25.28–42.17)</td> <td>402 (81)</td> <td>86 (66)</td> <td>1.22</td> <td>0.82</td> </tr> </tbody> </table>						Signs and symptoms	Sensitivity (%)	Specificity (%)	Laparoscopically diagnosed PID		Likelihood ratio* (Positive)	Post-test probability	Present (n=494)	Absent (n=129)	(95% CI)	(95% CI)	No (%)	No (%)	Vaginal discharge	74 (69.99–77.90)	24 (16.95–32.34)	366 (74)	98 (76)	0.98	0.79	Fever	47 (42.49–51.47)	64 (55.43–72.58)	234 (47)	47 (36)	1.30	0.83	Vomiting	14 (11.03–17.34)	88 (81.55–93.34)	68 (14)	16 (12)	1.11	0.81	Menstrual irregularity	45 (40.49–49.45)	57 (48.36–66.03)	223 (45)	56 (43)	1.04	0.80	Ongoing bleeding	25 (21.24–29.17)	77 (68.49–83.73)	124 (25)	29 (22)	1.12	0.81	Urinary symptoms	35 (30.81–39.41)	64 (55.43–72.58)	173 (35)	46 (36)	0.98	0.79	Proctitis symptoms	10 (7.43–12.90)	92 (86.21–96.22)	50 (10)	10 (8)	1.31	0.83	Tenderness of pelvic organs on bimanual examination	99 (97.65–99.67)	0.007 (<0.001–2.84)	489 (99)	128 (99)	1.00	0.79	Palpable adnexal mass or swelling	52 (47.52–56.51)	70 (61.06–77.54)	258 (52)	39 (30)	1.73	0.84	Erythrocyte sedimentation rate ≥15mm in 1 <sup>st</sup> hour	81 (77.23–84.34)	33 (25.28–42.17)	402 (81)	86 (66)	1.22	0.82
	Signs and symptoms	Sensitivity (%)	Specificity (%)	Laparoscopically diagnosed PID		Likelihood ratio* (Positive)				Post-test probability																																																																															
				Present (n=494)	Absent (n=129)																																																																																				
		(95% CI)	(95% CI)	No (%)	No (%)																																																																																				
	Vaginal discharge	74 (69.99–77.90)	24 (16.95–32.34)	366 (74)	98 (76)	0.98	0.79																																																																																		
	Fever	47 (42.49–51.47)	64 (55.43–72.58)	234 (47)	47 (36)	1.30	0.83																																																																																		
	Vomiting	14 (11.03–17.34)	88 (81.55–93.34)	68 (14)	16 (12)	1.11	0.81																																																																																		
	Menstrual irregularity	45 (40.49–49.45)	57 (48.36–66.03)	223 (45)	56 (43)	1.04	0.80																																																																																		
	Ongoing bleeding	25 (21.24–29.17)	77 (68.49–83.73)	124 (25)	29 (22)	1.12	0.81																																																																																		
	Urinary symptoms	35 (30.81–39.41)	64 (55.43–72.58)	173 (35)	46 (36)	0.98	0.79																																																																																		
Proctitis symptoms	10 (7.43–12.90)	92 (86.21–96.22)	50 (10)	10 (8)	1.31	0.83																																																																																			
Tenderness of pelvic organs on bimanual examination	99 (97.65–99.67)	0.007 (<0.001–2.84)	489 (99)	128 (99)	1.00	0.79																																																																																			
Palpable adnexal mass or swelling	52 (47.52–56.51)	70 (61.06–77.54)	258 (52)	39 (30)	1.73	0.84																																																																																			
Erythrocyte sedimentation rate ≥15mm in 1 <sup>st</sup> hour	81 (77.23–84.34)	33 (25.28–42.17)	402 (81)	86 (66)	1.22	0.82																																																																																			
<p>*Likelihood ratio interpretation: &gt;10 and &lt;0.1 (large difference between pretest and post-test probability), 5-10 and 0.1-0.2 (moderate), 2-5 and 0.5-0.2 (small), 1-2 and 0.05-1 (small and rarely important).</p>																																																																																									
<p>For detection of chlamydia only, four estimates for the accuracy of lower abdominal pain to detect chlamydia were available to pool. The pooled sensitivity for detecting chlamydia using a syndromic management approach (lower abdominal pain) is 48.0% (95% CI: 24.0–73.0), and pooled specificity is 61.7% (95% CI: 41.9–78.3).</p>																																																																																									
<p>For detection of trichomonas only, four estimates for the accuracy of lower abdominal pain to detect <i>Trichomonas</i> were available to pool. The pooled sensitivity for detecting <i>Trichomonas</i> using a syndromic management approach (lower abdominal pain) is 39.7% (95% CI: 19.6–63.9), and pooled specificity is 60.6% (95% CI: 41.0–77.4).</p>																																																																																									
<p><b>Other infections</b></p>																																																																																									
<p>About half of diagnosed pelvic inflammatory disease cases are caused by an STI such as chlamydia, gonorrhoea or <i>M. genitalium</i> infection (3). In the remaining cases, a specific cause is unclear, although pelvic inflammatory disease is polymicrobial (4). [Sharma 2014] There is evidence linking idiopathic pelvic inflammatory disease to vaginal microbiota dysbiosis, including recent bacterial vaginosis (a dysbiotic condition), and bacterial vaginosis organisms have been detected among women with pelvic inflammatory disease (5–7).</p>																																																																																									

	Judgement	Research evidence
Desirable effects	<p><b>How substantial are the desirable anticipated effects of syndromic approach?</b></p> <p> <input type="radio"/> Trivial  <input type="radio"/> Small  <input checked="" type="radio"/> Moderate  <input type="radio"/> Large  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	<p><b>Desirable effects</b></p> <p><b>Consequences of appropriate treatment (true positive)</b></p> <p>Immediate treatment of an acute pelvic inflammatory disease may avert adverse consequences such as chronic pelvic pain, ectopic pregnancy and infertility.</p> <p><b>Consequences of appropriate treatment (true negative)</b></p> <p>Alternative diagnoses possible Psychological benefit</p>
Undesirable effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <p> <input type="radio"/> Large  <input type="radio"/> Moderate  <input checked="" type="radio"/> Small  <input type="radio"/> Trivial  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	<p><b>Undesirable effects</b></p> <p><b>Consequences of missed cases (false negative)</b></p> <p>Onward transmission of STIs Cost of "wrong" treatment Vulnerability to HIV Pelvic inflammatory disease and its sequelae Loss of confidence in the health system if inappropriately managed Burden of STIs</p> <p><b>Consequences of unnecessary treatment (false positive)</b></p> <p>Cost of treatment (side-effects) Potential stigma or relationship strain Antimicrobial resistance (especially <i>N. gonorrhoeae</i>) Loss of confidence in the health system if inappropriately managed Delayed management of the true cause of disease</p> <p>When treatment is based on the syndromic approach, most women with pelvic inflammatory disease were identified with pelvic inflammatory disease, and there were few missed cases (8 of 1000 women with abdominal pain) compared with not assessing for pelvic inflammatory disease, although many women were overtreated.</p>
Certainty of the evidence of test accuracy	<p><b>What is the overall certainty of the evidence of test accuracy?</b></p> <p> <input type="radio"/> Very low  <input type="radio"/> Low  <input checked="" type="radio"/> Moderate  <input type="radio"/> High  <input type="radio"/> No included studies         </p>	
Certainty of the evidence of the effects of management	<p><b>What is the overall certainty of the evidence of effects of the management that is guided by the test results?</b></p> <p> <input type="radio"/> Very low  <input type="radio"/> Low  <input checked="" type="radio"/> Moderate  <input type="radio"/> High  <input type="radio"/> No included studies         </p>	<p>The evidence for management was based on current WHO recommendations for treating women with pelvic inflammatory disease.</p>



	Judgement	Research evidence
Certainty of effects	<p><b>What is the overall certainty of the evidence of effects of the test?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	
Values	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <p><input type="radio"/> Important uncertainty or variability</p> <p><input type="radio"/> Possibly important uncertainty or variability</p> <p><input checked="" type="radio"/> Probably no important uncertainty or variability</p> <p><input type="radio"/> No important uncertainty or variability</p>	<p>Higher value was placed on missing women with pelvic inflammatory disease based on the consequences of missing treatment for pelvic inflammatory disease (including damage to the reproductive tract). Value (although less) was placed on reducing the risk of onward transmission of STIs.</p> <p>Pelvic inflammatory disease after three years of follow-up: 18% infertility, 0.6% ectopic pregnancy, 29% chronic pelvic inflammatory disease (PEACH study (1))</p>
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favour the intervention or the comparison?</b></p> <p><input type="radio"/> Favours the comparison</p> <p><input type="radio"/> Probably favours the comparison</p> <p><input type="radio"/> Does not favour either the intervention or the comparison</p> <p><input type="radio"/> Probably favours the intervention</p> <p><input checked="" type="radio"/> Favours the intervention</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>There were few missed cases with a syndromic approach to lower abdominal pain, which was heavily valued. Although many women were treated unnecessarily, little value was placed on the overtreatment due to minimal side-effects.</p> <p>Therefore, assessing for pelvic inflammatory disease and managing syndromically was favoured over no treatment.</p>
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <p><input type="radio"/> Large costs</p> <p><input type="radio"/> Moderate costs</p> <p><input checked="" type="radio"/> Negligible costs and savings</p> <p><input type="radio"/> Moderate savings</p> <p><input type="radio"/> Large savings</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>We did not identify any published cost analysis related to lower abdominal pain syndrome.</p> <p>The average cost of pelvic inflammatory disease = £163 (range £96–960) (8).</p> <p>Average lifetime cost of pelvic inflammatory disease =US\$ 2400 (9).</p> <p>There was little difference in costs between treating all or not treating or assessing for pelvic inflammatory disease, although greater costs if molecular testing was used.</p>

	Judgement	Research evidence
Certainty of evidence of required resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	
Cost-effectiveness	<p><b>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Favours the comparison</li> <li><input type="radio"/> Probably favours the comparison</li> <li><input type="radio"/> Does not favour either the intervention or the comparison</li> <li><input type="radio"/> Probably favours the intervention</li> <li><input checked="" type="radio"/> Favours the intervention</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> No included studies</li> </ul>	<p>A pharmacist-managed syndromic intervention in Lima, Peru resulted in an estimated cost savings of US\$1.51 per case adequately managed using a societal perspective (10). This was primarily driven by the assumption that pharmacists will prescribe medications that are more effective and less costly compared with pharmacies in the control districts. However, this study did not truly have a societal perspective, only considering the medication cost but no other societal costs (includes women with vaginal discharge, lower abdominal pain – data not disaggregated for pelvic inflammatory disease syndrome).</p> <p>The Guideline Development Group agreed that, based on cost-effectiveness, assessing for pelvic inflammatory disease and managing syndromically is favoured rather than no assessment, treating all or molecular testing.</p>
Equity	<p><b>What would be the impact on health equity?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Reduced</li> <li><input type="radio"/> Probably reduced</li> <li><input checked="" type="radio"/> Probably no impact</li> <li><input type="radio"/> Probably increased</li> <li><input type="radio"/> Increased</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>We identified no studies.</p>
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> No</li> <li><input type="radio"/> Probably no</li> <li><input type="radio"/> Probably yes</li> <li><input checked="" type="radio"/> Yes</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p><b>Clinicians</b></p> <p>We found poor provider adherence to recommended guidelines for diagnosing pelvic inflammatory disease. For example, only 70% of women attending STI clinics in the United States of America (2010–2011) who were diagnosed as having pelvic inflammatory disease met the criteria for pelvic inflammatory disease in accordance with the guidelines of the United States Centers for Disease Control and Prevention (11).</p> <p><b>Patients</b></p> <p>We did not find any studies discussing the acceptability of syndromic management of lower abdominal pain.</p>

	Judgement	Research evidence
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>A randomized controlled trial of the feasibility and acceptability for pharmacy workers to recognize and manage STI syndromes was conducted in Lima, Peru (12). Standardized simulated patients visited the pharmacies in the control and intervention districts and found that pharmacy workers in the intervention districts were significantly better at recognizing and managing the STI syndromes (including pelvic inflammatory disease) – adequate for 61% of pharmacies in the intervention arm versus 19% in the control arm for pelvic inflammatory disease.</p> <p>However, the syndromic approach relies on the patient recognizing the symptoms (to seek consultation with a health-care provider) and the skill of the health-care provider in adequately managing a woman with lower abdominal pain.</p> <p>Pelvic inflammatory disease diagnosis such as laparoscopy, ultrasound and magnetic resonance imaging – not available in primary or secondary health care in resource -limited settings.</p>

## Summary of judgements

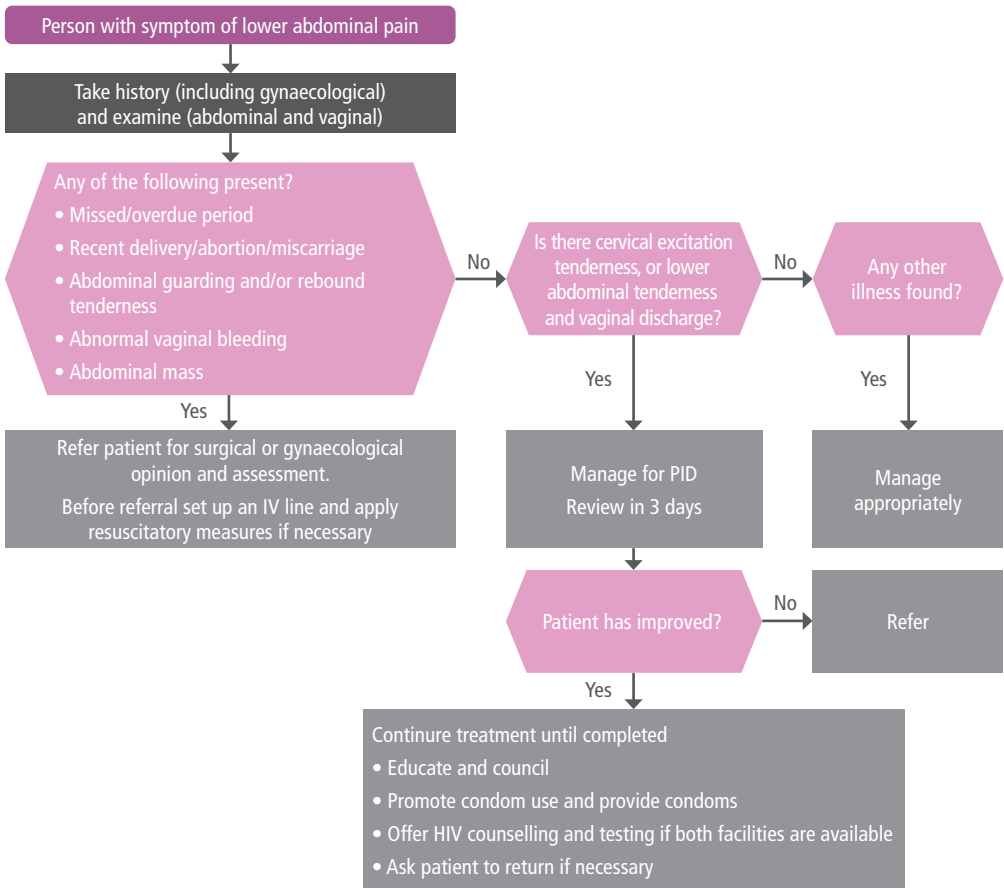
	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of the effects of management	Very low	Low	Moderate	High			No included studies
Certainty of effects	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

## Conclusions

### Should the current WHO syndromic management be recommended versus laboratory diagnosis, no treatment or treat all to identify pelvic inflammatory disease caused by STIs among women with lower abdominal pain?

Type of recommendation	○ Strong recommendation against the intervention	○ Conditional recommendation against the intervention	○ Conditional recommendation for either the intervention or the comparison	○ Conditional recommendation for the intervention	● Strong recommendation for the intervention
<b>Recommendation</b>	<p><b>Recommendations for management of women with lower abdominal pain</b></p> <p>For sexually active women with symptom of lower abdominal pain, we suggest assessing for pelvic inflammatory disease and treating syndromically.</p> <p>Good practice includes:</p> <ul style="list-style-type: none"> <li>• taking a medical and sexual history and assessing the risk of STIs;</li> <li>• performing a physical examination, including abdominal and pelvic examination, to assess for pelvic inflammatory disease, surgical conditions or pregnancy and vulvovaginal examination to visualize any lesions, overt genital discharge, vulval erythema and excoriations;</li> <li>• performing a bimanual digital examination of the vagina to (1) assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove; and</li> <li>• offering HIV and syphilis testing and other preventive services as recommended in other guidelines.</li> </ul> <p>For sexually active women with lower abdominal pain with either of the following features on clinical examination (bimanual palpation):</p> <ul style="list-style-type: none"> <li>• cervical motion tenderness; or</li> <li>• lower abdominal tenderness:</li> </ul> <p>We suggest the following.</p> <ol style="list-style-type: none"> <li>1. Treat for pelvic inflammatory disease on the same visit.</li> <li>2. Test for infection with <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> and, if available, <i>M. genitalium</i>, to support partner management when tests are available.</li> <li>3. Schedule follow-up assessment in three days to assess for clinical improvement, and if the woman has not improved, refer for further assessment.</li> </ol> <p>For women with lower abdominal pain with any of the following conditions, good practice includes referral to surgical or gynaecological assessment:</p> <ul style="list-style-type: none"> <li>• missed or overdue period;</li> <li>• recent delivery, abortion or miscarriage;</li> <li>• abdominal guarding and/or rebound tenderness;</li> <li>• abnormal vaginal bleeding in excess of spotting;</li> <li>• abdominal mass; and</li> <li>• detection of a suspected cervical lesion.</li> </ul>				
<b>Justification</b>	<p>Managing people presenting with lower abdominal pain based on a syndromic approach results in moderate benefits and little harm compared with treating all or no treatment. The syndromic approach would be feasible and acceptable and would not negatively affect equity (in some settings it may increase equity) and incur negligible costs.</p>				

**Fig. A5.1. Current WHO syndromic management guidelines for lower abdominal pain**



## References

1. Peipert JF, Ness RB, Blume J, Soper DE, Holley R, Randall H et al. Clinical predictors of endometritis in women with symptoms and signs of pelvic inflammatory disease. *Am J Obstet Gynecol.* 2001;184:856–63.
2. Eggert J, Sundquist K, van Vuuren C, Fianu-Jonasson A. The clinical diagnosis of pelvic inflammatory disease – reuse of electronic medical record data from 189 patients visiting a Swedish university hospital emergency department. *BMC Women’s Health.* 2006;6:16.
3. Goller JL, De Livera AM, Fairley CK, Guy RJ, Bradshaw CS, Chen MY et al. Population attributable fraction of pelvic inflammatory disease associated with chlamydia and gonorrhoea: a cross-sectional analysis of Australian sexual health clinic data. *Sex Transm Infect.* 2016;92:525–31.
4. Sharma H, Tal R, Clark NA, Segars JH. Microbiota and pelvic inflammatory disease. *Semin Reprod Med.* 2014;32:43–9.
5. Wang Y, Zhang Y, Zhang Q, Chen H, Feng Y. Characterization of pelvic and cervical microbiotas from patients with pelvic inflammatory disease. *J Med Microbiol.* 2018;67:1519–26.
6. Ness RB, Hillier SL, Kip KE, Soper DE, Stamm CA, McGregor JA et al. Bacterial vaginosis and risk of pelvic inflammatory disease. *Obstet Gynecol.* 2004;104:761–9.
7. Ness RB, Kip KE, Hillier SL, Soper DE, Stamm CA, Sweet RL et al. A cluster analysis of bacterial vaginosis–associated microflora and pelvic inflammatory disease. *Am J Epidemiol.* 2005;162:585–90.
8. Aghaizu A, Adams EJ, Turner K, Kerry S, Hay P, Simms I et al. What is the cost of pelvic inflammatory disease and how much could be prevented by screening for *Chlamydia trachomatis*? Cost analysis of the Prevention of Pelvic Infection (POPI) trial. *Sex Transm Infect.* 2011;87:312–7.
9. Yeh JM, Hook EW 3rd, Goldie SJ. A refined estimate of the average lifetime cost of pelvic inflammatory disease. *Sex Transm Dis.* 2003;30:369–78.
10. Adams EJ, Garcia PJ, Garnett GP, Edmunds WJ, Holmes KK. The cost–effectiveness of syndromic management in pharmacies in Lima, Peru. *Sex Transm Dis.* 2003;30:379–87.
11. Llata E, Bernstein KT, Kerani RP, Pathela P, Schwebke JR, Schumacher C et al. Management of pelvic inflammatory disease in selected U.S. sexually transmitted disease clinics: Sexually Transmitted Disease Surveillance Network, January 2010–December 2011. *Sex Transm Dis.* 2015;42:429–33.
12. Garcia P, Hughes J, Carcamo C, Holmes KK. Training pharmacy workers in recognition, management and prevention of, STDs: district-randomized controlled trial. *Bull World Health Organ.* 2003;81:806–14.

13. Wilkinson D, Sturm AW. Value of clinical algorithms to screen for gonococcal and chlamydial infection among women attending antenatal and family planning clinics. *S Afr Med J*. 1998;88(7 Suppl. 1):900–5.
14. Alary M, Laga M, Vuylsteke B, Nzila N, Piot P. Signs and symptoms of prevalent and incident cases of gonorrhoea and genital chlamydial infection among female prostitutes in Kinshasa, Zaire. *Clin Infect Dis*. 1996;22:477–84.
15. Meda N, Sangaré L, Lankoandé S, Sanou PT, Compaoré PI, Catraye J et al. Pattern of sexually transmitted diseases among pregnant women in Burkina Faso, west Africa: potential for a clinical management based on simple approaches. *Genitourin Med*. 1997;73:188–93.
16. Piper JM, Korte JE, Holden AE, Shain RN, Perdue S, Champion JD, Newton ER. Development of composite symptom variables for quantitative analysis of genitourinary symptomatology in women. *Int J STD AIDS*. 2005;16:128–32.
17. Vallely LM, Toliman P, Ryan C, Rai G, Wapling J, Gabuzzi J et al. Performance of syndromic management for the detection and treatment of genital *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study. *BMJ Open*. 2017;7:e018630.
18. Wiesenfeld HC, Hillier SL, Krohn MA, Amortegui AJ, Heine RP, Landers DV et al. Lower genital tract infection and endometritis: insight into subclinical pelvic inflammatory disease. *Obstet Gynecol*. 2002;100:456–63.
19. Woods JL, Scurlock AM, Hensel DJ. Pelvic inflammatory disease in the adolescent: understanding diagnosis and treatment as a health care provider. *Pediatr Emerg Care*. 2013;29:720–5.
20. Cohen CR, Manhart LE, Bukusi EA, Astete S, Brunham RC, Holmes KK et al. Association between *Mycoplasma genitalium* and acute endometritis. *Lancet*. 2002;359:765–6.
21. Grió R, Latino MA, Leotta E, Smirne C, Lanza A, Spagnolo E et al. Sexually transmitted diseases and pelvic inflammatory disease. *Minerva Ginecolog*. 2004;56:141–7.



**Table A5.1. Detection of any STIs for lower abdominal pain syndrome**

Algorithm	Year of study	Country	Country income level	Sample size	Where recruited	Sub-population	How a positive case is defined	Pathogen, diagnostic	True positive	False negative	False positive	True negative
Wilkinson & Sturm (13)	1998	South Africa	Upper middle	268	Antenatal clinic	100% pregnant women	Symptoms only	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> <i>C. trachomatis</i> = direct immunofluorescence <i>N. gonorrhoeae</i> = culture	13	38	48	170
Wilkinson & Sturm (13)	1998	South Africa	Upper middle	190	Family planning clinic	100% women	Symptoms only	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> <i>C. trachomatis</i> = direct immunofluorescence <i>N. gonorrhoeae</i> = culture	3	18	5	163
Alary et al. (14)	1988–1991	Zaire	Low	771	Unclear	100% female sex workers	Symptoms only	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> <i>C. trachomatis</i> = enzyme immunoassay <i>N. gonorrhoeae</i> = culture	100	125	217	329
Meda et al. (15)	1994	Burkina Faso	Low	397	Antenatal care	100% pregnant women	Symptoms only	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> <i>C. trachomatis</i> = enzyme immunoassay <i>N. gonorrhoeae</i> = culture	8	22	113	254
Piper et al. (16)	Unclear	United States	High	518	Public health clinic	100% ethnic minority women	Symptoms only	<i>C. trachomatis</i> , and <i>N. gonorrhoeae</i> and <i>T. vaginalis</i> <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> = NAAT (GenProbe) <i>T. vaginalis</i> = culture	106	279	20	113
Valley et al. (17)	2011–2015	Papua New Guinea	Lower middle	765	Antenatal clinic	100% pregnant women	Symptoms only	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> and <i>T. vaginalis</i> NAAT	60	267	106	332
Valley et al. (17)	2011–2015	Papua New Guinea	Lower middle	614	Well-woman clinic	100% women	Symptoms only	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> and <i>T. vaginalis</i> NAAT	46	108	154	306
Valley et al. (17)	2011–2015	Papua New Guinea	Lower middle	385	Sexual health clinic	100% women	Symptoms only	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> and <i>T. vaginalis</i> NAAT	109	36	173	67

**Table A5.2. Detection of gonorrhoea for lower abdominal pain syndrome**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostic	True positive	False negative	False positive	True negative
Wiesenfeld et al. (18)	1998–2000	United States	High	427	Hospital, sexual health clinic, ambulatory care sites	Excluded acute pelvic inflammatory disease	Subclinical pelvic inflammatory disease (endometrial biopsy)	Culture	15	26	57	329
Woods et al (19)	2013	United States	High	150	General practice, emergency department	100% diagnosed with pelvic inflammatory disease	Pelvic inflammatory disease diagnosis according to ICD criteria (symptoms + examination)	Unclear	19	6	98	27
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	765	Antenatal clinic	100% pregnant women	Symptoms only	PCR	15	94	151	505
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	614	Well-woman clinic	100% women	Symptoms only	PCR	15	34	185	380
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	385	Sexual health clinic	100% women	Symptoms only	PCR	46	17	236	86
Cohen et al. (20)	Unclear	Kenya	Lower middle	115	Sexual health clinic	100% had pelvic pain (14 days or less)	Endometritis (endometrial biopsy)	PCR	9	4	49	53

**Table A5.3. Detection of chlamydia for lower abdominal pain syndrome**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostic	True positive	False negative	False positive	True negative
Wiesenfeld et al. (18)	1998–2000	United States	High	403	Hospital, sexual health clinic, ambulatory care sites	Excluded acute pelvic inflammatory disease	Subclinical pelvic inflammatory disease (endometrial biopsy)	PCR	27	44	46	286
Woods et al. (19)	2013	United States	High	150	General practice, emergency department	100% diagnosed with pelvic inflammatory disease	Pelvic inflammatory disease diagnosis according to ICD criteria (symptoms + examination)	Unclear	31	14	86	19
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	765	Antenatal clinic	100% pregnant women	Symptoms only	PCR	30	145	136	454
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	614	Well-woman clinic	100% women	Symptoms only	PCR	19	27	181	387
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	385	Sexual health clinic	100% women	Symptoms only	PCR	62	16	220	87
Cohen et al. (20)	Unclear	Kenya	Lower middle	115	Sexual health clinic	100% had pelvic pain (14 days or less)	Pelvic inflammatory disease (endometrial biopsy)		4	2	54	55
Griro et al. (21)	1997–2001	Italy	High	5026	Hospital		Symptomatic for pelvic inflammatory disease	LCR using Abbot LCx system	49	38	1505	3434

**Table A5.4. Detection of trichomoniasis for lower abdominal pain syndrome**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostic	True positive	False negative	False positive	True negative
Wiesenfeld et al. (18)	1998–2000	United States	High	428	Hospital, sexual health clinic, ambulatory care sites	Excluded acute pelvic inflammatory disease Women 15–30 years old	Subclinical pelvic inflammatory disease (endometrial biopsy)	Culture	14	35	60	319
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	765	Antenatal clinic	100% pregnant women	Symptoms only		29	142	137	457
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	614	Well-woman clinic	100% women	Symptoms only		24	68	176	346
Vallely et al. (17)	2011–2015	Papua New Guinea	Lower middle	385	Sexual health clinic	100% women	Symptoms only		40	14	242	89
Griro et al. (21)	1997–2001	Italy	High	5516	Hospital	100% women	Symptomatic for pelvic inflammatory disease	LCR using Abbot LCx system	23	22	1697	3774

## ANNEX 6. EVIDENCE-TO-DECISION TABLE: GENITAL ULCER DISEASE

Should current WHO syndromic management be recommended versus laboratory diagnosis, no treatment or treat all to identify sexually transmitted infections among people with anogenital ulcers?

### Population:

Individuals presenting with anogenital ulcers

### Intervention and comparator:

Intervention: syndromic management approach versus comparison: laboratory diagnosis (or no treatment or treat all)

### Purpose of the approach:

To identify individuals for treatment of STIs

### Linked treatments:

Treatments for infections caused by genital herpes simplex virus, *Treponema pallidum* (syphilis), lymphogranuloma venereum and *Hemophilus ducreyi* (chancroid)

### Anticipated outcomes:

Number of people identified correctly as having or not having STI; number of people identified incorrectly as having or not having STI; consequences of appropriate or inappropriate treatment; patient and provider acceptability; and feasibility, equity and resource use

### Setting:

Outpatient

### Perspective:

Population level

### Subgroups:

High- or low-prevalence settings; settings with limited versus established laboratory capacity

### Background:

Syndromic management refers to a strategy for identifying and treating STIs based on specific syndromes (symptoms identified by a patient) and signs (clinically observed signs of infection) associated with clearly defined causes. Although etiological diagnosis is preferred, it is not always accessible or affordable.

Fig. A6.1 provides clinical guidelines for the syndromic management of genital ulcer syndrome in the 2003 guidelines for the management of sexually transmitted infections (1).

The Guideline Development Group agreed to update this approach for anogenital ulcers; ulcers are a break in the skin or mucosa and may present as ulcers, sores, or vesicles. Genital ulcers refer to those located on the genital or anorectal areas and may be painful or painless.

## Assessment

	Judgement	Research evidence	Additional considerations
Problem	<p><b>Is the problem a priority?</b></p> <p> <input type="radio"/> No  <input type="radio"/> Probably no  <input type="radio"/> Probably yes  <input checked="" type="radio"/> Yes  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	<p>STIs are important because of their magnitude, potential complications and increased risk of HIV. STIs have health, social and economic consequences. The consequences of STIs (such as HSV and syphilis) disproportionately affect women and newborn children. For example, women acquiring primary HSV in the third trimester of pregnancy may result in congenital herpes, leading to neurocognitive problems, developmental delays or death of infants. Congenital syphilis can also cause serious morbidity or death among infants.</p> <p>Presentation of genital ulcer disease is a major challenge for clinicians to distinguish STI-related versus non-STI-related causes. Many individuals keep having sex even in the presence of a genital ulcer. It has been proposed that timely diagnosis of STIs could reduce HIV incidence.</p> <p><b>High cost of molecular STI testing</b></p> <p>Molecular based tests enable etiological diagnosis to guide appropriate treatment (such as multiplex PCR test for HSV and syphilis) but are expensive and not available in many settings.</p>	
Test accuracy	<p><b>How accurate is the test?</b></p> <p> <input type="radio"/> Very inaccurate  <input checked="" type="radio"/> Inaccurate  <input type="radio"/> Accurate  <input type="radio"/> Very accurate  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	<p>We conducted a systematic review (2–4), searching up to September 2019, of the sensitivity and specificity of a syndromic management approach to identify multiple STIs related to anogenital ulcers. In summary, we identified four articles that assessed the diagnostic accuracy of the clinical diagnosis of a pathogen causing genital ulcer disease to detect any STI (Table A6.1), 15 studies for herpes (Table A6.2), 15 studies for syphilis (Table A6.3) and 13 studies for chancroid (Table A6.4). We found no studies on detecting lymphogranuloma venereum.</p> <p>For detecting herpes from a clinical diagnosis of herpes, 15 studies provided 20 estimates for pooling. The pooled sensitivity for detecting herpes using a syndromic management approach is 40.4% (95% CI: 23.0–60.6%), and pooled specificity is 88.0% (95% CI: 75.3–94.6%).</p> <p><b>For detection of syphilis</b> using clinical diagnosis of syphilis among individuals with genital ulcer disease, 15 studies provided 22 estimates for pooling. The pooled sensitivity for detecting syphilis is 64.4% (95% CI: 44.8–80.2%) and pooled specificity 83.7% (95% CI: 67.0–92.9%).</p> <p>The global distribution, incidence and prevalence of causal agents of genital ulcer disease varies widely by geographical region and population subgroup. This is important, since the positive and negative predictive values depend on the prevalence of pathogens.</p> <p><b>Other considerations related to the accuracy of tests</b></p> <p>We found that the accuracy of the syndromic approach depends on clinician skill and experience, clinical setting (STI centre versus primary care) and patient characteristics (membership of subpopulation(s)).</p> <p>The positive and negative predictive values may be worse among non-STI clinic attendees (because of lower prevalence of STIs among "general populations") (24).</p> <p>No difference in causal agents for genital ulcer disease between people living with HIV and those without HIV (12).</p>	

	Judgement	Research evidence	Additional considerations																								
Desirable effects	<p><b>How substantial are the desirable anticipated effects of syndromic approach?</b></p> <p>○ Trivial</p> <p>● Small</p> <p>○ Moderate</p> <p>○ Large</p> <p>○ Varies</p> <p>○ Don't know</p>	<p><b>Desirable effects and undesirable effects</b></p> <p>The potential consequences of true positive could include appropriate treatment, cure, side-effects, partner notification, reduced transmission of STIs and HIV, resistance, couple difficulties and costs.</p> <p>The potential consequences of true negative could include alternative diagnoses possible and psychological benefit.</p> <p>The potential consequences of false negative could include cure still possible, persistent symptoms, complications, STI and/or HIV transmission, no counselling and no partner notification.</p> <p>The potential consequences of false positive could include inappropriate treatment, side-effects, antimicrobial resistance, couple difficulties and costs.</p> <p><b>GRADE summary of findings table for clinical diagnosis and HSV</b></p> <p>Based on the sensitivity and specificity of clinical diagnosis of STIs, we calculated the number of people appropriately treated (true positive), the number of missed cases (false negative) and the number of people treated unnecessarily or overtreated (false positive).</p>	<p>The Guideline Development Group agreed that the desirable effects of syndromic management (few unnecessarily treated) were small compared with treating all.</p> <p>The Guideline Development Group also agreed that the undesirable effects (number of missed cases) were moderate compared with treating all in particular for syphilis (due to the consequences of transmission).</p> <p>Overtreatment may be acceptable if high morbidity and mortality from undetected cases requires controlling the STI in the population (such as syphilis).</p>																								
	<p><b>Treatment of people with HSV based on a clinical diagnosis</b></p> <p>Pooled sensitivity: 0.40 (95% CI: 0.23 to 0.61)   Pooled specificity: 0.88 (95% CI: 0.75 to 0.95)</p> <table border="1"> <thead> <tr> <th rowspan="2">Test result</th> <th colspan="2">Number of results per 100 patients tested (95% CI)</th> <th rowspan="2">Number of participants (studies)</th> <th rowspan="2">Certainty of the Evidence (GRADE)</th> </tr> <tr> <th>Prevalence 30% Typically seen in</th> <th>Prevalence 70% Typically seen in</th> </tr> </thead> <tbody> <tr> <td>True positives</td> <td>12 (7 to 18)</td> <td>28 (16 to 42)</td> <td rowspan="2">2667 (15)</td> <td>⊕⊕⊕⊕</td> </tr> <tr> <td>False negatives</td> <td>18 (12 to 23)</td> <td>42 (28 to 54)</td> <td>High<sup>a</sup></td> </tr> <tr> <td>True negatives</td> <td>62 (53 to 66)</td> <td>26 (23 to 28)</td> <td rowspan="2">2667 (15)</td> <td>⊕⊕⊕⊕</td> </tr> <tr> <td>False positives</td> <td>8 (4 to 17)</td> <td>4 (2 to 7)</td> <td>High<sup>a</sup></td> </tr> </tbody> </table> <p>CI: Confidence interval</p> <p><b>Explanations</b></p> <p><sup>a</sup> Some heterogeneity but confidence intervals not wide.</p>	Test result	Number of results per 100 patients tested (95% CI)		Number of participants (studies)	Certainty of the Evidence (GRADE)	Prevalence 30% Typically seen in	Prevalence 70% Typically seen in	True positives	12 (7 to 18)	28 (16 to 42)	2667 (15)	⊕⊕⊕⊕	False negatives	18 (12 to 23)	42 (28 to 54)	High <sup>a</sup>	True negatives	62 (53 to 66)	26 (23 to 28)	2667 (15)	⊕⊕⊕⊕	False positives	8 (4 to 17)	4 (2 to 7)	High <sup>a</sup>	<p>However, there is still a risk of unnecessary treatment and potential for STI-related stigma due to low specificity of syndromic management.</p> <p>Underdiagnosis of herpes may not be a problem (except for pregnant women) since adequate treatment with antiviral agents may not be easily accessible or too expensive in resource-limited settings.</p>
Test result	Number of results per 100 patients tested (95% CI)		Number of participants (studies)	Certainty of the Evidence (GRADE)																							
	Prevalence 30% Typically seen in	Prevalence 70% Typically seen in																									
True positives	12 (7 to 18)	28 (16 to 42)	2667 (15)	⊕⊕⊕⊕																							
False negatives	18 (12 to 23)	42 (28 to 54)		High <sup>a</sup>																							
True negatives	62 (53 to 66)	26 (23 to 28)	2667 (15)	⊕⊕⊕⊕																							
False positives	8 (4 to 17)	4 (2 to 7)		High <sup>a</sup>																							
	<p><b>GRADE summary of findings table for clinical diagnosis and syphilis</b></p> <p><b>Treatment of people with syphilis based on a clinical diagnosis</b></p> <p>Pooled sensitivity: 0.64 (95% CI: 0.45 to 0.80)   Pooled specificity: 0.84 (95% CI: 0.67 to 0.93)</p> <table border="1"> <thead> <tr> <th rowspan="2">Test result</th> <th colspan="2">Number of results per 100 patients tested (95% CI)</th> <th rowspan="2">Number of participants (studies)</th> <th rowspan="2">Certainty of the Evidence (GRADE)</th> </tr> <tr> <th>Prevalence 5% Typically seen in</th> <th>Prevalence 10% Typically seen in</th> </tr> </thead> <tbody> <tr> <td>True positives</td> <td>3 (2 to 4)</td> <td>6 (4 to 8)</td> <td rowspan="2">2667 (15)</td> <td>⊕⊕⊕○</td> </tr> <tr> <td>False negatives</td> <td>2 (1 to 3)</td> <td>4 (2 to 6)</td> <td>Moderate<sup>a</sup></td> </tr> <tr> <td>True negatives</td> <td>80 (64 to 88)</td> <td>75 (60 to 84)</td> <td rowspan="2">2667 (15)</td> <td>⊕⊕⊕○</td> </tr> <tr> <td>False positives</td> <td>15 (7 to 31)</td> <td>15 (6 to 30)</td> <td>Moderate<sup>a</sup></td> </tr> </tbody> </table> <p>CI: Confidence interval</p> <p><b>Explanations</b></p> <p><sup>a</sup> Estimates from studies varied widely, meaning wide confidence intervals and then absolute effects.</p>	Test result	Number of results per 100 patients tested (95% CI)		Number of participants (studies)	Certainty of the Evidence (GRADE)	Prevalence 5% Typically seen in	Prevalence 10% Typically seen in	True positives	3 (2 to 4)	6 (4 to 8)	2667 (15)	⊕⊕⊕○	False negatives	2 (1 to 3)	4 (2 to 6)	Moderate <sup>a</sup>	True negatives	80 (64 to 88)	75 (60 to 84)	2667 (15)	⊕⊕⊕○	False positives	15 (7 to 31)	15 (6 to 30)	Moderate <sup>a</sup>	
Test result	Number of results per 100 patients tested (95% CI)		Number of participants (studies)	Certainty of the Evidence (GRADE)																							
	Prevalence 5% Typically seen in	Prevalence 10% Typically seen in																									
True positives	3 (2 to 4)	6 (4 to 8)	2667 (15)	⊕⊕⊕○																							
False negatives	2 (1 to 3)	4 (2 to 6)		Moderate <sup>a</sup>																							
True negatives	80 (64 to 88)	75 (60 to 84)	2667 (15)	⊕⊕⊕○																							
False positives	15 (7 to 31)	15 (6 to 30)		Moderate <sup>a</sup>																							

	Judgement	Research evidence	Additional considerations
Desirable effects		<p><b>Prevalence of chancroid</b></p> <p>Chancroid</p> <p>A: Master B: Low income C: Middle income D: High income</p>	<p>There is a potential for the loss of confidence in the health system if genital ulcer disease is inappropriately managed.</p> <p>There is a lower likelihood of antimicrobial resistance with syphilis and HSV.</p>
Undesirable effects	<p><b>How substantial are the undesirable anticipated effects?</b></p> <p><input type="radio"/> Large</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> Small</p> <p><input type="radio"/> Trivial</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>Same-day treatment</b></p> <p>Prompt treatment (within 72 hours after genital lesions appear) of HSV with antiviral agents can reduce genital viral shedding and the duration of ulcers by 1–4 days (25–27).</p> <p><b>Considerations for the certainty of the evidence of accuracy</b></p> <p>Reference laboratory tests are not always equivalent in studies included in the meta-analysis.</p> <p>Clinical diagnosis can be highly variable between and within countries and settings since it depends on the skill of the clinician: previous experience, knowledge of risk factors and the prevalence of the pathogen (13).</p>	
Certainty of the evidence of test accuracy	<p><b>What is the overall certainty of the evidence of test accuracy?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>Global distribution and the incidence and prevalence of causal agents of genital ulcer disease vary widely by geographical region and population subgroup. This is important as the positive and negative predictive values depend on the prevalence of the pathogens.</p> <p>Studies relying on HSV and syphilis serology as the reference may overestimate positivity since they may not distinguish current infection (as the cause of the genital ulcer disease) or past treated infection.</p> <p>Untested pathogens could be a cause of anogenital ulceration, although they are less common, such as <i>C. trachomatis</i> lymphogranuloma venereum, <i>Haemophilus ducreyi</i> and <i>Candida glabrata</i>.</p> <p>All studies were convenience samples, and none had a truly random sample, so generalizing the results is difficult. Most were recruited from sexual health clinics, biasing the sample. Similarly, since the studies were cross-sectional, we were unable to assess temporal association between symptoms and STIs.</p>	
Certainty of the evidence of the effects of management	<p><b>What is the overall certainty of the evidence of effects of the management that is guided by the test results?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>The evidence for management was based on current WHO recommendations for treating women with pelvic inflammatory disease.</p>	



	Judgement	Research evidence	Additional considerations
Certainty of effects	<p><b>What is the overall certainty of the evidence of effects of the test?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>		
Values	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <p><input type="radio"/> Important uncertainty or variability</p> <p><input type="radio"/> Possibly important uncertainty or variability</p> <p><input checked="" type="radio"/> Probably no important uncertainty or variability</p> <p><input type="radio"/> No important uncertainty or variability</p>	The Guideline Development Group placed greater value on not missing cases than on unnecessary treatment.	
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favour the intervention or the comparison?</b></p> <p><input checked="" type="radio"/> Favours the comparison</p> <p><input type="radio"/> Probably favours the comparison</p> <p><input type="radio"/> Does not favour either the intervention or the comparison</p> <p><input type="radio"/> Probably favours the intervention</p> <p><input type="radio"/> Favours the intervention</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	Treating all was favoured since there were no missed cases in people presenting with ulcers, and there was little value placed on unnecessarily treating people.	

	Judgement	Research evidence	Additional considerations																																							
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Large costs</li> <li><input type="radio"/> Moderate costs</li> <li><input checked="" type="radio"/> Negligible costs and savings</li> <li><input type="radio"/> Moderate savings</li> <li><input type="radio"/> Large savings</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> Don't know</li> </ul>	<p>Need for better training for nurses working in primary health care settings in Botswana (28).</p> <p>Etiological diagnosis requires training, infrastructure, time and money.</p>																																								
Certainty of evidence of required resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <ul style="list-style-type: none"> <li><input type="radio"/> Very low</li> <li><input type="radio"/> Low</li> <li><input type="radio"/> Moderate</li> <li><input type="radio"/> High</li> <li><input checked="" type="radio"/> No included studies</li> </ul>	<p>Korenromp (29) reported the unit cost of treatment.</p> <table border="1" data-bbox="364 615 1084 875"> <thead> <tr> <th>STI or syndrome</th> <th>Treatment dose per day</th> <th>Drugs, per dose</th> <th>Treatment duration (days)</th> <th>Drugs per treatment</th> <th>Drugs + service delivery</th> </tr> </thead> <tbody> <tr> <td>Herpes</td> <td>Acyclovir 400 mg</td> <td>3</td> <td>7</td> <td>US\$ 0.04</td> <td>US\$ 11.05</td> </tr> <tr> <td>Syphilis</td> <td>Benzathine PCN 2.4 M</td> <td>1</td> <td>1</td> <td>US\$ 0.44</td> <td>US\$ 11.65</td> </tr> <tr> <td>Chancroid</td> <td>Azithromycin 500 mg</td> <td>2</td> <td>1</td> <td>US\$ 0.38</td> <td>US\$ 10.95</td> </tr> </tbody> </table> <table border="1" data-bbox="364 906 1084 1051"> <thead> <tr> <th>STI</th> <th>Test</th> <th>Cost</th> <th>Service delivery</th> <th>Total</th> </tr> </thead> <tbody> <tr> <td>Syphilis, herpes, chancroid</td> <td>mPCR</td> <td>??</td> <td>??</td> <td></td> </tr> <tr> <td>Syphilis</td> <td>Rapid test</td> <td>US\$ 0.50</td> <td>US\$ 3.00</td> <td>US\$ 3.50</td> </tr> </tbody> </table>	STI or syndrome	Treatment dose per day	Drugs, per dose	Treatment duration (days)	Drugs per treatment	Drugs + service delivery	Herpes	Acyclovir 400 mg	3	7	US\$ 0.04	US\$ 11.05	Syphilis	Benzathine PCN 2.4 M	1	1	US\$ 0.44	US\$ 11.65	Chancroid	Azithromycin 500 mg	2	1	US\$ 0.38	US\$ 10.95	STI	Test	Cost	Service delivery	Total	Syphilis, herpes, chancroid	mPCR	??	??		Syphilis	Rapid test	US\$ 0.50	US\$ 3.00	US\$ 3.50	
STI or syndrome	Treatment dose per day	Drugs, per dose	Treatment duration (days)	Drugs per treatment	Drugs + service delivery																																					
Herpes	Acyclovir 400 mg	3	7	US\$ 0.04	US\$ 11.05																																					
Syphilis	Benzathine PCN 2.4 M	1	1	US\$ 0.44	US\$ 11.65																																					
Chancroid	Azithromycin 500 mg	2	1	US\$ 0.38	US\$ 10.95																																					
STI	Test	Cost	Service delivery	Total																																						
Syphilis, herpes, chancroid	mPCR	??	??																																							
Syphilis	Rapid test	US\$ 0.50	US\$ 3.00	US\$ 3.50																																						
Cost-effectiveness	<p><b>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</b></p> <ul style="list-style-type: none"> <li><input checked="" type="radio"/> Favours the comparison</li> <li><input type="radio"/> Probably favours the comparison</li> <li><input type="radio"/> Does not favour either the intervention or the comparison</li> <li><input type="radio"/> Probably favours the intervention</li> <li><input type="radio"/> Favours the intervention</li> <li><input type="radio"/> Varies</li> <li><input type="radio"/> No included studies</li> </ul>	<p>Overall, the Guideline Development Group agreed that, although there are few differences between the costs of treating all, not treating and syndromic management, the costs of more cases missed with syndromic management made treating all the more cost-effective.</p> <p>Adams et al. (30) examined the cost-effectiveness of syndromic management (including genital ulcer disease) in pharmacies in Lima, Peru. They reported an overall cost saving of US\$ 1.51 per adequately managed case, from a societal perspective.</p> <p>The mean cost per syphilis treated for syndromic management of genital ulcer disease cases in China was US\$ 13.54 in 2003 (6).</p> <p>Cost-effectiveness analysis in Cambodia: cost per genital ulcer disease case = US\$ 43.21 (USD, 2002) for men from the general population, US\$ 43.56 for women from the general population and US\$ 44.05 for female sex workers.</p> <p>US\$ 10.15 per syndrome treated in the United Republic of Tanzania (in 1993) – no disaggregated data for genital ulcer disease (31).</p> <p>The average cost per STI treated in a primary care setting in the Central African Republic (including 7% with genital ulcer disease) was US\$ 3.90 (in 1993) (32).</p> <p>China, Taiwan: US\$ 14.30 (in 2005) for the cost of correctly treating syphilis using a syndromic approach versus US\$ 21.58 for an etiological approach (33). The authors conclude that, in Taiwan, China, syndromic management was more cost-effective than etiological diagnosis in terms of cost per person with STI treated (health-care provider perspective).</p>																																								

	Judgement	Research evidence	Additional considerations
Cost-effectiveness		<p>A modelling study to evaluate the incremental cost-effectiveness ratio of the WHO 2003 genital ulcer disease algorithm versus the 1994 genital ulcer disease algorithm reports that the incremental cost-effectiveness ratio for treating HSV-2 ranged from US\$ 0.50 to US\$ 8.50 depending on the prevalence of genital ulcer disease causes (<i>Haemophilus ducreyi</i>, true positive, HSV-2) (34).</p> <p>Syndromic management is likely to be cost-saving in rural South Africa, considering its potential impact on reducing HIV incidence (35).</p> <p>In Côte d'Ivoire, the mean drug cost per cure = US\$ 4.50 (in 1994) and mean direct cost per cure = US\$ 4.90 (36).</p>	
Equity	<p><b>What would be the impact on health equity?</b></p> <p><input type="radio"/> Reduced</p> <p><input type="radio"/> Probably reduced</p> <p><input checked="" type="radio"/> Probably no impact</p> <p><input type="radio"/> Probably increased</p> <p><input type="radio"/> Increased</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>The cost of antiviral agents might be prohibitive for some people or in some settings. The cost of STI management – including consultation, drugs and tests – might also be prohibitively high for some subpopulations.</p> <p>Partner notification processes in resource-limited settings are poorly described and largely non-existent.</p>	<p>Diagnostic test for ulcers (such as M-PCR) are costly, technically sophisticated, time-consuming and thus rarely affordable, available or accessible in resource-limited settings.</p> <p>If a diagnostic is used, the patient might need to return to discuss the results.</p>
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input checked="" type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>Clinicians</b></p> <p>Pharmacy and clinicians offered syndromic management in Peru – community randomized controlled trial (37).</p> <p>More than 90% of 100 clinicians from Pakistan were willing to attend educational sessions and follow the national STI treatment protocols (38).</p> <p>Concerns about how general practitioners treat people with genital ulcer disease in Namibia (39).</p> <p>Difficulties in providing syndromic STI management noted among health-care providers (doctors and midwives) in Karachi (40).</p> <p><b>Patients</b></p> <p>83% of patients in the United Republic of Tanzania reported satisfaction with STI services using syndromic management (41).</p> <p>For algorithms that required follow-up (such as that in Rwanda) (42), 50% failed to return for follow-up.</p>	<p>May be difficulties from health-care providers in communicating or discussing sensitive issues related to sex.</p> <p>Symptomatic patients may not disclose their symptoms for a variety of reasons (fear of stigma, lack of access, etc...)</p> <p>Immediate relief of symptoms may be preferred rather than waiting for test results</p>

	Judgement	Research evidence	Additional considerations
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input checked="" type="radio"/> Probably yes</p> <p><input type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>Etiological diagnosis requires skilled personnel and sophisticated equipment and is expensive and time-consuming.</p> <p><b>Successful use of syndromic management</b></p> <p>Syndromic management for genital ulcer disease has been implemented in many resource-limited settings with variable success: Ethiopia (43,44), Kenya (24,45), Malawi (46,47), Peru (23), United Republic of Tanzania (48), Peru (49), India (50–53), United Republic of Tanzania (41), Zambia (22), Namibia (39), China (6), Malawi (54), Zimbabwe (55), Karachi (40), South Africa (25,56–59), Bangladesh (53), Burkina Faso (54), Brazil (60), Central African Republic (32), Rwanda (42), Côte d'Ivoire (36), Swaziland (61), Gambia (62) and Mozambique (63).</p> <p>Standardized simulated patients visited pharmacies in the United Republic of Tanzania but found challenges for pharmacies to adequately manage genital ulcer disease syndromes (48). Pharmacy staff in Gambia were willing to offer syndromic management, but none of the simulated patients with genital ulcer disease would be treated appropriately (64).</p> <p>Rural clinics in South Africa – only 9% were correctly managed using a syndromic management approach (no disaggregated data for genital ulcer disease) (65).</p> <p>A survey of 43 doctors working in South Africa found that 23% had correct knowledge about managing genital ulcer disease (66).</p> <p>Only 9% of patients in South Africa received comprehensive syndromic management (67).</p> <p>None of the 50 general practitioners interviewed in Namibia could manage genital ulcer disease properly according to the syndromic management guidelines (39).</p> <p>Interviews with health-care workers from 240 health-care facilities in six countries in western Africa found suboptimal STI management, with effective treatment given to only 14% of the patients (68).</p> <p>Community pharmacies see many potential STIs, but none of the 85 head pharmacists from South Africa correctly identified the treatment for genital ulcers (69).</p> <p>Nurses in Rwanda could deliver STI syndromic management in country towns (42).</p> <p>Syndromic management protocol followed for 70% of genital ulcer disease cases presenting to Male Health Clinic in India (52).</p> <p>Interviews with 120 GPs and 244 occupational health nurses working in the private sector in South Africa in 1997 (59): 14% of GPs reported effective treatment for genital ulcer disease.</p> <p><b>Training</b></p> <p>A mixed-methods study of 250 clinicians in Ethiopia, including the use of mystery patients, found that only 13% were trained in the syndromic management of STIs (70), highlighting the need for training and supervision.</p> <p>Sixteen nurses from primary health centres in Nigeria were trained to manage STIs using a syndromic approach, demonstrating its acceptability and feasibility (62).</p> <p>Doctors and paramedics in India were successfully trained for syndromic case management (71).</p> <p><b>Surveillance of STIs</b></p> <p>Change in the causes of genital ulcer disease over time in Malawi (1992–1999) (52).</p>	<p>Syndromic management often provided at primary care level (including pharmacies) in low- and middle-income countries without clinical examination.</p> <p>A syndromic algorithm may be preferable to nothing, enabling health-care providers to make a diagnosis rapidly without special skills or sophisticated laboratory investigations.</p> <p>If syndromic management is to be scaled up, it is essential that adequate training and supervision is provided.</p> <p>Ongoing need for regular updating of syndromic management protocols in accordance with changing trends of STIs.</p> <p>Need ongoing evaluation of the quality of the services offering syndromic management, such as adherence to the algorithms.</p> <p>Intermittent etiological diagnosis to track changes in the underlying epidemiology of STIs causing the syndromes and thus whether the antibiotics prescribed need to be changed.</p>

## Summary of judgements

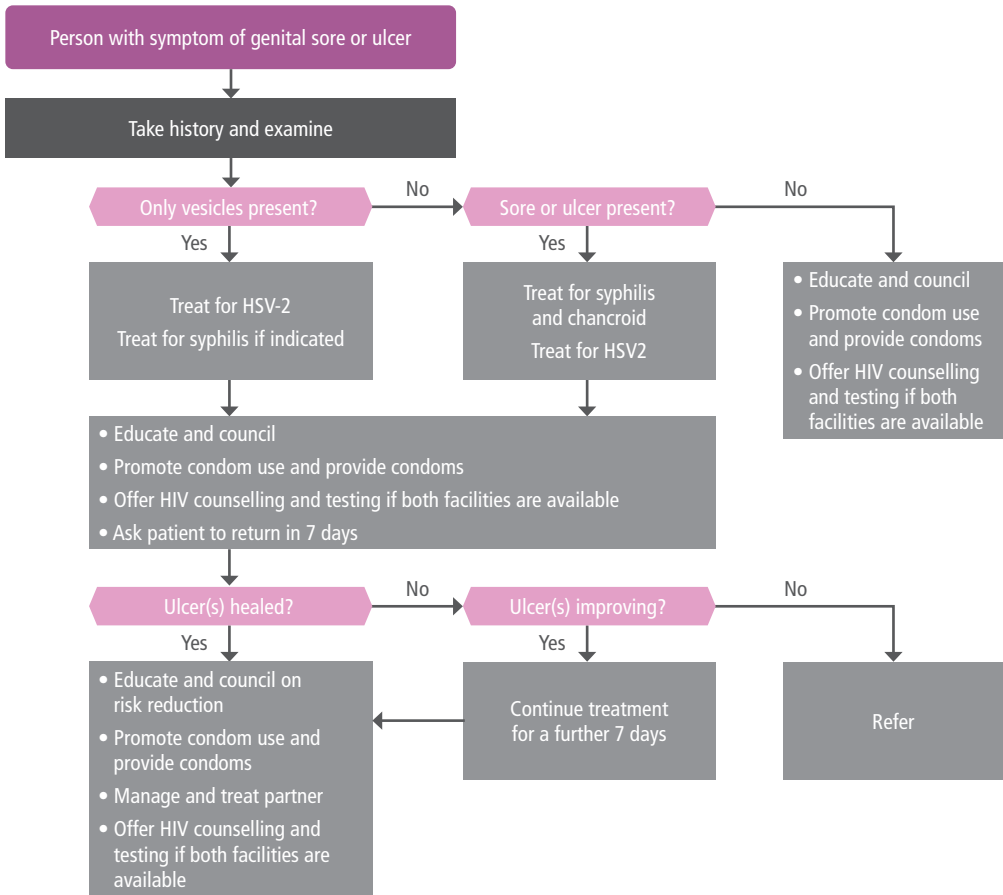
	Judgement						
Problem	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of the effects of management	Very low	Low	Moderate	High			No included studies
Certainty of effects	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

## Conclusions

### Should current WHO syndromic management be recommended versus laboratory diagnosis, no treatment or treat all to identify sexually transmitted infections among people with anogenital ulcers?

Type of recommendation	● Strong recommendation against the intervention	○ Conditional recommendation against the intervention	○ Conditional recommendation for either the intervention or the comparison	○ Conditional recommendation for the intervention	○ Strong recommendation for the intervention
Draft recommendation	<p><b>Recommendations for management of genital ulcer disease, including anorectal ulcers</b></p> <p>For people who present with genital ulcers (including anorectal ulcers), we recommend treatment based on quality-assured molecular assays of the ulcer. However, in settings with limited or no molecular tests or laboratory capacity, we recommend syndromic treatment to ensure treatment on the same day of the visit.</p> <p>Good practice includes:</p> <ul style="list-style-type: none"> <li>• taking a medical and sexual history and assessing the risk of STIs;</li> <li>• performing a physical examination of the genital and anal areas;</li> <li>• offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and</li> <li>• providing analgesics for pain.</li> </ul> <p><i>Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit</i></p> <p>For people with confirmed anogenital ulcers, we recommend to:</p> <ol style="list-style-type: none"> <li>1. Perform molecular assays (NAAT) from anogenital lesions to confirm or exclude herpes simplex virus and <i>Treponema pallidum</i> (syphilis).</li> <li>2. Perform molecular assays from anogenital lesions to confirm lymphogranuloma venereum in geographical settings and/or populations where cases are reported or emerging.</li> <li>3. Perform serological tests for syphilis, with appropriate interpretation for management depending on the test or tests used.</li> <li>4. Treat for syphilis and/or herpes simplex virus according to the results available on the same day of the visit or treat syndromically and revise management according to the results when available.</li> <li>5. Treat for lymphogranuloma venereum when the results are positive.</li> <li>6. Treat for chancroid only in geographical settings where cases are reported or emerging.</li> </ol>				

<p><b>Draft recommendation</b></p>	<p><i>Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing</i></p> <p>For people with confirmed anogenital ulcers, WHO suggests the following.</p> <ol style="list-style-type: none"> <li>1. Treat syndromically for syphilis and herpes simplex virus on the same day.</li> <li>2. Treat for herpes simplex virus if the ulcer is recurrent or vesicular, and treat for syphilis if the person has no history of recent treatment for syphilis (in the past three months).</li> <li>3. Treat for chancroid only in geographical settings where cases are reported or emerging.</li> </ol> <p>Good practice includes.</p> <ul style="list-style-type: none"> <li>• Performing serological tests for syphilis, including an RPR-equivalent test, if available, to attempt to identify active syphilis and for monitoring the response to treatment.</li> </ul> <p>Referring men with persistent anogenital ulcers to a centre with laboratory capacity and expertise to diagnose herpes or less common pathogens (lymphogranuloma venereum, donovanosis and chancroid) and other genital or gastrointestinal conditions.</p> <p><b>Remarks</b></p> <p>Genital ulcer disease refers to breaks in the skin or mucosa and may present as ulcers, sores or vesicles. Anogenital ulcers refer to those located on the genital or anal areas and may be painful or painless.</p> <p>A negative serological test for syphilis when anogenital ulcers have been present for less than three weeks does not definitively exclude syphilis, since antibodies may not yet be present to be detected by a serological test for syphilis. See WHO guidance on interpreting syphilis tests (see subsection 10.2).</p>
<p><b>Justification</b></p>	<p>Managing people presenting with anogenital ulcers based on a syndromic approach results in small benefits and moderate harms compared to molecular testing or treating all. Molecular testing may not be feasible in all settings and alternatively treating all would be feasible and the costs would be negligible. Treating all or conducting molecular testing would be acceptable to all and would not have a negative impact on equity (in some settings it may increase equity).</p>

**Fig. A6.1. Current WHO syndromic approach to management of genital ulcers**



## References

1. Guidelines for the management of sexually transmitted infections. Geneva: World Health Organization; 2003 (<https://www.who.int/hiv/pub/sti/pub6/en>, accessed 31 March 2021).
2. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, editors. *Cochrane handbook for systematic reviews of interventions version 5.1*. Cochrane; 2021 (<https://training.cochrane.org/handbook>, accessed 31 March 2021).
3. Appendix 9.1. Critical appraisal checklist. In: Aromataris E, Munn Z, editors. *JB I manual for evidence synthesis*. Adelaide: JBI; 2020.
4. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med*. 2001;20:2865–84.
5. Das A, Ghosh P, Ghosh I, Bhattacharya R, Azad Sardar AK, Goswami S et al. Usefulness and utility of NACO regime in the management of sexually transmitted infections: a pilot study. *Indian J Dermatol*. 2017;62:630–4.
6. Liu H, Jamison D, Li X, Ma E, Yin Y, Detels R. Is syndromic management better than the current approach for treatment of STDs in China? Evaluation of the cost–effectiveness of syndromic management for male STD patients. *Sex Transm Dis*. 2003;30:327–30.
7. Sanchez J, Volquez C, Totten PA, Campos PE, Ryan C, Catlin M et al. The etiology and management of genital ulcers in the Dominican Republic and Peru. *Sex Transm Dis*. 2002;29:559–67.
8. Behets FM, Andriamiadana J, Randrianasolo D, Randriamanga R, Rasamilalao D, Chen CY et al. Chancroid, primary syphilis, genital herpes, and lymphogranuloma venereum in Antananarivo, Madagascar. *J Infect Dis*. 1999;180:1382–5.
9. Behets FM, Brathwaite AR, Hylton-Kong T, Chen CY, Hoffman I, Weiss JB et al. Genital ulcers: etiology, clinical diagnosis, and associated human immunodeficiency virus infection in Kingston, Jamaica. *Clin Infect Dis*. 1999;28:1086–90.
10. Beyrer C, Jitwatcharanan K, Natpratan C, Kaewvichit R, Nelson KE, Chen CY et al. Molecular methods for the diagnosis of genital ulcer disease in a sexually transmitted disease clinic population in northern Thailand: predominance of herpes simplex virus infection. *J Infect Dis*. 1998;178:243–6.
11. Bhavsar C, Patel RM, Marfatia Y. A study of 113 cases of genital ulcerative disease and urethral discharge syndrome with validation of syndromic management of sexually transmitted diseases. *Indian J Sex Transm Dis AIDS*. 2014;35:35–9.
12. Bogaerts J, Vuylsteke B, Martinez Tello W, Mukantabana V, Akingeneye J, Laga M et al. Simple algorithms for the management of genital ulcers: evaluation in a primary health care centre in Kigali, Rwanda. *Bull World Health Organ*. 1995;73:761–7.
13. DiCarlo RP, Martin DH. The clinical diagnosis of genital ulcer disease in men. *Clin Infect Dis*. 1997;25:292–8.
14. Hina R, Tankhiwale SS, Surpam RB. Study of seroprevalence and syndromic validation of HSV2 among genito-ulcerative disease patients attending STI clinic in a tertiary care hospital. *J Evol Med Dent Sci*. 2017;6:2984–6.
15. Htun Y, Morse SA, Dangor Y, Fehler G, Radebe F, Trees DL et al. Comparison of clinically directed, disease specific, and syndromic protocols for the management of genital ulcer disease in Lesotho. *Sex Transm Infect*. 1998;74(Suppl. 1):S23–8.

16. Prabhakar P, Narayanan P, Deshpande GR, Das A, Neilsen G, Mehendale S et al. Genital ulcer disease in India: etiologies and performance of current syndrome guidelines. *Sex Transm Dis.* 2012;39:906–10.
17. Risbud A, Chan-Tack K, Gadkari D, Gangakhedkar RR, Shepherd ME, Bollinger R et al. The etiology of genital ulcer disease by multiplex polymerase chain reaction and relationship to HIV infection among patients attending sexually transmitted disease clinics in Pune, India. *Sex Transm Dis.* 1999;26:55–62.
18. Wang Q, Yang P, Zhong M, Wang G. Validation of diagnostic algorithms for syndromic management of sexually transmitted diseases. *Chin Med J.* 2003;116:181–6.
19. Wang QQ, Mabey D, Peeling RW, Tan ML, Jian DM, Yang P et al. Validation of syndromic algorithm for the management of genital ulcer diseases in China. *Int J STD AIDS.* 2002;13:469–74.
20. Fast MV, D'Costa LJ, Nsanze H, Piot P, Curran J, Karasira P et al. The clinical diagnosis of genital ulcer disease in men in the tropics. *Sex Transm Dis.* 1984;11:72–6.
21. Dangor Y, Ballard RC, da LEF, Fehler G, Miller SD, Koornhof HJ. Accuracy of clinical diagnosis of genital ulcer disease. *Sex Transm Dis.* 1990;17:184–9.
22. Hanson S, Sunkutu RM, Kamanga J, Hojer B, Sandstrom E. STD care in Zambia: an evaluation of the guidelines for case management through a syndromic approach. *Int J STD AIDS.* 1996;7:324–32.
23. Ndinya-Achola JO, Kihara AN, Fisher LD, Krone MR, Plummer FA, Ronald A et al. Presumptive specific clinical diagnosis of genital ulcer disease in a primary health care setting in Nairobi. *Int J STD AIDS.* 1996;7:201–5.
24. Otieno FO, Ndivo R, Oswago S, Ondiek J, Pals S, McLellan-Lemal E et al. Evaluation of syndromic management of sexually transmitted infections within the Kisumu Incidence Cohort Study. *Int J STD AIDS.* 2014;25:851–9.
25. Nilsen AE, Aasen T, Halsos AM, Kinge BR, Tjøtta EA, Wikstrom K et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet.* 1982;2:571–3.
26. Bryson YJ, Dillon M, Lovett M, Acuna G, Taylor S, Cherry JD et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir. A randomized double-blind controlled trial in normal subjects. *N Engl J Med.* 1983;308:916–21.
27. Reichman RC, Badger GJ, Mertz GJ, Corey L, Richman DD, Connor JD et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. A controlled trial. *JAMA.* 1984;251:2103–7.
28. Boonstra E, Lindbaek M, Klouman E, Ngome E, Romoren M, Sundby J. Syndromic management of sexually transmitted diseases in Botswana's primary health care: quality of care aspects. *Trop Med Int Health.* 2003;8:604–14.
29. Korenromp EL, Wi T, Resch S, Stover J, Broutet N. Costing of national STI program implementation for the global STI control strategy for the health sector, 2016–2021. *PLoS One.* 2017;12:e0170773.
30. Adams EJ, Garcia PJ, Garnett GP, Edmunds WJ, Holmes KK. The cost-effectiveness of syndromic management in pharmacies in Lima, Peru. *Sex Transm Dis.* 2003;30:379–87.
31. Gilson L, Mkanje R, Grosskurth H, Moshia F, Picard J, Gavyole A et al. Cost-effectiveness of improved treatment services for sexually transmitted diseases in preventing HIV-1 infection in Mwanza Region, Tanzania. *Lancet.* 1997;350:1805–9.

32. Parker KA, Koumans EH, Hawkins RV, Massanga M, Somse P, Barker K et al. Providing low-cost sexually transmitted diseases services in two semi-urban health centers in Central African Republic (CAR): characteristics of patients and patterns of health care-seeking behavior. *Sex Transm Dis.* 1999;26:508–16.
33. Tsai CH, Lee TC, Chang HL, Tang LH, Chiang CC, Chen KT. The cost–effectiveness of syndromic management for male sexually transmitted disease patients with urethral discharge symptoms and genital ulcer disease in Taiwan. *Sex Transm Infect.* 2008;84:400–4.
34. Vickerman P, Ndowa F, Mayaud P. Modelling the cost per ulcer treated of incorporating episodic treatment for HSV-2 into the syndromic algorithm for genital ulcer disease. *Sex Transm Infect.* 2008;84:243–8.
35. White RG, Moodley P, McGrath N, Hosegood V, Zaba B, Herbst K et al. Low effectiveness of syndromic treatment services for curable sexually transmitted infections in rural South Africa. *Sex Transm Infect.* 2008;84:528–34.
36. La Ruche G, Lorougnon F, Digbeu N. Therapeutic algorithms for the management of sexually transmitted diseases at the peripheral level in Côte d’Ivoire: assessment of efficacy and cost. *Bull World Health Organ.* 1995;73:305–13.
38. Khandwalla HE, Luby S, Rahman S. Knowledge, attitudes, and practices regarding sexually transmitted infections among general practitioners and medical specialists in Karachi, Pakistan. *Sex Transm Infect.* 2000;76:383–5.
39. Iipinge SN, Pretorius L. The delivery and quality of sexually transmitted infections treatment by private general practitioners in Windhoek Namibia. *Glob J Health Sci.* 2012;4:156–71.
40. Mahmood MA, Saniotis A. Use of syndromic management algorithm for sexually transmitted infections and reproductive tract infections management in community settings in Karachi. *J Pakistan Med Assoc.* 2011;61:453–7.
41. Grosskurth H, Mwijarubi E, Todd J, Rwakatare M, Orroth K, Mayaud P et al. Operational performance of an STD control programme in Mwanza Region, Tanzania. *Sex Transm Infect.* 2000;76:426–36.
42. Steen R, Soliman C, Mujyambwani A, Twagirakristu JB, Bucyana S, Grundmann C et al. Notes from the field: practical issues in upgrading STD services based on experience from primary healthcare facilities in two Rwandan towns. *Sex Transm Infect.* 1998;74(Suppl. 1):S159–65.
43. Beyene M, Gizachew Y, Afework K, Berihun M, Shitaye A, Bemnet A et al. Sexually transmitted infections based on the syndromic approach in Gondar town, northwest Ethiopia: a retrospective cross-sectional study. *BMC Public Health.* 2013;13(143).
44. Wolday D, Z GM, Mohammed Z, Meles H, Messele T, Seme W et al. Risk factors associated with failure of syndromic treatment of sexually transmitted diseases among women seeking primary care in Addis Ababa. *Sex Transm Infect.* 2004;80:392–4.
45. Chelugot B, Joesoef MR, Marum LH, Wandera C, Ryan CA, Decock KM et al. Changing patterns in sexually transmitted disease syndromes in Kenya after the introduction of a syndromic management program. *Sex Transm Dis.* 2004;31:522–5.
46. Chilongozi DA, Daly CC, Franco L, Liomba NG, Dallabetta G. Sexually transmitted diseases: a survey of case management in Malawi. *Int J STD AIDS.* 1996;7:269–75.

47. Behets FM, Liomba G, Lule G, Dallabetta G, Hoffman IF, Hamilton HA et al. Sexually transmitted diseases and human immunodeficiency virus control in Malawi: a field study of genital ulcer disease. *J Infect Dis.* 1995;171:451–5.
48. Garcia PJ, Gotuzzo E, Hughes JP, Holmes KK. Syndromic management of STDs in pharmacies: evaluation and randomised intervention trial. *Sex Transm Infect.* 1998;74(Suppl. 1):S153–8.
49. Garcia PJ, Holmes KK, Carcamo CP, Garnett GP, Hughes JP, Campos PE et al. Prevention of sexually transmitted infections in urban communities (Peru PREVEN): a multicomponent community-randomised controlled trial. *Lancet.* 2012;379:1120–8.
50. Goel SS. Study of syndromic management approach in the management of sexually transmitted diseases in rural population. *Indian J Sex Transm Dis.* 2012;33:146–7.
51. Mertens TE, Smith GD, Kantharaj K, Mugrditchian D, Radhakrishnan KM. Observations of sexually transmitted disease consultations in India. *Public Health.* 1998;112:123–8.
52. Sharma K, Chavan Y, Aras R, Khismatrao D. Syndromic management of STDs in a male health clinic in a primary health care setting. *Indian J Sex Transm Dis.* 2011;32:136–7.
53. Tankhiwale SS, Chavan SP. Comparative study of syndromic and etiological diagnosis of sexually transmitted infection except human immunodeficiency virus in sexually transmitted infection and reproductive tract infection clinic attendees in central India. *Int J Med Public Health.* 2013;3:347–51.
54. Lule G, Behets FMT, Hoffman IF, Liomba G, Dallabetta G, Hamilton HA et al. Choosing an effective and affordable antibiotic regimen for sexually transmitted diseases (STD) patients in Malawi. *Malawi Med J.* 1998;11:50–5.
55. Machiha A, Mugurungi O, Tshimanga M, Kilmarx P, Mungati M, Nyakura J et al. The aetiology of genital ulcer disease and association with HIV infection in Zimbabwe. *Sex Transm Infect.* 2015;91:A157.
56. Mark J, Hariri S, Ilunga R, Forhan S, Likibi M, M LK et al. Evaluation of sexually transmitted infection clinical services in Gauteng Province, South Africa: knowledge, attitudes, and beliefs among health care providers. *Sex Transm Infect.* 2011;87:A92–3.
57. Mathews C, van Rensburg A, Coetzee N. The sensitivity of a syndromic management approach in detecting sexually transmitted diseases in patients at a public health clinic in Cape Town. *S Afr Med J.* 1998;88:1337–40.
58. Moodley P, Sturm PD, Vanmali T, Wilkinson D, Connolly C, Sturm AW. Association between HIV-1 infection, the etiology of genital ulcer disease, and response to syndromic management. *Sex Transm Dis.* 2003;30:241–5.
59. Schneider H, Blaauw D, Dartnall E, Coetzee DJ, Ballard RC. STD care in the South African private health sector. *S Afr Med J.* 2001;91:151–6.
60. Moherdau F, Vuylsteke B, Siqueira LF, dos Santos Junior MQ, Jardim ML, de Brito AM et al. Validation of national algorithms for the diagnosis of sexually transmitted diseases in Brazil: results from a multicentre study. *Sex Transm Infect.* 1998;74(Suppl. 1):S38–43.
61. Meheus A, Van Dyck E, Ursi JP, Ballard RC, Piot P. Etiology of genital ulcerations in Swaziland. *Sex Transm Dis.* 1983;10:33–5.
62. Mabey DC, Wall RA, Bello CS. Aetiology of genital ulceration in the Gambia. *Genitourin Med.* 1987;63:312–5.

63. Mbofana FS, Brito FJ, Saifodine A, Cliff JL. Syndromic management of sexually transmitted diseases at primary care level, Mozambique. *Sex Transm Infect.* 2002;78:E2.
64. Leiva A, Shaw M, Paine K, Manneh K, McAdam K, Mayaud P. Management of sexually transmitted diseases in urban pharmacies in The Gambia. *Int J STD AIDS.* 2001;12:444–52.
65. Harrison A, Wilkinson D, Lurie M, Connolly AM, Karim SA. Improving quality of sexually transmitted disease case management in rural South Africa. *AIDS.* 1998;12:2329–35.
66. Uchenna C, Govender I. Knowledge, attitudes and practices of doctors at Jubilee Hospital, Tshwane District, regarding the syndromic management guidelines for sexually transmitted infections. *S Afr Fam Pract.* 2018;60:155–61.
67. Wilkinson D, Karim SS, Lurie M, Harrison A. Public-private health sector partnerships for STD control in South Africa – perspectives from the Hlabisa experience. *S Afr Med J.* 2001;91:517–20.
68. Bitera R, Alary M, Masse B, Viens P, Lowndes C, Baganizi E et al. [Quality of disease management of sexually transmitted diseases: investigation of care in six countries in western Africa]. *Sante.* 2002;12:233–9.
69. Ward K, Butler N, Mugabo P, Klausner J, McFarland W, Chen S et al. Provision of syndromic treatment of sexually transmitted infections by community pharmacists: a potentially underutilized HIV prevention strategy. *Sex Transm Dis.* 2003;30:609–13.
70. Alemayehu A, Godana W. Knowledge and practice of clinicians regarding syndromic management of sexually transmitted infections in public health facilities of Gamo Gofa Zone, south Ethiopia. *J Sex Transm Dis.* 2015;2015:310409.
71. Sharma R, Prajapati S, Patel B, Kumar P. Evaluation of skill-oriented training on enhanced syndromic case management (ESCM) of reproductive tract infections / sexually transmitted infections (RTI/STIs) of care providers from three-tier health-care system of Gujarat. *Indian J Community Med.* 2016;41:183–9.

**Table A6.1. Detection of any STI for genital ulcer syndrome (shaded rows represents studies testing presence of ulcer to detect any STIs)**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Pathogens	Diagnostics	True positive	False negative	False positive	True negative
Das et al. (5)	2013	India	Lower middle	297	STI and gynaecology outpatients	22% male 12% genital ulcer disease	Presence of ulcer	HSV, <i>Candida glabrata</i> , cytomegalovirus, true positive	VDRL, TPHA, Smear, HSV-Ab	14	215	27	41
Liu et al. (6)	2003	China	Upper middle	55	Sexual health clinic	100% male 14% genital ulcer disease	Presence of ulcer	HSV, true positive, <i>Haemophilus ducreyi</i>	PCR, RPR, TPPA	13	0	40	2
Sanchez et al. (7)	1995–1996	Dominican Republic	Upper middle	81	General practice	100% male 100% genital ulcer disease	Symptoms + examination	HSV, true positive, <i>Haemophilus ducreyi</i>	M-PCR	13	12	28	28
Sanchez et al. (7)	1995–1996	Peru	Upper middle	63	General practice	100% male 100% genital ulcer disease	Symptoms + examination	HSV, true positive, <i>Haemophilus ducreyi</i>	M-PCR	2	7	29	25

**Table A6.2.** Comparing the accuracy of clinical diagnosis of herpes with etiologic diagnosis of herpes

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostics	True positive	False negative	False positive	True negative
Behets et al. (8)	1997	Madagascar	Low	196	Sexual health clinic	71% men	Clinical diagnosis <sup>a</sup>	M-PCR	0	19	2	175
Behets et al. (9)	1996	Jamaica	Upper middle	304	Sexual Health clinic	83% men	Clinical diagnosis <sup>a</sup>	M-PCR	85	73	24	122
Beyrer et al. (10)	1995–1996	Thailand	Upper middle	38	Sexual health clinic	79% female sex workers	Clinical diagnosis <sup>a</sup>	M-PCR	21	11	3	3
Bhavsar et al. (11)	2011–2012	India	Lower middle	96	Hospital	79% men	Clinical diagnosis <sup>a</sup>	Tzanck smear IgM for HSV-2	33	0	38	25
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men	History and examination	Cytopathic effect on Vero cells	4	85	4	302
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men	History and examination + syphilis serology or darkfield microscopy	Cytopathic effect on Vero cells	4	85	4	302
Bogaerts et al. (13)	1990–1992	Rwanda	Low	395	General practice	63% men	Clinical diagnosis <sup>a</sup>	Cytopathic effect on Vero cells	43	46	87	219

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostics	True positive	False negative	False positive	True negative
DiCarlo & Martin (13)	1990-1992	United States	High	220	Sexual health clinic	100% men	Clinical diagnosis <sup>a</sup>	Culture	20	37	10	153
Hina et al. (14)	2015-2016	India	Lower middle	96	Sexual health clinic	75% men	Clinical diagnosis <sup>a</sup>	Tzanck smears, HSV2-IgM	33	2	36	25
Htun et al. (15)	1993-1994	Lesotho	Lower middle	92	Sexual health clinic		Clinical diagnosis <sup>a</sup>	MPCR	7	10	1	74
Htun et al. (15)	1993-1994	Lesotho	Lower middle	92	Sexual health clinic		Clinical diagnosis <sup>a</sup>	MPCR	5	19	3	65
Htun et al. (15)	1993-1994	Lesotho	Lower middle	92	Sexual health clinic		Clinical diagnosis <sup>a</sup>	MPCR	0	24	0	68
Prabhakar et al. (16)	2008-2009	India	Lower middle	181	Sexual health clinic	100% men	Clinical diagnosis <sup>a</sup>	M-PCR	59	31	37	54
Risbud et al. (17)	1994	India	Lower middle	302	Sexual health clinic		Clinical diagnosis <sup>a</sup>	M-PCR	48	47	32	175
Sanchez et al. (7)	1995-1996	Dominican Republic	Upper middle	81	General practice	100% men	Clinical diagnosis <sup>a</sup>	M-PCR	19	16	10	36
Sanchez et al. (7)	1995-1996	Peru	Upper middle	63	General practice	100% men	Clinical diagnosis <sup>a</sup>	M-PCR	15	12	17	19



Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostics	True positive	False negative	False positive	True negative
Wang et al. (18)	1998–1999	China	Upper middle	96	Sexual health clinic	52% men	Clinical diagnosis <sup>a</sup>	M-PCR	25	8	36	27
Wang et al. (19)	2000–2001	China	Upper middle	227	Sexual health clinic	90% men	Clinical diagnosis <sup>a</sup>	M-PCR	49	22	78	78
Fast et al. (20)	1980	Kenya	Lower middle	70	“Special treatment clinic”	100% men	Clinical diagnosis <sup>a</sup>	Culture	3	3	1	63
Dangor et al. (21)	Unclear	South Africa	Upper middle	210	Hospital	100% men	Clinical diagnosis <sup>a</sup>	Culture	5	2	21	182

<sup>a</sup> A diagnostic test is the clinician’s diagnosis of herpes (rather than the presence of an ulcer). Clinical diagnosis is based on physical examination and history.

**Table A6.3. Detection of syphilis using clinical diagnosis of syphilis in a population of individuals with genital ulcer disease**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostics	True positive	False negative	False positive	True negative
Behets et al. (8)	1997	Madagascar	Low	196	Sexual health clinic	71% men	Clinical diagnosis <sup>a</sup>	M-PCR	52	4	112	28
Behets et al. (9)	1996	Jamaica	Upper middle	304	Sexual Health clinic	83% men	Clinical diagnosis <sup>a</sup>	M-PCR	21	10	24	249
Beyrer et al. (10)	1995–1996	Thailand	Upper middle	38	Sexual health clinic	79% female sex workers	Clinical diagnosis <sup>a</sup>	M-PCR	0	1	1	36
Bhavsar et al. (11)	2011–2012	India	Lower middle	96	Hospital	79% men	Clinical diagnosis <sup>a</sup>	VDRL, TPHA	19	24	1	52
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men	History and examination	RPR, TPHA, Darkfield microscopy	108	2	279	6
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men	History and examination + syphilis serology or darkfield microscopy	RPR, TPHA, Darkfield microscopy	107	3	9	276
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men	Clinical diagnosis <sup>a</sup>	RPR, TPHA, Darkfield microscopy	20	90	31	254
DiCarlo & Martin (13)	1990–1992	United States	High	220	Sexual health clinic	100% men	Clinical diagnosis <sup>a</sup>	Darkfield microscopy	14	31	3	172
Hanson et al. (22)	1996	Zambia	Lower middle	95	Hospital	100% men	Clinical diagnosis <sup>a</sup>	Darkfield microscopy, RPR, TPHA	24	17	14	40
Hanson et al. (22)	1996	Zambia	Lower middle	131	Hospital	100% women	Clinical diagnosis <sup>a</sup>	Darkfield microscopy, RPR, TPHA	14	22	12	83

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostics	True positive	False negative	False positive	True negative
Htun et al. (15)	1993–1994	Lesotho	Lower middle	92	Sexual health clinic		Clinical diagnosis <sup>a</sup>	MPCR, RPR, FTA-Abs	5	18	1	68
Htun et al. (15)	1993–1994	Lesotho	Lower middle	92	Sexual health clinic		Clinical diagnosis <sup>a</sup>	MPCR, RPR, FTA-Abs	30	4	52	6
Htun et al. (15)	1993–1994	Lesotho	Lower middle	92	Sexual health clinic		Clinical diagnosis <sup>a</sup>	MPCR, RPR, FTA-Abs	33	1	52	6
Ndinya-Achola et al. (23)	1990–1991	Kenya	Lower middle	172	Primary care	47% men	Clinical diagnosis <sup>a</sup>	RPR	6	18	19	129
Prabhakar et al. (16)	2008–2009	India	Lower middle	181	Sexual health clinic	100% men	Clinical diagnosis <sup>a</sup>	M-PCR	26	18	72	78
Sanchez et al. (7)	1995–1996	Dominican Republic	Upper middle	81	General practice	100% men	Clinical diagnosis <sup>a</sup>	M-PCR	2	2	11	66
Sanchez et al. (7)	1995–1996	Dominican Republic	Upper middle	63	General practice	100% men	Clinical diagnosis <sup>a</sup>	M-PCR	2	4	8	49
Wang et al. (18)	1998–1999	China	Upper middle	96	Sexual health clinic	100% had “STI symptoms”	Clinical diagnosis <sup>a</sup>	M-PCR, RPR, TPPA	18	5	12	61
Wang et al. (19)	2000-1	China	Upper middle	227	Sexual health clinic	90% men	Symptoms + examination + risk factors	M-PCR, Darkfield microscopy, RPR, TPPA	94	12	6	115
Fast et al. (20)	1980	Kenya	Lower middle	70	“Special treatment clinic”	100% men	Clinical diagnosis <sup>a</sup>	RPR, Darkfield microscopy	6	4	4	56
Dangor et al. (21)	Unclear	South Africa	Upper middle	210	Hospital	100% male	Clinical diagnosis <sup>a</sup>	RPR, fluorescent treponemal antibody absorption, darkfield microscopy	22	3	25	160

<sup>a</sup> A diagnostic test is the clinician’s diagnosis of herpes (rather than the presence of an ulcer). Clinical diagnosis is based on physical examination and history.

**Table A6.4. Detection of chancroid using clinical diagnosis in a population with genital ulcer disease**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostics	True positive	False negative	False positive	True negative
Behets et al. (8)	1997	Madagascar	Low	196	Sexual health clinic	71% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	M-PCR	34	30	63	69
Behets et al. (9)	1996	Jamaica	Upper middle	304	Sexual Health clinic	83% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	M-PCR	54	18	57	175
Beyrer et al. (10)	1995–1996	Thailand	Upper middle	38	Sexual health clinic	79% female sex workers 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	M-PCR	0	0	6	32
Bhavsar et al. (11)	2011–2012	India	Lower middle	96	Hospital	79% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	Gram stain	2	1	1	92
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men 100% genital ulcer disease	History and examination	Culture	115	0	272	8
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men 100% genital ulcer disease	History and examination + syphilis serology or darkfield microscopy	Culture	83	32	188	92
Bogaerts et al. (12)	1990–1992	Rwanda	Low	395	General practice	63% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	Culture	74	41	67	213
DiCarlo & Martin (13)	1990–1992	USA	High	220	Sexual health clinic	100% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	Culture	40	78	6	96

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostics	True positive	False negative	False positive	True negative
Htun et al. (15)	1993–1994	Lesotho	Lower middle	92	Sexual health clinic	100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	MPCR	54	2	22	14
Htun et al. (15)	1993–1994	Lesotho	Lower middle	92	Sexual health clinic	100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	MPCR	51	4	31	6
Htun et al. (15)	1993–1994	Lesotho	Lower middle	92	Sexual health clinic	100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	MPCR	53	3	32	4
Ndinya-Achola et al. (23)	1990–1991	Kenya	Lower middle	156	Primary care	47% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	Culture	51	5	76	24
Prabhakar et al. (16)	2008–2009	India	Lower middle	181	Sexual health clinic	100% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	M-PCR	59	31	37	54
Risbud et al. (17)	1994	India	Lower middle	302	Sexual health clinic	100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	M-PCR	53	31	76	142
Sanchez et al. (7)	1995–1996	Dominican Republic	Upper middle	81	General practice	100% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	M-PCR	11	10	17	43
Sanchez et al. (7)	1995–1996	Peru	Upper middle	63	General practice	100% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	M-PCR	0	3	21	39
Fast et al. (20)	1980	Kenya	Lower middle	70	"Special treatment clinic"	100% men 100% genital ulcer disease	Clinical diagnosis <sup>a</sup>	Culture	42	6	8	14
Dangor et al. (20)	Unclear	South Africa	Upper middle	210	Hospital	100% genital ulcer disease	Clinical diagnosis <sup>a</sup>		117	30	14	49

<sup>a</sup> A diagnostic test is the clinician's diagnosis of herpes (rather than the presence of an ulcer). Clinical diagnosis is based on physical examination and history.

## ANNEX 7. EVIDENCE-TO-DECISION TABLE: ANORECTAL DISCHARGE

Should the current WHO syndromic management approach be recommended versus laboratory diagnosis, no treatment and treat all to identify sexually transmitted infections among people with anorectal discharge?

### Population:

Men and women (cis-men, cis-women, trans-women and transmen) presenting with anorectal discharge

### Intervention and comparator:

Intervention: current WHO syndromic approach versus comparison: laboratory diagnosis (or no treatment or treat all)

### Purpose of the test:

To detect *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis*; herpes simplex virus (HSV); *C. trachomatis* (serovars L1, L2 and L3) causing lymphogranuloma venereum and *Mycoplasma genitalium*

### Linked treatments:

Treatments for anorectal infections (see above)

### Anticipated outcomes:

Number of people identified correctly as having or not having STI; number of people identified incorrectly as having or not having STI; consequences of appropriate or inappropriate treatment; patient and provider acceptability, feasibility, equity and resource use

### Setting:

Outpatient

### Perspective:

Population level

### Subgroups:

High- or low-prevalence settings; settings with limited versus established laboratory capacity; key populations: sex workers, men who have sex with men, transgender people, people living with HIV

### Background:

Syndromic management refers to a strategy to identify and treat people with STIs based on specific symptoms identified by a patient and signs (clinically observed signs of infection) associated with clearly defined causes. Although etiological diagnosis is preferred, it is not always accessible or affordable.

Fig. A7.1 shows clinical guidelines for the syndromic management of anorectal syndrome in the 2003 WHO guidelines for the management of sexually transmitted infections.

## Assessment

	Judgement	Research evidence
Problem	<p><b>Is the problem a priority?</b></p> <p><input type="radio"/> No</p> <p><input type="radio"/> Probably no</p> <p><input type="radio"/> Probably yes</p> <p><input checked="" type="radio"/> Yes</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>Anorectal infection</b></p> <p>Anorectal STIs are possible for individuals practising anal sex. Among men who have sex with men, anorectal STIs are relatively common and frequently asymptomatic but can cause proctitis, presenting as anal discharge and/or pain. Possible causes include <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> including lymphogranuloma venereum, herpes simplex viruses (HSV-1, HSV-2) and <i>Treponema pallidum</i> (true positive). Proctitis can also be caused by non-infectious reasons. An individual with anorectal infections may also have concomitant infection at other anatomical sites. There is concern that, if people with anorectal STIs are not treated, this could increase HIV acquisition through inflammation and increased viral shedding.</p> <p><b>High cost of molecular STI testing</b></p> <p>Cheaper platforms, near-patient or point-of-care tests are needed for <i>C. trachomatis</i> and <i>N. gonorrhoeae</i>.</p> <p><b>Antimicrobial resistance</b></p> <p>There is increasing concern about the treatment of people with <i>N. gonorrhoeae</i>, since high rates of resistance to penicillin, tetracycline, and quinolone have been documented globally. Resistance to commonly used first-line medications (azithromycin) and reports of treatment failure and reduced susceptibility in <i>N. gonorrhoeae</i> to cephalosporin (a last-line treatment for <i>N. gonorrhoeae</i>) raise concern that <i>N. gonorrhoeae</i> could become untreatable.</p>
Test accuracy	<p><b>How accurate is the test?</b></p> <p><input type="radio"/> Very inaccurate</p> <p><input checked="" type="radio"/> Inaccurate</p> <p><input type="radio"/> Accurate</p> <p><input type="radio"/> Very accurate</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>We conducted a systematic review, searching up to September 2019, of the sensitivity and specificity of a syndromic management approach to identify multiple STIs related to anorectal discharge. In summary, we identified four studies that assessed the diagnostic accuracy of anorectal syndromic management to detect any STI (Table A7.1), five studies for anorectal chlamydia (Table A7.2) and five studies for anorectal gonorrhoea (Table A7.3).</p> <p><b>For detection of any STIs</b> (chlamydia or gonorrhoea), four studies provided five estimates for pooling. The pooled sensitivity for detecting anal chlamydia or gonorrhoea using a syndromic management approach (anorectal syndrome) is 32.4% (95% CI: 11.4–64.0%), and pooled specificity is 81.7% (95% CI: 43.1–96.43%).</p> <p><b>For detection of specific STIs</b></p> <p>For detection of anal chlamydia, five estimates were available to pool. The pooled sensitivity for detecting anal chlamydia using a syndromic management approach is 11.1% (95% CI: 2.2–40.3%), and pooled specificity is 94.8% (95% CI: 87.1–98.0%).</p> <p>For detection of anal gonorrhoea, five studies providing five estimates were available to pool; the pooled sensitivity for detecting anal gonorrhoea using a syndromic management approach is 14.2% (95% CI: 6.1–29.7%), and pooled specificity is 94.4% (95% CI: 84.8–98.1%).</p> <p>For detection of herpes or syphilis, no estimates were found for evaluating the accuracy of syndromic management.</p> <p>For detection of lymphogranuloma venereum, one study among men who have sex with men from sexual health clinics in the Netherlands provided an estimate for the sensitivity of syndromic management to detect lymphogranuloma venereum: 4.6% (95% CI: 1.3–11.4%) (7).</p> <p>Prevalence can vary widely (anorectal <i>N. gonorrhoeae</i>: 0.2–24%, anorectal <i>C. trachomatis</i> 2.1–23%) (8–14), and there are behavioural and network correlates of those with greater likelihood of an STI (15). Men who have sex with men are not homogeneous.</p>

	Judgement	Research evidence																																										
Test accuracy		<p>The evidence for the value of adding risk assessment to the history of symptoms is mixed.</p> <p>A study from India to detect anorectal <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> among 508 patients (in 2008–2009) reported the accuracy for detecting <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> in algorithms that used: (1) anorectal symptoms only (sensitivity of 0.8%), (2) receptive anal sex and/or anorectal discharge (sensitivity 41.7%, specificity 66.3%, positive predictive value 17.5%) and (3) addition of risk assessment (sensitivity 81.9%, specificity 20.1%, positive predictive value 14.9%) (1).</p> <p>A study of 698 men who have sex with men in Kenya (2) explored model-derived risk score based on correlates of anorectal <i>C. trachomatis</i> or <i>N. gonorrhoeae</i>. The risk score was based on three correlates (age 18–24 years versus ≥25 years (2 points), people living with HIV (2 points) and condomless sex with a male partner (1 point). They report a sensitivity of 81% and specificity of 66%, with a number needed to treat of 12 for anorectal <i>C. trachomatis</i> or <i>N. gonorrhoeae</i> that might be possible in their context for asymptomatic men who have sex with men (see the table below). The correlates of anorectal <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> among symptomatic men were people living with HIV (adjusted odds ratio (aOR) 17.1 [95% confidence interval (CI) 3.5–84]), receptive anal sex (aOR 53.5 [95% CI 6.4–444.9]) and versatile sex position (aOR 24.2 [95% CI 2.0–294.8]).</p> <table border="1" data-bbox="450 753 1082 1070"> <caption>Sensitivity, Specificity, NNT and Predictive Values of Risk Score at Different Cut Points</caption> <thead> <tr> <th>Risk Score Cut Point</th> <th>Sensitivity</th> <th>Specificity</th> <th>Proportion Offered PT</th> <th>NNT</th> <th>PPV</th> <th>NPV</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>95.2%</td> <td>12.3%</td> <td>88.0%</td> <td>36</td> <td>4.3%</td> <td>98.4%</td> </tr> <tr> <td>2</td> <td>85.7%</td> <td>39.5%</td> <td>61.4%</td> <td>24</td> <td>5.5%</td> <td>98.5%</td> </tr> <tr> <td>3</td> <td>81.0%</td> <td>66.1%</td> <td>35.7%</td> <td>12</td> <td>8.9%</td> <td>98.8%</td> </tr> <tr> <td>4</td> <td>28.6%</td> <td>97.5%</td> <td>3.6%</td> <td>3</td> <td>31.6%</td> <td>97.1%</td> </tr> <tr> <td>5</td> <td>19.1%</td> <td>98.8%</td> <td>1.9%</td> <td>2</td> <td>40.0%</td> <td>96.7%</td> </tr> </tbody> </table> <p>Abbreviations: NNT = number needed to treat; NPV = negative predictive value; PPV = positive predictive value</p> <p>However, a study of 787 men who have sex with men from Peru (in 2012–2014) reported that most anorectal <i>C. trachomatis</i> or <i>N. gonorrhoeae</i> were detected in men with no relevant risk behaviour with their three most recent sex partners (6). Other studies (8) also suggest that adding risk factors may not increase the accuracy of syndromic management, and its value should be assessed in specific contexts.</p>	Risk Score Cut Point	Sensitivity	Specificity	Proportion Offered PT	NNT	PPV	NPV	1	95.2%	12.3%	88.0%	36	4.3%	98.4%	2	85.7%	39.5%	61.4%	24	5.5%	98.5%	3	81.0%	66.1%	35.7%	12	8.9%	98.8%	4	28.6%	97.5%	3.6%	3	31.6%	97.1%	5	19.1%	98.8%	1.9%	2	40.0%	96.7%
Risk Score Cut Point	Sensitivity	Specificity	Proportion Offered PT	NNT	PPV	NPV																																						
1	95.2%	12.3%	88.0%	36	4.3%	98.4%																																						
2	85.7%	39.5%	61.4%	24	5.5%	98.5%																																						
3	81.0%	66.1%	35.7%	12	8.9%	98.8%																																						
4	28.6%	97.5%	3.6%	3	31.6%	97.1%																																						
5	19.1%	98.8%	1.9%	2	40.0%	96.7%																																						
Desirable effects	<p><b>How substantial are the desirable anticipated effects of syndromic approach?</b></p> <p><input type="radio"/> Trivial</p> <p><input checked="" type="radio"/> Small</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> Large</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>Desirable effects and undesirable effects</b></p> <p>The potential consequences of true positive could include appropriate treatment, cure, side-effects, partner notification, reduced transmission of STI and HIV, resistance, couple difficulties and costs.</p> <p>The potential consequences of true negative could include alternative diagnoses possible and psychological benefit.</p> <p>The potential consequences of false negative could include cure still possible, persistent symptoms, complications, STI and/or HIV transmission, no counselling and no partner notification.</p> <p>The potential consequences of false positive could include inappropriate treatment, side-effects, antimicrobial resistance, couple difficulties and costs.</p> <p>Based on the sensitivity and specificity of anorectal syndrome to detect STIs, we calculated the number of people appropriately treated (true positive), the number of missed cases (false negative) and the number of people treated unnecessarily or overtreated (false positive)</p>																																										



	Judgement	Research evidence																							
Undesirable effects	<p>How substantial are the undesirable anticipated effects?</p> <p><input type="radio"/> Large</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> Small</p> <p><input type="radio"/> Trivial</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p><b>GRADE summary of findings tables: detection of any chlamydia or gonorrhoea using anorectal discharge</b></p> <p>Pooled sensitivity: 0.32 (95% CI: 0.11 to 0.64)   Pooled specificity: 0.82 (95% CI: 0.43 to 0.96)</p> <table border="1"> <thead> <tr> <th rowspan="2">Test result</th> <th colspan="2">Number of results per 100 patients tested (95% CI)</th> <th rowspan="2">Number of participants (studies)</th> <th rowspan="2">Certainty of the Evidence (GRADE)</th> </tr> <tr> <th>Prevalence 20% Typically seen in</th> <th>Prevalence 50% Typically seen in</th> </tr> </thead> <tbody> <tr> <td>True positives</td> <td>6 (2 to 13)</td> <td>16 (6 to 32)</td> <td rowspan="2">2010 (4)</td> <td rowspan="2">⊕⊕⊕○ Moderate<sup>a</sup></td> </tr> <tr> <td>False negatives</td> <td>14 (7 to 18)</td> <td>34 (18 to 44)</td> </tr> <tr> <td>True negatives</td> <td>65 (34 to 77)</td> <td>41 (22 to 48)</td> <td rowspan="2">2010 (4)</td> <td rowspan="2">⊕⊕⊕○ Moderate<sup>a</sup></td> </tr> <tr> <td>False positives</td> <td>15 (3 to 46)</td> <td>9 (2 to 28)</td> </tr> </tbody> </table>	Test result	Number of results per 100 patients tested (95% CI)		Number of participants (studies)	Certainty of the Evidence (GRADE)	Prevalence 20% Typically seen in	Prevalence 50% Typically seen in	True positives	6 (2 to 13)	16 (6 to 32)	2010 (4)	⊕⊕⊕○ Moderate <sup>a</sup>	False negatives	14 (7 to 18)	34 (18 to 44)	True negatives	65 (34 to 77)	41 (22 to 48)	2010 (4)	⊕⊕⊕○ Moderate <sup>a</sup>	False positives	15 (3 to 46)	9 (2 to 28)
Test result	Number of results per 100 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)																				
	Prevalence 20% Typically seen in	Prevalence 50% Typically seen in																							
True positives	6 (2 to 13)	16 (6 to 32)	2010 (4)	⊕⊕⊕○ Moderate <sup>a</sup>																					
False negatives	14 (7 to 18)	34 (18 to 44)																							
True negatives	65 (34 to 77)	41 (22 to 48)	2010 (4)	⊕⊕⊕○ Moderate <sup>a</sup>																					
False positives	15 (3 to 46)	9 (2 to 28)																							
Certainty of the evidence of test accuracy	<p>What is the overall certainty of the evidence of test accuracy?</p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>CI: Confidence interval</p> <p><b>Explanations</b></p> <p><sup>a</sup> There was high heterogeneity across studies resulting in wide confidence.</p> <p>A false positive diagnosis could cause STI-related stigma for the patient and their sexual partner(s), and they might take unnecessary antibiotics, with potential risks of adverse side-effects and contributing to the development of antimicrobial resistance.</p> <p>Overtreatment is a key consideration. Antibiotic use can exert selection pressure, giving resistant strains advantage over susceptible strains, increasing the development of resistance. Resource-limited settings are an incubator of antimicrobial-resistant STIs since they have large STI burdens (16).</p> <p>Increasing consumption of antibiotics (both humans and animals) (17), reliance on syndromic STI management, weaker health systems and limited regulations for governing the access, use and quality of antibiotics.</p> <p><b>Considerations for certainty of test accuracy</b></p> <p>Evidence is derived largely from men who have sex with men; heterosexual women also practise receptive anal sex, but there are no data on syndromic management of anorectal syndrome for women.</p>																							
Certainty of the evidence of the effects of management	<p>What is the overall certainty of the evidence of effects of the management that is guided by the test results?</p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>	<p>We have evidence for treatment of the STIs related to anorectal discharge.</p>																							
Certainty of effects	<p>What is the overall certainty of the evidence of effects of the test?</p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input checked="" type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input type="radio"/> No included studies</p>																								

	Judgement	Research evidence																																										
Values	<p><b>Is there important uncertainty about or variability in how much people value the main outcomes?</b></p> <p><input type="radio"/> Important uncertainty or variability</p> <p><input type="radio"/> Possibly important uncertainty or variability</p> <p><input checked="" type="radio"/> Probably no important uncertainty or variability</p> <p><input type="radio"/> No important uncertainty or variability</p>	<p>The Guideline Development Group placed greater value on the false negatives (missed cases) than on the false positives (people unnecessarily treated).</p>																																										
Balance of effects	<p><b>Does the balance between desirable and undesirable effects favour the intervention or the comparison?</b></p> <p><input checked="" type="radio"/> Favours the comparison</p> <p><input type="radio"/> Probably favours the comparison</p> <p><input type="radio"/> Does not favour either the intervention or the comparison</p> <p><input type="radio"/> Probably favours the intervention</p> <p><input type="radio"/> Favours the intervention</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>Although fewer people would be treated unnecessarily if the previous WHO syndromic management approach were used, there would be more missed cases compared with treating all, and greater value was placed on avoiding missed cases. In addition, there would be no missed cases or unnecessary treatment if molecular testing is used.</p> <p>The Guideline Development Group therefore agreed that the balance of benefits and harm favours treating all or molecular testing.</p>																																										
Resources required	<p><b>How large are the resource requirements (costs)?</b></p> <p><input type="radio"/> Large costs</p> <p><input type="radio"/> Moderate costs</p> <p><input checked="" type="radio"/> Negligible costs and savings</p> <p><input type="radio"/> Moderate savings</p> <p><input type="radio"/> Large savings</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>We did not identify studies that evaluated the cost of anorectal syndrome management.</p> <p>Korenromp (18) reported the unit costs of diagnostic and treatment commodities:</p> <table border="1"> <thead> <tr> <th>STI</th> <th>Treatment</th> <th>Dose per day</th> <th>Treatment duration</th> <th>Drugs, per dose</th> <th>Drugs + service delivery</th> </tr> </thead> <tbody> <tr> <td>Gonorrhoea</td> <td>Ceftriaxone 250 mg</td> <td>1</td> <td>1 day</td> <td>US\$ 0.57</td> <td>US\$ 10.71</td> </tr> <tr> <td>Chlamydia</td> <td>Azithromycin 500 mg</td> <td>2</td> <td>1 day</td> <td>US\$ 0.38</td> <td>US\$ 10.95</td> </tr> <tr> <td>Trichomoniasis</td> <td>Metronidazole 500 mg</td> <td>4</td> <td>1 day</td> <td>US\$ 0.01</td> <td>US\$ 10.05</td> </tr> <tr> <td colspan="6"><b>Diagnostic test</b></td> </tr> <tr> <td>Gonorrhoea and chlamydia</td> <td colspan="4">NAAT: assuming a price reduction starting 2016, from US\$ 20 as of 2016 (specimen collection in primary care; testing in secondary and tertiary care facilities)</td> <td>US\$ 12.00<sup>a</sup></td> </tr> <tr> <td>Trichomoniasis</td> <td colspan="4">Wet mount (point of care)</td> <td>US\$ 4.00</td> </tr> </tbody> </table> <p><sup>a</sup> Current cost of NAAT US\$ 16.</p> <p>There are negligible differences in costs when treating all or when using the previous WHO syndromic approach, but the greatest cost with molecular testing.</p>	STI	Treatment	Dose per day	Treatment duration	Drugs, per dose	Drugs + service delivery	Gonorrhoea	Ceftriaxone 250 mg	1	1 day	US\$ 0.57	US\$ 10.71	Chlamydia	Azithromycin 500 mg	2	1 day	US\$ 0.38	US\$ 10.95	Trichomoniasis	Metronidazole 500 mg	4	1 day	US\$ 0.01	US\$ 10.05	<b>Diagnostic test</b>						Gonorrhoea and chlamydia	NAAT: assuming a price reduction starting 2016, from US\$ 20 as of 2016 (specimen collection in primary care; testing in secondary and tertiary care facilities)				US\$ 12.00 <sup>a</sup>	Trichomoniasis	Wet mount (point of care)				US\$ 4.00
STI	Treatment	Dose per day	Treatment duration	Drugs, per dose	Drugs + service delivery																																							
Gonorrhoea	Ceftriaxone 250 mg	1	1 day	US\$ 0.57	US\$ 10.71																																							
Chlamydia	Azithromycin 500 mg	2	1 day	US\$ 0.38	US\$ 10.95																																							
Trichomoniasis	Metronidazole 500 mg	4	1 day	US\$ 0.01	US\$ 10.05																																							
<b>Diagnostic test</b>																																												
Gonorrhoea and chlamydia	NAAT: assuming a price reduction starting 2016, from US\$ 20 as of 2016 (specimen collection in primary care; testing in secondary and tertiary care facilities)				US\$ 12.00 <sup>a</sup>																																							
Trichomoniasis	Wet mount (point of care)				US\$ 4.00																																							

	Judgement	Research evidence
Certainty of evidence of required resources	<p><b>What is the certainty of the evidence of resource requirements (costs)?</b></p> <p><input type="radio"/> Very low</p> <p><input type="radio"/> Low</p> <p><input type="radio"/> Moderate</p> <p><input type="radio"/> High</p> <p><input checked="" type="radio"/> No included studies</p>	No studies identified.
Cost-effectiveness	<p><b>Does the cost-effectiveness of the intervention favour the intervention or the comparison?</b></p> <p><input checked="" type="radio"/> Favours the comparison</p> <p><input type="radio"/> Probably favours the comparison</p> <p><input type="radio"/> Does not favour either the intervention or the comparison</p> <p><input type="radio"/> Probably favours the intervention</p> <p><input type="radio"/> Favours the intervention</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> No included studies</p>	<p>No studies identified.</p> <p>The Guideline Development Group agreed that, based on cost-effectiveness, treating all (the comparison) is favoured rather than the previous WHO syndromic approach.</p>
Equity	<p><b>What would be the impact on health equity?</b></p> <p><input type="radio"/> Reduced</p> <p><input type="radio"/> Probably reduced</p> <p><input checked="" type="radio"/> Probably no impact</p> <p><input type="radio"/> Probably increased</p> <p><input type="radio"/> Increased</p> <p><input type="radio"/> Varies</p> <p><input type="radio"/> Don't know</p>	<p>Most studies (seven of eight) involved men who have sex with men. We only identified one study that examined the accuracy of anorectal syndromic management among 345 trans-women in Brazil for detecting <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> (in 2015–2016) (5). In this study population, 48% were reported to be current sex workers. Those who reported more than five sexual partners in the preceding six months had higher odds for anorectal <i>C. trachomatis</i> (aOR 2.5 [0.9–6.9]).</p> <p>One study evaluated the value of presumptive treatment of anorectal <i>C. trachomatis</i> or <i>N. gonorrhoeae</i> (diagnosed using NAAT) among 277 men who have sex with men who were sex workers in Kenya (19). Among this high-risk group of men, one of 10 would have asymptomatic <i>C. trachomatis</i> or <i>N. gonorrhoeae</i>.</p> <p>A study of 698 men who have sex with men in Kenya reported that those with higher risk of anorectal <i>C. trachomatis</i> or <i>N. gonorrhoeae</i> were asymptomatic men aged 18–24 years (aOR 7.6 [1.7–33.2]), people living with HIV (aOR 6.9 [2.2–21.6]) and men who had condomless anal sex in the preceding three months (aOR 3.8 [1.2–11.9]) (2).</p>

	Judgement	Research evidence
Acceptability	<p><b>Is the intervention acceptable to key stakeholders?</b></p> <p> <input type="radio"/> No  <input type="radio"/> Probably no  <input checked="" type="radio"/> Probably yes  <input type="radio"/> Yes  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	No studies were identified.
Feasibility	<p><b>Is the intervention feasible to implement?</b></p> <p> <input type="radio"/> No  <input type="radio"/> Probably no  <input type="radio"/> Probably yes  <input checked="" type="radio"/> Yes  <input type="radio"/> Varies  <input type="radio"/> Don't know         </p>	No studies were identified.

## Summary of judgements

Problem	Judgement						
	No	Probably no	Probably yes	Yes		Varies	Don't know
Test accuracy	Very inaccurate	Inaccurate	Accurate	Very accurate		Varies	Don't know
Desirable effects	Trivial	Small	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	Small	Trivial		Varies	Don't know
Certainty of the evidence of test accuracy	Very low	Low	Moderate	High			No included studies
Certainty of the evidence of the effects of management	Very low	Low	Moderate	High			No included studies
Certainty of effects	Very low	Low	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
Certainty of evidence of required resources	Very low	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	No included studies
Equity	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		Varies	Don't know
Feasibility	No	Probably no	Probably yes	Yes		Varies	Don't know

## Conclusions

### Should the current WHO syndromic management approach be recommended versus laboratory diagnosis, no treatment and treat all to identify sexually transmitted infections among people with anorectal discharge?

Type of recommendation	● Strong recommendation against the intervention	○ Conditional recommendation against the intervention	○ Conditional recommendation for either the intervention or the comparison	○ Conditional recommendation for the intervention	○ Strong recommendation for the intervention
<b>Recommendation</b>	<p>Recommendations for management of anorectal discharge</p> <p>For people with symptom of anorectal discharge and report receptive anal sex, we recommend management based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, we recommend syndromic treatment to ensure treatment on the same day of the visit.</p> <p>Good practice includes:</p> <ul style="list-style-type: none"> <li>• taking a medical and sexual history and assessing the risk of STIs;</li> <li>• performing a physical examination of the genital and perianal areas and a digital rectal examination, if acceptable (and anoscopy, if available and acceptable);</li> <li>• offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and</li> <li>• referring for other investigations when anorectal discharge is unrelated to a sexually transmitted infection, such as other gastrointestinal conditions.</li> </ul> <p><i>Settings with quality-assured molecular testing in a laboratory with a fully operational quality management system and results available on the same day of the visit</i></p> <p>We recommend the following.</p> <ol style="list-style-type: none"> <li>1. Perform molecular assays (nucleic acid amplification test (NAAT)) using a self-collected or clinician-collected anorectal swab to confirm or exclude infection with <i>N. gonorrhoeae</i> and/or <i>C. trachomatis</i> and treat the individual infections detected.</li> <li>2. Treat, additionally, for herpes simplex virus if there is anorectal pain.</li> <li>3. Follow the genital ulcer guidelines if ulceration is present.</li> </ol> <p><i>Settings in which same-day treatment is not feasible with molecular testing or with limited or no molecular testing</i></p> <p>We suggest the following.</p> <ul style="list-style-type: none"> <li>• Treat for <i>N. gonorrhoeae</i> and <i>C. trachomatis</i> if discharge is present.</li> <li>• Treat, additionally, for herpes simplex virus if there is anorectal pain.</li> </ul> <p>Good practice includes.</p> <ul style="list-style-type: none"> <li>• Following the genital ulcer guidelines if ulceration is present.</li> <li>• Referring people with persistent anorectal discharge to a centre with laboratory capacity to diagnose <i>N. gonorrhoeae</i>, <i>C. trachomatis</i> (including lymphogranuloma venereum serovars) and <i>M. genitalium</i> and determine antimicrobial resistance for <i>N. gonorrhoeae</i> and <i>M. genitalium</i>.</li> </ul>				
<b>Justification</b>	<p>Managing people presenting with anorectal discharge based on a syndromic approach results in small benefits and moderate harm compared with molecular testing or treating all. Molecular testing may not be feasible in all settings and, alternatively, treating all would be feasible and the costs would be negligible. Treating all or conducting molecular testing would be acceptable to all and would not negatively affect equity (in some settings, it may increase equity).</p>				

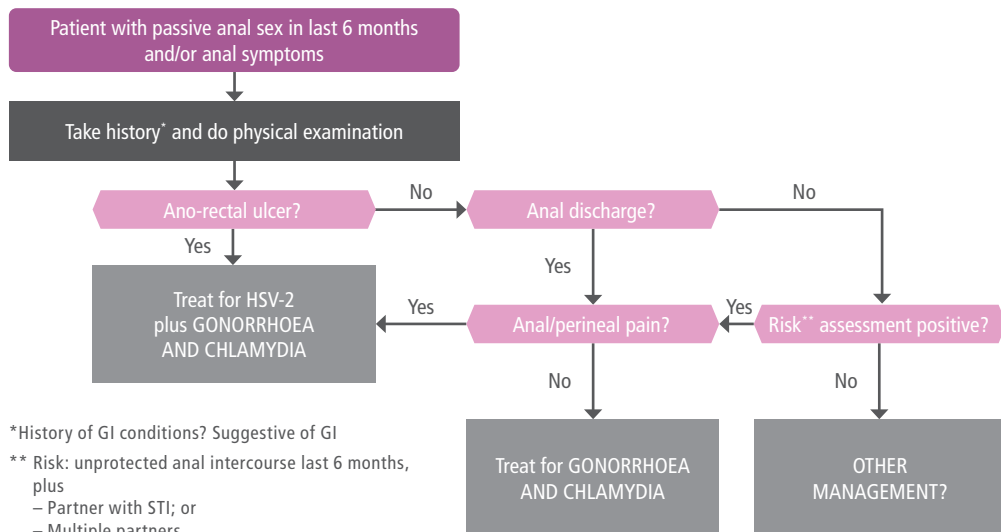
## References

1. Mugundu PR, Narayanan P, Das A, Morineau G. Assessing syndromic management algorithms for the diagnosis of rectal chlamydia and gonorrhoeae among men who have sex with men clinic attendees from two cities in India. *Sex Transm Infect.* 2013;89(Suppl. 1).
2. Quilter LAS, Obondi E, Kunzweiler C, Okall D, Bailey RC, Djomand G et al. Prevalence and correlates of and a risk score to identify asymptomatic anorectal gonorrhoea and chlamydia infection among men who have sex with men in Kisumu, Kenya. *Sex Transm Infect.* 2019;95:201–11.
3. Rebe K, Lewis D, Myer L, de Swardt G, Struthers H, Kamkuemah M et al. A cross sectional analysis of gonococcal and chlamydial infections among men-who-have-sex-with-men in Cape Town, South Africa. *PLoS One.* 2015;10:e0138315.
4. Sanders EJ, Wahome E, Okuku HS, Thiong'o AN, Smith AD, Duncan S et al. Evaluation of WHO screening algorithm for the presumptive treatment of asymptomatic rectal gonorrhoea and chlamydia infections in at-risk men who have sex with men in Kenya. *Sex Transm Infect.* 2014;90:94–9.
5. Caracas C, Jalil EM, Garcia ACF, Nazer SC, De Oliveira LP, Veloso V et al. High chlamydia and gonorrhoea prevalences and low performance of syndromic management among Brazilian trans-women. *AIDS Res Hum Retrovirus.* 2018;34(Suppl. 1):240.
6. Passaro RC, Segura ER, Perez-Brumer A, Cabeza J, Montano SM, Lake JE et al. Body parts matter: social, behavioral, and biological considerations for urethral, pharyngeal, and rectal gonorrhoea and chlamydia screening among men who have sex with men in Lima, Peru. *Sex Transm Infect.* 2018;45:607–14.
7. Van der Bij AK, Spaargaren J, Morre SA, Fennema HS, Mindel A, Coutinho RA et al. Diagnostic and clinical implications of anorectal lymphogranuloma venereum in men who have sex with men: a retrospective case-control study. *Clin Infect Dis.* 2006;42:186–94.
8. Chan PA, Robinette A, Montgomery M, Almonte A, Cu-Uvin S, Lonks JR et al. Extragenital infections caused by *Chlamydia trachomatis* and *Neisseria gonorrhoeae*: a review of the literature. *Infect Dis Obstet Gynecol.* 2016;2016:5758387.
9. Kent CK, Chaw JK, Wong W, Liska S, Gibson S, Hubbard G et al. Prevalence of rectal, urethral, and pharyngeal chlamydia and gonorrhoea detected in 2 clinical settings among men who have sex with men: San Francisco, California, 2003. *Clin Infect Dis.* 2005;41:67–74.

10. Soni S, White JA. Self-screening for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* in the human immunodeficiency virus clinic – high yields and high acceptability. *Sex Transm Dis.* 2011;38:1107–9.
11. Turner AN, Reese PC, Ervin M, Davis JA, Fields KS, Bazan JA. HIV, rectal chlamydia, and rectal gonorrhoea in men who have sex with men attending a sexually transmitted disease clinic in a midwestern US city. *Sex Transm Dis.* 2013;40:433–8.
12. Ross MW, Nyoni J, Ahaneke HO, Mbwambo J, McClelland RS, McCurdy SA. High HIV seroprevalence, rectal STIs and risky sexual behaviour in men who have sex with men in Dar es Salaam and Tanga, Tanzania. *BMJ Open.* 2014;4:e006175.
13. Kim EJ, Hladik W, Barker J, Lubwama G, Sendagala S, Ssenkusu JM et al. Sexually transmitted infections associated with alcohol use and HIV infection among men who have sex with men in Kampala, Uganda. *Sex Transm Infect.* 2016;92:240–5.
14. Muraguri N, Tun W, Okal J, Broz D, Raymond HF, Kellogg T et al. HIV and STI prevalence and risk factors among male sex workers and other men who have sex with men in Nairobi, Kenya. *J Acquir Immune Defic Syndr.* 2015;68:91–6.
15. Katz DA, Dombrowski JC, Bell TR, Kerani RP, Golden MR. HIV incidence among men who have sex with men after diagnosis with sexually transmitted infections. *Sex Transm Dis.* 2016;43:249–54.
16. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ.* 2019;97:548–62.
17. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis.* 2014;14:742–50.
18. Korenromp EL, Wi T, Resch S, Stover J, Broutet N. Costing of national STI program implementation for the global STI control strategy for the health sector, 2016–2021. *PLoS One.* 2017;12:e0170773.
19. Okuku HS, Wahome E, Duncan S, Thiongo A, Mwambi J, Sahfi J et al. Evaluation of presumptive treatment recommendation for asymptomatic anorectal gonorrhoea and chlamydia infections in at-risk men who have sex with men in Kenya. *J Int AIDS Soc.* 2012;15:99.



**Fig. A7.1. Current WHO syndromic approach to the management of anorectal syndrome**



\*History of GI conditions? Suggestive of GI

\*\* Risk: unprotected anal intercourse last 6 months, plus  
 – Partner with STI; or  
 – Multiple partners

Follow up after 1 week. If symptoms persist:

- Treat for LGV;
- Treat for HSV;
- Refer

**Table A7.1. Detection of any STI for anorectal syndrome**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Pathogens and test	True positive	False negative	False positive	True negative
Mugundu et al. (1)	2008–2009	India	Lower middle	868	Sexual health clinic	100% men who have sex with men	Receptive anal sex and/or anal discharge + subsequent proctoscopy ± smear findings	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> NAAT – Roche AmpliCor	53	74	250	491
Mugundu et al. (1)	2008–2009	India	Lower middle	868	Sexual health clinic	100% men who have sex with men	Adding “risk assessment” to above		104	23	592	149
Quilter et al. (2)	Unclear	Kenya	Lower middle	698	Community settings	99% men who have sex with men	Anal symptoms + “risk assessment” (model-derived risk score)	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> NAAT – Abbott Realtime	15	21	151	511
Rebe et al. (3)	2012	South Africa	Upper middle	200	Sexual health clinic	100% men who have sex with men	Symptoms only	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> , Aptima Combo 2	9	38	13	140
Sanders et al. (4)	2011–2012	Kenya	Lower middle	244	Unclear	100% men who have sex with men	Symptoms + “risk assessment”	<i>C. trachomatis</i> and <i>N. gonorrhoeae</i> Aptima Combo 2	3	28	1	212

**Table A7.2. Detection of anal gonorrhoea for anorectal syndrome**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostic	True positive	False negative	False positive	True negative
Caracas et al.(5)	2015–2016	Brazil	Upper middle	345	Unclear	100% trans-women	Symptoms only	Not reported	4	43	26	272
Passaro et al.(6)	2012–2014	Peru	Upper middle	787	Unclear	100% men who have sex with men	Symptoms only	NAAT	3	62	16	706
Quilter et al.(2)	Unclear	Kenya	Lower middle	698	Community settings	99% men who have sex with men	Anal symptoms + "risk assessment" (model-derived risk score)		12	15	154	517
Rebe et al.(3)	2012	South Africa	Upper middle	200	Sexual health clinic	100% men who have sex with men	Symptoms only		3	14	19	164
Sanders et al.(4)	2011–2012	Kenya	Lower middle	19	Unclear	100% men who have sex with men	Symptoms + "risk assessment"		4	3	11	1

**Table A7.3. Detection of anal chlamydia for anorectal syndrome**

Study	Year of study	Country	Country income level	Sample size	Where recruited	Subpopulation	How a positive case is defined	Diagnostic	True positive	False negative	False positive	True negative
Caracas et al. (5)	2015–2016	Brazil	Upper middle	345	Unclear	100% trans-women	Symptoms only	Not reported	22	28	8	287
Passaro et al. (6)	2012–2014	Peru	Upper middle	787	Unclear	100% men who have sex with men	Symptoms only	NAAT	3	122	16	646
Quilter et al. (2)	Unclear	Kenya	Lower middle	698	Community settings	99% men who have sex with men	Anal symptoms + "risk assessment" (model-derived risk score)		8	11	158	521
Rebe et al. (3)	2012	South Africa	Upper middle	200	Sexual health clinic	100% men who have sex with men	Symptoms only		2	14	20	164
Sanders et al. (4)	2011–2012	Kenya	Lower middle	244	Unclear	100% men who have sex with men	Symptoms + "risk assessment"		0	20	4	220

## ANNEX 8. SUPPLEMENTAL MATERIALS

Systematic review for urethral discharge

Systematic review for vaginal discharge

Systematic review for risk factors for gonorrhoea and chlamydial infection

Systematic review for lower abdominal discharge

Systematic review for genital ulcer

Systematic review for anorectal discharge

The role of *Mycoplasma genitalium* in acute and recurrent urethritis and pelvic inflammatory disease

Description of modelling of vaginal discharge





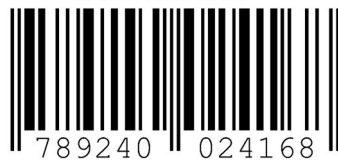
**For more information, contact:**

World Health Organization  
Department of Global HIV,  
Hepatitis and STI Programme  
20, avenue Appia  
1211 Geneva 27  
Switzerland

Email: [hiv-aids@who.int](mailto:hiv-aids@who.int)

[www.who.int/hiv](http://www.who.int/hiv)

9789240024168



9 789240 024168