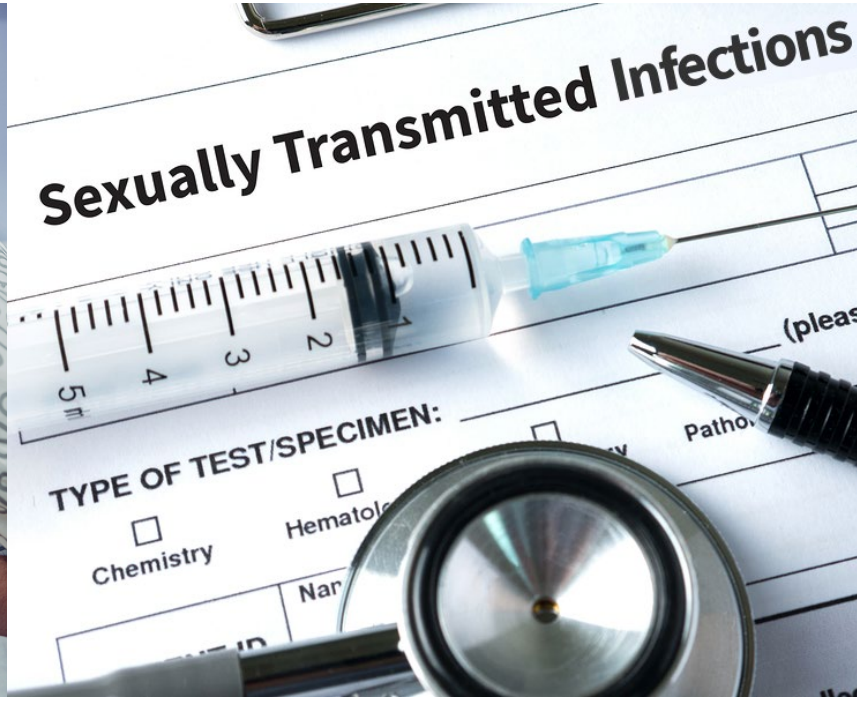
KCE REPORT 310Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SHORT REPORT

DIAGNOSIS AND MANAGEMENT OF GONORRHOEA AND SYPHILIS



KCE REPORT 310Cs
GOOD CLINICAL PRACTICE

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SHORT REPORT

DIAGNOSIS AND MANAGEMENT OF GONORRHOEA AND SYPHILIS

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SHORT REPORT

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AGREE	Appraisal of Guidelines Research and Evaluation
BAPCOC	Belgian Antibiotic Policy Coordination Committee
BPG	Benzathine Penicillin G
CDC	Centers for Disease Control and Prevention
CEBAM	Belgian Centre for Evidence-Based Medicine
CENTRAL	The Cochrane Central Register of Controlled Trials
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	Human Immunodeficiency Virus
ITM – IMT – ITG	Institute of Tropical Medicine (Institut de Médecine Tropicale – Instituut voor Tropische Geneeskunde)
IUSTI	International Union against Sexually Transmitted Infections
LGV	Lymphogranuloma venereum
MSM	Men who have Sex with Men
NAAT	Nucleic Acid Amplification Test
NGC	National Guideline Centre
NIHDI (INAMI – RIZIV)	National Institute for Health and Disability Insurance (Institut National d'Assurance Maladie-Invalidité – Rijksinstituut voor Ziekte- en Invaliditeitsverzekering)
Non-trep	Non-treponemal
PCR	Polymerase chain reaction
PICO	Participants–Interventions–Comparator–Outcomes
PoC	Point of Care
PrEP	Pre-exposure prophylaxis
QUADAS	Quality assessment tool for diagnostic accuracy studies
RCTs	Randomised Controlled Trials
RPR	Rapid Plasma Reagin
SDA	Strand Displacement Amplification
SSMG	Société Scientifique de Médecine Générale
STI(s)	Sexually transmitted infection(s)

Syp	Syphilis
TMA	Transcription Mediated Amplification
Trep	Treponemal
VBOV	Vlaamse Beroepsorganisatie van Vroedvrouwen
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

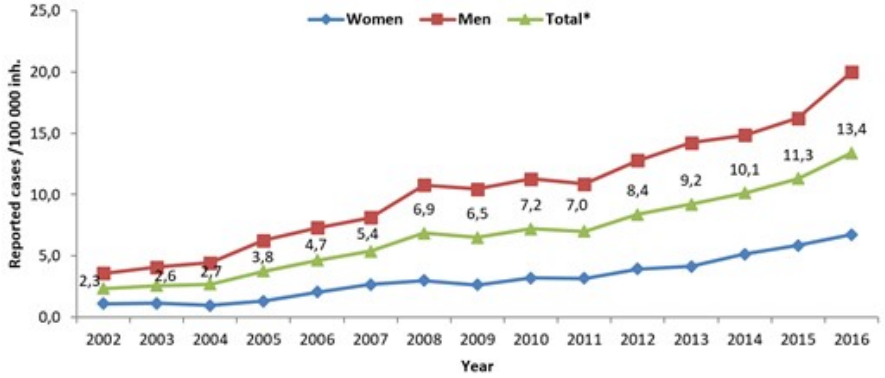
In Belgium, as in the rest of the world, a concerning incremental number of newly diagnosed sexually transmitted infections (STIs) has been reported (Figure 1).[1, 2] Suboptimal diagnostics, poor case reporting and limited surveillance has meant an underestimation of the incidence. *Chlamydia trachomatis* accounts for half of the new infections of which 50% occur in young people below 25 years, followed by gonorrhoea and syphilis being most common especially in men who have sex with men (MSM).[1, 3]

To halt this trend, an early detection of infections, effective treatment and good partner management are urgently needed in order to decrease onwards transmission and limit the risk of serious health sequelae.[1] STI diagnosis and treatment should be based on the best available scientific evidence avoiding inequality between patients, inappropriate use of resources and malpractice. Overuse of tests in low risk groups and underuse in high risk groups can lead to inappropriate use of resources and poor outcomes. In the same way, inadequate treatment also leads to potentially non justified costs, increase of resistance (e.g. to specific antibiotics) and poor outcomes, including high risk for dissemination, recurrence or infertility.

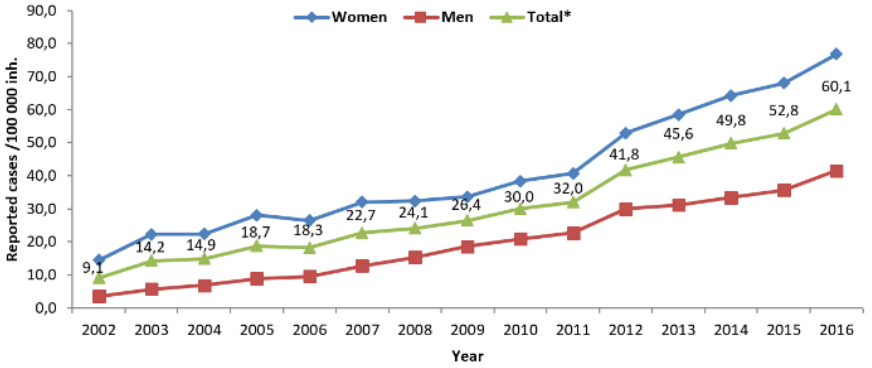
In the absence of a national guideline, certain clinics have developed and use their own clinic based testing strategies and refer to sexual health questionnaires based on Dutch, European or other guidelines.[4-8] In addition, five consensus based guidance documents were developed to inform and support the healthcare practitioners: a Domus Medica clinical practice tool for an STI consult intended for the general practitioner inclusive of a summary card (in Dutch),[9] a consultation guide for sex workers clinics (in Dutch),[10] a management guide for gonorrhoea and for syphilis (in Dutch),[11, 12] and a guide for antibiotic use (in French and Dutch).[13] A Belgian STI guideline would address the above mentioned issues including newly emerging challenges for the health professionals in the STI field e.g. gonorrhoea resistance to first-line treatment regimens,[1] increased incidence of pharyngeal gonorrhoea which is more difficult to treat,[1] the continued need to use culture for gonorrhoea resistance surveillance in an era of molecular amplification diagnostic platforms.

Figure 1 – Evolution of reported cases / 100 000 inhabitants for gonorrhoea, syphilis and chlamydia by gender, Belgium, 2002-2016

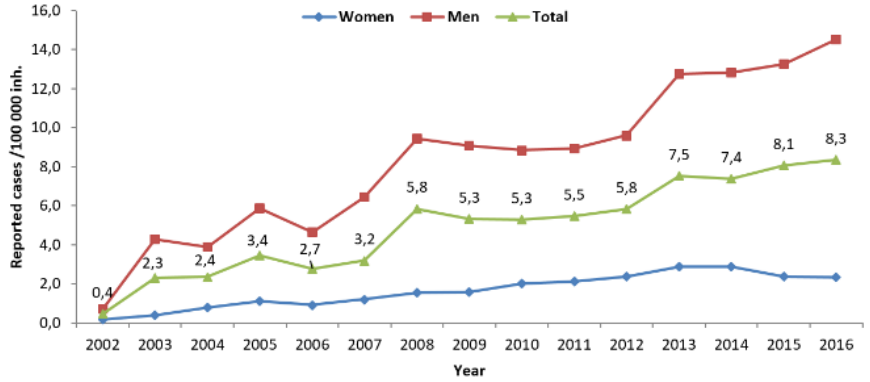
Gonorrhoea



Chlamydia



Syphilis



*Source: Vanden Berghe et al. 2018[2] *including cases for which gender was not reported; men include MSM and heterosexual men*

1.2 Remit of the guideline

1.2.1 Objectives of the guideline

The main objectives of this guideline are to provide information and best practices on STI management to a primary care physician with a focus on the diagnosis and treatment of gonorrhoea and syphilis. The scope of this guideline was defined in collaboration with experts and stakeholders and was restricted to:

- Primary care, more specifically the health care worker who would be the first contact of a patient with an STI or at risk of an STI;
- Opportunistic diagnostic testing in asymptomatic and symptomatic persons;
- Sexually active men and women (pregnant and non-pregnant women), including adolescents. Victims of sexual assault were excluded from this study due to particular situation and justice-related procedures.

This guideline provides recommendations for an evidence-based diagnosis and management of patients with sexually transmitted infections in Belgium. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation.

In parallel of this KCE guideline the following will be available: a **chlamydia guideline** developed by the Working group Development of primary Care Guidelines (http://www.ebpnet.be) in the context of the update of the 2004 Flemish guideline chlamydia for general practice[14] and a sexual health consultation **guidance** tool for STI testing (KCE). The guidance tool will summarise this guideline, the chlamydia guideline and add guidance for the other STIs.

1.2.2 Patient-centered care

The primary end clients of this guideline are primary health care providers involved in the detection, diagnosis and management of STIs. Additionally, this guideline is highly relevant to the policy makers and contributes to the HIV 2014-2019 plan and future plan. This comprehensive plan formulates recommendations for testing and access to care, specifying that a national testing strategy needs to be developed for HIV and STIs in accordance with existing regulations (action 37) and that opportunistic testing by general practitioners and specialists needs to be improved (action 38).

The choice of a diagnostic strategy possibly resulting in treatment should not only consider medical aspects but also patient preferences. Patients should be well and timely informed about all diagnostic options and all the treatment options and the advantages and disadvantages they offer. This information should be clear and repeated over time.

2 METHODOLOGY

2.1 The Guideline Development Group

This guideline is the result of a collaboration of first line health care professionals, infectious disease specialists, microbiologists, professional and patient associations and KCE researchers. Guideline development and literature review expertise, support, and facilitation were provided by the KCE Expert Team (V. Jespers, S. Stordeur and A. Desomer) and by a sub-contracting team, the National Guideline Centre (NGC) (S. Carville, C. Jones, S. Lewis, M. Perry), responsible for the literature review (search, quality appraisal, evidence tables) and the evaluation of the level of evidence using Grading of recommendations assessment, development and evaluation (GRADE) of the diagnosis and treatment of gonorrhoea and syphilis. The writing of the report, the conclusions and the recommendations remain the sole responsibility of the KCE team.

2.2 Clinical research questions

On June 30th 2017, a scoping group with representatives of professional and patient organisations, professional associations of general practitioners and midwives (e.g. Domus Medica, SSMG, VBOV), epidemiologists and scientists from clinical settings, university faculties or scientific institutes (e.g. Sciensano, IMT/ITG, Hôpital Saint-Pierre in Brussels) reviewed the original project demand: “How can existing STI practice guidelines be applied to the Belgian context with its specific target groups?” In preparation of the meeting a data search was performed to identify high quality guidelines. Medline was searched for comprehensive STI guidelines; chlamydia, syphilis, gonorrhoea infection specific guidelines; and, guidelines covering the STI consultation and the partner management. The decision of the scoping group was to focus on STI diagnosis and management in primary care and the following three broad research questions with nine sub-questions were withheld by the scoping group:

i. Management of patients with STIs

1. What is the clinical picture, diagnosis, treatment and management, inclusive of follow-up, and schedule of retesting for gonorrhoea and syphilis?

ii. What is the content and clinic flow for an STI primary care consultation?

2. How can opportunistic STI testing be offered?
3. What are the questions to ask for to identify risks and identify which tests to perform?
4. Which tests are to be performed for a pre-defined risk group?
5. Which specimen site(s) and test type is performed according to each STI?

iii. How is good partner management performed?

6. What are the process steps in partner(s) management?
7. How are the patient contacts identified?
8. What are the lookback periods?
9. And how is/are this/these partner(s) notified and managed?

For each broad question, specific research questions and PICO were derived; these can be found in the Scientific Report (Chapter 2.3., Table 6). The same approach was followed by the Working group Development of primary Care Guidelines for chlamydia. This chlamydia guideline is to be published by Ebpracticenet.

The **second and third broad questions** were planned as an implementation project of the KCE guideline and the chlamydia guideline. The outcome of this work consists of a sexual health consultation STI testing tool with extra information added in from a critical analysis of the literature. It will be reported in a subsequent publication.

Box 1 – What is in this report and what is not?

Included in this report

In this KCE report, the reader will find the following clinical recommendations separately for **gonorrhoea** and **syphilis**:

- Assessment of risk;
- Diagnosis: who to test, which sample to take, and which diagnostic tests to use;
- Treatment: information and advice for the patient; timing of initiation of therapy; when to refer to second line; treatment choice in men and women, in pregnant women and in people with an allergy to a recommended antibiotic; testing and surveillance for resistance;
- Test of cure, follow-up and testing frequency;
- Notification.

In this report, the first stages of the development of a sexual health consultation tool (methods and structure) are reported.

Not included in this report

The clinical recommendations for the management of **Chlamydia trachomatis** are reported in a separate report published by the Working group Development of primary Care Guidelines Ebpracticenet (http://www.ebpnet.be); this guideline can also be downloaded from the KCE Website (https://kce.fgov.be/en/publications).

The final tool (paper and online version) will be part of a further KCE report (to download from https://kce.fgov.be/en).

2.3 General approach

This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with members of the Guideline Development Group. A literature review was conducted, including a search for recent, high quality guidelines as well as grey literature. The ADAPTE method was used when high-quality, recent guidelines were available that were in line with the defined PICO (see http://processbook.kce.fgov.be/node/105). An additional literature search was conducted to update the evidence retrieved from the guidelines and to answer research questions not covered by the guidelines (e.g. combined diagnostic tests for gonorrhoea and chlamydia).

2.4 Quality assessment of studies

Retrieved diagnostic studies were assessed for the risk of bias and applicability concerns by means of the Quality assessment tool for diagnostic accuracy studies (QUADAS)-2 tool. The quality appraisal of randomised controlled trials (RCTs) and comparative observational studies for therapeutic interventions was performed using the "Cochrane Collaboration's tool for assessing risk of bias". All bias criteria were evaluated and described and scored as no serious risk, serious risk or very serious risk of bias. The GRADE approach was used to evaluate the quality of evidence (from very low quality to high quality) for each outcome and study.

2.5 Formulation of recommendations

The evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to guide the development of clinical practice recommendations and presented to the GDG, who formulated recommendations for clinical practice based on the evidence. In some cases, the GDG members added recommendations that are really important for practitioners but are not appropriate for formal ratings of quality of evidence according to the GRADE approach: 'Good practice statements' in blue tables. Good practice statements typically represent situations in which a large and compelling body of indirect evidence, made up of linked evidence including several indirect comparisons, strongly support the net benefit of the recommended action.[15] The same strategy was followed by WHO.[16]

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (KCE experts and NGC). This first draft was, together with the evidence tables, circulated to the guideline development group one to two weeks prior to the face-to-face meetings (30/3/2018, 08/06/2018, 06/09/2018, 10/09/2018, 04/10/2018, 22/10/2018 and 07/11/2018). Recommendations were changed if important new evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared and the summary table once more circulated to the guideline development group.

GDG members stated in the table if they agreed 'Yes' or 'No' and added comments whenever they disagreed. These comments were discussed at the next GDG meeting before a final approval and consensus was reached.

The final recommendations on all questions for gonorrhoea and syphilis were agreed with an evaluation by stakeholders via a mailed survey.

The strength of each recommendation was assigned using the GRADE system (Table 1). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study was conducted. For each recommendation, we provided its strength and the quality of the supporting evidence.

2.6 External review

The recommendations prepared by the GDG were circulated to sexual health associations involved in research, to citizens, patients and professionals working in sexual health, STI, and other modalities of STI prevention, screening, diagnosis and treatment (See colophon). All invited panellists received the scientific reports for all research questions and were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' (the panellists were also able to answer 'not applicable' if they were not familiar with the underlying evidence). If panellists disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. A summary table was made of the scores showing that the score was 4 to 5 for 89% of the recommendations. The comments were summarised and presented to the stakeholders at the meeting on December 7th 2018. Some minor and mostly textual changes were made to the recommendations accordingly.

2.7 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. This validation was done in two phases. First, the scientific content was assessed by two clinicians on January 29th 2019 (cf. names in the colophon). Second, the methodology was validated making use of the AGREE II checklist. This validation process was chaired by CEBAM on February 5th 2019 (cf. names in the colophon).

Table 1 – Strength of recommendations according to the GRADE system

Grade		Definition
Strong	**The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)***	
Meaning for:	Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
	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.
	Politicians	The recommendation can be adopted as policy in most situations.
Weak	**The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)***	
Meaning for	Patients	The majority of individuals in this situation would want the suggested course of action, but many would not.
	Clinicians	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
	Politicians	Policy-making will require substantial debate and involvement of various stakeholders.

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

3 CLINICAL RECOMMENDATIONS FOR MANAGEMENT OF GONORRHOEA

The details of the evidence used to formulate the recommendations and good practice statements below are available in the scientific report and its supplements. The tables follow the sequence of the chapters of the scientific report.

STI testing should aim to target those patients with high risk sexual behaviour or belonging to a group with the highest number of infections based on Belgian surveillance data. An **opportunistic testing approach** was preferred by the GDG even when the recommendation is to offer regular STI testing. Whether or not to be tested for STIs should be part of the decision-making process between the patient and the care provider. The primary care provider can thus use this guideline for his sexual health promotion activities.

3.1 Gonorrhoea diagnosis

3.1.1 Recommendations: Who to test for gonorrhoea

Based on a critical analysis of the type of patient proposed for gonorrhoea testing, the GDG defined the following patients or groups at risk for gonorrhoea infection.

The prevalence for Belgium was taken into account.[2] For young people, sexual activity rather than minimum age was proposed. The GDG agreed that competent minors can independently decide on low-risk medical interventions.[17] These may include tests or treatments with few side effects (e.g., taking blood samples, prescribing contraceptives, etc.) or interventions that pose few health risks (e.g. tooth extraction, etc.). Conducting an STI diagnostic test is a low-risk procedure. It is important to note that this concerns the ability to accept a diagnostic test. This should be distinguished from the ability to authorise acts that affect sexual integrity. Just because you were not legally considered capable of consenting to sexual intercourse does not mean that you could not legally consent to a (medical) act that is indirectly related to sexual intercourse.

Next to age, serial monogamous relationships are common and adolescents potentially switch from one partner to another, without being tested by the start of the relationship with a new partner (with an unknown HIV serological status). The experts would like to facilitate the implementation of a regular health consultation in the medical follow-up of adolescents. For any heterosexual relationship, the most important characteristics to keep in mind are the inconsistent use of a condom with a partner of whom the HIV serological status is unknown, or the relationships with concurrent partners. The GDG members emphasised the need to retest the pregnant women with high risk sexual behaviour or at increased risk for an STI, even with a primary negative test result, in the third trimester of the pregnancy in order to avoid gonorrhoea transmission to the foetus during delivery. The GDG reported difficulties in the process of contacting partners with suboptimal results. Currently, an online application is been set up to be used through Belgium. Partner notification is further discussed in section 5 as part of the implementation project.

Who to test for gonorrhoea	Strength of Recommendations	Level of Evidence
A. Patients with symptoms suspicious of gonorrhoea.	Weak	Very low
B. For asymptomatic patients with high risk sexual behaviour or at increased risk for gonorrhoea: 1. Sex worker of any gender 2. MSM with high risk behaviour • unprotected sexual contacts in non-exclusively monogamous relationships • who are on Pre-exposure prophylaxis (PrEP) • with a recent chlamydia, HIV or syphilis diagnosis 3. a) Patient or sex partner originates or travels to and from countries that are most affected: The WHO regions most affected are the African region, the Western Pacific region and the Americas. b) Patient or sex partner originates or travels to and from countries where multi-drug resistant gonorrhoea is prevalent: Southeast and East Asian countries 4. Heterosexual patient with unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships with/whenever • concurrent partners • multiple partners over a short time period • partner as defined above in classification 1, 2, or 3 • an STI diagnosis in the past year • partners in anonymous setting 5. Adolescents and young people up to the age of 29 years • who prefer to stop using condoms with their partner (expressed during a sexual health consultation) • who have unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships with/whenever ○ concurrent partners ○ multiple partners over a short time period ○ partner as defined above in classification 1, 2, or 3	Weak	Very low
C. All pregnant women in the first trimester or at the first antenatal visit if she or her partner belongs to classification 1 to 5. For pregnant women with high risk sexual behaviour or at increased risk for gonorrhoea as identified above, repeat test in the third trimester.	Weak	Very low
D. Test for gonorrhoea whenever: • a baby is born while the mother has an active infection • in case of abortion • sexual partner with suspected or confirmed gonorrhoea • all patients who are newly diagnosed with an STI including HIV • patients with a newly diagnosed hepatitis B or hepatitis C that may have been acquired through sexual transmission	Weak	Very low

3.1.2 Recommendations: Diagnostic tests for gonorrhoea

The diagnosis of uncomplicated gonorrhoea is established by identification of *N. gonorrhoea* in genital, rectal, or pharyngeal secretions mostly by Nucleic Acid Amplification Tests (NAATs). NAATs are widely used in Belgium and they are highly sensitive and specific diagnostic tests that can be conducted on a wide range of samples, including urine, and vulvovaginal, cervical and urethral swabs. The sensitivity varies by NAAT type and is frequently lower for rectal and pharyngeal samples. NAAT methodology involves amplification of specific *N. gonorrhoeae* DNA or RNA sequences by polymerase chain reaction (PCR), strand displacement assay (SDA), or transcription-mediated assay (TMA).

The full cost of the gonorrhoea molecular amplification amounts to 12.5€. Currently, no reimbursement limitation for gonorrhoea testing exists except for the combination of NAAT and culture, used for antibiotic sensitivity testing or surveillance, on the same prescription. For the monitoring of resistance, a culture is the only available option. This activity is performed at the reference laboratory in Antwerp at ITM.

Since co-infections of gonorrhoea and chlamydia are common, combined diagnostic test platforms have been developed testing for both organisms on the same sample. The reimbursement rules have not been adopted to this combined testing platform and this creates confusion and problems. For example, chlamydia is reimbursed for young people below the age of 21 years or when the patient is symptomatic and in both instances this is limited to a maximum of twice a year. The cost for the patient when not reimbursed for chlamydia is approximately 30€.

3.1.2.1 Recommendations: Diagnostic tests for gonorrhoea in men

Commercial NAATs, which are for the extra-genital samples (oropharyngeal and rectal) mostly not CE-labelled, need to be validated to evaluate the validity of the test insert specifics. Although both urine and urethral samples are adequate for NAATs the GDG pointed out that men prefer urine samples and both men and clinicians have an aversion for urethral swab taking as it is painful. Rectal self-collected sample collection is preferred by the patient but sample collection by the clinician has other advantages e.g. screening for anal cancer. Therefore, both rectal sampling methods can be considered.

Testing from multiple sites is expensive. Therefore, pooling of samples, thereby reducing the number of samples from 3 to 2 or even 1 may benefit the patient especially when testing is to be repeated every 3 to 6 months in individuals with high risk sexual behaviour. The pooling of an oropharyngeal, urine/urethral and rectal sample on site (clinician) or in the laboratory are both an area of research. Laboratory pooling has recently been tried in Belgium in MSM and although NAAT inhibition (a cause of false negatives) was less present , the study was too small to draw firm conclusions.[18]

Diagnostic tests for gonorrhoea in men	Strength of Recommendations	Level of Evidence
For asymptomatic and symptomatic men, offer NAAT test(s) from one or more sample sites according to their sexual behaviour o Insertive position (vaginal, anal, or oropharyngeal): use a first flow urine (asymptomatic) or an urethral sample (symptomatic) for a combined gonorrhoea-chlamydia NAAT o Anal receptive position: use a anorectal sample for a combined gonorrhoea-chlamydia NAAT o Oropharyngeal receptive position: use an oropharyngeal sample for a gonorrhoea NAAT	Strong	Urine and urethral: low (SDA), moderate (TMA) and high (PCR). Rectal and pharyngeal: very low (SDA, TMA)
For men who have sex with men known to have high sexual risk behaviour: sample all three sites	Weak	Very low
The use of a NAAT test on pooled samples (oropharyngeal, urine/urethral and rectal) was evaluated in one study. Currently, we suggest that 1st line healthcare practitioners take separate samples and send them to the laboratories with a prescription detailing the level of risk. There, a decision can be taken to use a NAAT test on pooled samples in specific situations (e.g. high risk setting, need for repetitive testing) when in-house validated technology and expertise is available.	Weak	Moderate
In men, do NOT offer culture testing for initial diagnosis.[μ]	Strong	Rectal: low to moderate. Pharyngeal: very low.

[μ]*Symptomatic men suspected of gonorrhoea could contribute to antimicrobial resistance surveillance and a culture should be taken at initial diagnosis, especially if they are treated presumptively (see recommendation 3.2.3). NAAT: nucleic acid amplification test; SDA: strand displacement amplification; TMA: transcription mediated amplification; PCR: polymerase chain reaction*

3.1.2.2 Recommendations: Diagnostic tests for gonorrhoea in women

Although based on the sensitivity results vaginal samples perform better than urine samples, the GDG agreed that urine samples can be useful when vaginal samples are not acceptable (e.g. for cultural reasons). We did not retrieve evidence on pharyngeal swabs and limited evidence on rectal swabs for women; we followed the IUSTI guideline recommending to use an oropharyngeal swab in women who engage in receptive oral sex and a rectal swab in women who engage in receptive anal sex, even if these tests are not EC-approved.[4] Similar considerations for combined testing of gonorrhoea and chlamydia on one sample with one test platform as in men were made by the GDG. There is no evidence for pooling of samples in women with high risk sexual behaviour as compared to MSM.

Diagnostic tests for gonorrhoea in women	Strength of Recommendations	Level of Evidence
For asymptomatic and symptomatic women, offer NAAT test(s) from one or more sample sites according to their sexual behaviour:		
• Vaginal receptive intercourse: use either (self-collected or clinician-collected) vaginal or first flow urine samples for a combined gonorrhoea-chlamydia NAAT	Strong	Vaginal samples: low to moderate (self-collected); moderate to high (clinician-collected). Endocervical samples: low to high. Urine sample: very low (SDA) to moderate (TMA and PCR).
• Oral receptive: oropharyngeal sample for a gonorrhoea NAAT	Weak	Very low
• Receptive anal: anorectal sample for a combined gonorrhoea-chlamydia NAAT	Weak	Rectal: moderate (SDA) to high (TMA)
For women with high sexual risk behaviour: offer NAAT test(s) from all three sites.	Weak	Very low
In women, do NOT offer culture testing for initial diagnosis.	Strong	High
Research recommendation: To perform a study in women with sexual high risk behaviour with pooling of urine or vaginal, pharyngeal and anorectal samples.		

NAAT: nucleic acid amplification test; SDA: strand displacement amplification; TMA: transcription mediated amplification; PCR: polymerase chain reaction

3.1.3 Diagnosis of gonorrhoea: Good practice statements

The following practices were stipulated by the experts at the GDG meetings.

Diagnosis of gonorrhoea: Good practice statements
The ideal time interval for time since last urinating to consider in providing a sample is 1 hour.
First flow (first void) urine sample is preferred over midstream sample both for chlamydia and gonorrhoea.
Specimen collection swabs for *C. trachomatis / N. gonorrhoea* NAAT and gonorrhoea culture must be synthetic. Other materials (e.g. cotton wool, wood) might inhibit testing (CDC, 2014).[19]
Urethral specimen collection for *C. trachomatis/ N. gonorrhoea* is invasive requiring insertion of a swab 2–3 cm into the male urethral followed by two or three rotations to collect sufficient cells.[19] Urine specimens are less invasive and are preferred over urethral specimens.
For the clinician, to collect an oropharyngeal swab, use a wooden tongue depressor to hold the tongue in place; without touching the sides of the mouth, use a sterile swab to swab the posterior nasopharynx and the tonsillar arches.[19]

NAAT: nucleic acid amplification test

3.2 Gonorrhoea treatment

3.2.1 Recommendations regarding information and advice for the patient

The advice preferred by the GDG stayed in line with the IUSTI and CDC guidelines.[4, 7]

Gonorrhoea information and advice for the patient	Strength of Recommendations	Level of Evidence
Patients should be advised to abstain from sexual contact for seven days after they and their partners have completed treatment and their symptoms have resolved.	Weak	Very low
All persons who receive a diagnosis of gonorrhoea should be tested for other STIs, including chlamydia, syphilis, and HIV.	Weak	Very low
Patients (and their sex partners) should be given information about their infection, including details about transmission, prevention and complications. Verbal information needs to be reinforced with written support or video material such as, hyperlinks towards scientific websites or organisations dedicated to STIs leaflets, brochures.	Weak	Very low

The following Belgian websites contain useful information for patients:

- **https://depistage.be/ (French)**
- **https://www.sidasos.be/ (French)**
- **https://www.sensoa.be/ (Dutch)**
- **http://www.alias-bru.be/ (for male sex workers; Dutch, French, English)**
- **https://domusmedica.be/richtlijnen/steekkaarten-implementatiemateriaal?s=hiv (Dutch) for HIV testing guidance Flanders – Hermetic: HIV European Research on Mathematical Modelling & Experimentation of HIV Testing In hidden Communities; https://www.medischcentrumhuisartsen.be/documents/focus/agenda/downloads.xml?loc=&lang=nl (Dutch)**
- **https://domusmedica.be/richtlijnen/themadossiers/themadossier-seksueel-overdraagbare-infecties (Dutch)**
- **Digital anonymous platform to inform sexual partners in case of a STD diagnosis: https://www.partneralert.be (Dutch and French)**
- **Vaccination for hepatitis B for adults: Hoge gezondheidsraad: https://www.health.belgium.be/nl/advies-8816-vaccinatie-volwassenen-hepatitis-b; https://www.health.belgium.be/en/node/20219**
- **Vaccination hepatitis B adolescents: https://www.health.belgium.be/nl/advies-8809-vaccinatie-tegen-hepatitis-b-kinderen-en-adolescenten**
- **http://www.hivsam.be/fr/: The HIV-SAM Project supports HIV prevention and sexual health promotion with Sub-Saharan African Migrants (SAM) in Flanders.**

3.2.2 Recommendations regarding testing and surveillance for resistance

WHO recommends that treatment guidelines are refined based on data from recent and quality-assured gonococcal antimicrobial resistance surveillance.[16] Therefore, the GDG recommended the following in regards to surveillance.

Gonorrhoea testing and surveillance for resistance	Strength of Recommendations	Level of Evidence
In case of suspected or confirmed gonorrhoea after travelling to Southeast and East Asia (suspicion for resistant gonorrhoea[μ]) the following measures should be taken (if not already done): • Take a detailed travel history to elicit assumed location (country, region) of infection • Sample all potentially infected sites for culture and NAAT	Weak	Very low
In case of highly suspicious symptomatic gonorrhoea take both a NAAT and culture before treatment is started.	Weak	Very low
Before treatment is given • At the time of the consultation for a positive gonorrhoea NAAT test, a sample should be taken for culture (if not already done). This pre-treatment culture sample is needed for the surveillance activities for gonorrhoea resistance in Belgium.	Weak	Very low

[μ] *The Belgian resistance data are presented in the full report. NAAT: Nucleic Acid Amplification Test*

3.2.3 Recommendation regarding initiation of therapy

Initiation of therapy for gonorrhoea	Strength of Recommendation	Level of Evidence

Treatment is to be started for the following reasons:
• Positive culture or NAAT from any site for *N. gonorrhoea*
• Without waiting for the results of the diagnostic tests:
  ○ On epidemiological grounds
  ▪ if a recent partner has confirmed gonococcal infection
  ▪ mother of neonate with confirmed gonococcal infection
  ○ In case of symptoms and after specimen collection for laboratory testing
  ▪ purulent urethral discharge in men
  ▪ proctitis in men who have sex with men
  ▪ mucopurulent cervicitis in women
  ○ If follow-up cannot be assured and after specimen collection for laboratory testing
	Weak	Very low

** NAAT: nucleic acid amplification test*

3.2.4 Referral to the second line for gonorrhoea: Good practice statements

The definition of complicated gonorrhoea stayed in line with the IUSTI and CDC guidelines.[4, 7]

When to refer to the second line[μ] for gonorrhoea: Good practice statements
Patients should be referred to the second line **before initiation of treatment**: • When first line therapy is not available or cannot be tolerated (failed) by patient • When cephalosporin allergy is already known or documented • When the patient presents with complicated[£] gonorrhoea
Patients should be referred to the second line **at the time of treatment failure:** • When first line treatment fails based on symptoms or laboratory testing • When the antibiotic sensitivity report indicates resistance to ceftriaxone and/or azithromycin

[μ] Referral to the appropriate specialist or medical colleague knowledgeable in gonorrhoea who consults at a dedicated STI / HIV clinic or an infectious disease clinic or hospital, is guided by the symptoms and their severity, or other characteristics such as pregnancy. [£]Complicated gonorrhoea defined as upper genital tract infection i.e. epididymo-orchitis and (suspicion of) pelvic inflammatory disease, disseminated gonococcal infection, gonococcal conjunctivitis in adults, arthritis and arthritis-dermatitis syndrome

3.2.5 Recommendation for treatment of gonorrhoea in women and men including young people

In Belgium the data for 2016 show 8% resistance for azithromycin and 0.34% for ceftriaxone (MIC EUCAST breakpoints on 597 isolates). [2]

The GDG proposed the same combination treatment regimens for all patients except pregnant women, for the following reasons:

- Currently, the combination treatment and the dosages are appropriate to avoid resistance;
- Same treatment is proposed whatever the infected site (for vaginal, urethral, pharyngeal and anal infections);
- The treatment is in line with the European guideline and the Belgian guidelines;[9-11, 13, 20]
- A consistent treatment across the first and the second lines is easy to remember and to communicate.

Currently, pharmaceutical companies market azithromycin in two packages: 3*500 mg (~9.5 euros) and 6*500 mg (~14.5 euros). The out-of-pocket payments amount respectively to 3.5 euros and 7 euros.

Ceftriaxone is marketed in 1g vials (+ 3.5 ml solvent for IM injection). The public price varies between 4 and 11 euros per 1g and the out-of-pocket payment varies between 1.5 and 4 euros.

Treatment of gonorrhoea in women and men including young people	Strength of Recommendation	Level of Evidence
First line therapy for uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx in sexually active non-pregnant women and men including young people is recommended as follows: **Dual therapy:** Ceftriaxone 500 mg IM in a single dose AND azithromycin 2 g orally for all cases in a single dose	Weak	Very low

3.2.6 *Treatment of gonorrhoea: Good practice statements*

Treatment of gonorrhoea: Good practice statements
Belgian resistance data should determine the choice of therapy for gonorrhoea
As dual therapy, ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously and under direct observation.
Azithromycin tablets may be taken with or without food but gastrointestinal side-effects can be less if taken after food.

3.2.7 *Recommendation for treatment of gonorrhoea in pregnant women*

For pregnant women, the GDG proposed single treatment with ceftriaxone for the following reasons:

- Currently, there have been no cases of resistance in the treatment of pregnant women;
- Same treatment for vaginal, urethral, pharyngeal and anal infections;
- The treatment is in line with the European guideline and the guideline published by the Agentschap zorg en gezondheid 2017.[4, 11]

Treatment of gonorrhoea in pregnant women	Strength of Recommendation	Level of Evidence
First line therapy for uncomplicated gonorrhoea of the urethra, cervix, rectum and pharynx in pregnant women is recommended as follows: **Single therapy:** Ceftriaxone 500 mg IM in a single dose for all cases	Weak	Very low

3.2.8 Treatment of gonorrhoea in pregnant women: Good practice statements

Treatment of gonorrhoea in pregnant women: Good practice statements
Belgian resistance data should determine the choice of therapy for gonorrhoea.
The diagnosis of gonorrhoea in pregnant women should be communicated with the gynaecologist to ensure follow-up of adverse events of treatment and complications of infection for the mother as well as the foetus or neonate.
Pregnant women found to have gonococcal infection should be treated immediately, and should have a test of cure 4 weeks after treatment.
Pregnant women found to have gonococcal infection should be retested during the third trimester to prevent maternal postnatal complications and gonococcal infection in the neonate.

3.2.9 Treatment of gonorrhoea in people with an allergy to cephalosporin: Good practice statement

Because of the complexities of cephalosporin allergy and the importance of treatment, the GDG decided that all these patients should be referred to the second line for management.

Treatment of gonorrhoea in people with an allergy to cephalosporin: Good practice statement
In case of allergy to penicillin/cephalosporin, patients with gonorrhoea of the urethra, cervix, rectum, or pharynx have to be referred to the second line to receive the most adequate treatment.

3.2.10 Recommendations for treatment of chlamydia and gonorrhoea co-infection

The GDG discussed the treatment options for a combined gonorrhoea chlamydia infection. For this, the recommendations for chlamydia were taken into account (will be published on https://www.ebpnet.be/nl/Pages/default.aspx). The GDG preferred not to administer triple therapy but advised to perform a test of cure (see next section) because of alternative regimen used.

Treatment of a co-infection gonorrhoea and chlamydia	Strength of Recommendations	Level of Evidence
Urogenital or oropharyngeal infection		
Ceftriaxone 500 mg IM in a single dose AND azithromycine 2 g orally in a single dose	Weak	Very low
Anorectal infection		
Ceftriaxone 500 mg IM in a single dose AND doxycycline 100 mg twice a day orally for 7 days	Weak	Very low
Anorectal infection in HIV positive men with unknown status of LGV		
Anorectal LGV infection		
Ceftriaxone 500 mg IM in a single dose AND doxycycline 100 mg twice a day orally for 21 days	Weak	Very low
Pregnant women		
Ceftriaxone 500 mg IM in a single dose AND azithromycine 1 g orally in a single dose	Weak	Very low

Currently, pharmaceutical companies market doxycycline in packages of 10 x 100mg oral. The public price amounts ~7 euros and the out-of-pocket payment ~1.5 euro.

3.3 Gonorrhoea test of cure and frequency of testing

3.3.1 Recommendations regarding a test of cure for gonorrhoea

A test of cure to ensure eradication of infection and/or identify emerging resistance adds an extra cost to the care package of the patient. For the individual patient with persisting symptoms, this strategy may be beneficial and improve care. A test of cure can also contribute to the public health and detect changes in resistance levels to antibiotics and inform public health surveillance on the correct antibiotic treatment.

Test of cure for gonorrhoea	Strength of Recommendations	Level of Evidence
Test of cure should be performed optionally in gonorrhoea cases to ensure eradication of infection and identify emerging resistance. Test of cure should be performed in case of: • Suspicion of treatment failure • Pharyngeal infection • When a different regimen is used than indicated in this guideline (e.g. monotherapy) • In case of treatment of a co-infection with chlamydia • Pregnant women • After travelling to Southeast and East Asia	Weak	Very low
Scheme of the test of cure If persistence of symptoms: culture with antibiotic susceptibility of all the relevant anatomic sites 3-7 days after treatment completion; if culture negative supplement with NAAT 14 days after completion of treatment; If asymptomatic: NAAT four weeks after treatment completion; if positive perform culture with antibiotic susceptibility testing of all the relevant anatomic sites before referral to second line and starting further treatment.	Weak	Very low

3.3.2 *Recommendations regarding testing frequency for gonorrhoea*

Whether or not to retest for STIs should be part of the decision-making process between the patient and the care provider STI testing and should aim to target those patients at highest risk or groups with the highest number of infections. The primary care provider can thus use this guidance for their sexual health promotion activities.

Testing frequency for gonorrhoea	Strength of Recommendations	Level of Evidence
Repeat testing interval every 3 to 12 months (same for other STIs) for asymptomatic patients with high risk sexual behaviour or at increased risk for gonorrhoea:		
1. Sex worker of any gender	Weak	Very low
2. MSM with high risk sexual behaviour • unprotected sexual contacts in non-exclusively monogamous relationships • who are on PrEP • with a recent HIV diagnosis • with a STI diagnosis in the past	Weak	Very low
3. Adolescents and young people up to the age of 29 years who continue to have unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships	Weak	Very low
4. Heterosexual patient who continues to have unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships	Weak	Very low

3.4 Mandatory notification of gonorrhoea

All cases of infections by *N. gonorrhoea* have to be notified in Brussels and Flanders using one of the three channels offered to healthcare practitioners to notify an infectious disease (phone, mail or website).

4 CLINICAL RECOMMENDATIONS FOR MANAGEMENT OF SYPHILIS

4.1 Syphilis diagnosis

4.1.1 Recommendations: Who to test for syphilis

The GDG considered the retrieved guidelines on syphilis[6, 21-24] and the KCE report regarding the diagnostic tests performed during pregnancy[22] to define the patient groups at risk for syphilis. The prevalence of syphilis for Belgium was taken into account for the formulation of recommendations for primary care.[2] Similar as for gonorrhoea, the considerations for young people and people in heterosexual relationships do hold for syphilis. The GDG reported difficulties in the process of contacting partners with suboptimal results. Currently, an online application is been set up to be used through Belgium. Partner notification is further discussed in section 5 as part of the implementation project.

Who to test for syphilis	Strength of Recommendations	Level of Evidence
All pregnant women in the first trimester or at the first antenatal visit. For pregnant women with high risk sexual behaviour or at increased risk for syphilis as identified below, repeat test in the third trimester whatever the result of the first test.	Strong	Moderate
Patients with symptoms suspicious of syphilis (see best practices for overview symptoms).	Weak	Very low
For asymptomatic patients with high risk sexual behaviour or at increased risk for syphilis: 1. Sex worker of any gender 2. MSM with high risk behaviour • unprotected sexual contacts (including deep kissing) in non-exclusively monogamous relationships • who are on PrEP • with a recent HIV diagnosis • with a syphilis diagnosis in the past 3. Patient or sex partner originates or travels to and from a country where the prevalence of syphilis is known to be high. See WHO map (https://www.who.int/gho/sti/en/). Countries with a prevalence above 1% include: • Sub-Saharan Africa: Mauritania, Mali, Senegal, Guinea, Liberia, Côte d'Ivoire, Ghana, Togo, Gabon, Chad, Sudan, Eritrea, Ethiopia, Central African Republic, South Sudan, Somalia, Kenya, Gabon, Democratic Republic of Congo, Rwanda, Uganda, United Republic of Tanzania, Zambia, Mozambique, Namibia, Botswana, South Africa, Madagascar, Zimbabwe • North African countries: Morocco, Algeria • Indonesia and Papua New Guinea • South and middle America: Venezuela, Colombia, Dominican Republic, Argentina, Paraguay • Romania, Mongolia	Weak	Very low

4. Heterosexual patient with unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships with/whenever • concurrent partners • multiple partners over a short time period • partner as defined above in 1, 2, or 3 • an STI diagnosis including HIV in the past year • partners in anonymous setting 5. Adolescents and young people up to the age of 29 years with unprotected oral, anal or vaginal intercourse in monogamous relationships with/whenever • a chlamydia, gonorrhoea, or HIV is diagnosed • partner as defined above in categories 1, 2, 3 or 4		
Test for syphilis whenever: • a newborn/baby or other whenever the other was diagnosed with syphilis • in case of abortion • sexual partner with suspected or confirmed syphilis • all patients who are newly diagnosed with an STI including HIV • patients with a newly diagnosed hepatitis B or hepatitis C that may have been acquired through sexual transmission	Weak	Very low

4.1.2 Recommendations: Which sample to take for syphilis

Although PCR can be used to directly detect *T. pallidum* from a syphilitic genital ulcer, we lack evidence confirming that in oral and anal ulcer specimens the commensal treponemas are not occasionally amplified. This can result in biological false positives.

An advantage of the direct detection methods is that it allows an early diagnosis of syphilis prior to a serologic response. Caution should be taken with PCR tests for *T. pallidum* as they are currently not internationally approved and a strict laboratory validation protocol with the use of controls has to be present for good quality.[25, 26]

Which sample to take for syphilis diagnosis	Strength of Recommendations	Level of Evidence
The cornerstone of diagnosis are serological tests: Sample venous blood for serologic tests.	Strong	High
In case of a chancre, i.e. a single painless, indurated, clean base, clear serum, no blistering ± regional lymphadenopathy, depending on the local laboratory procedures: Sample any suspicious anogenital or oral ulcer by swab for PCR.	Weak	High

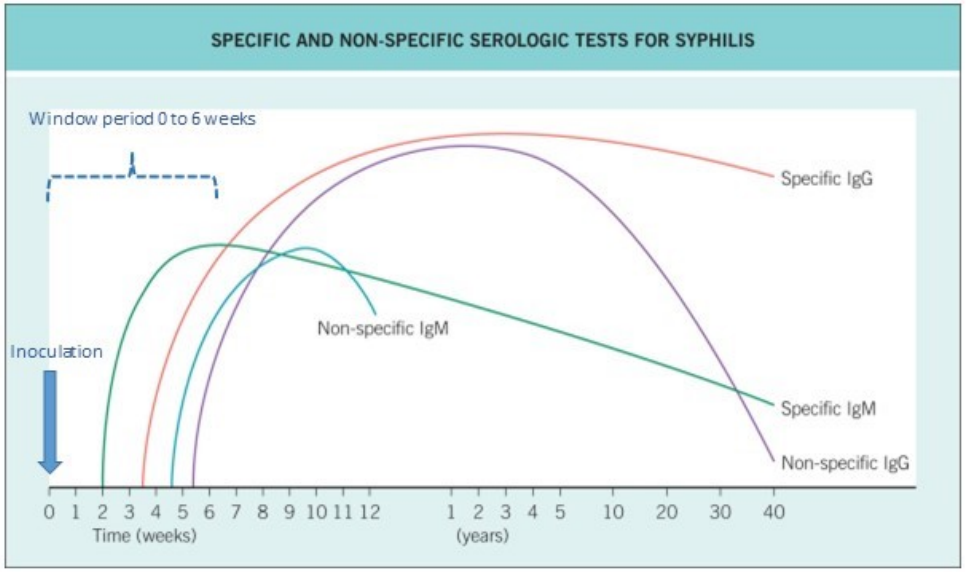
PCR: polymerase chain reaction

4.1.3 Recommendation: Which tests to use for syphilis

For a serological diagnosis of *Treponema pallidum* the result of one test does not suffice (Figure 2). Algorithms that combine both the results of treponemal and non-treponemal serological tests are used to define an active infection and its stage (primary, secondary or tertiary). The final result (positive, negative) should be based on a laboratory testing algorithm that makes use of more than one test performed on the same sample. Several algorithms are in place that combine serological tests, i.e. a traditional, a reverse, an updated reverse, and a hybrid algorithm. It can be difficult to define the exact stage of the infection solely on the basis of laboratory tests and especially when a patient is asymptomatic. ECDC advocates a flexible approach with combinations of the serological options and supports the updated reverse algorithm. In this 'updated' reverse algorithm a treponemal-specific test is used, followed by a second treponemal test and then followed by a non-treponemal test. The second treponemal test increases specificity and reduces the false positive results encountered on the automated analysers. Algorithms with a treponemal assay that do NOT add a non-treponemal assay into the testing scheme will have a high false positive rate as previously treated infections will be detected as well. Detailed information can be found in the IUSTI guideline.[6] In case of a negative non-treponemal test (after two positive treponemal tests), treponemal IgM is tested to detect a very early infection even in asymptomatic patients.

WHO and the European guidelines advise against the use of the syphilis point of care (PoC) tests in low syphilis prevalence settings, such as Belgium, as performance is low and access to laboratory high performance test is not an issue.[27] The use of any PoC test at clinical sites requires ongoing supervision by a reference laboratory, including provision of an external quality assurance programme.[28]

Figure 2 – Treponemal infection antibody patterns over time



Source: Personal communication Prof Henry de Vries

Which tests to use for syphilis diagnosis	Strength of Recommendation	Level of Evidence
On the basis of the current evidence we do not recommend to offer POC testing for the diagnosis of syphilis in first line.	Strong	Low

4.1.4 *Choice of tests for syphilis diagnosis: Good practice statements*

Choice of tests for syphilis diagnosis: Good practice statements
Because final diagnosis is made on grounds of clinical picture AND laboratory results: • Communicate with laboratory all relevant information from the patient's history and clinical diagnosis regarding symptoms, stage of infection, and previous infection, HIV status, pregnancy, and risk behaviours
Investigate ANY positive result: • After having sent samples to a laboratory, results could take 3 to 7 days. Make sure that the testing algorithm chosen by the laboratory is followed through (all diagnostic tests, including trep tests and non-trep tests are performed). If this is not clear, then discuss with laboratory. • If the results are difficult to interpret ask a colleague knowledgeable in syphilis for clarifications and / or refer.

4.2 Syphilis treatment

4.2.1 *Recommendations regarding syphilis information and advice for the patient*

Syphilis information and advice for the patient	Strength of Recommendations	Level of Evidence
Patients with early, infectious syphilis should be advised to abstain from sex until one week after start of treatment.	Weak	Very low
Patients (and their sex partners) should be given information about their infection, including details about transmission, prevention and complications. Verbal information needs to be reinforced with written support or video material such as, hyperlinks towards scientific websites or organisations dedicated to STIs leaflets, brochures.	Weak	Very low
All patients with a syphilis diagnosis should be offered testing for other STI including HIV.	Weak	Very low

4.2.2 Recommendation regarding initiation of syphilis therapy

Initiation of syphilis therapy	Strength of Recommendation	Level of Evidence
Treatment is to be started for the following reasons: • Active syphilis • Positive serological tests in combination with clinical information • On epidemiological grounds: Immediate epidemiological treatment for sexual contacts should be considered, especially of pregnant partners	Weak	Very low

4.2.3 Recognising syphilis clinical symptoms: Good practice statements

The GDG stressed that syphilis is uncommon in the first line and symptoms therefore might be missed.

Recognising syphilis clinical symptoms: Good practice statements

Patients with symptoms that are suspicious for syphilis

- Any chancre-like anogenital ulcer should be considered syphilis unless proven otherwise
- Primary syphilitic anogenital or oral ulcer / chancre
  - regional lymphadenopathy
  - single painless, indurated, clean base, clear serum, no blistering
  - atypical, multiple, painful, deep, indistinguishable from herpes
- Symptomatic secondary syphilis
  - non-itching skin rash (roseola, papular syphilids)
  - mucocutaneous lesions – condylomata lata
  - fever, generalized lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis and glomerulonephritis
  - meningitis, cranial nerve palsies
  - auricular and ophthalmic abnormalities (such as uveitis, retinitis, otitis and papilloedema)
- Symptomatic tertiary syphilis
  - gummatous syphilis: nodules/plaques or ulcers (skin, mucosae, visceral)
  - early or late neurosyphilis: stroke, myelitis, meningitis, cranial nerve dysfunction, general paresis, tabes dorsalis, unexplained sudden visual loss, unexplained sudden deafness
  - cardiovascular syphilis: aortic regurgitation, stenosis of coronary ostia, aortic aneurysm (mainly thoracic)

4.2.4 When to refer to the second line for syphilis: Good practice statements

When to refer to the second line for syphilis: Good practice statements
Patients should be referred to the second line [μ] before initiation of treatment: • pregnancy (also refer to gynaecologist) • clinical features of symptomatic late syphilis[£] • neurological symptoms or suspicion of neurosyphilis • suspicion of ocular syphilis • cardiovascular symptoms • complications
Guided by results serology after initiation of treatment • difficult interpretation of serologic tests that may affect treatment duration • repeat infections

[μ] Referral to the appropriate specialist or medical colleague knowledgeable in syphilis is guided by the symptoms and their severity, or other characteristics such as pregnancy; [£]gummatous disease, cardiovascular disease, ocular disease, neurological disease

4.2.5 Recommendations for treatment of syphilis in women and men including young people (excluding pregnant women)

Well-controlled clinical data are lacking on the optimal dose, duration of treatment and long-term efficacy of all antimicrobials, even for penicillin.[6] The GDG decision was guided by the following: Parenteral observed treatment is preferred over oral treatment as treatment of choice for better adherence:

- To maximize adherence with recommended therapies and reduce complications and transmission, medication for syphilis infection should be provided on site and directly observed.
- If medications are not available when treatment is indicated, linkage to an STI treatment facility should be provided for same-day treatment.

Stock out problems with BPG are universal and do exist in Belgium as well. At the present time BPG is imported from Portugal (Lentocillin S 1200) with an unlimited waiver. The IM route can be used in primary care settings but a prescription and extra consultation may be required before administration is done. Health insurance maximum reimbursement frequency rules apply: 6 times 1.2 million BPG Units per year.

Treatment of syphilis in women and men including young people excluding pregnant women	Strength of Recommendations	Level of Evidence
Early syphilis Give the following treatment to adults and adolescents with early syphilis (primary, secondary and early latent up to 1 year) including HIV positive patients:		
• First choice: BPG 2.4 million units at once intramuscularly on day 1	Strong	Low
• Second choice: Doxycycline 100 mg orally twice daily for 14 days (be aware of photosensitisation)	Strong	Very low
Late syphilis Give the following treatment to adults and adolescents with late syphilis (> 1 year), including HIV positive patients:		
• First choice: BPG 2.4 million units IM weekly for 3 consecutive weeks (day 1, day 8 and day 15)	Strong	Low
• Second choice: Doxycycline 100 mg orally twice daily for 28 days (be aware of photosensitisation)	Strong	Very low
In case of penicillin allergy		
• When in doubt, first assess the risk of anaphylaxis. If patients have a history compatible with an IgE mediated allergy then alternative therapies (such as doxycycline) should be used.	Strong	Very low
• Patients should also be referred for skin testing to confirm allergy and for consideration of penicillin desensitisation.	Weak	High

4.2.6 *Treatment of syphilis: Good practice statements*

Treatment of syphilis: Good practice statements
Administer BPG 2.4 million units by two injections of 1.2 million units in separate places (e.g. each buttock) and replacing part of solvent by the same volume of 1% lidocaine solution may reduce the pain associated with injection; check the solvent first as it may already contain lidocaine. Advise the patient to walk for 30 minutes to help the product resorb into the muscle.
Physicians should warn patients of the photo toxicity risk associated with doxycycline and advise patients on the use of a high sun protection factor (SPF) broad-spectrum sunscreen that offers good protection against UVB and UVA wavelengths; clothing, hat and behavioural avoidance of sun including shade are also important.
How to take doxycycline? • the tablets must be swallowed during the meal with a large glass of water • it is important not to lie down for an hour after taking the tablets. These conditions of intake must be respected due to possible digestive disorders, in particular oesophageal ulcerations.

4.3 Syphilis follow-up and frequency of testing

The following recommendations are in line with the European IUSTI and UK syphilis guideline.[6, 23]

4.3.1 Recommendations regarding follow-up of a treated patient

Follow-up of patients with treated syphilis	Strength of Recommendations	Level of Evidence
In case of a positive serology:		
1. Clinical and serological (non-trep RPR) follow-up should be performed • for early syphilis at three and six months • for late syphilis at three, six and 12 months	Strong	Very low
2. Referral [μ] is indicated when • recurrence of signs or symptoms • when RPR titres do not **decrease** four-fold within 6 months from day 1 of treatment for early syphilis (primary, secondary and early latent <1 year) • when RPR titres do not decrease four-fold within 12 months from day 1 of treatment for late syphilis (> 1 year**)**	Strong	Very low
In case of negative results (serum or PCR) in a suspected infected patient:		
1. Symptomatic patients with ulcer(s) treated for syphilis: • repeat serologic tests at 6 weeks after ulcer appearance to exclude diagnosis • optionally, perform serologic tests at 2 weeks after ulcer appearance to exclude diagnosis	Weak	Very low
2. Asymptomatic patients after an isolated high risk episode with exposure to syphilis: • repeat serologic test at 6 weeks (in all cases) • and at 12 weeks (optionally) after treatment according to laboratory procedures.	Weak	Very low

[μ] Referral to the appropriate specialist or medical colleague knowledgeable in syphilis who consults at a dedicated STI / HIV clinic or an infectious disease clinic or hospital.
RPR: rapid plasma reagin; PCR: polymerase chain reaction

4.3.2 *Testing frequency for syphilis: Good practice statements*

Testing frequency for syphilis: Good practice statements

Repeat testing interval every 3 to 12 months (same for other STIs) for asymptomatic patients with high risk sexual behaviour or at increased risk for syphilis:

1. Sex worker of any gender
2. MSM with high risk behaviour
   - unprotected sexual contacts (including deep kissing) in non-exclusively monogamous relationships
   - who are on PrEP
   - with a recent HIV diagnosis
   - with a syphilis diagnosis in the past
   -

A negative result will act as a baseline for future testing.

4.4 Mandatory notification of syphilis

All cases of infections by syphilis have to be notified in Brussels and Flanders using one of the three channels offered to healthcare practitioners to notify an infectious disease (phone, mail or website).

5 IMPLEMENTATION OF THIS GUIDELINE

5.1 Policy and other implementation of this guideline

5.1.1 Barriers and facilitators

An identified barrier was the nomenclature and reimbursement for diagnostic tests with NAATs and gonorrhoea culture for drug-resistance testing and surveillance. During the development of the guideline, KCE experts with members of the GDG shared this concern with NIHDI (RIZIV – INAMI) representatives. The following eventual policy *implications of the guideline for INAMI – RIZIV* were discussed:

- Is it possible to introduce a new nomenclature code for reimbursement of a combi NAAT chlamydia/gonorrhoea test in addition to the separate nomenclature codes for the diagnosis of gonorrhoea and chlamydia;
- The reimbursement modalities for the combi NAAT test need further discussions between NIHDI and experts from the field (including representatives of laboratories and clinical specialists treating STI, and representatives of main patients STI associations) in order to be revised.

An important facilitating aspect for this guideline is the existence of the working group across governmental cabinets ('Inter-kabinetten Werkgroep' or 'Groupe de travail inter-cabinets') which was installed to coordinate the governmental actions for STIs and HIV.

The *Flemish Agency 'Vlaams Agentschap Zorg en Gezondheid'* is currently rolling out the online partner notification (partneralert.be) and in this context the guideline will be applied.

The *Belgian Antibiotic Policy Coordination Committee* (BAPCOC) expressed its interested to apply the treatment recommendations to the guideline for primary care. This guideline is in alignment with the 'policy paper for the 2014-2019 term' (available at https://consultativebodies.health.belgium.be/en/documents/policy-paper-bapcoc-2014-2019).

5.1.2 Actors of dissemination and publication on Ebpractice net

As discussed already above, the implementation of this guideline and the online tool will be facilitated/conducted by SENSOA and SIDA'SOS. Several associations expressed an interest for the results to be presented to their local group of practitioners. SENSOA plans to promote the guideline through their website sensoa.be, through the SENSOA newsletter and the implementation project 'onder4ogen' which teaches the general physician to talk about sexual health. SENSOA will further promote the guideline through their stakeholders and the Flemish STI consortium (Vlaams SOA Overleg).

On the other hand the content of this guideline is intended to be disseminated by scientific and professional organisations. Domus Medica will promote both this guideline and the chlamydia guideline as part of the existing sexual health topic online for primary care physicians. The guideline will be placed on the 'evidence based practice' website in Dutch and French (https://www.ebpnet.be/nl/Pages/default.aspx). Organisations can make attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education e.g. laboratory education by the reference ITM laboratory, STI education sessions for GPs, presentation of prevalence and surveillance gonorrhoea and other STI data by Sciensano.

5.2 Translating the guideline into a primary care sexual health consultation STI testing instrument

To implement this guideline in the daily clinical practice of health care providers, a sexual consultation tool for STI testing is currently under development. The stakeholders and GDG were in favour of the development of a guidance tool as described below.

5.2.1 Clinical guidance

The number of international guidelines and online tools is high whereas a comprehensive tool is lacking for Belgium. The members of the GDG group emphasised the need for a hands-on tool, with the objective to better identify and target the patient and patient groups with the highest likelihood of being positive for an STI. The ideal guidance helps the physician with identifying: which test, the correct treatment and the correct way to follow up the patient. In short, the focus is on guiding the primary caregiver on the different steps in a sexual health consultation, for the detection and treatment of STIs (including HIV).

The guidance will come in paper format, supplemented with an electronic version. Well performing online 'interactive dynamic' tools or 'static' sexual health consultation tools were searched in the grey literature (Table 2). The basis of this new tool was created with the help of experts of the GDG and a critical analysis of the retrieved documents. This tool will summarise the newly developed guidelines on chlamydia, syphilis and gonorrhoea, but moreover it will refer to information from other Belgian sources, such as the website of stakeholders (SIDA'SOS, Sensoa), medical organisations (Domus Medica, SSMG), Sciensano STI surveillance information, etc.

5.2.2 Structure of the STI consultation instrument

The tool that was preferred and selected by the GDG was the nicely conceptualised online tool for an STI consultation proposed by the Australian New South Wales government: "STI/HIV testing tool: easy as 1 2 3" updated in September 2017 (https://stipu.nsw.gov.au/wp-content/uploads/STI-HIV-Testing-Tool-online.pdf).

The main reasons for the choice were: the scope of the tool, its applicability to the Belgian situation, the clarity of presentation, its recent update and the yearly revision of the tool. This tool covers three main topics answering the following questions: 'Starting a conversation about sexual health testing'; 'STI/HIV testing table (describing the patient and specific risk groups for STIs)'; 'How to test – Infection, specimen site and test type'; 'Contact tracing'. The tool is set in such a way that it lists for each of the groups at risk, the commonly encountered infections and the timeframe how often the patient should be tested. The specimen collection site is further described by gender for each infection including the preferred test.

The GDG preferred a Belgian tool to have a chronological order as for a normal consultation (Table 3). Next to the management of the patient, general tools and information will be available to inform the patient on STIs in general.

Table 2 – STI consultation instrument: overview of international and national guidance documents

Guidance documents, tools and websites	
Belgium	
Domus Medica 2017 - SOI[9]	https://www.domusmedica.be/documentatie/downloads/praktijkdocumenten/richtlijnen/1332-praktijktool-seksueel-overdraagbare-infecties-aanpak-in-de-huisartsenpraktijk.html
Domus Medica 2017 - HIV screening[29]	https://www.domusmedica.be/documentatie/downloads/praktijkdocumenten/steekkaarten-en-andere-hulpmiddelen/b-bloed-bloedvormende-organen-en-immuunstelsel/1328-advies-hiv-screening-door-huisartsen.html
Ghapro 2014 - Sex workers[10]	http://www.ghapro.be/nl/ghapro-publicaties_andere.html
BAPCOC 2012 - first line[20] **BAPCOC 2017 - hospital**[13]	http://overlegorganen.gezondheid.belgie.be/nl/advies-en-overlegorgaan/commissies/BAPCOC
European	
IUSTI 2012 - Consultation for STIs[30]	https://iusti.org/regions/Europe/euroguidelines.htm
The Netherlands 2013 - SOA consult[31]	https://www.nhg.org/standaarden/samenvatting/het-soa-consult
The Netherlands 2018 - Dermatology[32]	https://www.nhg.org/sites/default/files/content/nhg_org/uploads/multidisciplinaire_richtlijn_soa_herziening_2018.pdf
UK BASHH 2013 - national guideline for consultations requiring sexual history taking[33]	https://www.bashh.org/guidelines
UK BASHH STI 2015 – testing STI[34]	https://www.bashh.org/guidelines https://www.bashhguidelines.org/media/1084/sti-testing-tables-2015-dec-update-4.pdf
International	
Australia 2017 online[35]	https://stipu.nsw.gov.au
Australia 2014 - MSM[36]	https://www.clinicalguidelines.gov.au/portal/2489/australian-sexually-transmitted-infection-and-hiv-testing-guidelines-2014-asymptomatic
Australia 2017 - Silverbook[37]	http://ww2.health.wa.gov.au/Silver-book; https://stipu.nsw.gov.au/wp-content/uploads/STI-HIV-Testing-Tool-online.pdf
US CDC 2015[38]	https://www.cdc.gov/std/tg2015/default.htm
Canada 2010 & 2016 - STI guideline[39, 40]	https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections.html

Table 3 – An STI consultation tool: proposed structure

Structure of the tool	
STEP 1	Starting a conversation about sexual health testing
STEP 2	Sexual history questions for readiness, needs and risk assessment
STEP 3	STI Testing overview
STEP 4	How to test
STEP 5	Treatment overview - Test of cure - Follow up
STEP 6	Partner management and contact

6 GUIDELINE UPDATE

In view of the rapidly evolving evidence, this guideline should be updated every 5 years. If, in the meantime, important new evidence would become available, this should be taken into consideration.

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

RECOMMENDATIONS[a]

To the health care providers, professional and scientific societies involved in the care of patients with STIs

- **To disseminate and implement the guidelines.**

To the healthcare providers involved in the management of STIs including laboratories

- **To properly register and notify each STI as required by the federated entities,**
- **To optimise the communication between actors :**
  - **For clinicians to provide to laboratories the necessary clinical information why an STI is suspected. This is especially important for syphilis.**
  - **For laboratories to provide laboratory results in a readable format (including disease stage for syphilis and exact anatomical location of the positive test for syphilis and gonorrhoea) with guidance on test of cure for the healthcare practitioner.**

To the Belgian Antibiotic Policy Coordination Committee (BAPCOC)

- **To integrate these recommendations into the primary care Belgian guide for anti-infectious treatment for the section of gonorrhoea and syphilis.**

To the National Institute for Health and Disability Insurance (RIZIV – INAMI)

- **To evaluate the nomenclature codes for reimbursement for the diagnosis of gonorrhoea and chlamydia and consider :**
  - **the reimbursement of the combined gonorrhoea/chlamydia NAAT-test**
  - **to base the reimbursement of the combined test NOT on frequency of testing or age category.**
- **To consider, next to the existing nomenclature code for gonorrhoea culture for diagnosis, a nomenclature code for antibiotic resistance testing in symptomatic patients.**

[a] The KCE has sole responsibility for the recommendations.

To Sciensano

- **To continue to build a performing SOI surveillance registration and monitoring system.**

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COLOPHON

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- **The experts and stakeholders were consulted during the development of the scientific report. Their comments were discussed during meetings.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus process between the validators. The validators did not co-author the scientific report and did not necessarily agree with its content.**

- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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