Diagnosis and treatment of syphilis: 2019 Belgian National guideline for primary care

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Diagnosis and treatment of syphilis: 2019 Belgian National guideline for primary care

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ABSTRACT
Objectives: In the last 10 years, Belgium and countries of the European Economic Area and other high-income countries observed an increasing trend in syphilis diagnoses. Men who have sex with men (MSM) are the most affected population explained by high rates of unprotected sex, a greater number of sexual partners, and risk compensation as a result of pre-exposure prophylaxis use. The 2019 European Centre for Disease Prevention and Control (ECDC) technical report on syphilis proposed interventions such as enhanced screening of specific populations at risk. This guideline will address these issues.

Methods: We performed a systematic review of the evidence for diagnosing and treating syphilis.

Results: Based on the results, recommendations were formulated for primary health care professionals in Belgium. This syphilis guideline addresses prioritised testing, the sample and test for the diagnosis, the treatment of a person with syphilis including syphilis serology follow-up, and partner management.

Conclusion: The identification and management of patients with syphilis will benefit from the application of this guideline.

1. Aetiology, transmission, features

Syphilis is a systemic human disease due to infection with the spirochete bacterium Treponema pallidum subspecies pallidum (T. Performance and detection bias was common across studies) Rectal and oral transmission is common in men who have sex with men (MSM) [1–3]. Syphilis can also be passed on through infected blood when sharing needles or rarely via blood transfusion [1]. The infectious ulcer, the sign of primary disease, develops after incubation of generally 3 weeks (range 10–90 days), resolving 3–8 weeks later. Untreated, 25% of patients develop signs of early secondary syphilis affecting multiple organs e.g. generalised rash, hepatitis, uveitis, etc. Secondary syphilis resolves spontaneously in 3–12 weeks and the disease enters an asymptomatic latent stage. This is defined as early during the first year of infection by the European Centre for Disease Prevention and Control (ECDC), and late thereafter (ending with the development of tertiary disease) [4]. Reported cases in Belgium increased from 0.4 to 14 per 100,000 between 2002 and 2018 with registrations mostly in men aged 20–59 years [5].

2. Challenges

Belgian 1st line health professionals perform well on syphilis testing in pregnant women but the opposite is the case when prioritising other patients for testing e.g. patients or their partners presenting with a sexually transmitted infection (STI) diagnosis. The practitioners’ knowledge of symptoms, treatment, and importance of follow-up of the patient with a positive syphilis serology, is limited as most cases are detected and treated at HIV reference centres. For example, a suspicious chance may go unrecognised or may be mistaken for herpes and no syphilis testing will be performed.

The presented evidence-based recommendations for the diagnosis and management of patients with syphilis address the above challenges. Although targeting primary care practitioners in Belgium, the recommendations can be of interest to primary care settings abroad.

3. Methods

This guideline was developed by the Belgian Health Care Knowledge Centre (KCE, https://kce.fgov.be/) with a Guideline Development Group (GDG) consisting of clinicians, researchers, and representatives of STI not-for-profit associations. A standard methodology was followed based on a systematic review of the evidence (Appendix). The comprehensive guideline and its supplement provide full information regarding the composition of the GDG, research questions and descriptive patient problem with the PICO model, the
diagnostic framework PIRT (population, index test, reference standard, target condition), search strategies and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowcharts, quality appraisal of identified papers, lists of included and excluded studies, tables of evidence, statistical analyses and forest plots, summaries of findings tables and Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles [6]. The whole process of external review, as well as the methodological assessment and the scientific validation, are also extensively described.

4. Literature search and quality appraisal: results

4.1. Guidelines

Eight guidelines were identified of which two were comprehensive guidelines [7,8] discussing the management of STIs in general; 6 were dedicated to diagnosis and/or treatment of syphilis [1,9–14]. The Appraisal of Guidelines Research and Evaluation (AGREE) II instrument was used to evaluate the methodological quality of the identified, leading to the exclusion of one guideline [8].

4.2. Individual studies: syphilis diagnosis

An additional literature search was conducted in MEDLINE and The Cochrane Central Register of Controlled Trials (CENTRAL) to update the evidence retrieved from the guidelines. The following themes were included:

- Tests that detect syphilis in biological specimens, polymerase chain reaction (PCR) and test kits included.
- Strategies of different test sequences and comparison of strategies with each other.

Not included were methods for the visual demonstration of *T. pallidum* and tests used for confirming or excluding neurosyphilis, cardiovascular syphilis, ocular syphilis, and auricular syphilis.

Eighty-four unique references were identified from this literature search. Of these, 67 were excluded based on title and abstract and 7 full text papers were ordered. An additional 25 studies were retrieved from retained guidelines or identified by the GDG members. Of the final 42 full-text articles (i.e. 2 systematic reviews and 40 primary studies), 10 primary studies were selected and the remaining excluded with reason. None of the evidence could be meta-analysed and therefore the GRADE rating was applied to evidence from individual studies.

The applied GRADE rating was: one diagnostic-algorithm study of moderate [15] and one of low quality [16]. The remaining 8 studies were of low to very low quality [17–24]. Study quality was weakened by a serious risk of bias, mostly due to patient selection methods, the flow and timing of the study samples.

4.3. Individual studies: syphilis treatment

An additional search was performed in MEDLINE, PubMed, Embase and The Cochrane Database of Systematic Reviews from March 2013 till 19/04/2018 to update the evidence retrieved from the Centers for Disease Control and Prevention (CDC) guideline, the most recent guideline dedicated to the management of adult syphilis [9]. Of the 2565 unique references identified, 27 full text records were ordered. Together with an additional 17 records retrieved from guidelines, 44 full texts were assessed. In total, 18 randomised trials (RCTs) and observational studies were included in this review:

- 5 RCTs [25–29] from the CDC guideline and 4 RCTs [30–33] from the updated search.
- 9 observational studies of which 7 [34–40] were identified from the search, 1 study from the CDC guideline [41] and 1 study [42] was retrieved from a systematic review [43].
- The quality of the evidence was rated as low to very low by GRADE criteria. Performance and detection bias was common across studies.

5. Results and recommendations: syphilis diagnosis

5.1. Opportunities for syphilis testing

Next to routinely testing pregnant women [44], practitioners should spontaneously identify patients at risk for syphilis during daily practice by asking about:

- High-risk sexual behaviour: unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships;
- knowledge of the infection status of the partner;
- previous STI infections;
- drug use.

5.2. Indications for syphilis testing

The recommended patient or risk group is described in Table 1.

5.3. Diagnostic tests

5.3.1. Identification of *T. pallidum*

PCRs can detect *T. pallidum* directly with high sensitivity from a syphilitic genital ulcer whereas oral and anal ulcer PCRs can show false positives caused by commensal treponemas. Although detection of the
5.3.2. Serological tests before a serologic response, PCR is not widely available. Laboratory (VDRL) test performing well on Belgium, and the Venereal Disease Research NTTs are the rapid plasma reagin (RPR) common in against lipoidal antigens, and damaged host cells. The Two types of serological tests exist: Treponemal tests place [45, 46].

- Symptomatic secondary syphilis
  - non-itching skin rash (roseola, papular syphilids)
  - mucocutaneous lesions – condylomata lata
  - fever, generalised lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis, and glomerulonephritis
  - meningitis, cranial neuroapathies (e.g. auditory nerve with hearing loss with or without tinnitus)
  - ophthalmic abnormalities (such as uveitis, retinitis, and papillodema).

- Symptomatic tertiary syphilis
  - gummatous syphilis: nodules/plaques or ulcers (skin, mucosae, visceral)
  - general paresis, tabes dorsalis

- Neurosyphilis: stroke, myelitis, meningitis, cranial nerve dysfunction, unexplained sudden visual loss, unexplained sudden deafness.

(B) 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 Pre-exposure prophylaxis (PrEP)
   - with a recent HIV diagnosis
   - with a syphilis diagnosis in the past.
3. The patient or sex partner originates or travels to and from a country where the prevalence of syphilis is known to be high. See the 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.
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
   - partner as defined above in classification 1, 2, or 3
   - an STI diagnosis including HIV in the past year
   - partners in an anonymous setting.
5. Adolescents and young people up to the age of 29 years with unprotected oral, anal or vaginal intercourse in non-exclusively monogamous relationships with/whenever:
   - chlamydia, gonorrhoea, or HIV is diagnosed
   - partner as defined above in classification 1, 2, 3 or 4.
6. 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 above in B, repeat test in the third trimester.
7. A test for syphilis whenever:
   - a newborn/baby or mother 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.

* All the indications for testing have a Strength of Recommendation (SR) weak and a Level of Evidence (LoE) very low except for the recommendation C ‘testing pregnant women’: SR strong, LoE moderate

Table 1. Indications for syphilis testing.*

<table>
<thead>
<tr>
<th>(A)</th>
<th>Patients with symptoms that are suspicious for syphilis: Good practice statement:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>● Any chancre-like anogenital or pharyngeal ulcer should be considered syphilis unless proven otherwise.</td>
</tr>
<tr>
<td></td>
<td>● Primary syphilitic anogenital or oral ulcer/chancrhere</td>
</tr>
<tr>
<td></td>
<td>○ regional lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>○ single painless, indurated, clean base, clear serum, no blistering</td>
</tr>
<tr>
<td></td>
<td>○ atypical, multiple, painful, deep, may be confused with herpes.</td>
</tr>
<tr>
<td></td>
<td>● Symptomatic secondary syphilis</td>
</tr>
<tr>
<td></td>
<td>○ non-itching skin rash (roseola, papular syphilids)</td>
</tr>
<tr>
<td></td>
<td>○ mucocutaneous lesions – condylomata lata</td>
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<td></td>
<td>○ fever, generalised lymphadenopathy, hepatitis, splenomegaly, periostitis, arthritis, and glomerulonephritis</td>
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<td></td>
<td>○ meningitis, cranial neuroapathies (e.g. auditory nerve with hearing loss with or without tinnitus)</td>
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<tr>
<td></td>
<td>○ ophthalmic abnormalities (such as uveitis, retinitis, and papillodema).</td>
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<td>● Symptomatic tertiary syphilis</td>
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<td></td>
<td>○ gummatous syphilis: nodules/plaques or ulcers (skin, mucosae, visceral)</td>
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<td></td>
<td>- Neurosyphilis: stroke, myelitis, meningitis, cranial nerve dysfunction, unexplained sudden visual loss, unexplained sudden deafness.</td>
</tr>
</tbody>
</table>

* All the indications for testing have a Strength of Recommendation (SR) weak and a Level of Evidence (LoE) very low except for the recommendation C ‘testing pregnant women’: SR strong, LoE moderate

Two types of serological tests exist: Treponemal tests (TT) e.g. Enzyme Immunoassay (EIA) detecting T. pallidum proteins antibodies and Non-treponemal tests (NTT) detecting antibodies (IgG and IgM) directed against lipoidal antigens, and damaged host cells. The NTTs are the rapid plasma reagin (RPR) common in Belgium, and the Venereal Disease Research Laboratory (VDRL) test performing well on cerebrospinal fluid. In Belgium, the algorithm combining the TT as a primary test followed by an NTT is universally used (labelled the reverse strategy) [13].

To increase the specificity (reducing the false positives e.g. screening of asymptomatic persons and blood donors), a second TT test is added after the first TT (updated reverse strategy) [47]. Another approach used for highly suspicious cases combines an NTT and TT on the same sample followed by a confirmatory TT test when either test is positive. Finally, point-of-care (POC) rapid syphilis tests should not be used in Belgium; single TT rapid tests will lead to overtreatment because a TT assay remains positive after treatment [17,18]. This includes the recent HIV-
syphilis POC tests, all with a suboptimal performance for syphilis [17–20].

5.3.2.2.1. Results from diagnostic algorithms. None of the evidence could be meta-analysed and therefore the GRADE rating was applied to evidence from individual studies. The available evidence was from two observational studies. One diagnostic-algorithm study reporting moderate quality evidence [15] and one with low quality evidence [16], comparing traditional testing strategies with reverse testing strategies in men and women [15,16]. For both studies the reverse testing resulted in an increased number of diagnosed cases.

5.3.2.2.2. EIA tests on serum samples. Five studies [17–20,24] compared Chembio DPP syp (NTT+TT), SD syp (TT), HIV-syp (TT) and HIV-HCV-syp (TT) tests on serum and blood samples:

- Chembio syp (NTT+TT) test had higher sensitivities (89–97%) in the serum samples, for the TT and NTT compared to the blood samples (48–53%); specificities were high (95–99%) in both serum and blood [17,18]. The combined result of TT and NTT had a sensitivity of 90% and a specificity of 100% on blood sample. This dual test would be useful for hard-to-reach populations and/or health care settings where patients may fail to return for their laboratory results.
- The dual HIV-syphilis tests (Chembio (TT) [18,20] and SD (TT) [19]) serum samples sensitivity was 99% for Chembio and 70% for SD with specificities of 99–100%. Blood samples had low sensitivities of 46–47% with high specificities of 99–100%.
- The triple Chembio test [18] had a low sensitivity of 44% for syphilis while specificity remained high at 99%. For HIV and HCV, sensitivity and specificity were very high (100% and 99.9% for HIV; 91.8% and 99.3% for HCV) using blood samples.

For MSM:

- The Chembio syp (NTT+TT) had low sensitivities ranging from 58–69% using both serum and blood samples [24]. Specificities were 99–100%.
- The SD syphilis 3.0 assay (TT) had a sensitivity of 80–83% in serum samples compared to 51–54% in blood samples, while both had a specificity of 100% [24].

The recommendations for the choice of sample and diagnostic test for syphilis are presented in Table 2.

6. Results and recommendations: syphilis treatment

The following patients should be referred to the second line for treatment (good practice statement): pregnant women (and refer to gynaecologist); patients with clinical features of symptomatic late
syphilis, or neurological symptoms or suspicion of neurosyphilis, suspicion of ocular syphilis, cardiovascular symptoms, or complications.

6.1. Information and advice

- Advise patients with early, infectious syphilis to abstain from sex until one week after the start of treatment. (SoR weak; LoE very low)
- Give the following information to patients (and their sex partners): cause and symptoms of syphilis infection, details about transmission, prevention, and complications. Provide verbal and written support or video material such as hyperlinks towards scientific websites or organisations dedicated to STIs leaflets, brochures. (SoR weak; LoE very low)
- Offer patients testing for other STI including HIV. (SoR weak; LoE very low)

6.2. Initiation of therapy

Treatment is to be started for the following reasons (SoR weak; LoE very low):

- 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.

6.3. Treatment choice for syphilis: molecules and dosage

The length of treatment required varies between early and late syphilis. The recommended treatment and dosing scheme is summarised in Table 3. In general, long-acting Penicillin G Benzathine (BPG) 2.4 million units is the first-choice treatment, providing a treponemicidal penicillin level in the blood for up to 21–28 days. Daily parenteral treatment with procaine penicillin provides a ‘safety margin’ by giving courses lasting 10–14 days in early syphilis and 10–21 days in late syphilis but it is not available in Belgium. However, well-controlled clinical trials are lacking on the optimal dose, duration of treatment and long-term efficacy of all antimicrobials, even for penicillin [13]. Treatment recommendations are based mainly on laboratory considerations, biological plausibility, practical considerations, expert opinions, case studies, and past clinical experience [13]. Resistance to macrolides e.g. azithromycin is 100% in the samples tested in Belgium [48]. Parenteral observed treatment is preferred over oral treatment for better adherence.

Eighteen studies reported treatment comparisons for syphilis in mixed populations of men and women [25–32,34–43]. Of these, 2 RCTs [27,30] and 5 observational studies [34,35,37,39,40] included patients with both HIV and syphilis; although they were mixed populations they were predominately male. One RCT [30] reported a 95% male population and the other RCT [27] reported 81% in the penicillin group and 93% in the ceftriaxone group. The observational studies were also predominately male and reported 94% and above MSM populations apart from one study [34] that had a lower reported MSM of 47% and 40% in each arm. The evidence from these studies was of very low to low-quality.

There was no difference in treatment failure between combined treatment (BPG+amoxicillin+probenecid) compared to BPG [26]. However, there were more cases of diarrhoea in the combined therapy compared to BPG.

Table 3. Treatment of syphilis in women and men and young people excluding pregnant women.

<table>
<thead>
<tr>
<th>A. Recommendations</th>
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<tbody>
<tr>
<td>Treatment of syphilis in women and men including young people excluding pregnant women</td>
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<table>
<thead>
<tr>
<th>Early syphilis</th>
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<tbody>
<tr>
<td>First choice: BPG 2.4 million units at once IM on day 1</td>
</tr>
<tr>
<td>SoR</td>
</tr>
<tr>
<td>Strong</td>
</tr>
<tr>
<td>Second choice: Doxycycline 100 mg orally twice daily for 14 days (be aware of photosensitisation)</td>
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<td>Strong</td>
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<table>
<thead>
<tr>
<th>Late syphilis</th>
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<tbody>
<tr>
<td>First choice: BPG 2.4 million units IM weekly for 3 consecutive weeks (day 1, day 8 and day 15)</td>
</tr>
<tr>
<td>SoR</td>
</tr>
<tr>
<td>Strong</td>
</tr>
<tr>
<td>Second choice: Doxycycline 100 mg orally twice daily for 28 days (be aware of photosensitisation)</td>
</tr>
<tr>
<td>Strong</td>
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</tbody>
</table>

In the 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.
- Patients should also be referred for skin testing to confirm allergy and for consideration of penicillin desensitisation.

<table>
<thead>
<tr>
<th>B. Good practice statements</th>
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<tbody>
<tr>
<td>administer BPG 2.4 million units by two injections of 1.2 million units in separate places (e.g. buttocks); replacing part of solvent by the same volume of 1% lidocaine solution (if not already added) may reduce pain. Advise the patient to walk for 30 minutes to help the product resorb into the muscle.</td>
</tr>
<tr>
<td>Doxycycline</td>
</tr>
<tr>
<td>phototoxicity risk: to use a high sun protection factor (SPF) broad-spectrum sunscreen (protection UVB and UVA wavelengths); clothing, hat and staying out of the sun are important.</td>
</tr>
<tr>
<td>prevention of digestive disorders (in particular oesophageal ulcerations): Swallow tablets during the meal with a large glass of water; do not lie down for an hour after taking the tablets.</td>
</tr>
</tbody>
</table>
The RCT evidence of combined treatment consisting of BPG+ceftriaxone+doxycycline group may provide a benefit in increased number with a serological response at 3, 6 and 12 months compared to the BPG group. The evidence suggested that there was no difference in adverse events between groups [32].

The observational evidence suggested there was no difference in serological response at 2 years between BPG and minocycline [36].

The observational evidence suggested that there was no difference in serological response at 2 years between BPG and doxycycline. However, there was a benefit of more cases of serological cure at 6 months with BPG compared to doxycycline [35,41,42].

Single-dose BPG vs triple dose BPG: The observational evidence suggested that there was no difference in serological response at 3 and 6 months but the triple dose of BPG may provide a benefit in increased serological response at 12 months. There was no difference in adverse events [30,34,39].

Intramuscular (IM) daily ceftriaxone for 15 days [27], or intravenous (IV) ceftriaxone daily for 10 days [31,33] are considered too complicated for primary care administration. While several studies [25,28,29,40] recommended azithromycin this option is not acceptable for Belgium which due to 100% resistance [48].

6.4. Follow-up of patients with treated syphilis

- In case of positive serology, clinical and serological (NTT) follow-up should be performed (SoR strong; LoE very low):
  - for early syphilis at three and six months
  - for late syphilis at three, six and 12 months
- In case of positive serology, a referral is indicated when (SoR strong; LoE very low):
  - recurrence of signs or symptoms
  - when NTT-RPR titres do not decrease fourfold within 6 months from day 1 of treatment for early syphilis (primary, secondary and early latent <1 year)
  - when NTT-RPR titres do not decrease fourfold within 12 months from day 1 of treatment for late syphilis (> 1 year)
- In case of negative results (serology or PCR) in a suspected infected patient and asymptomatic after an isolated high-risk episode with exposure to syphilis (SoR weak; LoE very low):
  - Repeat the serologic test at 6 weeks (in all cases)
  - and at 12 weeks (optionally) after treatment according to laboratory procedures.

6.5. Syphilis testing frequency

Repeat testing interval (a negative result will act as a baseline for future testing) every 3 to 12 months for asymptomatic patients with high-risk sexual behaviour or at increased risk for syphilis (good practice statement):

- Sex worker of any gender
- 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

7. Mandatory notification of syphilis

All cases of infections by T. pallidum 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).

8. Referral of partners

In Belgium, no clear strategy currently exists for contacting partners of patients with an STI. Internationally, patient-initiated and provider-initiated referral are commonly used [49–51]. But legal limitations make that some methods are not applied in Belgium e.g. patient delivered partner therapy [52,53].

The strategy proposed by the GDG is first, to identify the last 1 to 5 partners or if too many those in the last month [54]. The lookback timeframes are to be used as a second option (SoR weak, LoE very low) [54]. Next, the patient receives a minimum referral package consisting of information on the STI; Advice for the partner to be tested; Letter to take to a physician explaining about the STI and why the partner comes for a sexual health consultation; A follow-up consultation with the patient. If the patient prefers provider-initiated referral there are two options: either the physician posts a letter with the minimum package information; or the online platform www.partneralert.be (Dutch, French, and English) is consulted by the health worker providing code(s) for a patient to anonymously inform the partner(s) via e-mail or phone text message. Subsequently, the partner receives a link.
and code to access further information about the STI in question and what to do.

9. Dissemination

This guideline was disseminated through an online consultation tool for STI testing (www.sti.kce.be) and is available in four languages, Dutch, French, German and English [54]. The management of chlamydia, gonorrhoea, HIV and hepatitis A, B and C (including referral to the second line) is included. The tool was reviewed and tested by a sample of end-users, found of high quality and considered a useful asset for general practice [54]. Further, this guideline will be available through the primary care online platform and database called EBPracticenet (www.ebpnet.be). Here, guidelines are available in Dutch and French for all primary care practitioners in a user-friendly, ready-to-use format. A clear, visible link to the online tool will be provided.

Acknowledgments

We are grateful to all the GDG members and stakeholders who contributed to the guideline development. GDG members other than authors are Sam Cordyn (Wit Gele Kruis Vlaanderen) Tine Cornelissen (Domus Medica), Céline Danhier (YES), Irith De Baetselier (Institute of Tropical Medicine), Anne-Sophie De Cannière (Violett), Nicole Dekker (University of Antwerp), Anja Desomer (KCE), Wouter Dhaeze (Agentschap Zorg en Gezondheid), Elizaveta Padalko (University of Ghent), Céline Danhier (YES), Tine Cornelissen (Domus Medica), Elizaveta Padalko (University of Ghent), Sandra Van den Eynde (Sensoa), and Thierry Van der Schueren (SSMG).

Disclosure statement

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Geolocation information

Location Names: Brussels, Belgium Health Care Knowledge Center (KCE)
Coordinate: 50°51′11.2″N 4°21′53.8″E
Latitude (in decimal degrees) 50.8531 and Longitude (in decimal degrees) 4.3649

Proposed review date

This guideline should be updated whenever research on diagnosis and treatment for syphilis evolves substantially or at least every 5 years.

References


[40] Yang CJ, Tang HJ, Chang SY, et al. Comparison of serological responses to single-dose azithromycin (2 g) versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients in an area of low prevalence of macrolide-resistant Treponema


