Development of an algorithm to facilitate the clinical management of syphilis

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Abstract

Background: Syphilis staging is important to determine treatment, post-treatment monitoring, and sexual partner follow-up. Many prescribers find syphilis staging to be challenging. Current guidelines for the management of patients diagnosed with syphilis provide little direction aside from an overview of some common symptoms and directing providers to stage cases in conjunction with experienced colleagues.

Local problem: In Canada and the United States, the rate of infectious syphilis has increased noticeably since 2000. Given the increase in rates of syphilis, it is important for all clinicians to understand how to appropriately manage patient care to reduce rates of infection.

Methods and interventions: A clinical algorithm was developed to stage infectious syphilis. This was tested among nurse practitioners and physicians in a sexually transmitted infection clinic. The algorithm was developed based on a review of the available United States, Canadian, and British practice guidelines.

Results: Project results demonstrated that this resource could be a relevant practice tool for providers in multiple clinical settings to ensure that patients receive appropriate diagnosis, staging, and treatment of syphilis infection. A case study of a patient who presented to the clinic as a contact is used to review the algorithm and demonstrate the appropriate clinical management of patients.

Conclusions: The algorithm appropriately guided practice and was useful to clinicians.

Keywords: Algorithm; clinical management; staging; syphilis.

Introduction

In 2000, with syphilis rates approaching zero, the US Centers for Disease Control asserted that syphilis could be eradicated by 2005 (Centers for Disease Control and Prevention [CDC], 2000). Since this time, however, the incidence of syphilis has increased by 103% in Canada, from 9.6/100,000 persons in 2011 to 19.5/100,000 in 2016, and by 107% in the United States, from 10.9/100,000 persons in 2013 to 22.6/100,000 in 2018 (CDC, 2019; Public Health Agency of Canada [PHAC], 2019). Although these increases have primarily been among men who have sex with men, they have also occurred among persons with opposite sex partners and pregnant women (CDC, 2018; Choudhri, Miller, Sandhu, Leon, & Aho, 2018).

One issue with these increases is that many clinicians are unfamiliar with syphilis, including its presentation, diagnosis, and management. Furthermore, many clinical guidelines do not provide sufficient detail to structure practice for syphilis. For example, PHAC (2016) states that “the interpretation of syphilis serology should be made in conjunction with a colleague experienced in this area.”

To surmount these challenges, an algorithm to stage syphilis was developed in a sexually transmitted infection (STI) clinic in Ottawa, Canada, where the local laboratories use the reverse syphilis screening pathway. The reverse pathway includes an antibody test followed by a treponemal test, followed by a non-treponemal test. This is in contrast to the pathway preferred in the United States.
project aims were to (1) facilitate clinician decision-making around syphilis diagnosis, staging, and treatment and (2) mitigate possible sequelae for patients which could occur from incorrect management. The question to answer was, “does a clinical algorithm help clinicians manage syphilis?” In presenting this algorithm, this article provides a clinical review of syphilis and uses a case study to show the algorithm in practice.

**Background**

Clinically, syphilis is a relapsing infection that is classified as infectious (≤12 months from inoculation) or noninfectious (>12 months) (PHAC, 2016; Singh & Romanowski, 1999; Sparling, Swartz, Mushner, & Healy, 2008). In its infectious state, syphilis progresses from a localized to a systemic infection and causes variable symptoms. Practitioners use this information about the natural history of syphilis, along with patient history and laboratory results to classify cases within the clinical stages of: primary infection (<3 months), secondary infection (2–6 months), early latent infection (≤12 months), late latent infection (>12 months), or tertiary infection (>1–46 years) (O’Byrne & MacPherson, 2019). Classically, primary syphilis presents as a single, painless, indurated genital ulcer with a nonexudative base; this is known as a chancre. Notably, chancres can be multiple or painful or exudative due to superinfection. Secondary syphilis, meanwhile, is a systemic infection, characterized by a diffuse maculopapular rash with possible palmar involvement and flu-like symptoms; patchy alopecia, neurologic deficits (particularly of cranial nerves II or VIII), and mucosal lesions (e.g., condylomata lata) may also manifest during this stage (Table 1). Syphilis then progresses to a latent phase (as early or late), where patients are asymptomatic with positive syphilis serology (O’Byrne & MacPherson, 2019). Finally, without treatment, about one quarter of persons progress to tertiary syphilis, involving irreversible damage, most commonly, to the neurologic, cardiovascular, and integumentary systems, although possibly to any organ (O’Byrne & MacPherson, 2019).

Syphilis staging is as follows: primary and secondary infections have symptoms, whether localized or systemic, respectively; latent syphilis is asymptomatic (Singh & Romanowski, 1999) (Table 1). To stage an infection as early latent, the patient must fulfill at least one of the following criteria within the last 12 months: (1) syphilis serology suggesting a new infection (i.e., previously negative results or previously a 4-fold, or lower, quantitative nontreponemal test result, such as the rapid plasma reagin [RPR] test), (2) symptoms that are unequivocally primary or secondary syphilis, or (3) a sexual contact with person known to have infectious syphilis (CDC, 2015; Kingston et al., 2016; PHAC, 2016). Otherwise, patients should be staged as having late latent syphilis or syphilis of unknown duration (O’Byrne & MacPherson, 2019) (Figure 1).

Syphilis staging is important because it determines (1) the treatment regimen, (2) what constitutes an adequate response to treatment, (3) how to rule out treatment failure (which can occur in 5–10% of cases), and (4) timeframes for notifying sexual partners who require testing and possible treatment (PHAC, 2016; CDC, 2015; Kingston et al., 2016) (Table 2). Owing to protean manifestations and complicated laboratory results (PHAC, 2016; Singh & Romanowski, 1999; Sparling et al., 2008), syphilis management can be clinically challenging. This clinical difficulty, in light of increasing rates, led to a quality improvement project. Contributing to the need for this project was that, at a transmission rate of 30–60%, syphilis is highly infectious (Singh & Romanowski, 1999). It is also associated with possible neurologic sequelae, including blindness, and can facilitate HIV acquisition (Singh & Romanowski, 1999; Sparling et al., 2008).

**Table 1. Syphilis-related symptoms**

| Stage           | Symptoms                                | Timing                  |
|-----------------|-----------------------------------------|-------------------------|
| Infectious      |                                         | 10–90 days (mean: 21 days) |
| Primary         | • Chancre at site of inoculation         |                         |
|                 | • Classically: single painless indurated |                         |
|                 |   genital ulcer with a clean base        |                         |
|                 | • Lesion can be oral, genital, perianal, |                         |
|                 |   or anal                                 |                         |
|                 | • Regional lymphadenopathy               |                         |
| Secondary       | • Rash                                   | 2–6 months (mean: 2–12 weeks) |
|                 | • Generalized lymphadenopathy            |                         |
|                 | • Malaise, fever, and headache           |                         |
|                 | • Mucous patches                         |                         |
|                 | • Condyloma lata                         |                         |
|                 | • Uveitis and retinitis                  |                         |
| Early latent    | • Asymptomatic                           | <12 months from infection|
| Non-infectious  |                                         |                         |
| Late latent     | • Asymptomatic                           | >12 months from infection|
| Tertiary        | • Cardiovascular                         | Early manifestations    |
|                 | • Neurologic                             | 12–18 months            |
|                 | • Gummatous                              | Late manifestations     |
|                 |   (dermatologic)                         | 5–25 years              |
Figure 1. Syphilis staging algorithm.
Methods

Context and intervention

This project occurred at the Ottawa STI clinic, which has >20,000 patient visits per year and accounted for 58% of Ottawa syphilis diagnoses in 2018. The algorithm was developed based on published guidelines (PHAC, 2016; CDC, 2015; Kingston et al., 2016), information on syphilis testing (Ratnam, 2005), and literature from CINAHL, EMBASE, and MEDLINE. The outcome was an algorithm that shows how to stage syphilis and manage serologic results using the reverse screening pathway.

Study of the intervention

Validation of this algorithm involved practitioners at the Ottawa STI clinic using a case study exercise and survey assessing clinical proficiency with syphilis pre-algorithm and post-algorithm use. Specifically, clinicians were surveyed about their confidence and skills regarding syphilis management. As part of this quality improvement evaluation, clinicians were asked about challenges they faced with syphilis diagnosis, staging, and management and to identify elements they would like to see incorporated into the algorithm to enhance their practice. The algorithm was designed based on a literature review of syphilis and in consideration of clinicians’ identified needs. Clinicians then reviewed a set of syphilis cases using the algorithm and completed a survey about their confidence and skills regarding syphilis management, including additional questions about ease of use, likelihood of use, and recommendations for improvement. This helped improve and validate the algorithm.

Survey questions were measured on a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). For evaluation, scaled questions were counted for frequencies (averages, percentages), and questions asking for a written response were coded based on similarities (for project evaluation and for modification of the algorithm). All responses were entered into an Excel spreadsheet and analyzed using descriptive statistics.

Results

Of the 18 prescribers at the Ottawa STI clinic, 15 were eligible to participate. Three were excluded because they helped develop the algorithm (all co-authors). All eligible prescribers at the STI clinic participated: four nurse practitioners and eight physicians. The prescribers reported seeing an average of 3.5 syphilis cases per month (range: 1–8).

Self-reported clinical proficiency pre-algorithm use

When prescribers were asked if they identified as “experts” in syphilis staging, 66.67% (n = 8) were “neutral” (neither agreed nor disagreed), and 33.33% (n = 4) “disagreed.” No participant identified as an “expert.” Half of all participants (n = 6) “agreed” with the statement they found syphilis difficult to stage, while another 42% (n = 5) stated they were “neutral” (neither agreed nor disagreed), and one participant stated they “strongly agreed.” Based on observed frequencies of responses, there were no identifiable differences in knowledge before using the algorithm between nurse practitioner and physician participants. See Table 3 for more details.
Self-reported clinical proficiency post-algorithm use

All 12 participants either “agreed” (66.67%) or “strongly agreed” (33.33%) that the algorithm made the process of staging syphilis clearer for them. Similarly, all participants identified that the algorithm was relevant to their practice, with 58% (n = 7) stating they “strongly agreed” and 42% (n = 5) stating they “agreed.” When asked how to increase clarity, no major modification were identified aside from some wording changes. Finally, participants were asked to rate their likelihood of using the algorithm in practice and of recommending it to colleagues. For both of these questions, 58% (n = 7) “strongly agreed” they would use and recommend the algorithm, and 42% (n = 5) “agreed.” More details about these results are present in Table 3.

These results showed that the new algorithm increased clinicians’ confidence and skills in managing this infection. As no such algorithm existed, this was considered a successful clinical tool to guide the management of an infection that, heretofore, was virtually eradicated and now confounds practitioners.

A review of the algorithm

Exemplar case

A 27-year-old male patient presented to clinic and reported that a male partner from 2.5 weeks ago “has syphilis.” The patient reported receiving and performing oral sex and condomless receptive anal sex with this person. The patient denied lesions, rash, and flu-like symptoms. He was last tested for STIs 2 years ago and had no previous STI diagnoses. Examination did not identify genital lesions or rash. Serology from this visit, which returned to clinic 1 week later, showed a reactive chemiluminescent assay, a nonreactive RPR, and a reactive Treponema pallidum particle agglutination (TPPA). What is the appropriate management for this patient?

Case review

Following the algorithm, at first visit, the patient presented “without a new result” and as a known “contact of syphilis,” which leads to “query infection (pathway C).” As the patient was asymptomatic, but a contact of syphilis, the algorithm indicates that, at the first visit, two items should occur: First, syphilis serology should be ordered and used as part of staging on receipt (if reactive), and second, the patient should be treated with 1 dose of intramuscular benzathine penicillin G 2.4 million units; this is the first-line treatment for persons diagnosed with, or who are the sexual contacts of persons diagnosed with, infectious syphilis (Table 2) (CDC, 2015; Kingston et al., 2016; PHAC, 2016). If a penicillin allergy were reported, doxycycline 100 mg oral tablets twice daily for 14 days can be used as a second-line agent (CDC, 2015; Kingston et al., 2016; PHAC, 2016). A referral for allergy testing should also be initiated because many suspected penicillin allergies are incorrect and needlessly result in second-line treatments (Barlam et al., 2016).

An important point in this case is that the absence of genital lesions and rash should not dissuade epidemiologic treatment because up to 60% of patients with confirmed syphilis do not recall a primary lesion (Singh & Romanowski, 1999). Also, although many men with female partners are diagnosed with primary syphilis, up to one third of men and women with male partners are not

Table 3. Survey results

| Survey Question | Participant Rating n/12 (%) |
|-----------------|---------------------------|
|                 | Strongly Agree | Agree | Neutral | Disagree | Strongly Disagree |
| Self-reported clinical proficiency post-algorithm use | | | | | |
| I have expert knowledge related to syphilis | 0 (0) | 0 (0) | 8 (66.67) | 4 (33.33) | 0 (0) |
| I find syphilis difficult to stage | 1 (8) | 6 (50) | 5 (42) | 0 (0) | 0 (0) |
| Do you find this algorithm made syphilis staging clearer? | 4 (33.33) | 8 (66.67) | 0 (0) | 0 (0) | 0 (0) |
| Do you find this algorithm relevant to your practice? | 7 (58) | 5 (42) | 0 (0) | 0 (0) | 0 (0) |
| I plan to use this algorithm in my practice | 7 (58) | 5 (42) | 0 (0) | 0 (0) | 0 (0) |
| I will recommend using this algorithm to my colleagues | 7 (58) | 5 (42) | 0 (0) | 0 (0) | 0 (0) |
diagnosed until the secondary stage, likely because chancres are painless and may be oral, rectal, or vaginal and difficult to visualize (Singh & Romanowski, 1999). Primary and secondary symptoms, such as the rash and mucous lesions, may also be subtle (Singh & Romanowski, 1999). Thus, as part of the physical assessment for syphilis, clinicians should inspect all mucosal membranes and not solely rely on patient report about being asymptomatic. Moreover, as primary syphilis lesions appear 10–90 days after inoculation (Singh & Romanowski, 1999), for the case study, it may also be that the patient has yet to develop a chancre, seeing as the reported exposure was 2.5 weeks earlier. Thus, an absence of symptoms within the first 90 days after a potential syphilis exposure may simply relate to the incubation period, not an absence of infection.

The next step is to review the laboratory results, once available. Returning to the algorithm, clinicians should follow the “new result” pathway in a patient “without a history of syphilis” and a “non-reactive RPR.” As the patient is asymptomatic, clinicians should follow the same algorithm pathway as at the first visit. For staging, in the absence of symptoms, the patient must have a latent infection. The question is whether this infection is early latent (<12 months), late latent (>12 months), or of unknown duration. For the patient in this case study, in the absence of symptoms and negative laboratory results within 12 months, staging early latent syphilis is possible because he reported a recent sexual contact with someone diagnosed with infectious syphilis.

An important point here, however, is that clinicians must to decide what constitutes a “contact.” Guidelines do not indicate if this must be a confirmed diagnosis or based exclusively on patient report. In the case study here, it is possible the patient is the index case and has had syphilis for >12 months, although this is less likely because syphilis is considered mostly non-infectious after 12 months of infection (CDC, 2015; Kingston et al., 2016; PHAC, 2016). Alternatively, the patient may have had syphilis for more than 12 months and was coincidentally named as a contact of infectious syphilis. Relevant considerations would be: Was the only contact 2.5 weeks ago? When was the partner tested? Did the partner have symptoms? Answers to these questions could increase clinicians’ confidence in staging as early latent or may lead to a suspicion that the infection was late latent or of unknown duration. In this case, the contact was receptive anal sex and only 2.5 weeks ago, signaling that symptoms of primary syphilis may be difficult to visualize or may not have materialized yet. These components of the history make the stage of early latent probable. However, when in doubt, clinicians can always stage the patient as having syphilis of unknown duration, which corresponds with the same treatment as late latent syphilis.

As the next step, follow-up serology should be scheduled based on stage. In the absence of a test-of-cure for syphilis, follow-up serology determines successful treatment and is considered a fourfold decrease in RPR by 12 months, if the RPR was initially reactive (CDC, 2015; Kingston et al., 2016; PHAC, 2016). The RPR, however, may be non-reactive in early or late syphilis and would not change in such cases; alternatively, the RPR may be < two-tube above non-reactive in which case a return to non-reactive is the best indicator of successful treatment. If an RPR test is positive initially and has decreased by less than fourfold in 12 months, referral to an infectious disease specialist may be needed to rule out neurosyphilis; a less than fourfold decrease by 12 months, however, may also occur due to re-infection or inadequate treatment, in which cases re-treatment may be all that is required; another possibility is that the person has a serofast or slowly decreasing titer (CDC, 2015; Kingston et al., 2016; PHAC, 2016). To ensure these RPR values are interpreted correctly after treatment, clinicians must order syphilis serology on the day of treatment, even if the original serology had been performed days previously. This is because the RPR titer can fluctuate within days and may be higher or lower than the previous value.

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**Table 4. Recommended STI services**

| Item                | Recommendations                                                                 |
|---------------------|---------------------------------------------------------------------------------|
| STI testing         | • Gonorrhea/chlamydia: urine, pharynx, rectum, vaginal, and/or endocervical testing based on sexual practices  |
|                     | • Syphilis/HIV: screen annually or more frequently if high risk                 |
|                     | • Hepatitis C: screen annually in men who have sex with men or more frequently if injection/inhalation drug use |
| Pregnancy testing   | • Do for all persons of childbearing age with cervix and uterus based on sexual practices |
|                     | • Offer contraception if ongoing risk identified                              |
| PrEP                | • Offer to anyone at risk of HIV                                               |
|                     | • Offer to all persons diagnosed with infectious syphilis                      |
| Vaccination         | • Hepatitis A: men who have sex with men and anyone who performs oral-anal sex |
|                     | • Hepatitis B: everyone                                                       |
|                     | • HPV: everyone                                                               |

*Note: HPV = human papilloma virus; PrEP = pre-exposure prophylaxis; STI = sexually transmitted infection.*
A final element is to offer pre-exposure prophylaxis (PrEP), which is the use of antiretroviral medication by HIV-seronegative persons to prevent HIV acquisition (Tan et al., 2017). Pre-exposure prophylaxis is important because, in studies, up to 20% of participants acquired HIV <12 months after syphilis infection (Solomon et al., 2014). This offer of PrEP, moreover, should occur irrespective of sex or sexual orientation. Relevant STI testing and vaccinations should also be provided (Table 4).

The algorithm also addresses modifications to the patient presentation, for example, identifying how to stage primary or secondary syphilis based on symptoms. It also addresses patients previously diagnosed with syphilis. In most cases, following the algorithm, the process is to query if there is a result, determine if the patient had syphilis previously, and use the clinical history and examination to determine care, and to test and treat when patients are contacts or symptomatic. In short, if a patient with risk factors for syphilis acquisition presents with symptoms suggestive of syphilis, treat empirically and order testing at that visit. The algorithm, as well, addresses the situation of when a patient has a continually non-reactive RPR or an inconclusive result: It could be that a patient has a new infection (with the RPR being ~70% sensitive during primary syphilis) or that s/he has an older infection with an RPR that waned (Singh & Romanowski, 1999). A nonreactive RPR, however, virtually rules out secondary syphilis because the RPR is nearly 100% sensitive during this stage, aside from prozone scenarios when the test is falsely negative due to titers that exceed the upper limit of detection (Kingston et al., 2016).

Another consideration in the algorithm relates to the management of patients who are living with HIV. Because persons living with HIV, compared with those who are HIV-seronegative, have elevated rates of neurosyphilis, clinicians should perform a detailed neurologic examination, with referral to an infectious disease specialist if this examination is abnormal (CDC, 2015; Kingston et al., 2016; PHAC, 2016). Such a referral may also be considered if the patient has a CD4+ count <350 cell/µL or an RPR ≥1:32 because these correspond with a threefold to sixfold increase in the occurrence of neurosyphilis (CDC, 2015; Kingston et al., 2016; PHAC, 2016). Otherwise, management remains unchanged, except that a re-test at 24 months after treatment might be indicated (CDC, 2015; Kingston et al., 2016; PHAC, 2016).

**Discussion**

Although research measuring prescribers’ confidence around staging infectious syphilis has not been well explored, the volume of published literature on syphilis management suggests this is a complicated subject and that clinicians could benefit from practical resources to support their practice. As such, the algorithm presented here could be used to facilitate syphilis diagnosis, staging, and treatment by clinicians of varying knowledge and experience levels. More specifically, this algorithm could help build primary care clinicians’ capacity to appropriately identify, diagnose, and treat syphilis in their practice. Furthermore, enhancing autonomy of primary care providers to more confidently manage syphilis infections could reduce specialist referrals or external consultations, thereby reducing health care costs (CDC, 2013).

Moreover, considering the >100% increase in infectious syphilis rates in Canada and the United States, this algorithm could be used in various clinical areas, such as primary care, emergency departments, and urgent care centers, to ensure patients receive appropriate management for syphilis regardless of where they access STI testing. From a population health perspective, this prompt identification of syphilis would be beneficial not only to reduce transmissibility of infectious syphilis (by treating patients sooner) but also to allow public health units who do syphilis case follow-up to be able to reach sexual contacts faster, thereby reducing ongoing risk of exposure and onward transmission of infection (CDC, 2015; PHAC, 2016).

One limitation of this project, however, is that the clinical algorithm is based on the reverse screening pathway (i.e., initial screening with treponemal enzyme-linked immunosorbent assay test, quantification of infection with nontreponemal RPR test, and confirmation with a second treponemal test, such as the TPPA) (Moreshed & Singh, 2015). As such, some components of this algorithm do not apply to the traditional screening pathway and is incompatible with the European CDC reverse algorithm (Moreshed & Singh, 2015). In addition, this algorithm does not detail the management of congenital or tertiary syphilis cases, which should involve infectious diseases specialist consultations. Finally, this project evaluation occurred in an STI clinic and involved clinicians who, despite their self-rated expertise, likely have more experience staging syphilis, compared with many clinicians in primary care. It is possible that evaluations of the clarity, relevance, and uptake of the algorithm might vary in other clinical settings.

**Conclusion**

Considering rising syphilis incidence and complicated clinical diagnosis and management, a syphilis algorithm was developed and validated among a group of STI clinicians. Above, the development and implementation of this algorithm—based on the reverse screening pathway—was reviewed, including a discussion about how to use it in primary care practice. This algorithm supplements Canadian and US guidelines (2016) and helps clinicians manage
patients independently, rather than relying on “experienced colleagues.” The use of this algorithm could enhance clinicians’ confidence in following up on syphilis diagnoses in a variety of clinical settings and patient populations. Fostering clinician’s autonomy in managing syphilis cases is important because clinicians are now more likely to encounter this infection in practice. As such, we feel the prompt identification of syphilis cases, supported by the use of this clinical algorithm in practice, can be a key strategy in attempting to reduce ongoing rates of syphilis transmission.

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References
Barlam, T. F., Cosgrove, S. E., Abbo, L. M., MacDougall, C., Schuetz, A. N., Septimus, E. J., ... Trivedi, K. K. (2016). Executive summary: Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society of Healthcare Epidemiology of America. Clinical Infectious Diseases, 62, 1197–1202.

CDC. (2000). Eliminating Syphilis from the United States. Retrieved from https://www.cdc.gov/stopssyphilis/FactPDF/usfact.pdf.

CDC. (2015). Sexually transmitted diseases treatment guidelines: Syphilis. Retrieved from https://www.cdc.gov/std/tg2015/syphilis.htm.

CDC. (2019). Sexually Transmitted Disease Surveillance, 2018. Retrieved from https://www.cdc.gov/std/stats18/syphilis.htm.

Centers for Disease Control. [CDC]. (2018). Syphilis. Retrieved from https://www.cdc.gov/std/stats17/syphilis.htm.

Centres for Disease Control and Prevention [CDC]. (2013). Incidence, prevalence, and cost of sexually transmitted infections in the United States. Retrieved from https://www.cdc.gov/std/stats/sti-estimates-fact-sheet-feb-2013.pdf.

Choudhri, Y., Miller, J., Sandhu, J., Leon, A., & Aho, J. (2018). Infectious and congenital syphilis in Canada, 2010–2015. Canada Communicable Disease Report, 44, 43–48.

Kingston, M., French, P., Higgins, S., Sukthankar, A., Stott, C., ... Sullivan, A. (2016). UK guidelines on the management of syphilis, 2015. International Journal of STD/AIDS, 27, 421–426.

Moreshed, M. G., & Singh, A. E. (2015). Recent trends in the serologic diagnosis of syphilis. Clinical and Vaccine Immunology, 22, 137–147.

O’Byrne, P., & MacPherson, P. A. (2019). Syphilis. BMJ, 365, i4759.

Public Health Agency of Canada [PHAC]. (2016). Canadian guidelines on sexually transmitted infections: Syphilis. Retrieved from https://www.canada.ca/en/health-canada/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/sexually-transmitted-infections/canadian-guidelines-sexually-transmitted-infections-27.html.

Public Health Agency of Canada [PHAC]. (2019). Update on sexually transmitted infections, 2016. Retrieved from https://www.canada.ca/en/health-canada/services/publications/diseases-conditions/update-sexually-transmitted-infections-canada-2016.html#ppnc.

Ratnam, S. (2005). The laboratory diagnosis of syphilis. Canadian Journal of Infectious Diseases and Medical Microbiology, 16, 44–51.

Singh, A., & Romanowski, B. (1999). Syphilis: Review with emphasis on clinical, epidemiologic, and some biologic features. Clinical Microbiology Reviews, 12, 187–209.

Solomon, M. M., Mayer, K. H., Glidden, D. V., Liu, A. Y., McMahan, V. M., Guanira, J. V., ... Grant, R. M. (2014). Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. Clinical Infectious Diseases, 59, 1020–1026.

Sparling, P. F., Swartz, M. N., Musher, D. M., & Healy, B. P. (2008). Clinical manifestations of syphilis. In K. K. Holmes, Sparling P. F. P., F. W. E. Stamm, P. Pirot, J. N. Wasserheit, L. Corey, M. S. Cohen & D. H. Watts (Eds.). Sexually transmitted diseases: (4th ed.) (pp. 661–688). China: McGraw-Hill Companies Inc.

Tan, D. H. S., Hull, M. W., Yoong, D., Tremblay, C., O’Byrne, P., Thomas, R., ... Shafrotn, S. (2017). Biomedical HIV Prevention Working Group of the CHIR Canadian HIV Trials Network. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. Canadian Medical Association Journal, 189, E1448–E1458.