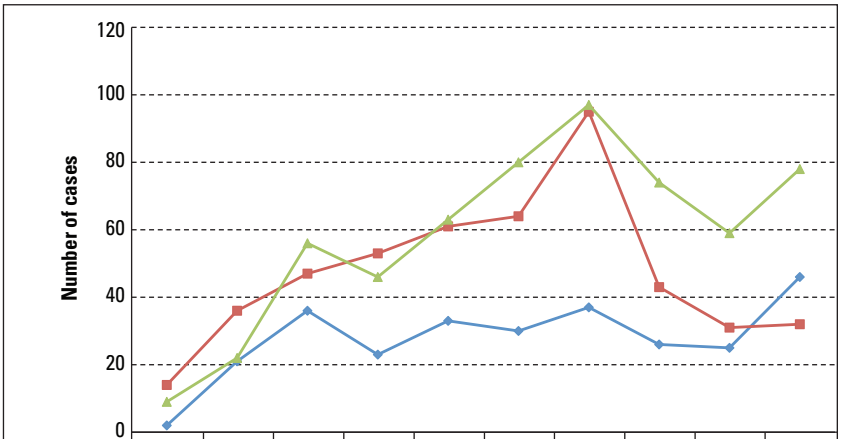
Better syphilis infection detection for better patient care and disease prevention

Syphilis, caused by the bacterium *Treponema pallidum* sub spp *pallidum*, is an infection recognized since antiquity. It was first reported in Italy at the end of 15th century.[1] Infections may be sexually transmitted as well as spread from an infected mother to her fetus or through blood transfusions. While *T pallidum* remains highly sensitive to penicillin, it remains a worldwide scourge. Globally, 25 million people are infected, with an estimated annual incidence of 12 million cases.[2] In British Columbia, syphilis infection rates are higher than the average Canadian rate, with an increasing number of infections in the men who have sex with men (MSM) population (**Figure**).[3]



	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
S-Primary	2	21	36	23	33	30	37	26	25	46
S-Secondary	14	36	47	53	61	64	95	43	31	32
S-Early Latent	9	22	56	46	63	80	97	74	59	78

Figure. MSM infectious syphilis case reports in BC by stage of infection 2002 to 2011.

Courtesy: Dr Mark Gilbert, Surveillance & Online Sexual Health Services, Clinical Preventions, BCCDC.

T pallidum causes disease in three stages. Entering through intact or abraded skin or mucous membrane and multiplying at the site of entry results in this spirochete causing painless ulcers in approximately 3 weeks (range 10 to 90 days) postexposure; this is the first stage of syphilis. Without treatment infections may resolve within 1 to 5 weeks. Humoral antibodies against cardiolipin (a nonspecific antigen that was discovered to cross-react well with *T pallidum* antigens) and treponemal antigen (from animal sources) usually do not appear until 1 to 4 weeks after the chancre. During the time the ulcer heals, *T pallidum*, when not stopped by treatment, spreads systemically; this is the second stage of syphilis. Multiple types of rashes and flu-like symptoms mimicking many other diseases may appear about 2 to 6 weeks later. The second stage (also known as secondary syphilis), if untreated, resolves within 2 to 6 weeks or the infection could go on to the third stage (called the latent or late stages of syphilis), as long as 30 years later. One-third of untreated patients with third-stage infections end up with chronic manifestations of disease including gummas (any tissue) and cardiovascular or neurological signs and symptoms.[4]

The laboratory diagnosis of syphilis infection is complex. Since this organism cannot be cultured, serology is used. Some of the issues related to serological diagnoses are that antibodies take time to appear after infection and serology screening tests require several secondary confirmatory tests that can produce complex results needing interpretation by experts in the field. *T pallidum* can be seen under the microscope from an appropriate clinical sample such as ulcer or cancre exudates; however, the sensitivity of this direct test is very low. *T pallidum* DNA may also be detected by polymerase chain reaction (PCR) from appropriate samples such as ulcer fluid, CSF, and biopsy tissue, but again test sensitivity is very low. Thus, despite its limitations, serology remains the mainstay for diagnosis.

Traditionally, syphilis serology screening tests such as the rapid plasma regain (RPR) tests have been done and have used non-treponemal (using cardiolipin antigens). When positive, results were confirmed using specific treponemal tests such as *Treponemaa pallidum* Particle Agglutination (TPPA),

This article is the opinion of the BC Centre for Disease Control and has not been peer reviewed by the BCMJ *Editorial Board.*

or fluorescent antibody-absorption (FTA-Abs). Since RPR positive titres correlated with disease activity, it was useful for monitoring treatment or re-infections. Recently, due to the need for efficiencies in high-volume screening and the need to address ergonomic stress of pipetting large numbers of samples, and with development of better tests, many laboratories in Canada have changed their diagnostic approach. Briefly, screening now uses semiautomated assays in which a blood sample is tested using an enzyme-linked immunosorbent assay (EIA). Screen positive samples are then tested with a quantitative non-treponemal test (e.g., RPR or VDRL). If any test results disagree, the specimen is also then tested using the TP-PA test as the confirmatory treponemal test. This new screening approach results in high-volume testing efficiencies, addresses ergonomic issues for technologists, and detects more cases (increased sensitivity) for early as well as latent syphilis.[5] One challenge with this new approach, however, is that there are more false positives due to increased test sensitivity.

Ideally, a screening test should be simple, easy to use, provide rapid results to enhance faster therapeutic interventions, and have the sensitivity, specificity, positive and negative predictive values suitable for use in both low- and high-prevalence populations. It also needs to be cost-effective. Meeting all these testing criteria is not simple. In the first instance, clinicians must remain aware that this "old mimicker of many diseases" (Sir William Osler)[6] is still very much alive and well in BC and that improvements in testing, albeit challenging to laboratories, are being implemented. This is yet another good example where clinical and laboratory interface is critical for patient care.

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Screening now uses semiautomated assays in which a blood sample is tested using an enzyme-linked immunosorbent assay.

Acknowledgments

The author would like to thank Mark Gilbert, Travis Hottes, and Stanley Wong.

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