National Collaborating Centre for Infectious Diseases
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Purple Paper

Rapid/Point of Care Testing for Syphilis: Canadian and International Perspectives

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Introduction

Syphilis remains a global problem with an estimated 12 million people infected annually (Gerbase, 1998). About 90% of these infections are in low-income countries (Peeling, 2004; Peeling, 2006). The World Health Organization (WHO) estimates that 2 million pregnant women each year are infected with syphilis globally and that approximately 1.2 million of these pregnant women with syphilis transmit the infection to their newborn resulting in still-birth and babies born with congenital syphilis (Salojee, 2004). In the developing world, many of these babies will die in the first year of life.

During the early and mid-1990s, Canada, like other high-income countries, set national goals to maintain disease rates for infectious syphilis below 0.5 per 100,000 population and to prevent all cases of endemic congenital syphilis (Proceedings, 1997). From 1994 to 1999, rates of infectious syphilis were 0.4–0.6/100,000 (PHAC, 2008). Between 1999 and 2008, reported rates of infectious syphilis increased in both genders: in men the rate increased by 870.7% (from 0.7 to 7.3 per 100,000) and in women by 123.4% (from 0.5 to 1.1 per 100,000). This has been driven by outbreaks among both men who have sex with men (MSM) as well as among heterosexual persons. Some of these outbreaks have been concentrated in street-involved persons and/or linked to the sex trade. The reported incidence of syphilis in 2008 was highest in Northwest Territories, British Columbia and Alberta, followed by Quebec and Ontario. Concurrent with the rise in heterosexually transmitted infections, a rise has been seen in congenitally acquired syphilis infections from 2 or less per year before 2005 to 7-8 cases per year between 2005 and 2007; the majority of reported cases were in Alberta (PHAC, 2008; Singh, 2007).

Syphilis rapid/point of care tests (RPOCT) are widely available for use in developing countries where they

Key Points

- Syphilis remains a global health problem with an estimated 12 million people infected annually.
- RPOCT may be defined as a “Point of Care Test” carried out in a clinical or non-clinical setting for which the result is available without testing at a laboratory and “Rapidly” enough (with test results typically available in < 20 minutes) to affect immediate patient management.
- More than a dozen commercially available syphilis RPOCT are available internationally.
- Immunochromatographic strip (ICS) tests, a type of treponemal test, have been widely evaluated using both whole blood and sera; the median reported sensitivity of ICS tests is 0.86 (interquartile range [IQR] 0.75-0.94) with median specificity of 0.99 (IQR 0.98-0.99).
- Antenatal cost-effectiveness of RPOCT shows that the ICS TT tests are cost-effective for the detection of maternal syphilis in low resource settings.
- Some of the inherent challenges of syphilis testing also exist with syphilis RPOCT. For example, because positive treponemal RPOCT may indicate new or old infections, a quantitative non-treponemal test is often helpful. No commercially available non-treponemal RPOCT is available as a single test at this time but two dual tests are commercially available.
- In Canada due to the low prevalence of infectious syphilis for many years, widespread availability of syphilis testing at laboratories and lack of a licensed syphilis RPOCT, there is no routinely used RPOCT for syphilis.
- In developed nations such as Canada, RPOCT for syphilis is potentially of greatest benefit in areas experiencing a resurgence of infectious syphilis and in hard-to-reach populations.

allow individuals to access a test at an earlier time point in their disease and expand the settings in which testing can be undertaken (Tucker, 2010; Ward, 2006).

Diagnosis of Syphilis

The diagnosis of syphilis is complex and depends on a combination of epidemiological data, clinical presentation and laboratory tests (PHAC, 2010). However, serological tests remain the mainstay of diagnosis of syphilis (Seña, 2010). Serological tests are divided into those which detect non-treponemal antibodies (or reagins) and those which detect treponemal antibodies. Two approaches to serological diagnosis of syphilis are now possible. In the traditional algorithm, a reactive non-treponemal test [NTT] (e.g. rapid plasma reagin [RPR]) is followed by one or more confirmatory assays, a treponemal test [TT] (e.g. *Treponema pallidum* particle agglutination [TPPA], fluorescent treponemal antibody – adsorbed [FTA-ABS]).

A second algorithm, commonly referred to as a reverse sequence algorithm (CDC, 2011), utilizes a TT, usually an enzyme immunoassay (EIA) using recombinant antigens, for screening, and if reactive, this is followed by a quantitative NTT and sometimes by a second confirmatory TT (Young, 1992). The use of these reverse sequence algorithms for syphilis has led to uncertainty in clinical management; positive test results could reflect greater sensitivity of the treponemal EIAs for untreated syphilis, a high frequency of treponemal false-positive results, or some combination thereof (Sena, 2010).

Both algorithms require the titration of reactive sera using the quantitative NTT in order to help stage the infection, follow response to treatment and assess for possible re-infection (Samoff, 2009).

Overview of Rapid/Point of Care Tests (RPOCT) for Syphilis

One definition of near-patient or "point of care" testing (RPOCT) is a test carried out in a clinical or non-clinical setting for which the result is available without testing at a laboratory and rapidly enough to affect immediate patient management (Dean, 2006). Most RPOCT for syphilis are available with a short turn around time, with test results available in $\leq$ 20 minutes (Tucker, 2010).

The characteristics of an ideal RPOCT as outlined by the World Health Organization Sexually Transmitted Diseases Diagnostics initiative in 2001(http://www.who.int/std_diagnostics/about_SDI/priorities.htm) are that the test should fulfill the ASSURED guidelines: **A**ffordable by those at risk of infection, **S**ensitive with few false negatives, **S**pecific with few false positives, **U**ser friendly or simple to perform with minimal training, **R**apid to enable treatment at the first visit, **R**obust, not requiring refrigeration or heating, **E**quipment free and **D**elivered to those who need it.

NTT including the RPR assay is not often used as a RPOCT because the tests need to be batched, and a power source is required for refrigeration of the reagents and to operate a shaker (Aledort, 2006). Currently there are more than a dozen commercially available RPOCT for syphilis internationally which test for the presence of treponemal antibodies (Greer, 2008). There are two varieties of rapid syphilis tests: *1) Immunochromatographic strip (ICS) tests* which work by having a test strip with a line that is impregnated with treponemal antigens that react with antibodies in whole blood or serum of a syphilis patient to produce a visual colour change on the test strip and 2) *Particle agglutination tests,* which use gelatin particles coated with treponemal antigens that clump together on a test tray when combined with whole blood or serum containing antibodies to syphilis.

A recent systematic review by Tucker *et al* summarizes the available literature on rapid syphilis testing using ICS since this type of TT has been evaluated in more clinical settings than particle agglutination tests (Tucker, 2010). A variety of specimen types have been used including whole blood primarily from finger prick specimens, whole blood from other than fingerprick specimens, and sera (Tucker, 2010). Two studies showed better sensitivity when serum specimens were used (Siedner, 2004; Herring, 2006). The median reported sensitivity of ICS tests was 0.86 (interquartile range [IQR] 0.75-0.94) with median specificity of 0.99 (IQR 0.98-0.99) and no difference between antenatal and STI clinic specimens. The ICS tests show a > 80% positive predictive value for syphilis when the syphilis prevalence was greater than 0.3%. Limited

data are available to confirm if the sensitivity is maintained in HIV-infected individuals (Montoya, 2006) and in those with high RPR titre infection (Benzaken, 2008; Montoya, 2006).

Because positive treponemal RPOCT may indicate new or old infections, a quantitative non-treponemal test is often helpful. However, there are no commercially available non-treponemal RPOCT available as a single test at this time.

Two commercially available dual tests are currently available. Castro *et al* evaluated a novel RPOCT (Chembio Diagnostics System Inc, Medford, NY) for the simultaneous detection of non-treponemal and treponemal antibodies in sera of 1601 patients (Castro, 2010). When compared to the RPR, the reactive concordance of the non treponemal result was 98.4% when the RPR titre was $\geq$1:2. However, when the RPR titre was $\leq$ 1:1, the sensitivity declined to 88%. When compared to the TPPA, the reactive and non-reactive concordance of the treponemal component of the test was 96.5% and 95.5%. This dual RPOCT is designed for use with serum, plasma and whole blood. Span Diagnostics (Gujarat, India) also makes a dual test (http://www.span.co.in/#) but no performance data from field trials are available.

The U.S. FDA recently licenced the Syphilis Health Check (Trinity Biotech, Jamestown, NY, USA), an ICS treponemal test (https://www.diagnosticsdirect2u.com/images/PDF/SyphilisHC.pdf; accessed October 4, 2011). This 10 minute test can be used with whole blood, serum or plasma specimens, requires 25-50 µL of blood and was originally distributed by Direct Diagnostics (Stone Harbor, NJ, USA). No published clinical data on test performance are available. There are currently no licensed RPOCT in Canada.

Available data on the antenatal cost-effectiveness of RPOCT show that the ICS TT tests are cost-effective for the detection of maternal syphilis in low resource settings when compared to either standard 2 test testing algorithms (i.e. NTT followed by TT) or a NTT alone (Terris-Prestholt, 2003;Levin, 2007; Rydzak, 2008). Owusu-Edesei and colleagues recently reported that a screening strategy employing an ICS TT was more cost saving than a dual-RPOCT (TT and NTT) strategy in a high prevalence setting but that the dual-RPOCT strategy may significantly reduce overtreatment (Owusu-Edesei, 2011). No cost-effectiveness data are available for developed countries.

Successes, Challenges and Failures of RPOCT Globally

RPOCT for syphilis have been used in many settings in developing nations to scale up STI prevention efforts especially in the prevention of mother to child transmission of syphilis (Peeling, 2006). However, many countries still fail to meet the goal set by the WHO in part related to initial funding costs, health system constraints and availability of adequately trained personnel. The ICS tests have provided the opportunity to address some of these concerns as they have been shown to be cost-effective, require no equipment and less stringent storage requirements and field personnel can be easily trained to conduct the tests. In addition, ICS tests are much easier to read than the RPR tests, especially when the results are borderline and hence it is easier to get reproducible results with ICS than with RPR. Further work is still needed to scale up existing efforts and to incorporate RPOCT for syphilis into existing well established HIV programs for Prevention of Mother to Child transmission (PMTCT) as well as at voluntary counseling and testing (VCT) sites (Peeling, 2006).

Choice of test kit and specimen type is important when deciding which kit will perform optimally in any given field setting as performance may vary depending on syphilis prevalence, type of kit and test and specimen type used. For example, Campos *et al* reported lower sensitivities with the use of whole blood (fingerprick) specimens which might have been due to inadequate lighting, lack of use of heparinized capillary tubes for collection of whole blood, false negatives due to previously treated syphilis and a low proportion of samples reactive at low RPR titres (Campos, 2006). Herring *et al* showed variability between test lots, day to day testing and differences between testers (Herring, 2006).

As RPOCT are often performed by non-laboratorians outside of a laboratory, and judgment is used on subjective interpretation of a band being positive or negative in an ICS or the strength of the agglutination reaction with antibodies in sera or whole blood, the results can be variable. Training protocols and quality assurance need to be in place.

Additionally, sufficient lighting should be provided to read results.

Some of the inherent challenges of syphilis testing also exist with RPOCT for syphilis. For example, the commercially available RPOCTs for syphilis detect treponemal antibodies and cannot distinguish active infection from prior treated syphilis, as these antibodies usually persist for decades (Herring, Nature Rev Microbiol 2006). Thus in areas of high syphilis prevalence, the test returns more positive results because there are more people who have prior treated infections who test positive on a treponemal test and may be subject to unnecessary re-treatment. For example, in a study by Montoya *et al*, 20% of women who tested positive by ICS were *Treponema pallidum* haemagluttination assay (TPHA) positive/RPR non-reactive; of whom 14% reported previous treatment for syphilis (Montoya, 2006). Despite this, the use of ICS tests in antenatal clinics has the potential to impact on prevention of mother-to-child transmission of syphilis even if up to 1% pregnant women have false positive test results and are treated unnecessarily (Tucker, 2010). False positive syphilis tests can occur with non venereal trepanematoses including yaws, pinta and bejel which are non-sexually transmitted infections typically acquired in childhood in some tropical countries (Antal, 2002). Alternatively, the test may provide a same-day screening test with active syphilis being confirmed by a non-treponemal test, allowing immediate treatment of high-risk patients unlikely to return for follow up and preventing onward transmission of infection.

Current Use of RPOCT for Syphilis in Canada

Currently, due to the low prevalence of infectious syphilis for many years, widespread availability of syphilis testing at laboratories and the lack of a licensed RPOCT for syphilis in the country, there is no routinely used RPOCT for syphilis in Canada. In the context of a recent resurgence of infectious syphilis in Alberta, Bergman *et al* recently reported preliminary data from the first field trial of RPOCT for syphilis in Edmonton (Bergman, 2011). The primary objective of this ongoing initiative is to evaluate the performance and utility of RPOCT for syphilis and HIV in hard-to-reach populations (including inner city, street-involved, incarcerated persons, MSM in bathhouses) in Edmonton, Alberta. The preliminary data (n=196) on the performance of finger prick (whole blood) specimens using the SD Bioline 3.0 test (Standard Diagnostics, Korea), a TT, showed a sensitivity of 80%, specificity of 100%, PPV of 100% and NPV 98.9%.

Potential Implications of Widespread Use of RPOCT in Canada

In Canada, syphilis is reportable at both the provincial/territorial level and notifiable at the national level. Since more false positive results can be expected when the disease prevalence is low, it is likely that all positive RPOCT tests for syphilis will require confirmatory testing and follow similar procedures for reporting developed for positive RPOCT for HIV in some provinces (e.g. Ontario). In Alberta since the implementation of the RPOCT project, similar reporting procedures have been employed to that used with traditional testing procedures. In an attempt to avoid unnecessary overtreatment in those who have been previously positive, a centralized syphilis registry is checked for prior syphilis history before offering treatment. For individuals with a history of previous treatment, RPOCT treatment is offered if the testing nurse feels that the patient is unlikely to return for follow up; the study is still underway to evaluate the efficacy of this approach. The use of a dual test RPOCT also has the potential to offset some overtreatment but the efficacy of such an approach in low prevalence settings needs to be evaluated.

If used for screening in low prevalence settings in Canada (e.g. the general population without specific risk factors), it is likely that a higher rate of false positives would be identified through treponemal (e.g. ICS) RPOCT. This rate of false positives would not be expected to be higher, however, than reverse sequence algorithms using the syphilis EIA (a treponemal test) which have become more widely used in Canada over the last few years (Tsang, 2011).

Potential Uses of RPOCT for Syphilis in Canada and International

Perhaps the greatest impact of RPOCT can be achieved in high prevalence settings in developing countries. The WHO has recommended that all pregnant women be screened for syphilis during pregnancy (WHO, 1991). Although prenatal screening for syphilis is policy in almost all countries

in the developing world, only about 30% of pregnant women get screened, because of lack of access to laboratories or clinics where syphilis testing is available. Syphilis in pregnancy is estimated to cause more than 500,000 perinatal deaths annually worldwide. RPOCT, which do not require laboratory equipment, and give a result in 15 minutes, offer an unprecedented opportunity to increase access to screening, and immediate treatment for those with syphilis.

On-site RPOCT has been shown to be feasible and allows for the test and treatment to be conducted in a single visit with the potential to significantly reduce perinatal mortality (Mabey, 2006; Bronzan, 2007). Other studies have suggested however that such a strategy may be of limited benefit in settings with well-functioning laboratory and clinical services already in place (Myer, 2003). In some countries, the introduction of rapid tests has met with opposition or even hostility from laboratory professionals. It is important to clarify that rapid tests are tools to supplement and not to replace laboratory testing. In fact, as testing is decentralized, the laboratory plays an important role in assuring the quality of tests and testing.

The proposed advantage of diagnosis and treatment in a single visit is not limited to developing countries (Greer, 2008). In STI clinics in the U.S and Canada, non return for the results of STI/HIV testing is a common problem (Singh, 1999, Swain, 2004; Greenwald, 2006; Kendrick, 2005). In addition, even for compliant patients with positive tests, there is a delay between testing and treatment during which infection can be spread, unknowingly, to others (Swain, 2004; Mahilum-Tapay, 2007).

In developed nations such as Canada, RPOCT for syphilis is potentially of greatest benefit in areas experiencing a resurgence of infectious syphilis and in hard-to-reach populations such as street-involved, transient, inner city and also MSM in some settings such as bathhouses or bars, etc. Such testing offered in high volume clinics, e.g. STI clinics enables rapid testing and treatment at a single visit as well and therefore to allow for immediate interviewing for partners. RPOCT also have the potential to allow RPOCT treatment in remote or rural areas of Canada where there may be significant delays in transport of specimens (Lee, 2011). Other potential opportunities for such testing might be for women in labour who have not received prenatal screening earlier in pregnancy or those who previously screened negative but may have been at risk (e.g. sex trade) for re-infection after an earlier negative screen. Interestingly, recognizing this trade-off, the U.S. Centers for Disease Control and Prevention recommends rapid screening and treatment for positive test results at the first prenatal visit in populations in which use of "prenatal care is not optimal" (CDC, 2006). Incorporating syphilis screening into existing RPOCT strategies for HIV which are already widely established and available in many countries will also allow for expanded screening in certain populations. As the rapid test technology has become sufficiently robust for self-testing, which is well received in studies in Africa, the debate for self-testing of syphilis will need to be considered (Choko, 2011).

In summary, RPOCT for syphilis in Canada have the potential to provide immediate and rapid access to testing and therefore treatment in "hard-to-reach populations" or in non-traditional venues and to mitigate the spread of syphilis. In order to take full advantage of rapid diagnostic tests, proposed studies must evaluate their utility, acceptance, effectiveness, potential adverse events and cost-effectiveness in clinics and field-based settings in Canada. Obtaining regulatory approval for rapid syphilis tests has been a continuing challenge in many countries including the U.S. in spite of the potential public health advantage of increasing access to hard-to-reach populations who are often the core transmitters of infection. Regulatory authorities may be risk adverse and reluctant to approve tests that do not show non-inferiority in test performance to the last approved test for a disease. Further data to support the utility and cost benefit of RPOCT for syphilis prevention and control in various settings are needed to assist with the regulatory reviews required for approval of these tests in many countries.

To quote Ward – "it is not a case of whether near-patient testing will improve STI control but rather how we ensure that it does." (Ward, 2006).

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Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada.
The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.