IHE Report

Cost-effectiveness in the Detection of Syphilis

February 2007

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INSTITUTE OF HEALTH ECONOMICS
ALBERTA CANADA

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EVALUATION OF ENZYME IMMUNOASSAY AND IMMUNOBLOT TESTING FOR THE DIAGNOSIS OF SYPHILIS IN ALBERTA

Final Report

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Supported by a financial contribution from Alberta Health and Wellness through its Alberta Health Technologies Decision Process: the Alberta Model for health technology assessment and policy analysis.

The views expressed herein do not necessarily represent the official policy of Alberta Health and Wellness.

EXECUTIVE SUMMARY

Objective

A new protocol for testing and diagnosing syphilis has been proposed in Alberta. The protocol proposes replacing rapid plasma reagin (RPR) with enzyme immunoassay (EIA) as the standard initial test and replacing Treponema pallidum (T. pallidum) particle agglutination assay (TPPA) and fluorescent treponemal antibody-absorbed (FTA-Abs) with Inno-Lia (IL) as the standard confirmatory test. The primary aim of this report is to provide a cost effectiveness analysis (CEA) of the proposed protocol (EIA+IL). Information regarding Social and System Demographics and Technology Effects and Effectiveness is also provided.

Social and System Demographics

Syphilis is a sexually transmitted infection caused by the bacterium T. pallidum. The primary mode of transmission is by sexual contact, but is also commonly transferred across the placenta in pregnant women. Untreated adult syphilis can ultimately develop into tertiary syphilis which is characterized by severe physiological and neurological damage that may not be reversible. Untreated cases of syphilis in pregnant women can lead to complications during pregnancy and delivery including neonatal death, still birth, blindness, deafness, abnormal bone growth, and/or mental retardation. Antibiotic (penicillin) treatment is relatively inexpensive and effective.

Recently infection rates in both Alberta and Canada have been increasing. In 2005, the rate of infectious syphilis cases in Alberta was higher than the national rate in Canada. Non-infectious and infectious syphilis have become the fourth and fifth most common notifiable sexually transmitted diseases in Alberta.

Technology Effects and Effectiveness

Current syphilis testing protocols have two major limitations potentially leading to higher rates of unidentified cases and unnecessary costs (i.e. unneeded testing of false positives and follow up testing of true negative indeterminates). First, RPR is a non-treponemal antigen targeted assay and therefore may not identify individuals early in primary syphilis or late in its progression. Second, confirmatory testing with TPPA and FTA-Abs requires a technologist to subjectively evaluate whether there is adequate fluorescent reactivity in the blood sample introducing potential bias. Consequently, confirmatory tests with TPPA and FTA-Abs may lead to both false positive and false negative results if the fluorescence intensity is misinterpreted.[1]

In contrast to RPR, EIA is a treponemal antigen targeted assay able to detect syphilis in all stages of untreated and treated syphilis. It has also been associated with greater diagnostic precision, although at a higher cost per test. Moreover, Inno-Lia (IL) is a multiparameter line immunoassay that uses recombinant and synthetic polypeptide antigens derived from T. pallidum proteins1 and in contrast to TPPA and FTA-Abs confirmatory testing, employs simpler interpretation criteria which further minimizes subjectivity. Confirmatory testing with IL is considered the diagnostic gold standard for the confirmatory testing of syphilis.

Another advantage of the EIA+IL over RPR is that it is available in automated platforms. This offers several advantages when conducting large volumes of tests including high throughput capacity, reduced staff training time, improved quality control, and expeditious turn around times.

Cost Effectiveness Analysis

A probabilistic cohort simulation model was constructed to determine, from a health systems perspective, the cost-effectiveness of EIA+IL versus Current Protocols. Using 2006 Alberta testing utilization levels from the Provincial Laboratory of Alberta (ProvLab) for prenatal and non-prenatal populations, the model simulated the cohort of individuals from each population (separately) according to the protocol (EIA+IL or Current) to generate costs and outcomes. Estimates of prevalence, testing utilization levels, test costs, labour costs, and test characteristics were valued based on provincial data and existing available literature.

Cost outcomes included syphilis tests, resource costs associated with falsely diagnosed true positive, treatment, treatment follow up, contact tracing, follow up of indeterminate cases (i.e. suspected syphilis but not confirmed), and community search and patient contacting for treatment and follow up. All cost outcomes were made to reflect 2006 Canadian dollars and would have occurred in 2006. Effectiveness was operationalized as the additional number of correct diagnoses.

Expected value calculations of costs and effectiveness were based on 100,000 Monte Carlo simulations. Incremental cost effectiveness ratios (ICER) were calculated based on the expected value of cost and effectiveness between EIA+IL and current protocols. An ICER below $25,000 per additional correct diagnosis and an ICER below $10,000 per additional correct diagnosis were used as benchmarks to indicate whether there was economic evidence to support replacing the current protocol with EIA+IL in the prenatal and non-prenatal population respectively.

CEA Results

In the prenatal population the cost of current protocols was $1,904,935, while the cost of EIA+IL was $1,914,439. In the non-prenatal population the cost of

the current protocol was $2,320,967 while the cost of EIA+IL was $2,234,914. The total cost of current protocols (prenatal and non-prenatal) was $4,225,902 and the total cost of EIA+IL was 4,149,353. In the prenatal population the total number of correct diagnoses was 51,510 for the current protocol and 51,517 for EIA+IL; the additional number of correct diagnoses was therefore seven with EIA+IL. In the non-prenatal population the total number of correct diagnoses was 37,876 for the current protocol and 38,035 for EIA+IL; the additional number of correct diagnoses was therefore 159 with EIA+IL.

In the prenatal population the ICER of EIA+IL (compared to current) is $1,358 per additional correct diagnosis (i.e. more costly and more effective). In the non-prenatal population the ICER v EIA Evaluation of EIA+IL is -$541 per additional correct diagnosis and dominates the current protocol (i.e. less costly and more effective). Overall (prenatal and non-prenatal), the ICER of EIA+IL is -$461 per additional correct diagnosis and dominates the current protocol (i.e. is less costly and more effective).

Discussion

Results should be evaluated in light of four caveats. First, the analysis is entirely founded on the assumption that persons testing negative on EIA and IL do not receive further confirmatory testing or follow up. Although in actual conditions there will be variation in how EIA+IL is used depending on clinical presentation and patient history, protocols for EIA+IL outlined in this report should be adhered to (at least in general) in order to achieve the cost effectiveness outcomes described.

Second, the economic advantages of a more sensitive but expensive test is positively correlated with the prevalence of disease. It is reasonable to assume that if implemented, EIA+IL will correctly identify more seropositive individuals leading to more correct diagnosis of true positives, which will eventually reduce prevalence. However, the economic impact of reducing syphilis in the testing population will not be affected in the short-run because it is the prevalence of seropositives in the testing population that affects laboratory testing results. That is, the prevalence of seropositive individuals will decrease at a much slower rate than the prevalence of syphilis cases and the economic effectiveness of EIA+IL will continue until the prevalence of both seropositive individuals and syphilis decrease.

Third, the analysis does not include the testing volumes from testing service providers other than the ProvLab (excluded due to limitations in the data). There were 32,640 estimated tests conducted by CLS, DKML, and other hospital laboratories in 2006. Assuming that 32,640 tests is representative of the testing volumes conducted outside the ProvLab, the estimated incremental test cost (initial test only) of EIA (compared to the current protocol) is $82,580.

Fourth, the net cost savings of EIA+IL is driven by reducing the number of symptomatic neurosyphilis compared to the current protocol. While the savings associated with prevented symptomatic neurosyphilis reflect the value of future savings had they occurred in 2006, no actual savings to the health care system would occur until neurosyphilis develops (may take up to 30 years).

Conclusion

Based on the CEA which only includes testing utilization levels from the ProvLab, at current prevalence levels compared to the current protocol, EIA+IL would generate cost savings to the health care system while also generating more correct diagnoses overall. Therefore, there is economic evidence to support replacing the current Alberta protocol with EIA+IL for pre-natal screening and for diagnosis in patients likely to have syphilis given that clear diagnostic guidelines are developed and continuing education is provided for clinicians on how to best use EIA and IL.

List of Acronyms

AHW – Alberta Health and Wellness

CEA – cost-effectiveness analysis

CLS – Calgary Lab Services

DAM – decision analytic modeling

DKML – Dynacare Kasper Medical Laboratories

EIA – enzyme immunoassay

FN – false negative

FP – false positive

FTA – Abs fluorescent treponemal antibody-absorbed

GP – general practitioner

HRQL – health related quality of life

ICER – incremental cost effectiveness ratio

ICEP – incremental cost effectiveness plane

IDMC – infectious disease medical consultant

IL – immunoblot assay (Inno-Lia)

RHAs – regional health authorities

RPR – rapid plasma reagin

STD – sexually transmitted disease

TN – true negative

TP – true positive

TPPA – *Treponema pallidum* particle agglutination assay

WTP – willingness to pay

Table of Contents

Executive Summary i

List of Acronyms iv

Objective 1

Social and System Demographics 1

- Clinical Manifestation and Burden of Disease 1
- Testing/Diagnosis 2
- Treatment 2
  - Table 1: Overview of treatment for syphilis 3
- Epidemiology in Alberta and Canada 5
  - Figure 1: Infectious syphilis rates in Alberta[1] and Canada[2] 5
  - Figure 2: Infectious and non-infectious syphilis cases in Alberta 2001-2006[1] 6
- Service Utilization 7

Technology Effects and Effectiveness 7

- Technology Effects 7
- EIA Distributors 8
- Technology Effectiveness 8
- Automation 9
- Table 2: Values of sensitivity and specificity 10

Economic Evaluation 12

- Review of Economic Evaluations of EIA or Inn o-Lia 12
  - Search Strategy 12
  - Selection Criteria 12
  - Results 12
- Testing and Diagnostic Protocols 13

Current Testing and Diagnostic Protocols 14
Comparator 15
Background for Understanding
Cost Effectiveness Analysis 16
Incremental Cost Effectiveness Ratios (ICER. 16
Expected Value Calculations 17
Handling Uncertainty. 18
Analysis 18
Model Inputs 19
Table 3A: Inputs –
population and diagnostic tests 20
Table 3B: Inputs –
treatment and routine follow ups 21
Table 3C: Inputs –
outcomes for false negatives and costs 22
Alberta Sources 23
Cost Outcomes 24
Diagnostic Outcomes. 25
Incremental Cost Effectiveness Ratio (ICER 25
Sensitivity Analysis 26
Model Assumptions 26
Results 27
Costs. 27
Effectiveness 28
Table 4: Cost, effectiveness,
and incremental cost effectiveness. 28
Incremental Cost Effectiveness 28
Sensitivity Analysis 29
Figure 3 Incremental Cost
Effectiveness Plane – Prenatal 29

Figure 4 Incremental Cost Effectiveness Plane – Non-Prenatal 30
Figure 5: Acceptability curve of EIA + IL in prenatal and non-prenatal populations. 31
Cost Attribution 31
Table 5: Incremental (Compared to Current) Cost Savings/Additions of EIA + IL 32
Discussion 33
General 33
Costs and Effectiveness 33
Reliability of Findings 34
Caveats 34
References 37
Appendices 40
Appendix A: Search Strategy 40-41
Appendix B: Simulation Models 42-43

Objective

A new laboratory testing protocol for the serological diagnosis of syphilis has been proposed for Alberta. The protocol proposes replacing rapid plasma reagin (RPR) with enzyme immunoassay (EIA) as the standard initial test. It also proposes replacing Treponema pallidum (T. pallidum) particle agglutination assay (TPPA) and fluorescent treponemal antibody-absorbed (FTA-Abs) with an immunoblot assay (Inno-Lia, IL) as the standard confirmatory test.

The primary aim of this report is to provide an economic evaluation of the newly proposed protocol (EIA+IL) while also providing contextual information (Social and System Demographics and Technology Effects and Effectiveness). Specifically, the economic evaluation compares the cost and outcomes of EIA+IL to those of the current protocol over a one year time period from a health systems perspective.

Social and System Demographics

Clinical Manifestation and Burden of Disease

Syphilis is a sexually transmitted infection caused by the bacterium T. pallidum. The primary mode of transmission is by sexual contact between partners where the probability of transmission exceeds 60%.[2] Clinical manifestations of syphilis can be categorized into three stages: primary, secondary, and tertiary.[3] Primary syphilis is characterized by chancre sores and regional lymphadenopathy which may be absent or go unnoticed. Often there is no clear demarcation between primary and secondary syphilis. The findings in secondary syphilis are diverse but often include rashes (particularly on the palms and soles), fever, malaise, lymphadenopathy, mucosal lesions, condyloma lata, alopecia, or meningitis. Transmission can occur during primary or secondary syphilis.[3]

Approximately 15% to 40% of untreated syphilis cases progress to the tertiary stage. In tertiary syphilis, 16% of affected persons will develop gummas and necrotic masses (which may form anywhere in the body) which lead to a wide range of functional problems. Ten percent will develop cardiovascular damage, particularly in the aorta leading to aneurysm and heart valve dysfunction. Seven percent of cases develop tertiary neurosyphilis characterized by muscle coordination problems, paralysis, blindness, psychoses, dementia, and death. Damage caused by tertiary neurosyphilis is irreversible.[3] Symptoms of neurosyphilis have a variable temporal onset. Estimates vary from as little as 5 years to as much as 30 years after initial infection.[4]

Syphilis also readily crosses the placenta in pregnant women, infecting the developing fetus.[5] Nearly half of all infants infected with syphilis during gestation die shortly before or after birth. The incidence of still birth and neonatal death is as high as 25% and 14% respectively.[6] Surviving infants may suffer from such disorders as blindness, deafness, abnormal bone growth, and/or mental retardation. Some infants with congenital syphilis may be initially asymptomatic

and develop symptoms later in life. The health system costs associated with treating infants with congenital syphilis for the first year has been estimated at $18.4 million ($11,031 per case) in 1995 in the United States.[7]

Testing/Diagnosis

The clinical findings of syphilis are variable, often mimicking many other diseases, or they can be absent altogether. Consequently, the diagnosis of infection is dependant on laboratory testing. While the organism can be detected in the exudates from early lesions by microscopy, the vast majority of syphilis tests are serological (i.e. blood tests). Serological tests for syphilis can be categorized into non-treponemal and treponemal tests (refer to Current Testing and Diagnostic Protocols Section for testing protocols in Alberta).

Non-treponemal tests include the Venereal Disease Research Laboratory (VDRL) and the RPR.[8] These tests detect antibodies against cardiolipin which are often present in the sera of syphilis cases. Although non-treponemal tests are widely available and inexpensive, they lack sensitivity in their ability to correctly identify positive cases, particularly in early infection or in the late latent stage. RPR may also be falsely positive in various conditions including tuberculosis, mononucleosis, pregnancy, and autoimmune disease. As the non-treponemal tests decline or revert to non-reactive after successful therapy, they are also used to monitor a patient's response to treatment (i.e. stage the infection).

Treponemal tests include TPPA and FTA-Abs. These tests use lyophilized T. pallidum or a lysate of pathogenic T. pallidum. As these tests detect antibodies to the organism itself, they have higher sensitivity and specificity than non-treponemal tests.

Treatment

Modern treatment of syphilis is with benzathine penicillin. Treatment of syphilis cases eradicates symptoms, arrests the progression of the late complications, and prevents spread to partners. If syphilis is untreated, the neurological and cardiovascular damage that occurs in the later stages may be irreversible. Determining the appropriate treatment of syphilis is based on the stage of syphilis infection, co-infection with HIV, pregnancy, and allergy to penicillin. Treatment of syphilis is described in The Canadian Guidelines on Sexually Transmitted Infections, 2006 Edition (available on line at: http://www.phac-aspc.gc.ca/std-mts/sti_2006/sti_intro2006_e.html).

Congenital syphilis can be prevented if the mother's infectious syphilis is detected early and effectively treated. In Alberta, all pregnant women accessing antenatal care are routinely tested for syphilis in order to detect and prevent transmission of the infection to the fetus.

Treatment of a pregnant woman infected with syphilis is based on both the stage of syphilis infection and the stage of pregnancy. If a newborn is determined to be at risk for congenital syphilis or is determined to have congenital syphilis, treatment with intravenous Penicillin G is necessary.

A comprehensive overview of treatment genesis for syphilis is found in Singh and Romanowski (refer to Current Testing and Diagnostic Protocols Section for treatment protocols in Alberta).[3] Table 1 summarizes the general recommendations for the treatment of syphilis from The Canadian Guidelines on Sexually Transmitted Infections, 2006 Edition.

Table 1: Overview of treatment for syphilis

Stage	Preferred treatment	Alternative treatment for penicillin-allergic patients
All **non-pregnant** adults – **Primary** – **Secondary** **Early latent** (<1 year duration)	Benzathine penicillin G 2.4 million units IM as a single dose* [A-II; A-III for HIV- infected individuals]	– Doxycycline 100 mg PO bid for 14 days [B-II] Alternative agents (to be used in exceptional circumstances)† – Ceftriaxone 1 g IV or IM daily for 10 days [B-II]
Pregnant women – **Primary** – **Secondary**‡ – **Early latent** (<1 year duration)	Benzathine penicillin G 2.4 million units IM as a single dose* [A-II]	– There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy; insufficient data exist to recommend ceftriaxone in pregnancy – Strongly consider penicillin desensitization followed by treatment with penicillin [A-III]
All **non-pregnant** adults – **Late latent** syphilis – **Latent** syphilis of unknown duration – **Cardiovascular syphilis** and other **tertiary syphilis** not involving the central nervous system	Benzathine penicillin G 2.4 million units IM weekly for 3 doses [A-II]	– Consider penicillin desensitization – Doxycycline 100 mg PO bid for 28 days [B-II] Alternative agents (to be used in exceptional circumstances)† – Ceftriaxone 1 g IV or IM daily for 10 days [C-III]
Pregnant women – Late latent syphilis – Latent syphilis of unknown duration – Cardiovascular syphilis and other tertiary syphilis not involving the central nervous system	Benzathine penicillin G 2.4 million units IM weekly for 3 doses [A-II]	– There is no satisfactory alternative to penicillin for the treatment of syphilis in pregnancy; insufficient data exist to recommend ceftriaxone in pregnancy – Strongly consider penicillin desensitization followed by treatment with penicillin [A-III]

Table 1: Overview of treatment for syphilis (continued)

Stage	Preferred treatment	Alternative treatment for penicillin-allergic patients
All adults – Neurosyphilis	Penicillin G 3–4 million units IV q 4 h (16–24 million units/day) for 10–14 days [A-II]	– Strongly consider penicillin desensitization followed by treatment with penicillin – Ceftriaxone 2 g IV/IM qd x 10–14 days [B-II]
Congenital syphilis[3,4]	Early (<1 month) Crystalline penicillin G 50,000 units/kg IV every 12 hours for the first week of life and every 8 hours thereafter for 10 days of total therapy [A-II]	
	Late (≥1 month) Crystalline penicillin G 50,000 units/kg/ IV every 6 hours for 10–14 days [A-II]	– If no neurologic involvement and normal CSF: benzathine penicillin G 50,000 units/kg IM (max 2.4 million units) weekly for 3 successive weeks [B-II] – No data are available to recommend penicillin alternatives in the case of penicillin allergy
Epidemiological treatment of sexual contacts in the preceding 30 days to primary, secondary and early latent syphilis[§,††]	Benzathine penicillin G 2.4 million units IM as a single dose [B-II]	See comment below on Azithromycin[††]

* Some experts recommend three weekly doses (total of 7.2 million units) of benzathine penicillin G in HIV-infected individuals.

† The efficacy data supporting the use of these agents is limited and, as such, should only be used in exceptional circumstances and when close patient follow-up is assured.

‡ Secondary syphilis in late pregnancy (>20 weeks gestation) should be treated with two doses of benzathine penicillin G 2.4 million units given 1 week apart (see note under Pregnancy below).

§ If sexual contact is unreliable or unable to test, then epidemiological treatment should be strongly considered.

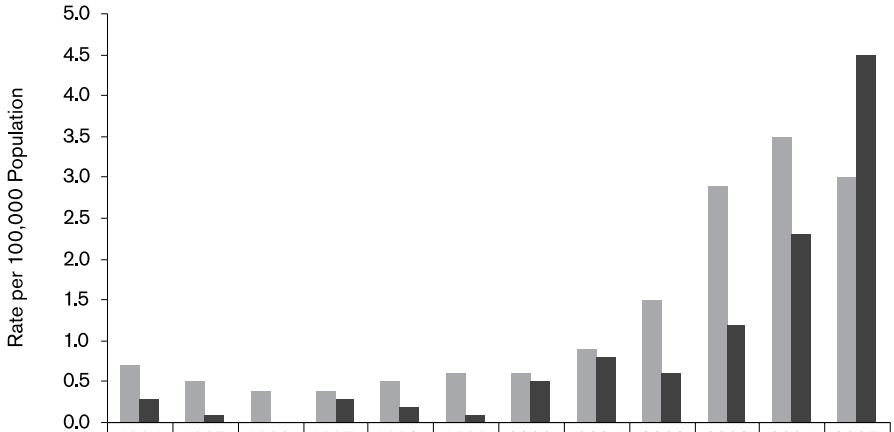
†† Azithromycin

In light of recent reports of failure of azithromycin for the treatment of early syphilis and the rapid development of azithromycin resistance in T. pallidum, this agent should not be routinely used as a treatment option for early or incubating syphilis unless adequate and close follow up can be ensured, and only in jurisdictions where little to no azithromycin genotypic resistance in T. pallidum has been demonstrated. It should be noted, however, that at the present time very limited Canadian data on the prevalence of Azithromycin resistance in T. pallidum is available.

Epidemiology in Alberta and Canada

Figure 1 presents infectious syphilis rates in Alberta and Canada since 1994. Before 2000, rates were relatively low. Since the year 2000, the rates in both Alberta and Canada have been increasing. In 2005, the rate of infectious syphilis in Alberta was higher than the national rate.

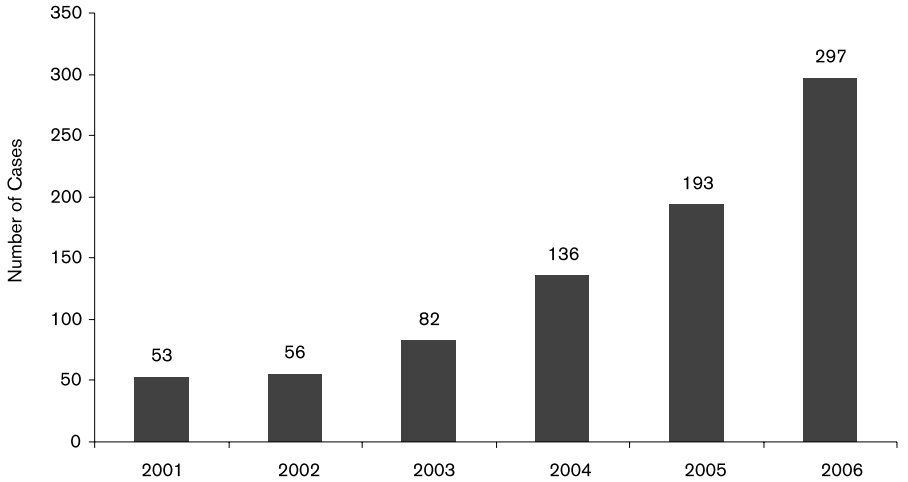
Figure 1: Infectious syphilis rates in Alberta[1] and Canada[2]



	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Canada	0.7	0.5	0.4	0.4	0.5	0.6	0.6	0.9	1.5	2.9	3.5	3.0
Alberta	0.3	0.1	0.0	0.3	0.2	0.1	0.5	0.8	0.6	1.2	2.3	4.5

Figure 2 shows the number of all diagnosed syphilis cases including infectious (stage 1 or stage 2) and non-infectious (stage 3) cases in Alberta from 2001-2006. The prevalence of syphilis has steadily increasing. In 2006, there were 297 confirmed cases, a 460% increase since 2001. Non-infectious and infectious syphilis are now the fourth and fifth most common notifiable sexually transmitted diseases in Alberta.

Figure 2: Infectious and non-infectious syphilis cases in Alberta 2001-2006[1]



Rates of syphilis differ by gender and ethnicity.[9] In Alberta, syphilis is more prevalent in men than in women.[10] While visible minorities (i.e. non-Caucasian) comprised only 31% of all cases in 2000, they comprised 56% of positive cases in 2005. First Nations populations accounted for 40% of the cases from visible minorities.[10] Syphilis affects all ages but peaks at 30-34 years of age and is followed by a gradual decline as age increases.[10] Over 80% of syphilis cases are transmitted by heterosexual contact[10] and approximately a third of the cases are linked to the sex trade.[10] Many cases report multiple sexual partners and use of injection drugs. Control of syphilis in this population is challenging as individuals and sexual partners may be difficult to contact and locate for testing and treatment.

Most syphilis cases in Alberta were found in Calgary and Edmonton. Of newly reported syphilis cases diagnosed in 2000, 2001 and 2002, Calgary accounted for 69%, 74% and 65% respectively. However, in the following three years (2003 to the end of 2005) Edmonton accounted for 71%, 69% and 77% of the cases respectively.[10]

Service Utilization

In 2006 there were a total of 96,244 total serum samples tested (from 89,647 individuals) for syphilis at the Provincial Laboratory of Alberta (ProvLab). Calgary Lab Services (CLS), Dynacare Kasper Medical Laboratories (DKML), Medicine Hat, Red Deer, and Lethbridge Regional Hospitals tested approximately 14,300, 15,600, 520, 720 and 1,500 sera in 2006 respectively. Therefore, total testing services for Alberta in 2006 is estimated to be 128,884. (The total number of tests conducted prior to 2006 was unavailable at the time of this report). This high volume of tests reflects the incidence and prevalence of syphilis in Alberta, including universal syphilis screening during pregnancy.

It is important to note that it is not known whether estimates from CLS, DKML, Medicine Hat, Red Deer, and Lethbridge represent the total number of tests, or the total number of individuals tested, since these numbers are derived not from administrative databases but rather from personal communications with laboratory managers. Our economic analysis will therefore be conducted using the ProvLab estimates.

Technology Effects and Effectiveness

Since enzyme immunoassay (EIA) is an alternative test for the testing of syphilis and may ultimately replace RPR as the standard initial test, the paramount question is whether EIA is as effective as, or more effective than, RPR at testing for syphilis.

Technology Effects

Currently RPR is the initial laboratory test for syphilis in Alberta. Two treponemal antigen tests, TPPA and the FTA-Abs, are used to confirm the diagnosis of syphilis in persons testing positive with RPR. However, the current diagnostic protocol has three major limitations that potentially lead to higher rates of incorrect diagnosis and unnecessary costs (i.e. unneeded testing of false positives and follow up testing of true negative indeterminate).

First, RPR (current initial test) is a non-treponemal antigen targeted assay and therefore may not identify individuals early in primary syphilis or late in its progression (late latent and tertiary stages). Second, RPR results are confounded by various conditions including tuberculosis, mononucleosis, pregnancy, and autoimmune disease which lead to false positive results. Third, confirmatory testing with TPPA and FTA-Abs is subjective, requiring a technologist to evaluate whether there is adequate fluorescent reactivity[a] in the blood sample. Consequently, confirmatory testing with TPPA and FTA-Abs may lead to both false positive and false negative results if the fluorescence intensity is misinterpreted.[1]

In contrast to RPR, EIA is a treponemal antigen targeted assay able to detect syphilis in all stages of untreated and treated syphilis and has been associated with greater diagnostic precision,[11;12] although at a higher cost per test. An additional advantage of EIA is high throughput automation and the electronic generation and dissemination of results (minimizing transcriptional errors) making it suitable for large volume applications (i.e. well suited for use as an initial test).[13]

Inno-Lia (IL) is a multiparameter line immunoassay that uses recombinant and synthetic polypeptide antigens derived from T. pallidum proteins,[1] and in contrast to TPPA and FTA-Abs confirmatory testing, employs simpler interpretation criteria which reduces the degree of subjectivity when interpreting results.[14] Confirmatory testing with IL is also more accurate than the current TPPA and FTA-Abs test. It is considered the diagnostic gold standard for the confirmatory testing of syphilis.[1]

EIA Distributors

Several commercial EIA tests have been developed worldwide: Murex ICE Syphilis distributed by Somagen Diagnostics; Captia Syphilis TA distributed by Trinity Biotech; Pathozyne Syphilis Competition distributed by Omega; Enzygnost distributed by Dade Behring; TrepChek distributed by Phoenix Biotech; and Architect Syphilis TP distributed by Abbot Diagnostics. TrepChek, TrepSure, Enzygnost, Captia Syphilis TA, and Architect Syphilis TP have been licensed by Health Canada.

Technology Effectiveness

Table 2 summarises the diagnostic characteristics of RPR, EIA, TPPA, FTA-Abs, and IL found in the literature. In general, RPR has a lower sensitivity than EIA but specificity varies in different studies. For every one false positive diagnosis with EIA, RPR has been shown to have as much as eight false positive diagnoses.[15] Therefore, in terms of technological effectiveness, EIA is more effective than RPR in correctly diagnosing individuals who have syphilis (i.e. correctly diagnosing a true positive while minimizing biological false positives). Both TPPA and FTA-Abs have lower sensitivity and specificity than IL. Thus, IL is more effective than TPPA/FTA-Abs in correctly diagnosing true positives and negatives.

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a. Fluorescence is defined as luminescence that occurs from electromagnetic radiation usually ultraviolet light. Therefore, adequate fluorescent reactivity refers to the technologist determining whether there is adequate visible florescent light emitted.

Minimizing false positives reduces health service resources wasted on confirmatory testing and reduces the harm (e.g. stigma and anxiety) caused to individuals and their families when wrongly diagnosed with an STI. Furthermore, correctly identifying cases will reduce the societal burden of disease by helping to reduce transmission, incidence and prevalence of disease.

Therefore, the technological effectiveness of EIA over RPR and of IL over TPPA/FTA-Abs can be significant when considering the volume of syphilis tests currently being conducted in Alberta. It is important to note, however, that EIA would not entirely replace RPR as RPR titrations are used for clinical management and staging of infection, and for following response to treatment.

Automation

While RPR is technically simple, it is a manual test and requires experienced technologists to interpret results (i.e. subjective).[16] EIA in contrast, is available on automated platforms (e.g. TrepChek, Enzygnost, Captia Syphilis TA, and Architect Syphilis TP). Automated platforms provide several advantages when conducting large volumes of tests.

Automated platforms have high throughput capacity allowing for large numbers of tests to be analyzed simultaneously (e.g. 200 tests per hour). It also allows for a single user interface that controls automation and management of chemistry and testing processes. Consequently, automated platforms can reduce staff training time while offering the advantage of improved quality control (through automation) and expeditious turn-around times. Determination of test results is performed spectrophotometrically which further reduces subjectivity when interpreting results.[15] Results can also be transferred and disseminated electronically, minimizing transcription errors.[16]

A potential disadvantage of automated platforms is the need for sophisticated instrumentation requiring the transfer of blood samples to a more centralized laboratory for cost efficient performance of high volume tests. Equipment can be expensive, although costs will ultimately depend on service contracts negotiated with distributors of the EIA kits.

Table 2: Values of sensitivity and specificity

Test	All stages		Primary	
	Sensitivity	Specificity	Sensitivity	Specificity
RPR	86 - 100%	93 - 98%		
	79.9 - 98.7%	99 - 100%		
		85 - 99%	78-86%	
	86.1%	99.4%		
	96.4%	97.5%		
EIA			84%	
	100%	99.9%		
	100%	98.2%		
	99.5%	99.4%		
	96.7%	98.3%	NA	
TPHA-TPPA	85 - 100%	98 - 100%		
			96%	
FTA-abs	70 - 100%	94 -100%		
	91.7%	92%		
		96%	84%	
	98.5 - 99.9%	98.1 - 99.9%		
Inno-Lia	100%	99.3%		
	93.8%	100%		

Note. Blank cells indicate that the information was not reported in the primary source.

							Source
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	
	100%		95-98%				17 18 19 20 21
							22 20 21 23 24
							17 22
	100%		100%		100%		17 25 26 14
							1 25

Economic Evaluation

Review of Economic Evaluations of EIA or Inno-Lia

Search Strategy

A search was conducted for economic evidence that describes the potential cost effectiveness of EIA compared to RPR. We searched selected databases (see Appendix A) on October 17 and 18, 2006 to find published health economic research that investigated the use of EIA for syphilis testing. A preliminary search indicated that the number of economic studies conducted on syphilis testing was limited. Therefore, PUBMED, MEDLINE®, EMBASE®, and HEALTHSTAR® were searched using MeSH headings, descriptors and text words for the disease/infection and screening tests (i.e., RPR and EIA) but not economic key words (e.g. cost-effectiveness).

Using the same search headings and keywords, we also searched Centre for Reviews and Dissemination (DARE, NHS EED, HTA), EBM Reviews-Database of Abstracts of Reviews of Effects, EconLit, ECRI, CADTH, Canadian Task Force on Preventive Healthcare, and The Cochrane Register of Controlled Trials.

Selection Criteria

The inclusion and exclusion criteria for the retrieval and review of identified articles are listed below:

Inclusion Criteria

1. Studies are full economic evaluations (i.e. comparative analysis of both costs and outcomes).
2. Studies are conducted in the context of laboratory testing.
3. Studies evaluate EIA with some comparator or standard.

Exclusion Criteria

1. Studies that focus on the diagnostic performance characteristics of initial tests only.

Results

There were 293 published documents identified from the literature search. None of the documents contained economic evaluations or economic analyses nor did any meet the inclusion criteria. Therefore, no documents were retrieved.

Testing and Diagnostic Protocols

Current Testing and Diagnostic Protocols

It is important to recognize that positive test results do not necessarily identify a new case since the presence of antibodies against T. pallidum can be present in both new cases and previously infected individuals. Therefore, the objective of laboratory testing is to identify seropositive individuals (i.e. presence of antibodies against T. pallidum) in the testing population in order to inform the clinical decision of diagnosis at the clinic or by the IDMC (i.e. identify new cases of syphilis).

In the prenatal population, the initial RPR test blood is drawn at the local community lab and forwarded to the ProvLab for analysis. The non-prenatal population can be divided into individuals presenting at non-STI clinic locations (e.g. GP offices) and those presenting at STI clinics. In STI clinics, for the initial RPR test, blood is drawn at the clinic and forwarded to the ProvLab for analysis. In the non-STI setting, for the initial RPR test, blood is drawn at the local community lab and forwarded to CLS or DKML (or other private lab) for analysis. All positive RPR tests from CLS, DKML, and other laboratory hospitals are then forwarded to the ProvLab for confirmatory testing (which includes the reprocessing of RPR).

The current testing and diagnostic protocols for syphilis are as follows (see also Appendix B):

Prenatal Population:

1. Prenatal: All pregnant women are screened for syphilis. Pregnant women are identified when they first visit their clinician (e.g., family physician, obstetrician, or midwife). It is the clinician who orders the blood tests.
2. Blood is drawn at a local lab and forwarded to the ProvLab for analysis. The blood sample is tested using RPR. Those who test negative are censored from further testing. Those who test positive receive confirmatory testing at the ProvLab.
3. Titrate RPR for all who tested positive on RPR. Note that RPR titration is conducted for purposes of patient management (i.e. staging the infection).
4. Test the blood sample using TPPA (first confirmatory test) for all who tested positive on RPR. Those who test negative are censored from further testing. Those who test positive receive further confirmatory testing using FTA-Abs.

5. Test the blood sample using FTA-Abs (final confirmatory test) for all who tested positive on TPPA. Those who test negative are considered indeterminate. Results from those who test positive are forwarded to their physician for a final clinical decision. Individuals who test positive are not immediately diagnosed as a new case because antibodies against T. pallidum are present in previously treated cases.
6. For positive cases, the Infectious Diseases Medical Consultant (IDMC) is contacted and gives authorization for treatment. Treatment is authorized by a clinician.
   a. All positive cases are interviewed for a list of their sexual partners. These sexual partners are contacted and scheduled for syphilis testing. While the goal is to contact all sexual partners, it is difficult to contact all sexual partners particularly from persons who are involved in the sex trade or from those who engage in anonymous intercourse.
   b. All positive and treated cases are followed up and monitored with RPR blood testing at 1, 3, 6, 12 and 24 months.[27] In the prenatal population, all positive results are reviewed by the IDMC.
7. For indeterminate cases, follow up monitoring is conducted consisting of blood tests with RPR, TPPA and FTA-Abs (simultaneous testing) within two to four weeks. All results are reviewed by the IDMC.
   a. Based on the follow up test results, the IDMC makes the diagnosis for syphilis. For positive cases, the IDMC gives the authorization for treatment and follows the protocols outlined in point 5 above. Negative cases are censored from further testing or follow up.

Non-Prenatal:

Testing protocols in non-STI clinic settings and STI clinics differ slightly. For simplification, the economic model follows the testing protocol for non-STI clinic settings. The testing and diagnostic protocols at non-STI clinic settings are identical to those occurring in the prenatal population except the following:

1. In point #1, diagnostic testing (not screening) is conducted for individuals who either self-refer to a GP, or who were identified as a sexual partner from a diagnosed case.
2. In point #6-b, 10% of the results are reviewed by the IDMC.

The testing and diagnostic protocols at STD clinics are identical to those occurring in the prenatal population except the following:

1. In point #1, diagnostic testing (not screening) is conducted for individuals who either self-refer to a STI clinic, or who were identified as a sexual partner from a diagnosed case.
2. In point #2, individuals testing negative on the initial test of RPR are not censored. These individuals continue to receive RPR titration and further confirmatory testing (i.e. treated as if they tested positive on RPR).

3. In point #6-b, all results are reviewed by the IDMC (not only those with discrepant findings).

It is important to note that treatment, follow up blood tests (for treated and indeterminate cases) and testing of sexual partners are conducted at a testing facility (e.g. STI clinic). Hence, for each testing service, the individual or sexual partner(s) must be contacted, located, and booked for an appointment at a care facility. Every effort is made to locate and contact these individuals. Furthermore, in all testing contexts (i.e. prenatal and non-prenatal) during contact tracing, names and locating information must be provided on a STD notification form and forwarded to STD services and the disease control and prevention branch at Alberta Health and Wellness.[27] Options for contact tracing include:

1. The physician or case manager provides contact names and location information on the contact form. STD services will coordinate the contact tracing process with the regional partner notification nurse.
2. The physician or case manager provides contact names and location information on the contact form. However the physician/case manager has the option of indicating on the form that they will undertake the testing and/or treatment of the sex partners. If the testing and/or treatment of the contact is not confirmed, STD services will co-ordinate follow up with the regional partner notification nurse.
3. The index case is asked to notify and refer sexual partners for testing and treatment. If contact testing or treatment is not confirmed, further follow up by a physician/case manager is necessary.

Comparator

The alternative protocol of conducting initial syphilis testing with EIA and confirmatory testing with IL is identical to those listed under the section Current Testing and Diagnostic Protocols except the initial/confirmatory test substituted. The alternative protocol is as follows:

1. EIA Test and IL Confirm with no Follow Up on Negative Tests (EIA+IL): Replace RPR with EIA as the initial test in all treatment contexts. Replace TPPA and FTA-Abs with IL as confirmatory test. IL is considered the diagnostic gold standard test. Accordingly, individuals who test negative on IL are diagnosed as not having syphilis (i.e. are not considered indeterminate) and are precluded from any follow up.

A search of syphilis testing protocols in other health contexts and countries was conducted to identify how EIA has been incorporated in other health systems. EIA has already been adopted in the UK as the initial test using either TPPA or IL as the confirmatory test.[28] EIA has been proposed as the initial test with confirmatory testing with FTA-Abs in the United States, but it is uncertain whether it has been adopted in any states.

Background for Understanding Cost Effectiveness Analysis

A complete economic evaluation is defined as the comparative analysis of alternate courses of action in terms of both their costs and outcomes.[29] Information on costs related to syphilis testing protocols are readily available. In a full economic analysis, we must also include health-related outcomes, since differences in costs, by themselves, are not an adequate indication of the relative performance of the tests. Health related quality of life (HRQL) indicators including the often used (but difficult to measure) "utility" measure, are the conceptual ideal. Utility is a combined measure of health status and mortality, that ranges from 0 (death) to 1 (full health). However, health-related outcomes are rarely found in economic assessments in this area. A search of the available published literature on syphilis revealed that there are no outcome measures quantified in terms of health related quality of life (HRQL) in persons with syphilis. Therefore, the level of economic analysis that can be conducted is an economic assessment that incorporates costs, with the outcome measure being the number of correct diagnoses.

An economic evaluation that evaluates costs and non-monetary outcomes such as the number of correct diagnosis is called a cost effectiveness analysis (CEA). In CEA, costs and effectiveness are summated for each alternative. The differences in costs between each alternative are divided by the difference in effectiveness between each alternative to produce an incremental cost effectiveness ratio (ICER).

Incremental Cost Effectiveness Ratios (ICER)

The ICER informs how much it costs to produce one additional unit of effectiveness. It can be considered the price of producing one additional unit of effectiveness by switching from one alternative to another. However, ICERs only inform how much it would cost to produce an additional unit of effectiveness and do not inform whether the additional effectiveness is worth the cost. Consequently, determining whether a more costly but more effective technology is worth adopting requires knowing what society is willing to pay (WTP) to produce an additional unit of effectiveness. Therefore, for a technology that is more costly but more effective, the technology is cost effective if its ICER is below what society is WTP for the additional effectiveness. However, the principal limitation of basing decisions on ICER is that there are no guidelines informing the appropriate WTP for an additional unit of effectiveness and will vary between health and clinical contexts.

Furthermore, it is important to recognize that decisions based on ICER are only relevant in decision situations where the new alternative produces greater costs and greater effectiveness or less costs and less effectiveness (i.e. in non-dominance situations). For situations where the new alternative produces greater costs and less effectiveness the baseline alternative should be maintained (i.e. the new alternative is dominated by the baseline alternative). For situations where the new

alternative produces less costs and greater effectiveness the new alternative should be adopted (i.e. the baseline alternative is dominated by the new alternative).

Decision Analytic Modeling

Cost and effectiveness associated with a technology are affected by multiple factors including (but not limited to) population characteristics, health care system, time horizon, and perspective (e.g. societal versus payer). Therefore, generating estimates of costs and effectiveness associated with a technology often require the use of decision analytic modeling (DAM). A DAM provides a schematic representation of how the technology impacts costs and effectiveness and is defined by a framework of parameters. Parameters refer to the relevant inputs that affect costs and effectiveness, which often include (but are not limited to) probabilities (e.g. probability of developing neurosyphilis), costs (e.g. cost of a RPR test), and population characteristics (e.g. prevalence of syphilis).

Expected Value Calculations

DAMs can calculate expected costs and effectiveness using single point estimates for parameters (i.e. use only one input that does not vary). However, there are two major limitations associated with using single point estimates for model parameters. First, point estimates do not account for the inherent variance or likelihood of possible values observed in actual conditions. Second, they do not account for potential interactions between parameters.[29]

The incidence and prevalence of syphilis is constantly varying and the challenge is to provide accurate estimates for resource utilization and costs in the present and in the future despite fluctuations. Therefore, to incorporate the fluctuations observed in actual conditions in the present analysis, expected value calculations are conducted using a probabilistic DAM. To create a model that incorporates the possible variation in inputs, a distribution is fitted to the input using the standard errors listed in Tables 3A to 3C (i.e. distribution parameters are fitted to an input based on existing evidence regarding the potential variance of the input). During each simulation called a Monte Carlo simulation, for each parameter with a fitted distribution, a value is randomly sampled (i.e. generated) from the distribution and the costs and effectiveness are calculated for the simulation.[30] One hundred thousand such "Monte Carlo" simulations are conducted and the expected value of costs and outcomes are calculated from the 100,000 simulations. This method of calculating expected values provides an ICER that incorporates the likelihood of potential values observed in actual conditions (i.e. incorporates the uncertainty associated with each parameter) including the potential interactions between inputs; this method generates more valid results and more credible conclusions.

Handling Uncertainty

As stated above, expected costs and effectiveness generated from a probabilistic DAM incorporate the uncertainty associated with each parameter into a single analysis. This uncertainty can be represented as a distribution of costs and effectiveness on the incremental cost effectiveness plane (ICEP). On the ICEP, the distribution of costs and effectiveness estimates can be divided into four quadrants: NW, NE, SE and SW. Simulations falling in the NW quadrant indicate that, compared to the baseline alternative, the new alternative is less effective and more costly. Simulations falling in the NE quadrant indicate that the new alternative is more effective but at additional costs. Simulations falling in the SE quadrant indicate that the new alternative is more effective but also less costly. Simulations falling in the SW quadrant indicate that the new alternative is less effective, but also less costly.

The ICEP can be converted into an acceptability curve. An acceptability curve depicts the proportion of ICERs that fall below a range of WTP thresholds for an additional correct diagnosis. This allows decision makers to choose a variety of thresholds (i.e. what an extra correct diagnosis might be worth) and observe what proportion of ICERs (generated from the model) fall below each chosen threshold. For example, if a decision maker concluded that the WTP for an additional correct diagnosis is $20,000 (i.e. a correct diagnosis is worth at least $20,000 to society), he/she would be able to observe the proportion of ICERs that were below $20,000 per additional correct diagnosis. This proportion would represent the probability that the new alternative is cost effective (compared to the baseline alternative) at the threshold of $20,000 per additional correct diagnosis.

Analysis

The analytical approach was to develop a DAM that compares current Alberta protocols with the proposed protocol incorporating EIA and IL. All analyses were conducted using Microsoft Excel 2003 and TreeAge Pro Suite (TREEAGE software Inc; Williamstown, MA).

We used the demand and utilization of syphilis testing services reported for 2006 for the ProvLab, which represent at least 75 per cent of all provincial testing, as our measure of the number of tests provided. Service utilization from CLS, DKML, and other hospital laboratories were not included for two primary reasons already noted: First, it is unknown whether these estimates represent total number of tests or total number of individuals tested. Second, the estimates were not generated from administrative databases but rather based on personal communications with laboratory managers.

In 2006, the ProvLab conducted 89,647 tests. Of this total, 51,523 were conducted for testing in the prenatal population and 38,124 were conducted for diagnostic purposes in the non-prenatal population (i.e. STI clinics and GP Offices). These populations are analyzed separately since differences in disease prevalence in the two testing populations will affect the predictive values of initial and confirmatory tests and will therefore have a significant impact on both costs and number of correct/incorrect diagnoses. The prevalence of syphilis and prevalence of seropositives in the prenatal population is considerably lower than the prevalence found in the non-prenatal population.

Model Inputs

With the exception of the prenatal population, syphilis testing is not actively conducted in the population. Rather, testing is conducted for individuals who self-refer to a GP Office/STI clinic or for individuals who are identified as a sexual partner from a laboratory confirmed case (i.e. sexual partners identified from contact tracing). The prevalence and demand of services for the present analysis reflects the demand of services from the prenatal population and for those presenting at GP offices and STI clinics (but not for the entire Alberta general population).

Inputs for the model parameters were derived primarily from Alberta data. Inputs for which Alberta data was unavailable was supplemented with estimates obtained from published research. Cost factors for which there was limited information available were estimated through consultation with experts and from available data. Tables 3A, 3B and 3C show the model inputs and their sources of valuation for Population and Diagnostic Tests, Treatment and Routine Follow Ups, and Outcomes for False Negatives and Costs respectively. The Standard Error and Distribution columns in these tables present additional information about the expected variability of the estimates, which are used in the sensitivity analysis.

Table 3A: Inputs – population and diagnostic tests

Model Parameters	Input	Standard Error	Distribution[a]	Source
Population Characteristics				
Individuals Tested in Alberta ProvLab 2006	89,647	NA	NONE	31
– Number from Prenatal	51,523	NA	NONE	31
– Number from Non-Prenatal	38,124	NA	NONE	31
– Prevalence of Seropositives - Prenatal Testing	0.076%	0.012%	BETA	31;32
– Prevalence of Seropositives – Non-Prenatal Testing	1.94%	0.07%	BETA	31;32
Test Characteristics				
RPR				
– Sensitivity	70.6%	1.22%	BETA	31
– Specificity	99.5%	0.22%	BETA	31
EIA [b]				
– Sensitivity	93.0%	1.2%	BETA	18
– Specificity	98.9%	1.0%	BETA	18
TPPA				
– Sensitivity	92.3%	1.2%	BETA	31
– Specificity	98. 0%	1.4%	BETA	17
FTA-Abs				
– Sensitivity	87.8%	2.5%	BETA	31
– Specificity	94.0%	2.4%	BETA	17
Inno-Lia				
– Sensitivity	94.6%	0.03%	BETA	31
– Specificity	99.5%	0.04%	BETA	14

Note: A 5% adjustment was conducted to lower sensitivities of all tests in the model to better reflect test performance in actual conditions (adjusted value shown).

a. Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (i.e. inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation. Distributions are fitted based on primary data. In general, parameters estimated from larger sample sizes generate smaller ranges of possible values (consistent with statistical theory). Therefore, inputs with very small standard errors indicate they were fitted from large sample sizes.

b. Based on the performance of Enzygnost, Architect & Trepsure. Value is average over three kits.

Table 3B: Inputs – treatment and routine follow ups

Model Parameters	Input	Standard Error[a]	Distribution[b]	Source
Community Search and Patient Contacting[c]				
– Clerical Services	18 min	NA	NONE	33
– Outreach Team – Community RN and Clerical Support	210 min	60 min	GAMMA	33
– Search Coordination Typical Case – RN	22 min	7 min	GAMMA	33
– Search Coordination Atypical Case – RN	60 min	20 min	GAMMA	33
– % of Atypical Cases	75%	21.7%	BETA	33
Treatment				
– New Case (Clinical Judgement)–Prenatal Testing	41%	7.9%	BETA	31:32
– New Case (Clinical Judgement)–Non-Prenatal Testing	38%	1.9%	BETA	31;32
– Patient Visit (history/assessment, paging IDMC, treatment)–RN	90 min	30 min	GAMMA	33
– Case Coordination–Provincial STI Medical Director (IDMC)	15 min	NA	NONE	33
– Average Number of Sexual Partners per Diagnosed Case	5	11	GAMMA	32
Follow Ups				
– Number of follow ups for Treated Patients (1, 3, 6, 12, 24 months)	5	NA	NONE	27
– Average Number of follow ups for Patients with Indeterminate Diagnosis (within 2 – 4 weeks)	3	1	GAMMA	§
– Drawing Blood – RN	30 min	15 min	GAMMA	33
Chart Reviews of Follow Up Blood Samples – IDMC				
From Treated Patients				
– Chart Review	10 min	NA	NONE	§
– % of Charts Reviewed from Prenatal Testing	100%	NA	NONE	33
– % of Charts Reviewed from Non-Prenatal Testing	10%	9.5%	BETA	§
From patients with Indeterminate Diagnoses				
– Chart Review	30 min	NA	NONE	§
– % of Charts Reviewed	100%	NA	NONE	33

Note: Typical cases are patients who are easily contacted and located and who are also cooperative. A-typical cases are patients who are difficult to contact and locate and who are also uncooperative.

a. Standard errors are estimated.

b. Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (i.e. inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation.

c. Search is conducted for contacting patient for scheduling treatment, treatment follow up visit, and follow up visit for indeterminate diagnosis.

§ Personal communication from IDMC.

Table 3C: Inputs – outcomes for false negatives and costs

Model Parameters	Input	Standard Error[a]	Distribution[b]	Source
Outcome for Untreated False Negative				
– Probability of Developing Neurosyphilis	6.1%	3.1%	BETA	34
– Probability of Developing Congenital Syphilis	100%	NA	NONE	3
Costs				
Cost per tests (kit, labour and supplies)				
– RPR	$2.22	NA	NONE	35
– RPR Titration	$22.20	NA	NONE	35
– EIA[c]	$4.75	NA	NONE	35
– TPPA	$5.14	NA	NONE	35
– FTA-Abs	$7.70	NA	NONE	35
– Inno-Lia	$37.30	NA	NONE	35
Antibiotic–Benzathine (cost per treatment)	$0.90	NA	NONE	33
Labour				
– Registered Nurse	$42 per hour	NA	NONE	36
– Clerical Services	$20 per hour	NA	NONE	33
– Infectious Diseases Medical Consultant	$171.40 per hour	NA	NONE	37
– Outreach Team	$62 per hour	NA	NONE	33
– GP (code 03.03A)	$29.30 per visit	NA	NONE	38
Untreated False Negative				
– Neurosyphilis[d]	$77,149 per case	NA	NONE	39
– Discount Rate for Neurosyphilis	5%	NA	NONE	NA
– Congenital Syphilis[e]	$16,017 per case	NA	NONE	7

a. Standard error is estimated.

b. Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (i.e. inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation.

c. Final cost per test is dependent on service contract.

d. Neurosyphilis is an irreversible condition. Cost reflects the management of the condition including eventual nursing home care. Cost is adjusted to Canadian 2006 dollars using the Canadian Consumer Price Index.

e. Hospital services for caring for newborn infants with syphilis. This cost is the incremental cost compared to healthy infants (i.e. cost attributable to congenital syphilis). Cost is adjusted to Canadian 2006 dollars using the Canadian Consumer Price Index.

Alberta Sources

The Public Health Act mandates that all syphilis infections be reported to the Chief Medical Officer of Health in Alberta. AHW and the regional health authorities provide a comprehensive program that includes diagnosis, treatment, partner notification, prevention, surveillance, research and education. Patient care services are provided by the RHAs, with AHW coordinating case management and the notification of sexual contacts. Therefore, a number of sources were used to estimate the parameters for the model.

Demand and testing utilization data for 2006 was collected by the ProvLab and AHW and contains information regarding the number of individuals tested, number of confirmatory tests conducted, and number of positive and indeterminate diagnoses made.[31] As previously noted, data from other labs were excluded. Based on this data, we were able to estimate 1) the number of individuals requiring testing in 2006 in prenatal and non-prenatal testing populations; 2) the prevalence of seropositive individuals in prenatal and non-prenatal testing populations; and 3) the proportion of diagnosed cases from individuals testing positive for T. pallidum antibodies.

The presence of antibodies is highly dependent on the stage of disease (i.e. the earlier the patient is tested, the higher the proportion who have not yet developed antibodies). Therefore the analytic strategy adopted was to use lower performance characteristics in our model which was obtained from available information for test characteristics in order to more accurately reflect test performance under actual conditions (i.e. early testing).

The ProvLab has recently conducted an evaluation of EIA.[18] The sensitivity and specificity values of EIA are based on this evaluation and are similar to other values found in the published literature. The sensitivity and specificity of RPR and the sensitivity of TPPA are based on calculations conducted by the ProvLab to inform this analysis.[31] The specificity of TPPA and the sensitivity and specificity of FTA-Abs and IL were derived from the available literature. A 5% correction was used to deflate the sensitivity values of all tests to better reflect test performance in actual conditions including early cases.

A key cost driver in the delivery of syphilis testing services is the labour resources required for searching and locating individuals (i.e. community search and patient contacting), administering treatment, contacting sexual partners, and reviewing charts. Information relating to service delivery were obtained from several Alberta sources.[27;33;36;40] Estimates of labour time associated with specific tasks were obtained from STI directors, managers, and nurses. Further, costs of tests and labour were obtained from Alberta sources (ProvLab accounting, Alberta union contracts, Alberta Alternative Relations Plan and Alberta Health Care Insurance Plan).[35-38]

Information that is not based on Alberta data relates to outcomes associated with false negative tests. Information relating to the probability of the outcome and resource costs associated with the outcome was derived from the published literature. Costs of neurosyphilis reflect the management of the condition including eventual nursing home care. Costs of congenital syphilis reflect the incremental hospital cost (compared to healthy infants) for caring for the newborn infant (i.e. reflects the cost attributable to congenital syphilis). Costs of neurosyphilis and congenital syphilis are based on American data and were adjusted to Canadian 2006 dollars using the Canadian Consumer Price Index.

Cost Outcomes

The economic evaluation compares the cost and outcomes of the newly proposed protocol to those of the current protocol over a one year time period (refer to Objectives section). Therefore, all costs were made to reflect 2006 Canadian dollars. Cost savings and cost additions observed for each protocol are attributable to the proportion of patients presenting at each outcome in each simulation model: We made the following assumptions about cost:

1. Testing and confirmatory tests.
   a. In protocols incorporating EIA, individuals testing positive on EIA, require RPR titration for patient management. Therefore, the cost of RPR is also incurred for individuals testing positive on EIA.
2. Resource cost associated with positive cases wrongly diagnosed (i.e. false negatives).
   a. In general, the number of true positives in the testing population comes from the seropositive population within the testing population. Therefore, not all wrongly tested seropositive individuals develop late latent and tertiary symptoms (i.e. they do not have syphilis and do not incur false negative cost outcomes).
   b. Not all true positives with incorrect test results (i.e. false negatives) develop neurosyphilis even if left untreated. Therefore, costs of neurosyphilis were calculated based on the probability of developing symptomatic neurosyphilis.
   c. The cost of neurosyphilis represents United States cost data and was adjusted to Canadian 2006 dollars using the Canadian Consumer Price Index. Nevertheless, the cost input for neurosyphilis may be overestimated because of systemic differences in healthcare systems between countries. The method of deriving costs of neurosyphilis in the original study was not available for scrutiny.
   d. Symptoms of neurosyphilis may not occur for up to 30 years after initial infection. A gain or a loss occurring in the future has less value/cost than if it occurs in the present. Discounting is a technique of weighting (i.e. valuating) future gains or losses to reflect the present value/cost of

gains or losses. To convert future costs to 2006 values, costs associated with neurosyphilis are discounted at a rate of 5% and is assumed to occur in 30 years. Note that this is a very conservative procedure, since neurosyphilis may occur considerably earlier than 30 years. Therefore these calculated costs must be considered as a lower bound.

3. Costs of physician visits for initial consultation and treatment (if applicable).
4. Treatment.
5. Treatment follow up.
6. Chart reviews and treatment consultations by the IDMC
7. Contact tracing.
   a. It is noteworthy to mention that EIA+IL will identify more TP (i.e. higher sensitivity) than the current Alberta protocol, and consequently, more sexual partners will be identified generating more testing and community search and patient contacting costs.
8. Follow up of indeterminate diagnoses.
9. Community search and patient contacting for treatment, follow ups and contact tracing.

Diagnostic Outcomes

The outcome selected for the economic evaluation is the number of correct diagnoses (i.e. True Positive + True Negative). Effectiveness is therefore the additional number of correct diagnoses.

Incremental Cost Effectiveness Ratio (ICER)

Our analysis will identify additional costs (or savings) and additional effectiveness between EIA+IL and the current Alberta protocol. If costs are less and effectiveness more, further analysis is unnecessary; the decision is to adopt the more effective and less costly alternative. However, if costs are more and effectiveness more, decision makers must decide whether the additional benefits are worth the additional costs. There are no guidelines informing the appropriate societal willingness to pay (WTP) for an additional correct diagnosis of syphilis.

Syphilis is easily treated by antibiotics and if treatment is administered early, severe complications (e.g. neurosyphilis) can be prevented and permanent damage avoided. In the prenatal population, the value of a correct diagnosis is high. Failure to diagnose syphilis during pregnancy is associated with high mortality and morbidity before the delivery or shortly after birth. Consequently, the potential loss in quality of life can be severe if the syphilis test fails to identify all positive cases within the seropositive population.

A value of $25,000 is arbitrarily considered to be appropriate in our context for prenatal testing and $10,000 for non-prenatal testing. Although the loss

of quality of life is substantial in the non-prenatal population, the threshold WTP value for a correct diagnosis is placed higher for the prenatal population than in the non-prenatal population. Therefore, an ICER below $25,000 per additional correct diagnosis and an ICER below $10,000 per additional correct diagnosis are used as benchmarks to indicate whether there is economic evidence to support replacing current protocol with EIA+IL in the prenatal and non-prenatal population respectively.

Sensitivity Analysis

Decisions should be based solely on expected values and not on the uncertainty of making an incorrect decision given that decisions must be made with current available evidence. Still, it is important to provide information regarding the distribution of potential costs and effectiveness generated from the Monte Carlo simulations (refer to Expected Value Calculations section under the heading Background for Understanding Cost Effectiveness Analysis) to enable decision makers to evaluate the credible range of potential costs and outcomes. Therefore, the distribution of costs and effectiveness estimates will be presented in a diagram of the ICEP.

As previously mentioned, there are no guidelines that can provide the correct benchmark to be used by a decision maker for determining society's WTP for a correct diagnosis in syphilis. Therefore, based on the scatter plots, an acceptability curve will also be provided to illustrate the probability that EIA+IL is cost effective for a range of WTP thresholds. This allows decision makers to choose a variety of thresholds (i.e. what an extra correct diagnosis might be worth) and observe the probability that EIA+IL is cost effective at each threshold.

Model Assumptions

No model can perfectly capture what is observed in reality and a number of assumptions are adopted. The major assumptions incorporated into the simulation models are as follows:

1. The process of community search and patient contacting can be challenging given the characteristics of the patient population (refer to Epidemiology in Canada and Alberta section). To incorporate the resource cost associated with community search and patient contacting, the analysis will be stratified by Typical (individuals who are easily contacted) and A-typical cases (individuals who are not easily contacted). It is assumed that all patients in the prenatal population can be readily contacted.
2. The labour time associated with community search and patient contacting for sexual partners will be the same as that used for primary case (e.g. if primary case was categorized as a-typical, then the labour time required to contact their sexual partner is also "a-typical").

3. While there are three options for contact tracing, the analysis assumes STD services will coordinate the contact tracing process with the regional partner notification nurse (option 2 listed in Current Testing and Diagnostic Protocols).
4. Blood tests and delivery of other materials are routinely conducted in Alberta. It is assumed that if implemented, EIA testing will be incorporated into existing infrastructure and capacity. Therefore, there are no shipping costs associated with EIA.
5. The treatment regime for a positive case of syphilis is dependent on whether syphilis is in the primary or latent stage. However, the stage of syphilis infection cannot be determined based on our available data. Therefore, our analysis applies the treatment regime associated with primary syphilis and assumes no allergy to penicillin.
6. Positive cases identified from contact tracing generate further testing and contact tracing which can be an interminable cycle. For the cohort of individuals requiring syphilis testing in Alberta for 2006, the calculation of costs and outcomes will be calculated up to and including the costs associated with contact tracing. That is, costs and outcomes will not be calculated for the second order individuals (i.e. sexual partners identified from the initial list of sexual partners).
7. For indeterminate diagnosis: Follow up of biological true positives will eventually be correctly diagnosed as a positive case and receive all treatment protocols. Follow up of biologically false negatives will eventually be correctly diagnosed as a negative case.
8. As stated above analysis is based on 2006 data obtained from the ProvLab STD database and does not include the testing volumes of other testing service providers in Alberta. The ProvLab testing volume accounts for 75% of all testing services conducted in Alberta in 2006 and is assumed to be representative of the demand of services found in Alberta.

Results

Costs

Table 4 summarizes results from the cost effectiveness analysis. In the prenatal population, cost of the current protocol was $1,904,935 while cost of EIA+IL was $1,914,439. In the non-prenatal population, cost of the current protocol was $2,320,967 while cost of EIA+IL was $2,234,914. Thus, the total cost of current protocols (prenatal and non-prenatal) was $4,225,902 and the total cost of EIA+IL (prenatal and non-prenatal) was $4,149,353.

Effectiveness

In the prenatal population, the current protocol generated 51,510 (13 TP and 51,497 TN) correct diagnoses. EIA+IL generated 51,517 (14 TP and 51,503 TN) correct diagnoses producing seven additional correct diagnoses. In the non-prenatal population, the current protocol generated 37,876 (224 TP and 37,652 TN) correct diagnoses. EIA+IL generated 38,035 (247 TP and 37,787 TN) correct diagnoses producing 159 additional correct diagnoses.

Table 4: Cost, effectiveness, and incremental cost effectiveness

	Cost	Incremental Cost	Effectiveness (# of correct diagnoses)			Incremental Effectivness	ICER $ per Additional Correct Diagnosis
			TP	TN	TP+TN		
Prenatal n = 51,523							
Current	$1,904,935		13	51,497	51,510		Not Dominated[a]
EIA + IL	$1,914,439	$9.504	14	51,517	51,517	7	$1,358
Non-Prenatal n = 38,124							
Current	$2,320,967		224	37,652	37,876		Dominated[b]
EIA + IL	$2,234,914	-$86,053	247	37,787	38,035	159	-$541
Total N = 89,647							
Current	$4,225,902		237	89,149	89,386		Dominated[b]
EIA + IL	$4,149,353	-$76,549	261	89,290	89,522	166	-$461

a. Not dominated means that the current protocol is less costly and less effective than EIA+IL.

b. Dominated means that the current protocol is more costly and less effective than EIA+IL.

Incremental Cost Effectiveness

In the prenatal population, the ICER of EIA+IL (compared to the current protocol) is $1,358 per additional correct diagnosis (i.e. EIA+IL will cost $1,358 to produce one additional correct diagnosis). In the non prenatal population, the ICER of EIA+IL is -$541 per additional correct diagnosis (i.e. EIA+IL will save $541 to produce one additional correct diagnosis). Overall (prenatal and non-prenatal), the ICER of EIA+IL is -$461 per additional correct diagnosis (i.e. EIA+IL will save $461 to produce one additional correct diagnosis).

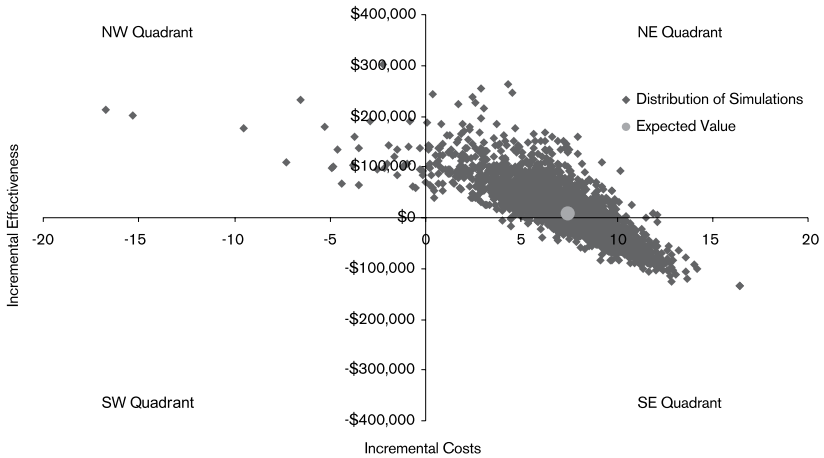
Sensitivity Analysis

Figures 3 and 4 show the distribution of incremental costs (i.e. differences in cost between current and EIA+IL) and incremental effectiveness (i.e. differences in number of correct diagnoses between current and EIA+IL) from each simulation on the ICEP for prenatal and non-prenatal populations respectively. Each blue dot represents the incremental cost and effectiveness between EIA+IL and current protocols from one simulation. Together they illustrate the distribution of possible incremental costs and effectiveness from the simulations. The pink dot represents the expected incremental cost and effectiveness of EIA+IL.

In the prenatal population EIA+IL falls in NW, NE, and SE quadrants indicating that EIA+IL can have large variations in potential effects in terms of costs and outcomes in the prenatal population in Alberta. However, the expected value of EIA+IL in the prenatal population falls in the NE quadrant meaning that, based on current information compared to the current protocol, EIA+IL is most likely to be more effective but at additional costs (i.e. EIA+IL will cost an additional $1,358 per additional correct diagnosis).

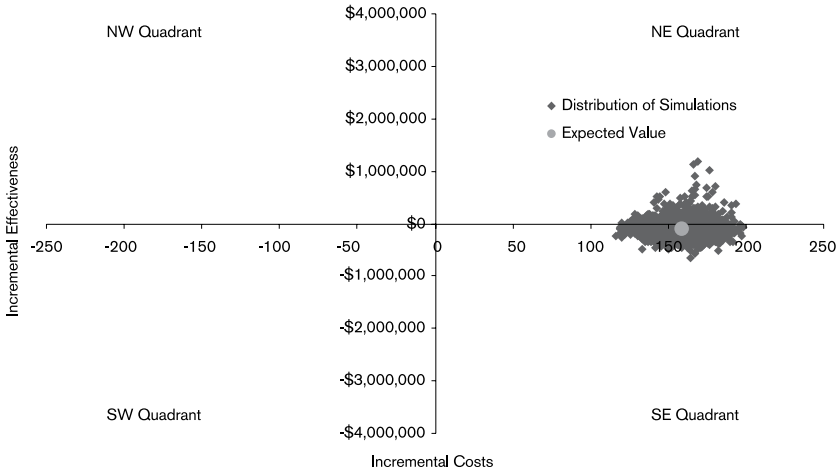
In the non-prenatal population, EIA+IL falls in the NE and SE quadrant indicating that EIA+IL is always more effective but can be more costly or less costly than the current protocol. However, the expected value of EIA+IL in the non-prenatal population falls in the SE quadrant meaning that based on current information, compared to the current protocol, EIA+IL is most likely to be more effective and less costly (i.e. EIA+IL will save an additional -$541 per additional correct diagnosis).

Figure 3 Incremental Cost Effectiveness Plane – Prenatal



Note. Each dark grey dot represents the incremental cost and effectiveness between the current protocol and EIA+IL from one simulation (100,000 simulations in total). Together they illustrate the distribution of incremental costs and effectiveness from the simulations. The light grey dot represents the expected (average) incremental cost and effectiveness of EIA+IL in the prenatal population.

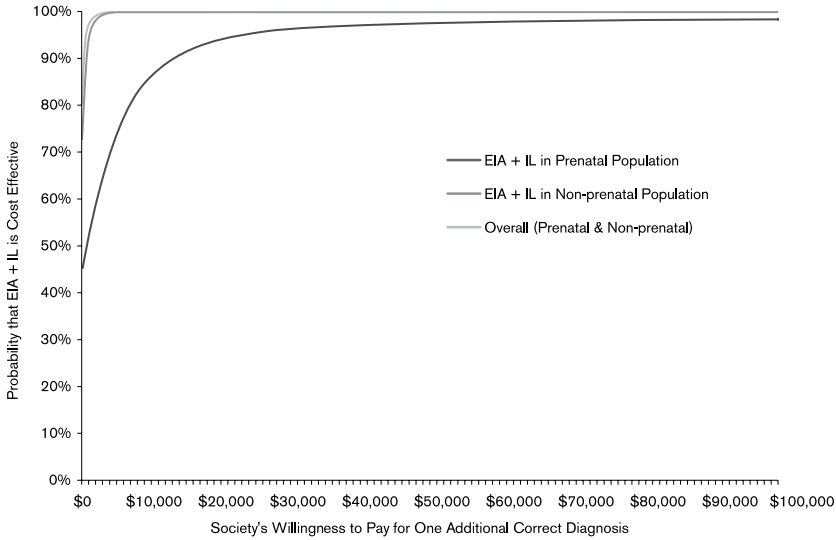
Figure 4 Incremental Cost Effectiveness Plane – Non-Prenatal



Note. Each dark grey dot represents the incremental cost and effectiveness between the current protocol and EIA+IL from one simulation (100,000 simulations in total). Together they illustrate the distribution of incremental costs and effectiveness from the simulations. The light grey dot represents the expected (average) incremental cost and effectiveness of EIA+IL in the non-prenatal population.

Figure 5 shows the acceptability curve which depicts the proportion of simulations that had ICER of EIA+IL (compared to the current protocol) below a range of cost per additional correct diagnosis thresholds. In the prenatal population, at a WTP of $0 per additional correct diagnosis (i.e. if society was WTP nothing to have more correct diagnoses in syphilis), EIA+IL is 45% cost-effective compared to the current protocol (this is due to the proportion of simulations falling in the SE quadrant–dominates the current protocol). The probability that EIA+IL is cost effective asymptotes to 98% above a WTP of $25,000 per additional correct diagnosis. In the non-prenatal population, the probability of EIA+IL being cost-effective is 80% at a WTP of $0 per additional correct diagnosis and 100% above a WTP of $10,000 per additional correct diagnosis. Overall results are similar to the results in the non-prenatal population.

Figure 5: Acceptability curve of EIA + IL in prenatal and non-prenatal populations



Note. Using current protocols as the comparator, the curve depicts the proportion of ICER from EIA+IL that were below a range of cost per additional correct diagnosis thresholds. Therefore, the curve represents the probability that EIA+IL is cost effective (compared to current protocols) at particular cost per additional correct diagnosis thresholds.

Cost Attribution

Table 5 shows the incremental costs of EIA+IL (compared to the current protocol) separated into six cost categories (NB. analysis is based on testing services reported for 2006 for the ProvLab): testing, physician visits, search and patient contacting, IDMC, congenital syphilis and neurosyphilis. For the prenatal population, EIA+IL generated an additional $154,165 of testing costs, $2,189 of antibiotic costs, $319 in physician visit costs and $801 in search and patient contacting costs. EIA+IL would generate cost savings of $1,565 attributed to reduced IDMC time, $134,693 attributed to reduced congenital syphilis and $11,712 attributed to reduced symptomatic neurosyphilis. In non-prenatal testing, EIA+IL would generate an additional $134,573 in testing costs, $1,911 to antibiotic costs, $4,719 in physician visit costs and $15,547 in search and patient contacting costs. EIA+IL generated cost savings of $15,043 attributed to reduced IDMC time and $277,760 attributed to reduced symptomatic neurosyphilis. Overall, EIA+IL would generate an additional $288,738 to testing costs, $4,100 in antibiotic costs, $5,038 in physician visit costs and $16,348 in search and patient contacting costs. EIA+IL would

generate cost savings of $16,608 attributed to reduced IDMC time, $134,693 attributed to reduced congenital syphilis and $239,472 attributed to reduced symptomatic neurosyphilis.

As previously mentioned, the economic evaluation compares the cost and outcomes of the newly proposed protocol to those of the current protocol over a one year time period. Therefore all cost outcomes reflect 2006 Canadian dollars and would have occurred in 2006 with the exception of symptomatic neurosyphilis (refer to Cost Outcomes section). Although the savings associated with prevented symptomatic neurosyphilis were discounted to reflect the value of future savings had they occurred in 2006, no actual savings to the health care system will occur until neurosyphilis develops (may take up to 30 years). Conversely, in the year 2037, actual cost savings to the health care system from prevented symptomatic neurosyphilis would be $1,034,984. This is a very conservative estimate, since many of the cases will appear earlier, but we have no information on when these cases might appear.

Table 5: Incremental (Compared to Current) Cost Savings/Additions of EIA + IL

	Testing	Anti-biotics	Physician Visits	SPC	IDMC	Congenital Syphilis	Neuro-syphilis[a]	Net Costs/ Savings
Prenatal	$154,165	$2,189	$319	$801	-$1,565	-$134,693	-$11,712	$9,504
Non-Prenatal	$134,573	$1,911	$4,719	$15,547	-$15,043	—	-$227,760	$86,053
Overall	$288,738	$4,100	$5,038	$16,348	-$16,608	-$134,693	-$239,472	-$76,549

Note. Analysis is based on 2006 data obtained from the ProvLab STD database and does not include the testing volumes from CLS, DKML, and other hospital laboratories. Testing conducted in CLS, DKML and other hospital laboratories may add an additional $82,580 of testing costs.

IDMC – Infectious Diseases Medical Consultant

SPC – Search and Patient Contacting

a. Although the costs associated with neurosyphilis reflect the present value of future savings associated with preventing symptomatic neurosyphilis (i.e. reflect value if occurring in 2006), no actual savings to the health care system would occur until neurosyphilis develops which may take up to 30 years.

Discussion

General

The burden of disease and associated health care costs of syphilis are significant in light of the relatively inexpensive and effective treatment available. Therefore, testing and correctly diagnosing syphilis is critical. We evaluated the economic impact of EIA+IL separately in the prenatal and non-prenatal population due to the inherent differences between the populations in prevalence levels.

Based on the CEA which only includes testing utilization levels from the ProvLab, in the prenatal population, current syphilis testing and managing protocols generated a cost of $1,904,935 in 2006. EIA+IL would generate an estimated cost of $1,914,439 creating $9,504 of additional health care costs. In the non-prenatal population, current syphilis testing and management protocols generated an estimated cost of $2,320,967. EIA+IL would generate an estimated cost of $2,234,914 creating a cost savings of -$86,053 to the health care system. When looking at the syphilis testing population as a whole there is a net savings of $76,549 to the health care system of which, 96% and 4% would be attributable to a reduction in the number of false negatives and a reduction in IDMC time respectively.

When evaluating effectiveness, the current syphilis testing protocol generated 51,510 total correct diagnoses while EIA+IL would generate 51,517 total correct diagnoses (seven additional correct diagnoses) in the prenatal population. In the non-prenatal population, the current syphilis testing protocol generated 37,876 total correct diagnoses while EIA+IL would generate 38,035 (159 additional correct diagnoses). Overall, EIA+IL would produce an additional 166 correct diagnoses, the majority of which would be attributed to correctly diagnosing true positives. This has significant implications on incidence and prevalence of syphilis in Alberta as correctly identifying true positives directly impacts rates of transmission and re-infection.

Costs and Effectiveness

In the prenatal population, EIA+IL has an ICER of $1,358 per additional correct diagnosis (i.e. reduces costs and produces more correct diagnoses). In the non-prenatal population, EIA+IL has an ICER of -$541 per additional correct diagnosis. Overall (prenatal and non-prenatal) EIA+IL had an ICER of -$461 per additional correct diagnosis. Therefore, there is economic evidence to support replacing the current protocol with EIA+IL for all syphilis testing populations in Alberta.

Reliability of Findings

Although the results were generated from 100,000 simulated sample sets and therefore incorporate the potential variability within inputs and potential interactions between inputs, the sensitivity analysis indicates to decision makers the degree of uncertainty associated with making an incorrect decision.

The sensitivity analysis indicates that EIA+IL had a wide distribution of potential economic effects in the prenatal population ranging from being more costly and more effective (compared to the current protocol) to being less costly and more effective. However, 55% of the simulations were more costly and more effective. There was less variation in the non-prenatal population with economic effects of EIA+IL ranging from being more costly and more effective to less costly and more effective. Eighty percent of the simulations were less costly and more effective. The high percentage of simulations aggregating in one quadrant (refer to Figures 3 and 4) indicates a relatively high degree of reliability in the results.

This is verified by the acceptability curve. At a WTP threshold of $10,000 per additional correct diagnosis, the probability of EIA+IL being cost effective is greater than 85% in the prenatal population. In the non-prenatal population and total Alberta population overall, even if society was WTP nothing for an additional correct diagnosis, the probability of EIA+IL being cost effective is 80% and 72% respectively.

Note that the analysis is primarily based on 2006 data obtained from the ProvLab STD database. While the data obtained from the ProvLab is assumed to be a valid and reliable estimate of syphilis testing services, verifying the validity and reliability of this data is beyond the scope of this report. We have not reflected on the possible errors that might be included in the database. Nevertheless, this is the most accurate contextually relevant information available.

Caveats

There are four major caveats in this analysis. First, it is uncertain how EIA+IL will be implemented and how clinicians will ultimately use the test. While the analysis suggests there is evidence to support replacing the current protocol with EIA+IL, it is entirely founded on the assumption that persons testing negative on EIA and IL do not receive further confirmatory testing or follow up. Although in actual conditions there will be variation in how EIA+IL is used depending on clinical presentation and patient history, protocols for EIA+IL outlined in this report should be adhered to (at least in general) in order to achieve the cost effectiveness outcomes described. Thus, clear diagnostic

protocols and education for clinicians ordering syphilis tests will be critical to the implementation of the EIA+IL protocol.

Second, the economic advantages of a more sensitive but expensive test is positively correlated with the prevalence of disease. It is reasonable to assume that if implemented, EIA+IL will correctly identify more seropositive individuals leading to more correct diagnosis of true positives, which will eventually reduce prevalence. However, the economic impact of reducing syphilis in the testing population will not be affected in the short-run because it is the prevalence of seropositives in the testing population that affects laboratory testing results. That is, the prevalence of seropositive individuals will decrease at a much slower rate than the prevalence of syphilis cases and the economic effectiveness of EIA+IL (i.e. a cost per correct diagnosis less than $10,000) will continue until the prevalence of both seropositive individuals and syphilis decrease.

Third, the analysis does not include the testing volumes from testing service providers other than the ProvLab (excluded due to limitations in the data– refer to Economic Modeling section). Therefore, the cost of testing services in the analysis does not reflect the total volume of testing services conducted in Alberta, although it does include confirmatory testing of all positive RPR tests. There were 32,640 estimated tests conducted by CLS, DKML, and other hospital laboratories in 2006. Assuming that 32,640 tests is representative of the testing volumes conducted outside the ProvLab, the estimated incremental test cost (initial test only) of EIA (compared to the current protocol) is $82,580.[b] However, it is important to note that potential cost savings (e.g. prevented congenital syphilis or symptomatic neurosyphilis) from these tested individuals have not been included either.

Fourth, cost savings observed for each protocol is attributable to the proportion of persons presenting at each outcome in each simulation model (refer to Appendix B). All costs were made to reflect Canadian 2006 dollars and would have occurred in 2006. However, the *net cost savings* of $239,472 associated with EIA+IL is driven by reducing the number of symptomatic neurosyphilis in the non-prenatal population; EIA produces 22.4% less false negatives (i.e. EIA has 22.4% higher sensitivity) than RPR. While the savings associated with prevented symptomatic neurosyphilis reflect the value of future savings had they occurred in 2006, no actual savings to the health care system would occur until neurosyphilis develops (may take up to 30 years). Conversely, by the year 2037, actual cost savings to the health care system from prevented symptomatic neurosyphilis would be $1,034,984. Still, as noted previously, the choice of 30 years and 5% discount rate is conservative (i.e. neurosyphilis can occur earlier than 30 years and 5% is a relatively high rate) and the savings associated with prevented symptomatic neurosyphilis can be considered the lower bound.

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b (EIA test cost – RPR test cost) × 32,640

CONCLUSION

Economic considerations are secondary to health outcomes and quality of life. Providing EIA+IL will result in more correct diagnoses and ultimately improve quality of life, particularly for positive cases that would have been missed with the current protocol. Based on the CEA which only includes testing utilization levels from the ProvLab, at current prevalence levels, compared to the current protocol EIA+IL would generate cost savings to the health care system while also generating more correct diagnoses. Therefore, based on the economic analysis there is economic evidence to support replacing the current Alberta protocol with EIA+IL for pre-natal screening and for diagnosis in patients likely to have syphilis given that clear diagnostic guidelines are developed and continuing education is provided for clinicians on how to best use EIA and IL.

REFERENCES

1. Hagedorn HJ, Hagedorn AK, De Bosschere K et al. Evaluation of INNO-LIA Syphilis Assay as a Confirmatory Test for Syphilis. Journal of Clinical Microbiology 2002; 40(3):973-978.
2. Garnett GP, Aral O, Hoyle DV et al. The natural history of syphilis. Implications for the transmission dynamics and control of infection. Sexually Transmitted Diseases 1997; 24:185-200.
3. Singh AE, Romanowski B. Syphilis: Review with emphasis on clinical, epidemiologic, and some biological features. Clinical Microbiology Reviews 1999; 12(2):187-209.
4. Carr J. Neurosyphilis. Practicval Neurology 2003; 3:328-341.
5. Stokes JH, Beerman H, Ingraham NR. Modern clinical syphilology. Philadelphia, PA: The W.B. Saunders Co, 1944
6. Ingraham NR. The value of penicillin alone in the prevention and treatment of congenital syphilis. Acta Dermato-Venereol 1951; 31 (Suppl 24):60-88.
7. Bateman DA, Phibbs CS, Joyce T et al. The hospital cost of congenital syphilis. Journal of Pediatrics 1997; 130(5):752-758.
8. Sartin JS, Perry HO. From mercury to malaria to penicillin: the history of the treatment of syphilis at the Mayo Clinic. J Am Acad Dermatol 1995; 32:255-261.
9. Centers for Disease Control and Prevention. Primary and secondary syphilis–United States, 1981–1990. Morbid Mortal Weekly Rep 1991; 40:314-315.
10. Disease Control and Prevention Branch. 6-5-2006. Alberta Health and Wellness.
11. Young H, Moyes A, Seagar L et al. Novel recombinant-antigen enzyme immunoassay for serological diagnosis of syphilis. Journal of Clinical Microbiology 1998; 36(4):913-917.
12. Castro R, Prieto ES, Santo I et al. Evaluation of an enzyme immunoassay technique for detection of antibodies against treponema pallidum. Journal of Clinical Microbiology 2003; 41(1):250-253.
13. Young H, Moyes A, McMillan A et al. Enzyme immunoassay for anti-treponemal IgG: screening or confirmatory test? Journal of Clinical Microbiology 1992; 45:37-41.
14. Ebel AL, Vanneste L, Cardinaels M et al. Validation of the INNO-LIA Syphilis kit as a confirmatory assay for Treponema pallidum antibodies. Journal of Clinical Microbiology 2000; 38:215-219.

15. Rodriguez I, Alvarez EL, Fernandez C et al. Comparison of a recombinant-antigen enzyme immunoassay with Treponema pallidum hemagglutination test for serological confirmation of syphilis. Mem Inst Oswaldo Cruz 2002; 97(3):347-349.
16. Young H, Moyes A, Seagar L et al. Novel recombinant-antigen enzyme immunoassay for serological diagnosis of syphilis. J Clin Microbiol 1998; 36(4):913-917.
17. Peeling RW, Ye H. Diagnostic tools for preventing and managing maternal and congenital syphilis: an overview. Bulletin of the World Health Organization 2004; 82(6):439-446.
18. Tilley P. ProvLab Syphilis Enzyme Immunoassay Evaluation. 2006. Provincial Lab of Alberta.
19. Barclay L. USPSTF Updates guidelines for syphilis screening. Ann Fam Med 2004; 2:362-365.
20. Hooper NE, Malloy DC, Passen S. Evaluation of a Treponema pallidum enzyme immunoassay as a screening test for syphilis. Clin Diagn Lab Immunol 1994; 1(4):477-481.
21. Silletti RP. Comparison of CAPTIA syphilis G enzyme immunoassay with rapid plasma reagin test for detection of syphilis. J Clin Microbiol 1995; 33(7):1829-1831.
22. Manavi K, Young H, McMillan A. The sensitivity of syphilis assays in detecting different stages of early syphilis. Int J STD AIDS 2006; 17(11):768-771.
23. Ebel A, Bachelart L, Alonso JM. Evaluation of a new competitive immunoassay (BioElisa Syphilis) for screening for Treponema pallidum antibodies at various stages of syphilis. J Clin Microbiol 1998; 36(2):358-361.
24. Halling VW, Jones MF, Bestrom JE et al. Clinical comparison of the Treponema pallidum CAPTIA syphilis-G enzyme immunoassay with the fluorescent treponemal antibody absorption immunoglobulin G assay for syphilis testing. J Clin Microbiol 1999; 37(10):3233-3234.
25. Byrne RE, Laska S, Bell M et al. Evaluation of a Treponema pallidum Western Immunoblot Assay as a confirmatory test for syphilis. Journal of Clinical Microbiology 1992; 30(1):115-122.
26. Nelson HD. Screening for syphilis: brief update for the US preventive services task force. www.preventiveservices.ahrq.gov. 2006.
27. Alberta Health and Wellness. Alberta treatment guidelines: Sexually transmitted infections in adolescents and adults. 2003.
28. Egglestone SI, Turner AJ. Serological diagnosis of syphilis. PHLS Syphilis Serology Working Group. Commun Dis Public Health 2000; 3(3):158-162.

29. Drummond MF, Sculpher MJ, Torrance GW et al. Methods for the economic evaluation of health care programmes. 3rd ed. New York: Oxford University Press, 2005
30. Briggs A. Handling uncertainty in cost effectiveness models. PharmacoEconomics 2000; 17(5):479-500.
31. ProvLab STI Database. 2006.
32. Alberta Health and Wellness. STD Database.
33. Alberta Health and Wellness. Evaluation and Management of STI Clinics Patients. 2006.
34. Rosahn PD. Autopsy studies in syphilis. J Vener Dis Infect 1947; 21(Suppl).
35. ProvLab. Provincial Laboratory of Alberta Internal Accounting. 2006.
36. Alberta Health and Wellness. Alberta Union Contracts. 2006.
37. Alberta Health and Wellness. Alternative Relations Plan. 2006.
38. Alberta Health and Wellness. Alberta health care insurance plan: Medical price list. 2006.
39. Chesson HW, Blanford JM, Gift TL et al. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. Perspectives on Sexual and Reproductive Health 2004; 36(1):11-19.
40. Alberta Health and Wellness (draft). AHW Partner Notification Manual. 2006.

Appendix A: Search Strategy

Table A: Search Strategy

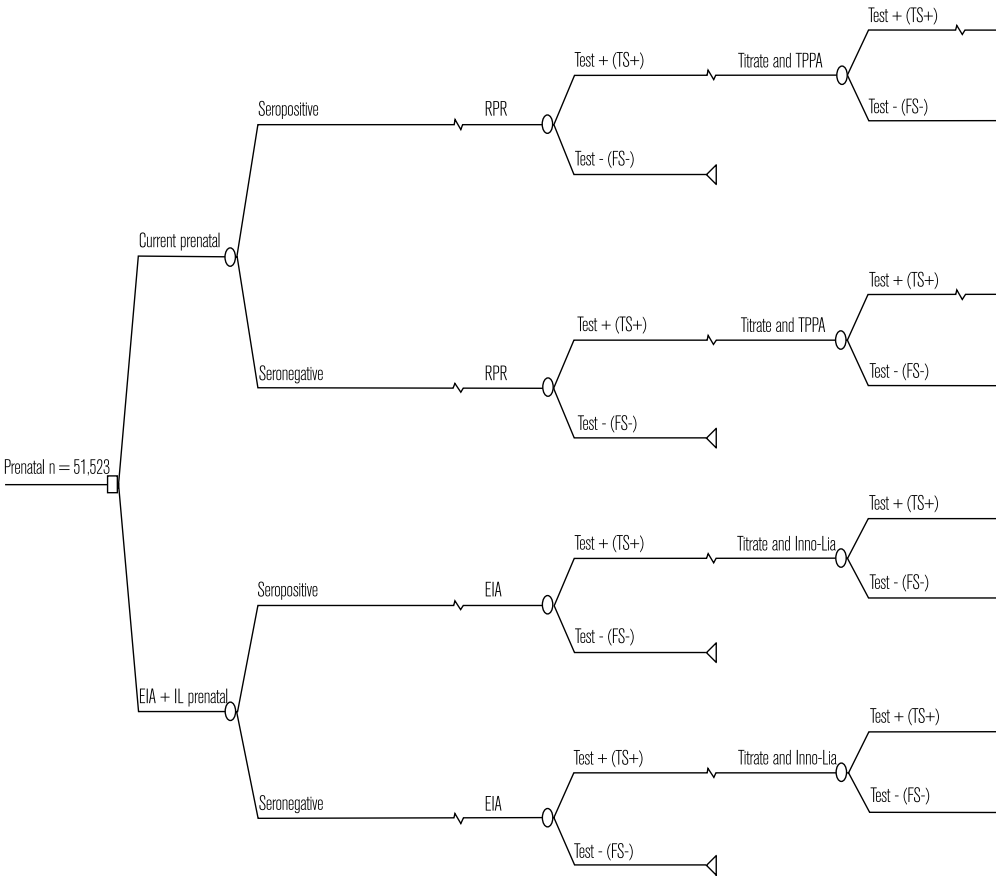
Database	Platform	Edition or date searched	Search terms	# Results
PubMed	www.pubmed.gov	October 17, 2006	(Syphylis[MeSH] OR Treponema pallidum [MeSH]) AND (Enzyme immunoassay OR EIA OR rapid plasma regain OR RPR)	419
HealthStar	(Ovid)	October 17, 2006	(exp Syphilis/ OR exp Treponema pallidum) AND ("rapid plasma reagin" or RPR or enzyme immunoassay or EIA)	146
EMBASE	(Ovid)	October 17, 2006	(exp SYPHILIS or exp Treponema Pallidum) AND (exp Reagin Test or rapid plasma reagin.mp or enzyme immunoassay.mp or exp Enzyme Immunoassay or EIA.mp or RPR.mp	365
Cochrane Database of Systematic Reviews	Cochrane Library www.thecochranelibrary.com	October 18, 2006	(MeSH syphilis OR MeSH Treponema pallidum) AND ((rapid NEXT plasma NEXT regain) OR (enzyme NEXT immunoassay) OR RPR OR EIA OR screen OR screening OR screens)	1
Health Technology Assessment Database	CRD Databases (DARE, HTA, NHS, EED) http://www.nhscrd.york.ac.uk	October 18, 2006	(Syphilis OR treponema pallidum) AND (enzyme immunoassay OR EID OR rapid plasma regain OR RPR OR screen OR	0

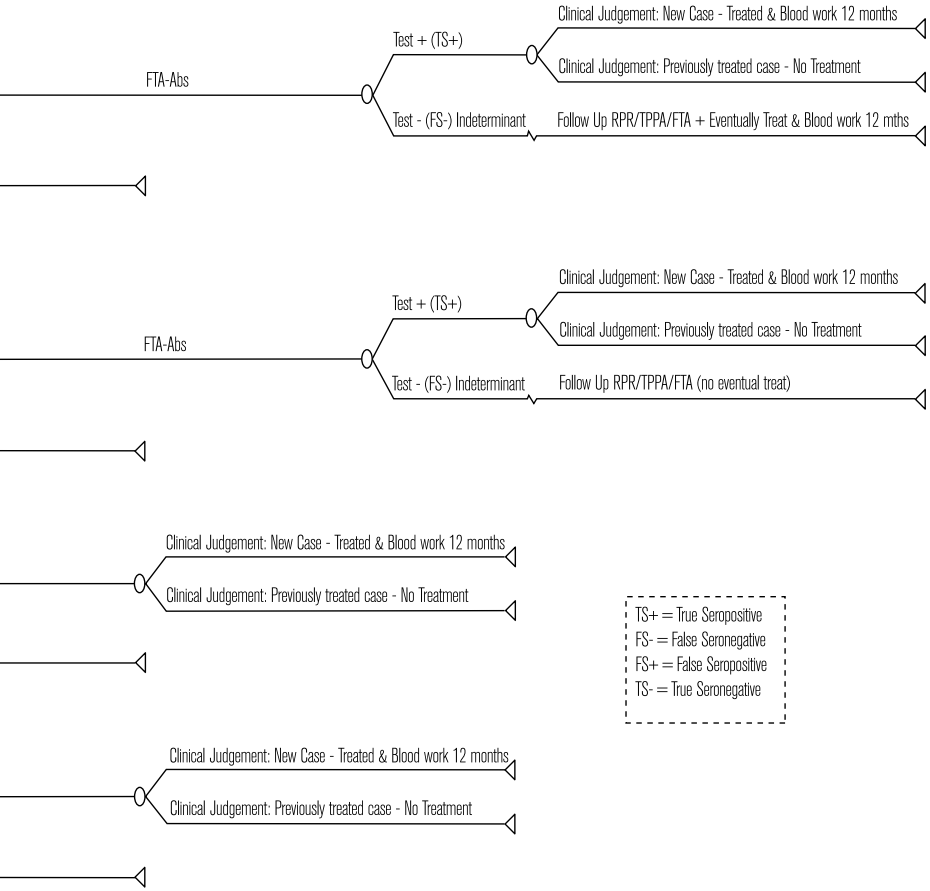
Table A: Search Strategy (continued)

Database	Platform	Edition or date searched	Search terms	# Results
NHS Economic Evaluation Database (NHS EED)	CRD Databases (DARE, HTA, NHS EED) http://www.nhscrd.york.ac.uk	October 18, 2006	(Syphilis OR treponema pallidum) AND (enzyme immunoassay OR EID OR rapid plasma regain OR RPR OR screen OR screening OR screens)	13
Database of Abstracts of Reviews of Effects (DARE)	CRD Databases (DARE, HTA, NHS EED) http://www.nhscrd.york. ac.uk	October 18, 2006	(Syphilis OR treponema pallidum) AND (enzyme immunoassay OR EID OR rapid plasma regain OR RPR OR screen OR screening OR screens)	1
Canadian Task Force on Preventative Healthcare	http://www.ctfphc.org	October 18, 2006	Scanned topics and systematic reviews	0
CADTH	http://www.cadth.ca	October 18, 2006	Syphilis	0
EconLit	EBSCO Host	October 18, 2006	Syphilis AND (screen OR screening OR screens)	0
ECRI	www.ecri.org	October 18, 2006	Syphilis	IHTA Abstracts – 21

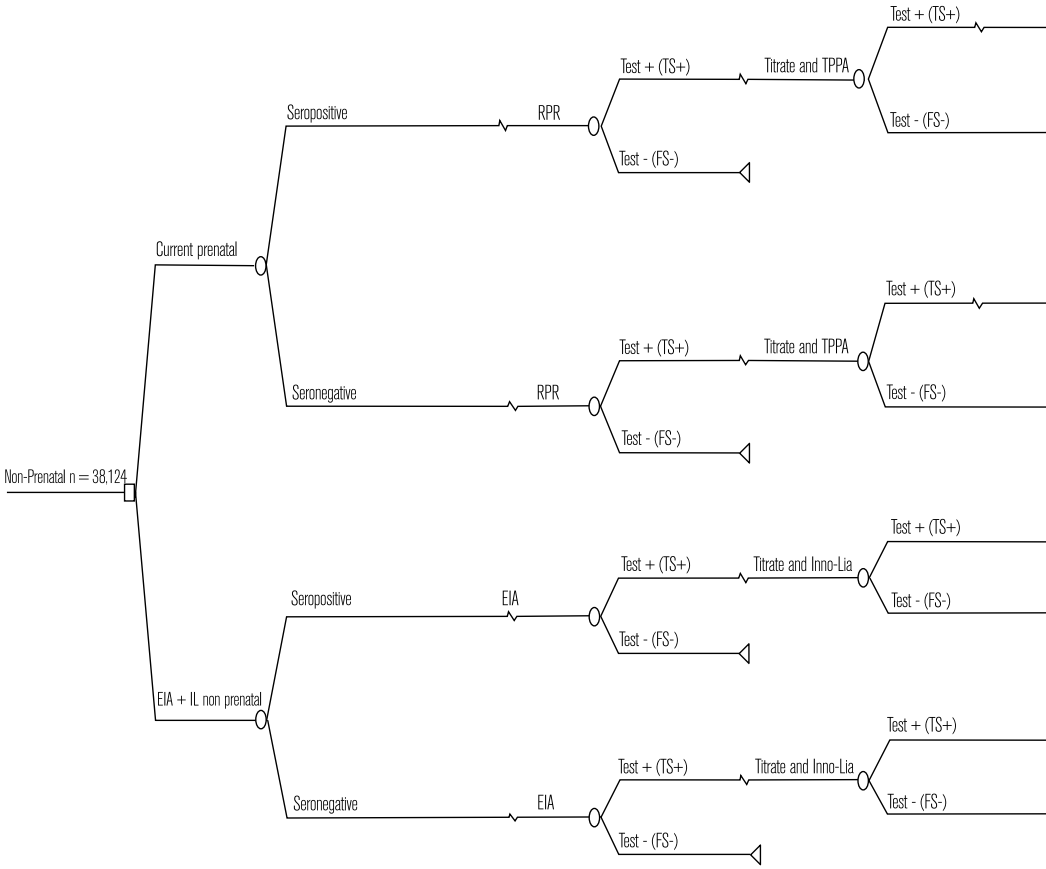
Appendix B: Simulation Models

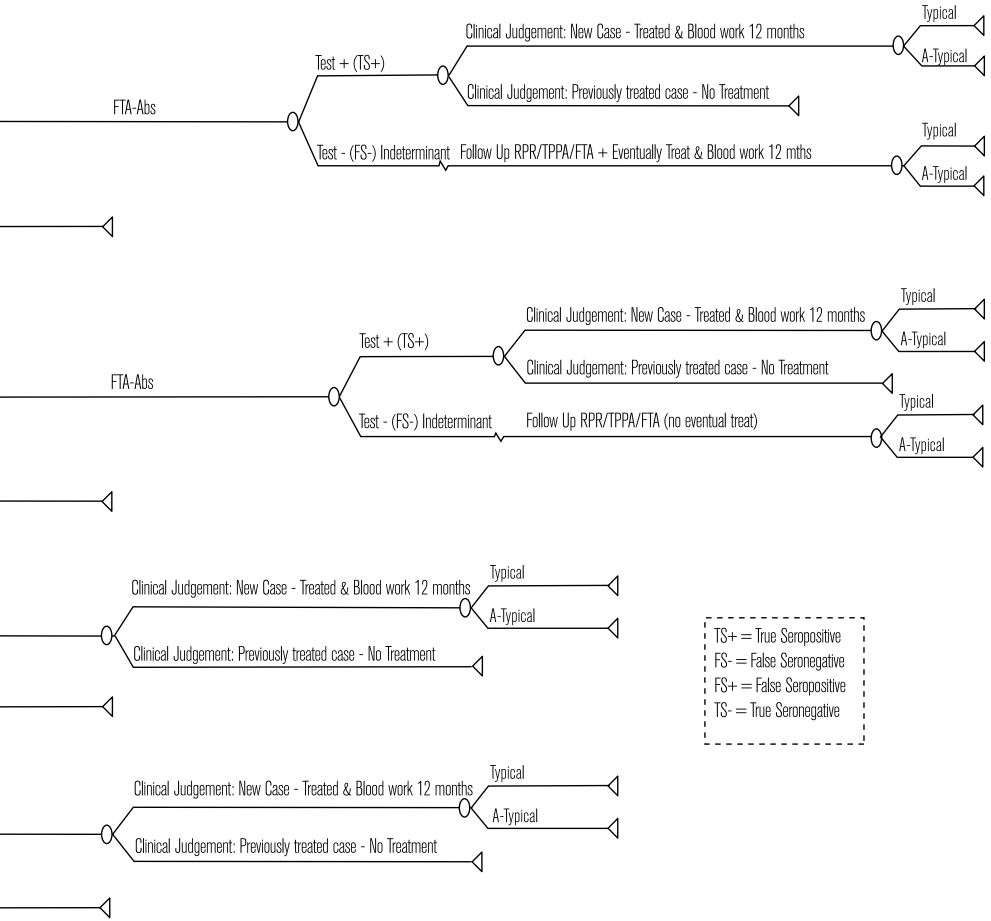
Prenatal Population




FTA-Abs
Test + (TS+)
Clinical Judgement: New Case - Treated & Blood work 12 months
Clinical Judgement: Previously treated case - No Treatment
Test - (FS-) Indeterminant
Follow Up RPR/TPPA/FTA + Eventually Treat & Blood work 12 mths
FTA-Abs
Test + (TS+)
Clinical Judgement: New Case - Treated & Blood work 12 months
Clinical Judgement: Previously treated case - No Treatment
Test - (FS-) Indeterminant
Follow Up RPR/TPPA/FTA (no eventual treat)
Clinical Judgement: New Case - Treated & Blood work 12 months
Clinical Judgement: Previously treated case - No Treatment
Clinical Judgement: New Case - Treated & Blood work 12 months
Clinical Judgement: Previously treated case - No Treatment
TS+ = True Seropositive
FS- = False Seronegative
FS+ = False Seropositive
TS- = True Seronegative

Non-prenatal Population




FTA-Abs
Test + (TS+)
Clinical Judgement: New Case - Treated & Blood work 12 months
Typical
A-Typical
Clinical Judgement: Previously treated case - No Treatment
Test - (FS-) Indeterminant
Follow Up RPR/TPPA/FTA + Eventually Treat & Blood work 12 mths
Typical
A-Typical
FTA-Abs
Test + (TS+)
Clinical Judgement: New Case - Treated & Blood work 12 months
Typical
A-Typical
Clinical Judgement: Previously treated case - No Treatment
Test - (FS-) Indeterminant
Follow Up RPR/TPPA/FTA (no eventual treat)
Typical
A-Typical
Clinical Judgement: New Case - Treated & Blood work 12 months
Typical
A-Typical
Clinical Judgement: Previously treated case - No Treatment
TS+ = True Seropositive
FS- = False Seronegative
FS+ = False Seropositive
TS- = True Seronegative
Clinical Judgement: New Case - Treated & Blood work 12 months
Typical
A-Typical
Clinical Judgement: Previously treated case - No Treatment

Notes

IHE Publications

- Cost-effectiveness in the detection of syphilis
- The use and benefit of teleoncology services
- Screening newborns for hearing
- Screening newborns for cystic fibrosis
- The use of nitric oxide in acute respiratory distress syndrome
- Rountine pre-operative testing – is it necessary?
- Consensus Statement on Self-monitoring in Diabetes
- Consensus Statement on How to Prevent Low Birth Weight

A new protocol for testing and diagnosing syphilis has been proposed in Alberta. The protocol proposes replacing rapid plasma reagin (RPR) with enzyme immunoassay (EIA) as the standard initial test and replacing Treponema pallidum (T. pallidum) particle agglutination assay (TPPA) and fluorescent treponemal antibody-absorbed (FTA-Abs) with Inno-Lia (IL) as the standard confirmatory test. The primary aim of this report is to provide a cost effectiveness analysis (CEA) of the proposed protocol (EIA+IL). Information regarding Social and System Demographics and Technology Effects and Effectiveness is also provided.

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ISBN 978-1-897443-00-2 (print)
ISBN 978-1-897443-17-0 (online)