ORIGINAL ARTICLE

Performance and costs of a rapid syphilis test in an urban population at high risk for sexually transmitted infections

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Key words

Cost-effectiveness • Rapid test • Syphilis

Summary

Introduction. *Rapid syphilis screening could facilitate case-identification in populations at high risk for sexually transmitted infections (STI). The aim of this study was to compare the performance and the cost-effectiveness of a rapid immunochromatography syphilis test with a traditional ELISA screening test in patients with suspected infectious syphilis or patients at high risk for STI/syphilis.*

Methods. *Consecutive patients attending a STI clinic cosensually underwent serological testing with two different tests. Sensitivity, specificity, Positive Predictive Values, Negative Predictive Values and effectiveness of the two tests were evaluated with respect to definitive diagnosis.*

Results. *In our population, the immunochromatography essay (Abbott Determine Syphilis TP) had a sensitivity of 95.0% (95% CI 88.7-97.8) and a specificity of 97.7% (95% CI 94.7-99.0). The ELISA test had a sensitivity of 95.0% (95% CI 88.8-97.9) and a specificity of 97.2% (95% CI 94.1-98.7). The Positive Predictive Value for ELISA was 94.1% (95% CI 87.6-97.3) and 95.0% (95% CI 88.7-97.8) for the rapid test. The Negative Predictive Value was 97.7% (95% CI 94.7-99) for both ELISA and the rapid tests.*

The cost-effectiveness analysis showed that the rapid test was less expensive than ELISA (€ 26.46 vs € 40.57) and yielded a similar number of right diagnoses.

Conclusions. *The Abbott Determine Syphilis TP test is an accurate, easy and inexpensive test that could facilitate the rapid detection of syphilis in high-risk urban patients.*

Introduction

The number of syphilis cases in North-Western Europe has risen steadily since 1996, while a surge in new cases has been reported in the former Soviet Union and other Eastern European countries [1-10]. In Western society, the populations most at risk for sexually transmitted infections (STI) are young persons, men who have sex with men (MSM), immigrant groups and inner city residents, whereas intravenous drug use is the leading cause and is mainly related to sex for drugs in Eastern Europe [11-14].

Outbreaks of primary-secondary syphilis occurred in major Italian cities in the late 1990s; in some settings, prevalently among MSM, the number of cases increased by 400-700% within just a few years [15-18].

Of paramount importance in the control of the disease is early diagnosis, yet diagnosis poses many challenges, despite the wide range of laboratory tests available [19]. Easy access to laboratory testing is thought to be a cornerstone in the control of syphilis. An on-site rapid test delivered at the first visit as part of STI screening in high-risk individuals or as a confirmatory test of clinical suspicion would be extremely useful in hard to reach populations.

Over twenty rapid tests for the serological diagnosis of syphilis are commercially available [19]. The fundamental features of a rapid test are: availability of results within 30 minutes, easy to perform (no expert staff needed), clear interpretation of results and low cost. STI clinics, medical practitioners, emergency departments, youth clubs and community-based centers for intravenous drug users or drop-in centers are ideally suited places where these tests could be administered to identify individuals requiring treatment. Few studies on test validity and utility in such facilities have been carried out. Most have been conducted in rural or underdeveloped areas [20-24]. In industrialized countries, the use of rapid tests should be strongly promoted to contain the mounting numbers of contagious cases.

Several studies on the cost-effectiveness of alternative strategies for syphilis prevention and control have compared selective screening and partner notification [25, 26]; others have focused on syphilis screening of specific populations such as pregnant women in or military recruit applicants [27, 28], finally other studies have evaluated cost-effectiveness of rapid plasma reagin test with postponed result end treatement and a rapid test with immediate results and treatement among pregnant women for maternal syphilis [29-31].

The aim of this study was to evaluate the performance and the cost-effectiveness of an immunochromatography essay for syphilis rapid diagnosis in high-risk patients attending an urban STI clinic.

Materials and methods

The HIV/STI clinic in Turin (an industrial city in North-Western Italy with 1 million inhabitants) is based on the

British walk-in-clinic model and offers confidential, voluntary self-referral services for the early diagnosis and free treatment of STIs. The clinic operates at Amedeo di Savoia Hospital, an infectious disease tertiary care institution. Between 01 June 2003 and 30 September 2006, consecutive patients with dermatological lesions suggestive of infectious syphilis or with ulcerative genital disease or patients at high risk of acquiring syphilis were offered a rapid test along with traditional treponema testing. After being interviewed, patients gave consent to clinical examination; microbiological samples were collected for the most common sexually transmissible pathogens. From each patient 7 ml of blood were drawn by trained personnel using the Vacutainer blood collection system (Becton-Dickinson, Rutherford, NJ, USA). EDTA-containing tubes were used for the rapid tests. Specimens were stored at 4°C until testing with ELISA within 24 hours at the hospital's microbiology laboratory.

Serological screening for syphilis was carried out using the ELISA test (BEIA Mab Syphilis Screen, Bouty-Italia). Positive specimens were then retested with Rapid Plasma Reagin (RPR Slide-Test, BioMérieux, France), Treponema pallidum-Particle agglutination (SERODIA-TP-PA, Fujirebio, Japan), ELISA IgM (BEIA Mab SYPHILIS IgM Capture, Bouty-Italy) according to the manufacturer's instructions. After reviewing World Health Organization (WHO) results and Italian market availability, we selected Determine Syphilis TP, an immunochromatographic rapid test, (Abbott Laboratories, Chicago, IL, USA) to detect antibodies for 57 KD antigen of *Treponema pallidum* in collected specimens. In brief, whole blood was collected in EDTA-containing vacutainer tubes; 50 ml of blood were transferred from the tube to the immunochromatographic strip by means of a micropipetter. As the sample migrates through the conjugate pad, it reconstitutes and mixes with the *Treponema pallidum* antigen-selenium colloid conjugate. The mixture continues to migrate through the solid phase to the immobilized *Treponema pallidum* antigens at the patient window site. A red line appears when anti-Treponema antibodies bind to the selenium-antigen colloid in the patient window. If the sample contains no antibodies, the red line does not appear because the *Treponema pallidum* antigen-selenium colloid flows past the patient window. To ensure test validity, an internal procedural control bar was incorporated. At least 15 minutes are needed before the result can be read. Two independent readers were chosen to interpret the results.

Definitive syphilis diagnosis was confirmed by combining clinical stage of disease (presence of dermatological lesions suggestive of infectious syphilis – such as aphthosis orogenital, candidiasis, condylomas, urethritis, vaginitis – or ulcerative genital disease – such as herpetic infections) and positive screening test result (ELISA) and positive confirmatory tests result (RPR, TP-PA or ELISA IgM). Test sensitivity, specificity, Positive Predictive Values, Negative Predictive Values and effectiveness (expressed as the number of right diagnoses) were measured against definitive diagnosis. The fraction of indeterminate tests was calculated as a marker for test failure frequency.

The economic evaluation was carried out from the hospital's point of view. To determine the cost of the tests, we referred to the data provided by the Amedeo di Savoia Hospital. The direct internal costs to the hospital for carrying out the tests were calculated taking the value of: test price, supplies (test tubes, gloves, micropipetters, biotransport), labor costs laboratory technicians, nurses, support personnel, medical staff and personal assistants to perform the test and write up the medical report.

The costs of the ELISA test (specimen transport from ambulatory to laboratory, exhibit transport from laboratory to ambulatory), and second medical examination were also included. There were no additional laboratory equipment costs because they are included in the kit price. Hospital administration and overhead costs were also included in the calculation. The total costs and the average cost per test unit are expressed in euros. All costs are expressed in euros and were calculated in relation to rates 2006.

Results

During the study period, 316 consecutive patients (244 men, median age 36 years; 72 women, median age 28.5 years) either symptomatic for dermatological or genital lesions or asymptomatic patients but belonging to an at-risk group were examined at the STI clinic; 78% were Italian nationals, 11% were from Eastern Europe, 6.5% from North Africa and 4.5% from other countries.

Table I summarizes the results of the two tests.

In this sample, the ELISA test had a sensitivity of 95.0% (95% CI 88.8-97.9) and a specificity of 97.2% (95% CI 94.1-98.7); the rapid test had a sensitivity of 95.0% (95% CI 88.7-97.8) and a specificity of 97.7% (95% CI 94.7-99.0).

Tab. I. Results of the Rapid and ELISA test.

Rapid test	Definitive Syphilis Diagnosis*			ELISA	Definitive Syphilis Diagnosis*		
	+	-	Total		+	-	Total
+	94	5	99	+	95	6	101
-	5	212	217	-	5	210	215
Total	99	217	316	Total	97	216	316

* Definitive syphilis diagnosis was confirmed by combining clinical stage of disease (presence of dermatological lesions suggestive of infectious syphilis – such as aphthosis orogenital, candidiasis, condylomas, urethritis, vaginitis –, or ulcerative genital disease – such as herpetic infections) and positive screening test result (ELISA) and positive confirmatory tests result (RPR, TP-PA or ELISA IgM).

The Positive Predictive Value of ELISA was 94.1% (95% CI 87.6-97.3) and that of the rapid test was 95.0% (95% CI 88.7-97.8). The Negative Predictive Value was 97.7% (95% CI 94.7-99) for both tests.
A breakdown of the unit costs per single test (in euros) is illustrated in Table II. The cost item that weighed most on the ELISA test was "second medical examination". The "second medical examination" was needed for report delivery and therapeutic prescription, whereas performing rapid syphilis test the "second medical examination" was not necessary being contextual.
Evaluation cost-effectiveness, Table III, determines less expensive rapid test for right diagnosis.
The difference in the costs and results of the two tests is readily apparent: with the rapid test – € 4,277.38 are saved per the additional right diagnosis.
This result remained the same even when a one-way sensitivity analysis was applied and the cost item that weighs the greatest, i.e. the "second medical examination", was eliminated, since even after this cost is eliminated, the cost of the rapid test is still less than that of the ELISA.

Discussion

The return of syphilis in many parts of the world requires accurate and rapid diagnosis for effective control. Paradoxically, the diagnosis of syphilis in the developed countries is not an easy task. Three different approaches are generally used: recognizing signs and symptoms in exposed individuals, direct demonstration of *Treponema* spp. by dark field microscopy and serological testing. The last is of paramount importance in the diagnostic process and for public health issues as well. In STI clinics, antenatal services, marginalized people centers and other such settings where many clients are not likely to return, rapid syphilis diagnosis is warranted. This means that treatment needs to be delivered at the same time as the provisional diagnosis.
Our study shows that the rapid test has a high sensitivity and specificity, confirming the results of previous studies on Abbott Determine Syphilis TP (Tab. IV). Our results also show that its sensitivity and specificity are comparable to those of the ELISA screening test and to the manufacturer's data (sensitivity 92.3%, specificity 100%).
As expected, the Positive Predictive Value was high, since the test was administered to a patient group with a high prevalence of syphilis (31.6%); likewise, there was a high probability of not having a definitive diagnosis of syphilis if the test result was negative. Moreover, the rapid test is less expensive than the ELISA test.
Based on these considerations, the rapid test could replace the traditional syphilis test for screening in high-risk population-based ambulatories.
In brief:
– routine administration of the test to urban high-risk

Tab. II. Estimated average cost (€) and incremental cost of the rapid and the ELISA test.

Resources	Rapid Test (a)	ELISA (b)	Incremental cost (c) = (b) - (a)
Staffing			
– medical	14.62	13.28	- 1.34
– laboratory technician/nurse	2.10	3.90	+ 1.80
– support personnel		0.88	+ 0.88
– personal assistant	0.50	0.50	0
Supplies	0.13	0.24	+ 0.11
Test price	4.00	1.38	- 2.62
Second medical examination	12.45	12.45	0
Other*	4.27	6.53	+ 2.26
Total	25.62	39.16	+ 13.54

*includes administration and overhead costs

Tab. III. Cost-effectiveness of the rapid and the ELISA test in 316 patients.

Test	Total Costs (€)	No. of right diagnoses	Costs/ No. of right diagnoses
Rapid Test	8,095.92	306	26.46
ELISA	12,373.30	305	40.57

Tab. IV. Comparison of sensitivity and specificity of the rapid test in different studies.

	Study population	WHO [20]	Lien [21]	Sato [22]	Diaz [23]	Siedner [24]
Sensitivity	95.0%	97.2%	100%	93.7%	96.9-98.5%	88%
Specificity	97.7%	94.1%	98.6%	95.2%	95.7-97.3%	

populations is recommended since it yields a result within 15 minutes, does not require sophisticated laboratory equipment or specifically trained personnel;
- high-risk populations typically seek treatment for acute episodes during clinic visits and are not likely to return a second time for test results;
- diagnosis and treatment at the same visit can aid in reducing the spread of the disease and the related costs of treatment.

Nevertheless, these statements should be interpreted within the correct perspective. The first limitation is linked to the rapid test's characteristics. Like all rapid tests, it is unable to discriminate between previous syphilis infection and re-infection since anti-Treponema antibodies continue to remain present in the blood, making the test useless for monitoring treatment or progress of the infection.

The second is that its use as a screening test for populations at low risk for syphilis is not currently advised, or at least not until the data from large-scale WHO studies have been evaluated. Similarly, the results can change completely for the general population, which has a significantly lower prevalence of syphilis. The test's sensitivity and specificity in a hypothetical Italian population of 100,000 habitual blood donors (Treponema pallidum Hemoagglutination [TPHA] Test prevalence of 0.12%) would yield disappointing results, thus discouraging its use for general population screening. As prevalence diminishes, so does the test's positive predictive value, while the negative predictive value increases.

The results of our study suggest that the rapid test could meet the need for an inexpensive, noninvasive, rapid screening test for syphilis, but larger sample sizes are needed to corroborate our conclusions.

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■ Received on May 30, 2007. Accepted on November 16, 2007.

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