

An Evaluation of a Novel Dual Treponemal/Nontreponemal Point-of-Care Test for Syphilis as a Tool to Distinguish Active From Past Treated Infection

Louise M. Causer,¹ John M. Kaldor,¹ Damian P. Conway,¹ David E. Leslie,² Ian Denham,³ Theo Karapanagiotidis,² Claire Ryan,⁴ Handan Wand,¹ David A. Anderson,⁴ Peter W. Robertson,⁵ Anna M. McNulty,⁶ Basil Donovan,¹ Christopher K. Fairley,⁷ and Rebecca J. Guy¹

¹Kirby Institute, University of New South Wales, Sydney, ²Victorian Infectious Diseases Reference Laboratory, Melbourne, ³Melbourne Sexual Health Centre, Carlton, ⁴Burnet Institute, Melbourne, ⁵SEALS Laboratory, Prince of Wales Hospital, Randwick, ⁶Sydney Sexual Health Centre, and ⁷Central Clinical School, Monash University, Melbourne, Australia

Background. Most syphilis point-of-care (POC) tests detect treponemal antibodies, which persist after successful treatment. Subsequent POC tests are positive, despite no active infection, and can lead to unnecessary treatment. We evaluated a new POC test, incorporating a nontreponemal component, to distinguish active from past infection.

Methods. Sera stored at 2 Australian laboratories were tested with DPP Screen and Confirm Assay. Treponemal and nontreponemal test lines were compared to corresponding conventional treponemal and nontreponemal reference test results: immunoassays and rapid plasma reagin (RPR), respectively, with RPR quantification by endpoint titration. POC test outcome concordance with conventional test results was assessed according to serological and clinical categories.

Results. Among 1005 serum samples tested, DPP treponemal line sensitivity was 89.8% (95% confidence interval [CI], 87.3%–91.9%) and specificity was 99.3% (95% CI, 97.0%–99.9%). DPP nontreponemal line sensitivity was 94.2% (95% CI, 91.8%–96.0%) and specificity was 62.2% (95% CI, 57.5%–66.6%). DPP test outcome (pair of test lines) was concordant with both reference test results for 94.3% of 404 high-titer infections, 90.1% of 121 low-titer infections, 27.5% of 211 past/treated infections, and 78.1% of 242 infections classified as not syphilis. Among 211 past/treated infections, 49.8% were incorrectly identified as active infection and a further 22.8% as not syphilis.

Conclusions. DPP test use would result in identification of >93% of active syphilis infections, whereas just over half of past infections would be diagnosed as past or not syphilis, avoiding unnecessary treatment compared with other POC tests. This may be at the expense of missing some active infections; thus, its potential benefits will depend on the prevalence of past vs active infection in a population.

Keywords. syphilis; point-of-care test; diagnosis.

Timely diagnosis and treatment of syphilis is crucial to minimize morbidity and onward transmission. Of particular concern is maternal syphilis, estimated at 1.36

million cases globally in 2008 [1], which can lead to fetal loss, perinatal death, prematurity, low birth weight, and a range of serious malformations in surviving children [2, 3]. These outcomes are preventable with accurate screening and prompt treatment for maternal infection [4–7], but many pregnant women with syphilis remain undiagnosed, particularly in developing countries. Screening for syphilis is also indicated for population groups that are at increased risk through sexual contact. These groups vary by setting but may include sex workers, men who have sex with men, and sexual contacts of those found to have syphilis.

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Correspondence: Louise M. Causer, MBBS, MScPH, DTM&H, The Kirby Institute, University of New South Wales, Sydney NSW 2052, Australia (lcauser@kirby.unsw.edu.au).

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Despite the importance of testing [8–10], it is widely recognized that the reliable diagnosis of active syphilis is challenging. Tests detecting treponemal antibodies are specific for syphilis (outside areas with endemic yaws or other treponemal infections) but are positive for life following infection in most cases, even after successful treatment. Tests for “nontreponemal” antibodies, such as RPR (rapid plasma reagin) and TRUST (toluidine red unheated serum test), are better indicators of active infection and can provide a quantitative result but, if used alone, can yield false-positive results due to cross-reactions with other antigens. They are also subject to false negativity in active syphilis because of biological fluctuations. Moreover, their accuracy and safe use depend on levels of operator skill and experience that are not insubstantial.

The recent development of easy-to-use, accurate, rapid point-of-care (POC) treponemal tests can transform syphilis control strategies. In endemic situations, these tests are now recommended for antenatal screening [11], even though it is understood that a proportion of women detected as positive and offered treatment will have past adequately treated syphilis rather than active infection. In addition to unnecessary treatment, the diagnosis of an infection that is primarily sexually transmitted may lead to psychosocial trauma including stigma and partner violence. In many settings, it is already challenging for women to deal with the consequences of such a true diagnosis, and false-positive test results can compound this burden further. There is therefore an urgent need for a syphilis POC test that can make the distinction between active and past treated infection.

The DPP Syphilis Screen and Confirm Assay is a commercially available POC test for syphilis that simultaneously detects treponemal and nontreponemal antibodies from the same specimen. Published evaluations suggest that the treponemal and nontreponemal test components have good sensitivity and specificity compared with selected treponemal and nontreponemal laboratory reference tests [12–14]; however, no studies have quantified the test’s ability to reduce the extent of false-positive diagnoses in past treated syphilis. We recently reported a laboratory-based evaluation of 4 syphilis POC tests [15], including the DPP assay, in a side-by-side comparison of the tests’ treponemal components using a well-characterized panel of stored serum specimens. Here we report specifically on the unique dual detection capability of the DPP test.

METHODS

Study Design

We used a cross-sectional design to assess the performance of the DPP test using stored sera. DPP test results were compared to the results of routinely performed conventional laboratory reference treponemal and nontreponemal tests. Routinely recorded clinical data were extracted from patient medical records

and used to characterize sera in regard to demographic and clinical factors.

Setting

Sera were selected from 2 major laboratories in Australia’s 2 largest cities, the Victorian Infectious Diseases Reference Laboratory (VIDRL) in Melbourne and South Eastern Area Laboratory Service (SEALS) in Sydney. These laboratories are the primary pathology providers for large, urban sexual health clinics that have extensive clinical expertise in sexually transmitted infection diagnosis and management and provide health services to substantial numbers of gay men. In both cities, very high rates of syphilis have recently been reported among gay men [16], particularly those with human immunodeficiency virus (HIV) [17].

DPP Screen and Confirm Assay

The DPP Syphilis Screen and Confirm Assay (Chembio Diagnostic Systems Inc, Bedford, New York) is designed as a POC test. It uses an immunochromatographic strip platform for simultaneous detection of treponemal and nontreponemal antibodies indicated by separate colored lines (T1 and T2), with a separate control line, C. It can be used with serum, plasma or whole blood (including fingerprick specimens [13]) without requiring refrigeration. Visual interpretation is made at 10–15 minutes.

Laboratories and Serological Reference Tests

VIDRL and SEALS routinely conduct reference treponemal testing using the Trepanostika TP recombinant enzyme immunoassay (bioMérieux, Boxtel, the Netherlands) and Architect Syphilis TP chemiluminescence assay (Abbott, Wiesbaden, Germany), respectively. Both assays are highly sensitive and specific [18, 19]. In this paper, these treponemal reference tests are collectively referred to as immunoassays (IA). Both laboratories also use TPPA (*Treponema pallidum* particle agglutination) to confirm the reference treponemal IA. In both laboratories, the nontreponemal reference test was a quantitative RPR assay using BD Macro-Vue RPR Card Tests (Becton, Dickinson and Co). Following Australian guidelines, a “reverse” screening algorithm is used, with the treponemal test conducted first, followed by a quantitative nontreponemal test for reactive IA specimens [20]. Both laboratories participate in an ongoing external quality assurance program (Royal College of Pathologists of Australia Quality Assurance Program).

Clinical and Laboratory Data

For each specimen, information on demographic, behavioral, and biological characteristics were obtained from the laboratory and clinical records (for those attending Melbourne and Sydney Sexual Health Centres).

Specimen Categorization

Serological

Specimens were categorized by treponemal (IA) and by nontreponemal (RPR) reference test results as active high RPR titer syphilis (IA reactive, RPR ≥ 8); active low RPR titer syphilis (IA reactive, RPR of 1, 2, or 4); past syphilis (IA reactive, RPR nonreactive); no syphilis (IA and RPR nonreactive/RPR ≤ 1); and biological false positives (IA nonreactive, RPR ≥ 2). As specimens from a person with a previously documented reactive treponemal reference test go directly for RPR testing, these were considered IA reactive for the study analyses.

Clinical

Using methods previously described [15], specimens were categorized into clinical stages (primary syphilis, secondary syphilis, early latent syphilis, late latent or unknown duration syphilis, past treated syphilis) based on clinicians' diagnosis documented in the corresponding medical records and according to the definitions in [Supplementary Text Box 1](#).

Sample Size and Specimen Selection

We selected approximately 1000 specimens, aiming for adequate numbers in each serological category to ensure that the estimate for sensitivity and specificity would have a 95% confidence interval (CI) of $\pm 10\%$ or less. Stored specimens were sequentially selected by date until the desired quota was reached.

Conduct of the DPP Test

Technicians performing the DPP test completed training to ensure consistency in test conduct and interpretation. Specimens were tested according to the manufacturer's instructions by 1 study technician blinded to the reference results. DPP test results were recorded on a data record sheet. A second study technician, blinded to both the reference test and first technician's results, interpreted and recorded the test result within 1 minute of the first read. Discrepancies were discussed and consensus recorded.

Data Analysis

The sensitivity and specificity of the individual DPP test lines (T1 and T2) compared to corresponding reference test results (IA and RPR), with quantitation by RPR endpoint titration, were calculated by standard methods (Stata software, version 12; StataCorp, College Station, Texas).

The DPP test outcome (pair of DPP test lines) was compared with dual reference test results categorized (*i*) by serological status and (*ii*) within clinical categories, to determine concordance. CIs were calculated [21] for estimates (sensitivity and specificity) with statistical significance of a difference between categories based on nonoverlapping CI.

Clinical consequence of using the DPP test—that is, the potential reduction in overdiagnosis of syphilis—was assessed among serum specimens determined to be “past syphilis”

based on the reference test results. Among these, we calculated the proportion yielding a reactive T1 and nonreactive T2 result on the DPP test.

Ethical Approval

Ethical approvals were granted by relevant committees: South East Sydney and Illawarra Area Health Service, Melbourne Health,

Table 1. Selected Characteristics of Study Population (N = 1005)

Variable	No. (%)
Sex	
Male	852 (84.8)
Female	153 (15.2)
Age, y	
Median	37
Range	18–85
Additional clinical information	
Available	681 (67.8)
Unavailable	324 (32.2)
Among men, same sex partner in last 12 mo	
Yes	504 (50.1)
No	83 (8.3)
Unknown	94 (9.4)
Unavailable	324 (32.2)
HIV status	
Positive	139 (13.8)
Negative	542 (53.9)
Unavailable	324 (32.2)
CD4 count, cells/ μ L, among HIV positive	
<200	2 (0.2)
200–499	59 (5.9)
≥ 500	55 (5.5)
Unknown	23 (2.3)
Unavailable	866 (86.2)
Clinical syphilis diagnosis ^a	
Primary	53 (5.3)
Secondary	70 (7.0)
Early latent	91 (9.1)
Late latent/unknown duration	25 (2.5)
Past treated	248 (24.7)
Syphilis, no stage specified	4 (0.4)
Not syphilis	190 (18.9)
Unavailable	324 (32.2)
Serological syphilis categorization	
IA reactive/RPR reactive (R ≥ 8)	404 (40.2)
IA reactive/RPR reactive (R = 1:1, 2, or 4)	121 (12.0)
IA reactive/RPR nonreactive	211 (21.0)
IA nonreactive/RPR reactive (R ≥ 2)	27 (2.7)
IA nonreactive/RPR nonreactive (RPR ≤ 1)	242 (24.1)

Abbreviations: HIV, human immunodeficiency virus; IA, immunoassay; R, reactive; RPR, rapid plasma reagin.

^a As documented in medical records for patient specimens.

RESULTS

Sample Characteristics

A total of 1005 specimens (678 from Melbourne and 327 from Sydney), characterized by treponemal and nontreponemal reference tests, were tested using the DPP assay. The median age of the cases was 37 years (range, 18–85 years), and 852 (84.8%) were men. Additional patient demographic and clinical data were available for 681 (67.8%) specimens. Table 1 describes the selected demographic, clinical, and laboratory characteristics of specimens tested.

Clinical Syphilis Categorization

Clinical and laboratory diagnoses of syphilis were documented for 491 cases, and 190 were documented as not having syphilis. On the basis of the records, 53 cases were classified as primary (5.3%), 70 (7.0%) secondary, 91 (9.1%) early latent, 25 (2.5%) late latent or unknown duration, 248 (24.7%) past/treated infections, and 4 (0.4%) as syphilis stage unspecified.

Serological Syphilis Classification

Of the 1005 sera tested, 525 (52.2%) were classified as having active syphilis infection, 211 (21.0%) were classified with past syphilis infection, and 27 (2.7%) were biological false positives. The remaining 242 (24.1%) were classified as not syphilis.

Stratifying active syphilis specimens by RPR titer, there were 404 specimens with high-titer and 212 with low-titer syphilis.

Sensitivity and Specificity of Individual T1 and T2 Lines

Table 2 describes the sensitivity and specificity of the 2 DPP test lines individually compared with the corresponding reference tests. Sensitivity of T1 compared to reference IA was 89.8% (95% CI, 87.3%–91.9%) and specificity was 99.3% (95% CI, 97.0%–99.9%). Sensitivity of T2 compared to reference RPR (reactive = RPR \geq 1) was 94.2% (95% CI, 91.8%–96.0%) and specificity 62.2% (95% CI, 57.5%–66.6%).

Among specimens with a reactive RPR ($n = 553$) stratified by category of RPR titer, T2 sensitivity was 98.3% (95% CI, 96.3%–99.2%) and 83.2% (95% CI, 76.2%–88.8%) at high and low titers, respectively. These were significantly different as indicated by nonoverlapping CIs. Restricting the analysis to IA reactive specimens ($n = 525$) only, sensitivity among low-titer specimens was 95% (95% CI, 98.1%–98.0%) and no longer significantly different from that of high-titer specimens (98.3% [95% CI, 96.3%–99.2%]). Figure 1 shows distribution of RPR titers among treponemal (IA) reference test–reactive specimens ($n = 525$) and DPP test T2 reactivity by RPR titer.

There was no statistically significant difference in performance of T1 or T2 by HIV status (Supplementary Table 1).

Concordance of DPP Test Outcome by Serological Syphilis Category

The DPP test outcome was concordant for 93.3% of 525 (correctly identified) specimens classified as active infections. Table 3 describes the concordance of DPP test outcomes with the 2 reference test results defined by serological category.

The DPP outcome was concordant with both treponemal and nontreponemal reference test results (correctly identified) for 94.3% of 404 high-titer infections, 90.1% of 121 low-titer infections, 27.5% of 211 past infections, and 78.1% of 242 classified as no syphilis. Among those with no syphilis but reactive DPP test lines ($n = 53$), 51 had reactive T2 line only, 1 had reactive T1 line only, and 1 had reactive T1 and T2 lines.

As T2 is not a quantitative result, concordance within the high- and low-titer categories is based only on reactive or non-reactive T2 result within the category.

Among 211 past infections, 49.8% were incorrectly identified as active infection and an additional 22.8% incorrectly as not syphilis. Table 4 describes further the concordance of DPP outcome among those with past infection by reference tests.

Concordance of DPP Test Outcome by Clinical Syphilis Category

Table 5 presents concordance of the DPP test outcome with both reference test results by clinical syphilis category. DPP test outcome is concordant with both reference tests for 88.6% of 44 primary syphilis cases, 90.0% of 69 secondary

Table 2. DPP T1 (Treponemal) Line Performance Versus Immunoassay (Treponemal) Reference Result and DPP (Nontreponemal) T2 Line Performance Versus Rapid Plasma Reagin (Nontreponemal) Reference Test Result (N = 1005)

DPP Test Line	DPP Reactive	Reference Laboratory Test Reactive	Sensitivity, % (95% CI)	DPP Nonreactive	Reference Nonreactive	Specificity, % (95% CI)
DPP T1 ^a	661	736	89.8 (87.3–91.9)	267	269	99.3 (97.0–99.9)
DPP T2 ^b	521	553	94.2 (91.8–96.0)	281	452	62.2 (57.5–66.6)

Abbreviation: CI, confidence interval.

^a Compared to reference immunoassay result.

^b Compared to reference rapid plasma reagin (RPR) result; for T2 sensitivity calculation, a reactive RPR was R \geq 1; for specificity calculation, RPR was nonreactive.

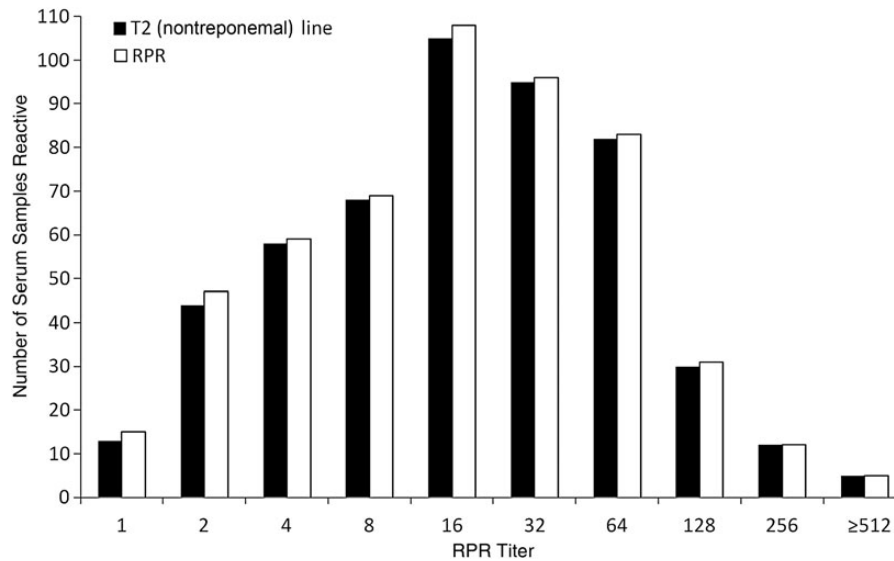


Figure 1. Distribution of rapid plasma reagin (RPR) titers among RPR (nontreponemal) reactive and immunoassay (treponemal) reactive reference test specimens (n = 525) and DPP T2 test line reactivity.

syphilis cases, 94.8% of 77 early latent syphilis cases, and 85.0% of 20 late latent syphilis cases with dual reactive reference tests.

Clinical Diagnostic and Treatment Consequences Based on DPP Test Outcome

Among those with past syphilis (n = 211), 50.2% (n = 106) would be correctly attributed to this category by the DPP test outcome whereas 49.8% (n = 105) would be incorrectly classified as having active syphilis. Assuming that a highly sensitive treponemal-only POC test would have detected all of these cases as positive, the use of the DPP test would have successfully categorized 50.2% of them as not active syphilis.

Among those with active syphilis (n = 525), 93.3% (n = 490) would be correctly diagnosed, with 35 being incorrectly classified. In this instance, assuming as above that a highly sensitive

treponemal-only POC test would have detected all of these cases as reactive, the use of the DPP test would have incorrectly classified 35 cases (which subsequently would have received no treatment).

DISCUSSION

Our laboratory-based study is the first to evaluate clinical implications and performance of the DPP Screen and Confirm Assay, the only currently available POC test for detection of both treponemal and nontreponemal antibodies, in regard to its ability to distinguish active from past syphilis. We found that the DPP test was able to correctly identify 93% of active syphilis infections, 28% of past syphilis infections, and 78% nonsyphilis infections.

Table 3. Concordance of DPP Outcome With Treponemal and Nontreponemal Reference Test Results by Serological Syphilis Category

Serological Syphilis Category	Reference Test Result			DPP Result			% Concordance	95% CI
	IA	RPR	No.	T1	T2	No.		
Active (overall)	R	R	525	R	R	490	93.3	90.8–95.2
Active (high titer)	R	≥8	404	R	R	381	94.3	91.6–96.4
Active (low titer)	R	<8	121	R	R	109	90.1	83.3–94.7
Past	R	NR	211	R	NR	58	27.5	21.6–34.0
No syphilis	NR	NR/≤1	242	NR	NR	189	78.4	72.3–83.1
Biological false positive	NR	≥2	27	NR	R	8	29.6	13.7–50.2

Abbreviations: CI, confidence interval; IA, reference immunoassay (treponemal) result; NR, nonreactive; R, reactive; RPR, reference rapid plasma reagin (nontreponemal) result (reactive = R ≥1); T1, DPP treponemal line; T2, DPP nontreponemal line.

Table 4. Concordance of DPP Test Outcome Among Past Serological Syphilis Category

DPP			Past Syphilis (n = 211) ^a	
T1	T2	No.	Concordance, %	95% CI
R	NR	58	27.5	21.6–34.0
R	R	105	49.8	42.8–56.7
NR	R	15	7.1	4.0–11.4
NR	NR	33	15.6	11.0–21.3

Abbreviations: CI, confidence interval; NR, nonreactive; R, reactive; T1, DPP treponemal line; T2, DPP nontreponemal line.

^a Past syphilis category defined by serological reference tests as immunoassay (treponemal) reactive and rapid plasma reagin (nontreponemal) nonreactive.

Among those past syphilis infections, compared to a highly sensitive treponemal-only POC as the next best alternative in POC testing, the use of the DPP test would have successfully detected 50.2% as not active syphilis.

Serological testing to detect treponemal and nontreponemal antibodies is critical to determine the infection status of an individual and need for treatment. Treatment is usually indicated when both these antibodies are detected, indicating active infection. Except in very early primary syphilis, presence of treponemal antibody in the absence of nontreponemal antibody suggests past treated infection. Among populations with high prevalence of syphilis infection, this may account for a large proportion of the population. In addition, infections with

Table 5. Concordance of DPP Outcome With Reference Test Results by Clinical Syphilis Category

Clinical Syphilis Category (Total)	Reference Test			DPP Test			DPP Test Outcome Concordance With Reference Tests, %
	IA	RPR	No.	T1	T2	No.	
Primary (n = 53) ^a	R	≥1	44	R	R	39	88.6
	R	NR	7	R	NR	1	14.3
	NR	NR	2	NR	NR	1	50.0
Secondary (n = 70)	R	≥1	69	R	R	62	90
	R	NR	1	R	NR	0	0.0
Early (n = 91)	R	≥1	77	R	R	73	94.8
	R	NR	14	R	NR	2	14.3
Late (n = 25)	R	≥1	20	R	R	17	85.0
	R	NR	5	R	NR	0	0.0

Clinical stage = documented in medical records for patient specimens.

Abbreviations: IA, reference immunoassay result; NR, nonreactive; R, reactive; RPR, reference rapid plasma reagin result (reactive = R ≥1); T1, DPP treponemal line; T2, DPP nontreponemal line.

^a Among “primary” syphilis, 2 specimens were IA nonreactive but polymerase chain reaction positive.

other *T. pallidum* subspecies causing illnesses such as yaws and bejel (endemic syphilis) can produce an indistinguishable antibody profile, complicating diagnosis of syphilis further in regions where these infections are also endemic.

POC tests capable of detecting treponemal antibodies alone are widely available and have been shown to perform well both in the field and laboratory settings compared to standard reference treponemal assays [15, 22–26]. POC syphilis tests have also been shown to be cost-effective in some settings [27–29]. In a number of countries, POC syphilis tests have been adopted as national policy, particularly as part of antenatal screening programs aiming to eliminate the mother-to-child transmission of syphilis [30]. As our study population included few women, with very few likely to be pregnant (B. Donovan, personal communication), the generalizability of our results to such screening programs may be limited.

The major limitation of these more widely used POC syphilis tests remains their inability to distinguish active, infectious syphilis from past treated infection. As a result, overdiagnosis and subsequent unnecessary treatment inevitably occur. This situation is likely to be of most concern among populations where syphilis (or other treponemal infection resulting in presence of treponemal antibodies such as yaws) is prevalent. Furthermore, the psychosocial ramifications of a “positive” syphilis test are often far-reaching and worthy of consideration.

As we have previously reported [15], the sensitivity of the individual DPP treponemal line compared to the conventional laboratory reference treponemal test was lower (89.8%) than that previously published [12–14], but specificity (99.3%) was similar.

In our study, the DPP nontreponemal line sensitivity compared to a reactive nontreponemal laboratory test (RPR ≥1:1) was 94.2% (95% CI, 91.8%–96.0%). The increased sensitivity among high-titer specimens (98.3% [95% CI, 96.3–99.2]) is consistent with findings reported elsewhere [12, 13, 31]. Among those with active syphilis infection, T2 sensitivity among low-titer RPR specimens improved to 95.0% (95% CI, 89.1%–98.0%). In our study, T2 specificity compared to a nonreactive reference nontreponemal test was poor (62.2%), and is in contrast to specificities noted by Castro et al (98.6%) [12], Yin et al (95%) [13], and Ayove et al (92.5%) [31]. There was no statistically significant difference in T2 specificity by HIV status, although the number of HIV-infected participants was limited. Despite standardized training on performing these tests, this poor specificity might be explained by technicians being overly cautious and recording even very faint shadows at the nontreponemal line region as reactive. Further exploration of this finding by stratifying DPP nontreponemal line specificity by reference treponemal test reactivity suggested that specificity was lower among treponemal reactive specimens (43.1%) vs nonreactive specimens (78.8%).

To our knowledge, we are the first to report the clinical implications of the DPP test’s ability to distinguish active from past

syphilis. Among those with serologically determined past syphilis, the DPP test outcome correctly identified more than one-quarter (27.5%) of cases. In a clinical setting, these cases would not receive treatment. The incorrectly identified cases here could be considered as biological false positives (7.1%), no syphilis (15.6%), and misdiagnosed active infection (49.8%). Of these, only those called active infection would be offered treatment, and represent the ongoing “overdiagnosis” and “overtreatment” occurring with the use of a POC test.

Our conclusion that the use of the DPP test would successfully detect 50.2% of past cases as not active syphilis is likely to be true only if patients who do have lesions of early primary syphilis are excluded. This is explained by the fact that a number of patients with polymerase chain reaction-positive early primary lesions and some treponemal antibody marker positivity have negative nontreponemal tests (up to 20% at VIDRL; D. Leslie, personal communication). In light of this, the DPP test may have a different potential under screening and clinical presentation with a genital ulcer.

Although it appears that most active infections would be detected (>93%), our previously published data show that the sensitivity of the DPP treponemal line is lower than that of some other treponemal-only syphilis POC tests, such as Determine TP [15]. In considering the use of this novel dual test, although there is evidence that it can improve identification of past cases and avoid unnecessary treatment, it is important to note that this may come at the expense of a somewhat reduced treponemal sensitivity, resulting in missing cases that may truly require treatment. The balance between possible reduction in overtreatment offered by the DPP test and loss of sensitivity is important to consider in the context of the population at risk. Unless there is a substantial prevalence of past/treated infection (or yaws), a treponemal-only POC test may be preferred or, alternatively, a treponemal-only test might be considered as first line, followed by the dual test to minimize overdiagnosis and subsequent treatment. Another setting in which the DPP test may prove useful is that of yaws eradication and monitoring programs, which usually occur in regions where standard laboratory methods are highly impractical.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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