Evaluation of the BioPlex 2200 syphilis total screen (IgG/IgM) with reflex to an automated rapid plasma reagin test

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Abstract
Background: We evaluated the recently FDA cleared BioPlex 2200 Syphilis Total Screen and automated rapid plasma reagin (RPR) assay for the detection of total (IgG/IgM) treponemal and non-treponemal antibodies in the reverse syphilis algorithm.

Methods: Prospectively submitted samples (n = 885) were assayed by both the IgG/IgM BioPlex Syphilis Screen and the original IgG BioPlex Syphilis Screen. The IgG screen reactive samples were reflexed to traditional RPR, and IgG/IgM screen reactive samples were reflexed to the automated RPR. Nonreactive RPR samples were tested by the Treponemal Pallidum Particle Agglutination test (TP-PA). Additional samples were collected (n = 404 total samples) to directly compare the automated and traditional RPR assays with each other.

Results: The sensitivity and specificity of the IgG/IgM screen with automated RPR was 95.6% (95% confidence interval [CI] 87.0-99.1) and 99.6% (CI 99.2-99.8) while the sensitivity and specificity of the BioPlex IgG screen with traditional RPR was 97.8% (CI 89.1-99.9) and 99.3% (CI 98.8-99.4). The sensitivity and specificity of the BioPlex RPR compared with traditional RPR was 95.8% (CI 93.9-97.0) and 94.1% (CI 89.4-91.1) and 95.3% (CI 92.6-97.1). The mean of the titer differences between the BioPlex RPR and the traditional RPR was 1.0 ± 0.9 SD titers.

Conclusion: The addition of the detection of treponemal IgM antibodies to the IgG/IgM screen did not significantly affect the sensitivity and specificity compared to the original IgG screen. However, the addition of the comparable BioPlex RPR assay to the instrumentation significantly reduces the overall labor of syphilis screening and confirmation.

Keywords: rapid plasma reagin, syphilis, TP-PA, Treponema pallidum

1 | INTRODUCTION

The laboratory diagnosis of syphilis depends on serologic methods, since Treponema pallidum, the causative agent of syphilis, cannot be cultured in vitro. The traditional algorithm in which sera are initially tested for the presence of non-treponemal antibody, such as the rapid plasma reagin (RPR), has been superseded in many laboratories by the reverse algorithm, in which a treponemal enzyme immunoassay (EIA) or chemiluminescent immunoassay (CLIA) is used as the initial screening assay. If the treponemal screening test is...
reactive, a non-treponemal test, such as the RPR, is performed and an endpoint titer is determined if the test is reactive. In the case of a nonreactive non-treponemal test, the Centers for Disease Control and Prevention (CDC) recommends that the sera be analyzed by the T. pallidum passive particle agglutination test (TP-PA). A reactive TP-PA usually indicates either a past, treated, or late/latent syphilis infection, while a nonreactive TP-PA would indicate a false-negative treponemal screen. However, since about 30% of patients with early syphilis will have a nonreactive non-treponemal test, some reactive TP-PA results may represent early syphilis, given that treponemal antibodies are detected a little before non-treponemal antibodies are detected.

The false-reactive rate of the treponemal EIA/CLIA screening assays varies based on the prevalence of syphilis in the population being tested, with low prevalence areas giving the highest false positivity rates. South Carolina is considered a moderately high prevalence area for syphilis infections. The rate of primary and secondary syphilis was 5.7 per 100,000 in 2013. The state ranks 11th in rates of syphilis among 50 states. A number of studies have demonstrated a high percentage of falsely reactive tests using EIA/CLIA methods in the reverse syphilis screening algorithm. Reverse algorithm screening often results in a higher false-reactivity rate than traditional testing does in areas with both a low and high prevalence of syphilis. In our previous study of the BioPlex IgG screen, the overall false-reactive rate was 1.0%. The BioPlex IgG screen false-reactivity rate was more consistent with rates seen in low prevalence populations.

Our institution has been using the BioPlex IgG screen for our syphilis screening assay based its automation, high throughput, and ease of use. However, other syphilis screening assays are available, such as the Lumipulse G TP-N chemiluminescent immunoassay, TrepSure EIA, and LIASON CIA, that detect both a treponemal IgM antibody in addition to an IgG antibody. Since the IgG BioPlex screening does not detect IgM treponemal, very early cases of syphilis may not be detected. Recently, BioPlex developed a Syphilis Total Screen which includes the simultaneous detection of total (IgG/IgM) treponemal antibodies and non-treponemal antibodies, or RPR, with reflex quantitation and titer for use with the BioPlex instrument. This study is an analysis of effect on accuracy with the addition of the detection of IgM treponemal antibodies in the IgG/IgM screen compared to the IgG screen along with an analysis of the automated RPR compared with the traditional RPR assay.

2. MATERIALS AND METHODS

2.1 Study samples

Between July 2, 2018 and July 31, 2018, a total of 885 serum samples were sent to the Medical University of South Carolina (MUSC) immunology laboratory for reverse algorithm syphilis testing. Procedures were followed in accordance with ethical standards established by MUSC in accordance with the Helsinki Declaration of 1975. The protocol used was approved by the MUSC Institutional Review Board (no. 44260) to meet the Health Information Portability and Accountability Act guidelines. Specimens were usually run within a few hours of receipt for the BioPlex IgG testing and then stored at 2-8°C for approximately 1-2 days prior to IgG/IgM screen testing, automated RPR, traditional RPR and TP-PA testing.

An additional 275 traditional RPR reactive samples were collected between May 16, 2016 and April 19, 2018 and tested by the automated RPR assay offered with the IgG/IgM screen to provide an adequate number of samples for the analysis of titer differences between the automated RPR assay and the traditional RPR assay.

Following patient sample testing, relevant clinical information including reason for testing, final clinical interpretation of results, and antibiotic treatment was obtained from the electronic medical record on patient samples that were discrepant between the two BioPlex screen methods, RPR methods, or discrepant with the TP-PA method.

2.2 Treponemal screening test

All samples were tested using both the BioPlex 2200 syphilis IgG and the BioPlex 2200 syphilis IgG/IgM screen and RPR multiplex flow immunoassay (MFI) Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer’s instructions. The syphilis IgG and IgG/IgM screen kits differ by the dyed beads coated with recombinant T. pallidum antigens. The BioPlex IgG screen uses three different sets of beads coated with 15, 17 and 47 kDa T. pallidum proteins for the detection of IgG treponemal antibodies. The BioPlex IgG/IgM screen and automated RPR uses beads coated with 17 kDa, 47 kDa for detection of total (IgG/IgM) treponemal antibodies and cardiolipin proteins for the automated RPR test. In this two-step assay design, the Bioplex 2200 system combines patient sample, bead reagent, and sample diluent in a reaction well. The sample is put through two incubation and wash cycles and finally read by a flow-cytometry based detector. The detector identifies the fluorescence of the dyed beads and quantifies the amount of antibody or antibody index (AI) in the sample. The results are classified as nonreactive (<0.9), equivocal (0.9-1.0), and reactive (>1.0).

2.3 Reflex to non-treponemal tests

All samples testing reactive by the IgG BioPlex and/or the IgG/IgM BioPlex screen were tested by both the automated RPR and the traditional RPR assay. The automated RPR assay was performed on the BioPlex 2200 system according to the manufacturer’s instructions. Qualitative RPR results were classified as nonreactive (<1.0 AI) and reactive (>1.0 AI). Samples that were BioPlex RPR reactive were titrated to endpoint using the onboard dilution procedure. The dilutions selected by the user were based on the antibody index of the neat sample. Available titers onboard were 1:4, 1:8, 1:16, 1:32, and 1:64. Manual dilutions were performed on samples <1:4 or >1:64. The final titer was reported as the highest titer dilution that produced an onboard reactive result.
The traditional RPR assay was performed with the 18 mm circular quantitative card test according to the manufacturer’s protocol (Cardinal Health, Dublin, OH). Any samples reactive by RPR were titrated to endpoint. Samples were reported as nonreactive, or with the highest titrer dilution that produced a reactive result.

2.4 | Treponemal confirmatory tests

All samples that were IgG or IgG/IgM BioPlex reactive, but RPR non-reactive or discrepant between the two RPR methodologies were further tested by Serodia TP-PA (Fujiribio Diagnostics, Inc., Seguin, TX), a gelatin particle agglutination assay. This assay was performed according to the manufacturers’ protocol. The results were read as nonreactive, borderline, or reactive.

2.5 | Statistical analysis

Comparisons of the IgG BioPlex screen algorithm with the IgG/IgM BioPlex screen algorithm and the tradition RPR with the BioPlex RPR were analyzed using a Yates’ corrected chi-square test to determine the overall agreement, clinical sensitivity, clinical specificity, and 95% confidence intervals for sensitivity and specificity. Other statistical calculations were performed using an Excel spreadsheet (Microsoft Corp., Redmond, WA).

3 | RESULTS

3.1 | Reverse algorithm screening results

Figure 1 outlines the reverse algorithm study design for the IgG/IgM BioPlex screen (Figure 1A) and the IgG BioPlex screen (Figure 1B). Among 885 patients tested, 46 (5.2%) of patients were reactive with the IgG/IgM BioPlex screen, while 50 (5.6%) were reactive with the IgG screen. Of the 46 patients with IgG/IgM BioPlex screen reactive results, the automated RPR was also reactive in 16 (34.8%) and nonreactive in 30 (65.2%) for an overall positivity rate for active syphilis of 1.8%. Of the 50 patients with IgG BioPlex screen reactive results, the traditional RPR was also reactive in 18 (36%) and nonreactive in 32 (64%) for an overall positivity rate for active syphilis of 2.0%.

Among the 30 IgG/IgM BioPlex screen reactive/automated RPR nonreactive sera, TP-PA was reactive in 27 (90.0%) and nonreactive in 3 (10%). For the 32 IgG reactive/traditional RPR nonreactive sera, TP-PA was reactive in 26 (81.3%) and nonreactive in 6 (18.7%). The overall false-reactive rate for the IgG/IgM BioPlex screen was 0.34%, while the false-reactive rate for the IgG screen was 0.67%.

When the IgG/IgM BioPlex screen (Table 1) and the IgG BioPlex screen (Table 2) reactivity was compared to TP-PA as the gold standard, the calculated sensitivity, specificity, and agreement of the IgG/IgM BioPlex screen was 95.6% (CI 87.0-99.1), 99.6% (CI 99.2-99.8), and 99.4% (CI 98.6-99.9) and the calculated sensitivity, specificity, and agreement of the IgG BioPlex screen was 97.8% (CI 89.1-99.9), 99.3% (CI 98.8-99.4), and 99.2% (CI 98.3-99.4). The overall false-nonreactive rate for the IgG/IgM BioPlex screen was 0.2%, while the false-nonreactive rate for the BioPlex IgG screen was 0.1%. There is overlap between the 95% confidence intervals for the calculated sensitivity, specificity, and agreement for both the IgG/IgM and the IgG screening assays indicating that there is no statistical difference for these parameters between the two assays.

3.2 | False nonreactive samples on IgG/IgM BioPlex screen or IgG BioPlex screen

Table 3 lists the test results and patient clinical information for results that were discrepant between the IgG/IgM BioPlex screen or IgG BioPlex screen with TP-PA and discrepant results between the automated BioPlex RPR with the traditional RPR. The two
false-nonreactive IgG/IgM BioPlex screen samples and the one false-nonreactive IgG BioPlex screen were from patients thought to have either had a past syphilis infection with unknown treatment status or had past known treated syphilis infection. The false-nonreactive samples were from patients either screened for pretransplant workup, dementia, or at risk for a sexually transmitted disease (STD).

3.3 | False-reactive samples on IgG/IgM BioPlex screen or IgG BioPlex screen

The false-reactive screens for the IgG/IgM BioPlex screen and IgG BioPlex screen were from patients who were either screened prenatally, screened for pretransplant workup, or were patients at risk for a STD.

There were five samples that were reactive only by the IgG screen and found nonreactive by TP-PA. Three samples were from patients undergoing prenatal screen, one patient had a rash on soles of feet and another was a high-risk patient undergoing an STD screen.

There were two samples that were reactive only by the Syphilis Total (IgG/IgM) screen. One patient was undergoing a pretransplant screen and another was undergoing routine STD screening.

3.4 | Samples discrepant on the traditional and automated RPR

There were 10 samples that were discrepant on the traditional and automated RPR (Lower half of Table 3). All except one sample were from patients who were treated in the past for syphilis. Four samples were nonreactive by traditional RPR, but reactive by the automated RPR, with 3 of the 4 samples having a titer of 1:1 and one having a titer at 1:4. All samples were positive with the TP-PA and both screening EIAs.

Six samples were reactive by traditional RPR, but nonreactive by automated RPR. Four of the six samples had a titer of 1:1, and two of the samples had a titer of 1:2 by the automated RPR.

3.5 | Analysis of the BioPlex automated RPR compared to traditional RPR

Titer differences between the BioPlex automated RPR compared to the traditional RPR were analyzed by testing additional serum samples that were reactive for the traditional RPR with the automated RPR for a total of 404 samples. When the titers for the traditional RPR reactive samples were compared to the titers for the automated RPR result, the correlation coefficient was 0.5294 (Figure 2). The mean of the titer difference between the BioPlex RPR and the traditional RPR was 1.0 ± 0.9 titers. The concordance rate at ±2 titer and = or ±1 titer dilutions between the BioPlex RPR and the traditional RPR was 93.8% and 71.1%, respectively. In instances where the BioPlex RPR had a titer result >1:64 (n = 39) and a manual titer was performed, the ±2 titer and = or ±1 titer concordance rate was 94.9% and 64.1%, respectively.

The Bioplex automated RPR screen was compared to the traditional RPR as the gold standard for 457 samples that were tested.

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**TABLE 2** Summary of results comparing the IgG screen with the results of the TP-PA

| Syphilis screening assay | TP-PA |
|-------------------------|-------|
|                         | Reactive | Nonreactive |
| IgG screen              |         |             |
| Reactive                | 44      | 6           |
| Nonreactive             | 1       | 834         |

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**FIGURE 2** A logarithmic plot of the inverse titer of the traditional rapid plasma reagin (RPR) value versus the inverse titer of the BioPlex automated titer for 275 samples reactive by the traditional RPR
### TABLE 3  Analysis of discrepant results on the reverse syphilis algorithm

| Category | TP-PA | IgG screen | IgM&IgG screen | Traditional RPR | Bio-Rad RP | Age | Gender | Reason for screen | Clinical impression |
|----------|-------|------------|----------------|-----------------|------------|-----|--------|-------------------|---------------------|
| Syphilis screen discrepant results |       |            |                |                 |            |     |        |                   |                     |
| False Nonreactive IgG screen | Reactive | 0.3 NEG | 1.2 POS | Not Done | Nonreactive | 68 | F | Declining mental status | Past infection. Declining mental status thought due to multiple lacunar infarcts |
| False Nonreactive IgM&IgG screen | Reactive | 1.0 POS | 0.2 NEG | Nonreactive | Nonreactive | 54 | M | STD screen HIV positive | Past treated syphilis infection in 2015 Past syphilis infection |
| False Positive IgG screen and IgM&IgG screen | NEG | 6.6 POS | 0.9 POS | Nonreactive | Nonreactive | 62 | M | Pre kidney transplant workup | False positive screen |
| False Positive IgG screen | NEG | 0.9 POS | 0.3 NEG | Nonreactive | Nonreactive | 25 | F | Prenatal screen | False positive screen |
| False Positive IgG screen | NEG | 1.4 POS | 0.5 NEG | Nonreactive | Nonreactive | 53 | M | Rash on soles of feet | False positive screen |
| False Positive IgG screen | NEG | 0.9 POS | <0.2 NEG | Nonreactive | Nonreactive | 44 | F | HIV positive Routine screen | False positive screen |
| False Positive IgG screen | NEG | 1.7 POS | <0.2 NEG | Nonreactive | Nonreactive | 25 | F | Prenatal screen | False positive screen |
| False Positive IgG screen | NEG | 1.7 POS | <0.2 NEG | Nonreactive | Nonreactive | 28 | F | Prenatal screen | False positive screen |
| False Positive IgM&IgG screen | NEG | <0.2 NEG | 1.9 POS | Nonreactive | Nonreactive | 27 | M | Routine STD screen | False positive screen |
| False Positive IgM&IgG screen | NEG | <0.2 NEG | 5.3 POS | Nonreactive | Nonreactive | 72 | F | Pre kidney transplant workup | False positive screen |
| RPR discrepant results |       |            |                |                 |            |     |        |                   |                     |
| RPR discrepant Traditional RPR Reactive | Reactive | 3.8 | 1.5 | Nonreactive | Reactive Titer 1:1 | 41 | M | HIV positive | Past treated infection 2009 |
| RPR discrepant Traditional RPR Nonreactive Bio-Rad RPR Reactive | Reactive | 2.3 | 3.3 | Nonreactive | Reactive Titer 1:1 | 63 | M | HIV positive | Past infection many years ago |
| RPR discrepant Traditional RPR Reactive; Bio-Rad RPR Nonreactive | Reactive | >8.0 | 8.0 | Nonreactive | Reactive Titer 1:1 | 26 | M | HIV positive | Past treated infection 2007 Past infection many years ago |
| RPR discrepant Traditional RPR Reactive | Reactive | >8.0 | >8.0 | Nonreactive | Reactive Titer 1:2 | 21 | F | Prenatal screen | Past treated infection 2017 |
| RPR discrepant Traditional RPR Reactive | Reactive | >8.0 | >8.0 | Reactive Titer 1:1 | Reactive Titer 1:2 | 57 | M | HIV positive | Past treated infection 2010 Past infection many years ago |
| RPR discrepant Traditional RPR Reactive; Bio-Rad RPR Nonreactive | Reactive | >8.0 | >8.0 | Nonreactive | Reactive Titer 1:1 | 37 | F | Pre kidney transplant workup | Recent treated infection 7/2018 |
| RPR discrepant Traditional RPR Reactive | Reactive | >8.0 | >8.0 | Reactive Titer 1:2 | Nonreactive | 30 | M | HIV positive | Past treated infection 2013 |
| RPR discrepant Traditional RPR Reactive; Bio-Rad RPR Nonreactive | Reactive | >8.0 | >8.0 | Reactive Titer 1:1 | Nonreactive | 41 | M | HIV positive | Past treated infection 2015 Past infection many years ago |
| RPR discrepant Traditional RPR Reactive | Reactive | >8.0 | >8.0 | Reactive Titer 1:1 | Nonreactive | 53 | M | HIV positive | Past treated infection 2017 |


by both assays, including all nonreactive RPR results (Table 4). The calculated sensitivity, specificity, and agreement of the BioPlex RPR compared with traditional RPR was 96.2% (CI 94.2-97.4), 94.1% (CI 89.4-97.0), and 95.5% (CI 92.8-97.3). Not included in the calculations were 53 samples from patients with a past diagnosis of syphilis considered serofast reactive with the traditional RPR, but were negative with the BioPlex automated RPR.

Of the eleven results that were traditional RPR reactive but BioPlex RPR nonreactive seven had a titer of 1:1, two with a titer of 1:2 and one each with a titer of 1:4 and 1:8. No record of previous syphilis testing was found in the medical record for these patients. Ten of the eleven patients were not suspected of having active syphilis, but were being screened for syphilis either because they were high risk for a sexually transmitted disease (STD) (ie, HIV infection or prior other STD), being screened for possible future organ transplantation or prenatal screening. One patient, however, was tested for syphilis infection because of a rash on the palms and soles that was suspicious for secondary syphilis infection. The traditional RPR titer in this patient was 1:1. Since traditional RPR was reported as positive in the medical record for the eleven patients being screened for syphilis, and there were no previous syphilis results, they were assumed by the physicians to have active syphilis.

Six of the seven traditional RPR negative but BioPlex reactive RPR results were from patients that were considered by the clinician to have a past infection. One of the seven specimens was considered a false positive BioPlex screen since the TP-PA was nonreactive. Four of the seven had documented past syphilis infection 2-3 years prior to their current testing, and the other two were assumed to have had past syphilis based on the nonreactive traditional RPR.

### DISCUSSION

With the introduction of automated treponemal tests, a new reverse syphilis algorithm is now used by many clinical laboratories. Our institution has been using the IgG BioPlex screen for our syphilis screening assay based on ease of use, high throughput, and automation. However, other syphilis screening assays, such as the LIASON T pallidum specific assay, however, detect both a treponemal IgM antibody in addition to an IgG antibody. Since the BioPlex IgG screening assay does not detect IgM treponemal antibodies, it is possible that it may not detect very early cases of syphilis. Recently, FDA has cleared the BioPlex 2200 IgG/IgM BioPlex screen and automated RPR assay for the detection of treponemal and non-treponemal antibodies in the reverse syphilis algorithm. In our current study, we found that the clinical performance of the BioPlex IgG/IgM screen was very similar to the original BioPlex IgG screen.

In our previous evaluation of the BioPlex IgG screen, 5.0% of the 10,060 patients tested were reactive on initial screen. Of those patients that were reactive on the initial BioPlex IgG screen, 29.9% were reactive by RPR and nonreactive in 70.1% for an overall positivity rate for active syphilis of 1.5%. In the present study, both the BioPlex IgG screen and the BioPlex Syphilis Total (IgG/IgM) screen demonstrated similar percentages to our previous evaluation of the BioPlex IgG screen, with 5.6% and 5.2% of 885 patients reactive on initial screen, with 36.0% and 34.8% reactive by RPR and nonreactive in 64% and 65.2% with an overall positivity rate for active syphilis of 2.0% and 1.8%, respectively. The calculated sensitivity, specificity, and agreement of the BioPlex IgG screen and the BioPlex IgG/IgM screen all had overlapping 95% confidence intervals, indicating that there was no statistical difference in performance between the old and the new BioPlex syphilis screen. One might expect increased sensitivity of the BioPlex IgG/IgM screen for syphilis infection due to the addition of the IgM treponemal antibody detection. It is possible, however, that the sample size of 885 patients with a fairly low positivity rate of 5.2%-5.6% for active syphilis and 2.9%-3.1% for past syphilis (RPR nonreactive, treponemal reactive) is not large enough to be able to detect a statistical difference in sensitivity between the two assays.

As observed in our previous study, nearly all of the specimens with falsely reactive BioPlex syphilis screening results had very low AIs (range 0.9-1.7 AI), for both the IgG screen and the IgG/IgM screen. Many of the falsely reactive BioPlex results were from patients being screened for syphilis because of HIV infection, pretransplant workup or for prenatal screening for pregnancy. Pregnancy has been well recognized as a cause of false-reactive non-treponemal tests.1

The BioPlex automated RPR showed comparable results to the traditional RPR. And although manual dilutions were needed for specimens with a BioPlex RPR titer <1:4 and >1:64, the methods still compared well.

These findings are very similar to the results of the study by Tesfazghi et al which compared the BioPlex RPR to the Wampole Impact RPR card test and found 78% concordance within ±1 dilution and 94% concordance within ±2 dilutions.

At the time of their study, a prior offline dilution step was not supported on the BioPlex 2200. Our study was able to assess the BioPlex offline dilution step for RPR titers >1:64 and still found a good correlation between the traditional RPR method and the BioPlex RPR for titers >1:64 and for the 1:2 titers. The need for a manual offline dilution step for RPR titers >1:64 and titers of 1:2 should be pointed out as a limitation to the automated BioPlex RPR assay, as the assay is not actually 100% automated for high titer RPR results.
This study confirms that the clinical performance of the BioPlex IgG/IgM screen and automated RPR assay compares well with the original BioPlex IgG screen and the traditional RPR methods. Although increased sensitivity for the detection of syphilis infection was not observed with the BioPlex IgG/IgM screen this may be due to sampling error and low incidence of detection of very early syphilis infections. Overall, the high sensitivity and specificity of this assay and the automation of the RPR should be an ideal diagnostic test for high-volume testing laboratories.

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