MAJOR ARTICLE

Analysis of 3 Algorithms for Syphilis Serodiagnosis and Implications for Clinical Management

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Background. Algorithms for the diagnosis of syphilis continue to be a source of great controversy, and numerous test interpretations have perplexed many clinicians.

Methods. We conducted a cross-sectional study of 24 124 subjects to analyze 3 syphilis testing algorithms: traditional algorithm, reverse algorithm, and the European Centre for Disease Prevention and Control (ECDC) algorithm. Every serum sample was simultaneously evaluated using the rapid plasma reagin, *Treponema pallidum* particle agglutination, and chemiluminescence immunoassay tests. With the results of clinical diagnoses of syphilis as a gold standard, we evaluated the diagnostic accuracy of the 3 syphilis testing algorithms. The κ coefficient was used to compare the concordance between the reverse algorithm and the ECDC algorithm.

Results. Overall, 2749 patients in our cohort were diagnosed with syphilis. The traditional algorithm had the highest negative likelihood ratio (0.24), a missed diagnosis rate of 24.2%, and only 75.81% sensitivity. However, both the reverse and ECDC algorithms had higher diagnostic efficacy than the traditional algorithm. Their sensitivity, specificity, and accuracy were 99.38%–99.85%, 99.98%–100.00%, and 99.93%–99.96%, respectively. Moreover, the overall percentage of agreement and κ value between the reverse and the ECDC algorithms were 99.9% and 0.996, respectively.

Conclusions. Our research supported use of the ECDC algorithm, in which syphilis screening begins with a treponemal immunoassay that is followed by a second, different treponemal assay as a confirmatory test in high-prevalence populations. In addition, our results indicated that nontreponemal assay is unnecessary for syphilis diagnosis but can be recommended for determining serological activity and the effect of syphilis treatment.

Keywords. syphilis; serodiagnosis; treponemal antibody test; nontreponemal antibody test.

Syphilis remains a public health concern worldwide [1–3]. The accuracy of diagnostic tests is critical for the successful control of epidemic syphilis outbreaks, including case findings, prompt therapy delivery to infected individuals, and partner management [4]. *Treponema pallidum*, the bacterium that causes syphilis, can only be cultured in vivo and cannot be examined with simple laboratory stains. New molecular tests for syphilis are unlikely to replace serology in the short term because they are fairly expensive and require sophisticated techniques, such as polymerase chain reaction (PCR) or DNA sequencing technology [4]. As a result, serologic testing is still regarded as the mainstay for diagnosing syphilis and for monitoring the efficacy of subsequent antibiotic treatment [4]. Currently, there are 2 common approaches to the diagnosis of syphilis using serological tests: the traditional algorithm and the reverse algorithm [5]. The US Centers for Disease Control and

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Prevention (CDC) recommends the traditional algorithm. In this algorithm, syphilis serologic screening begins with a nontreponemal test, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test. This screening is followed by confirmation using one of several treponemal tests [6, 7]. However, the Association of Public Health Laboratories [8], the United Kingdom Health Protection Agency [9], and the International Union Against Sexually Transmitted Infections [10] all encourage the use of a reverse algorithm that begins with a treponemal assay. In the reverse algorithm, a reactive treponemal screening assay is followed by a quantitative nontreponemal assay. In fact, there are 2 implementation schemes for the reverse algorithm. The more widely accepted procedure involves a reactive treponemal screening assay, followed by a quantitative nontreponemal assay [1, 6, 8, 11, 12]. When the treponemal screening assay is reactive but there is a negative nontreponemal assay result, a second and different treponemal assay is performed to resolve the discordant results [6]. Another method is recommended by the European Centre for Disease Prevention and Control (ECDC): A reactive treponemal screening assay (primary screening test) is followed by a second, different treponemal assay that is used as a confirmatory test; this procedure is not followed by a quantitative nontreponemal assay [10]. In this article, these 2 schemes are designated the "reverse algorithm" and the "ECDC algorithm," respectively, for ease of identification. The basic difference between these 2 reverse algorithms is whether a quantitative nontreponemal assay is performed following the reactive treponemal assay in the syphilis serodiagnostic procedure, which is an important clinical issue.

To the best of our knowledge, there have been few studies and scarce clinical data involving a detailed analysis of the different algorithms for detecting syphilis. Similarly, no peer-reviewed publications have evaluated the quantitative nontreponemal assay in the reverse algorithm for syphilis diagnosis. Therefore, this study was primarily aimed at illustrating the key differences among the 3 different syphilis diagnostic methods: the traditional, reverse, and ECDC algorithms (Figure 1). Moreover, we examined whether the quantitative nontreponemal assay (eg, the RPR/VDRL test) is necessary for syphilis diagnosis.

METHODS

Study Population and Ethics Statement

We conducted a cross-sectional analysis of patients with results of syphilis serological testing performed at Zhongshan Hospital, Medical College of Xiamen University, China, between December 2011 and May 2013. During this period, the syphilis serologic testing for each sample (from 24 124 subjects) was performed using RPR (InTec, Xiamen, China), *Treponema pallidum* particle agglutination (TPPA) (Fujirebio, Tokyo, Japan), and a new, automated chemiluminescence immunoassay (CIA) (Boson Biotechnology, Xiamen, China) according to the manufacturer's instructions, after duplicate tests were excluded. All the serological testing was performed on the same specimen, and the results of all 3 tests were reported simultaneously.

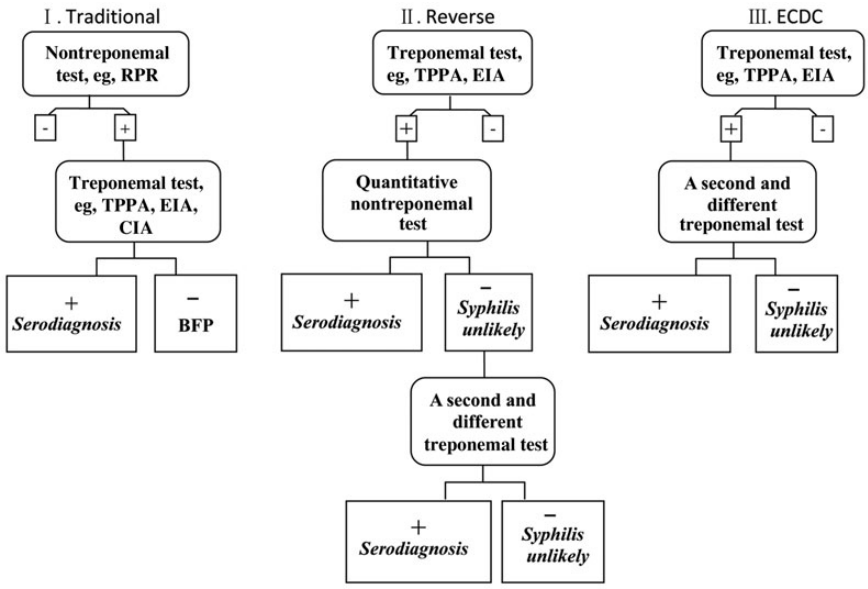

Figure 1. Syphilis testing algorithms. Abbreviations: BFP, biological false positive; CIA, chemiluminescence immunoassay; ECDC, European Centre for Disease Prevention and Control; EIA, enzyme immunoassay; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

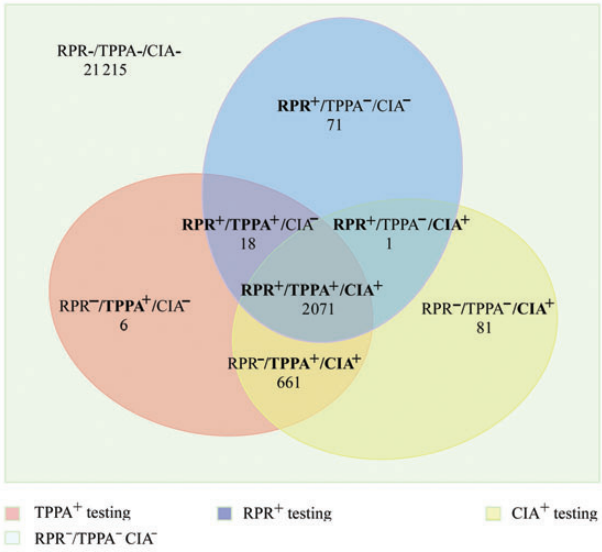

Figure 2. Serologic results. Boldface font represents positive results. Abbreviations: CIA, chemiluminescence immunoassay; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

The subjects of this study included outpatients, inpatients, and populations undergoing routine health examinations. These subjects underwent syphilis testing for screening (if asymptomatic), for diagnosis (if symptomatic), or to monitor their response to syphilis treatment. This study was approved by the Institutional Ethics Committee of Zhongshan Hospital, Medical College of Xiamen University, and it was in compliance with national legislation and the Declaration of Helsinki guidelines.

Clinical Diagnosis of Syphilis

Based on the US CDC [7] and ECDC [10] guidelines, syphilis was clinically diagnosed by combining serodiagnosis and personal history (including clinical characteristics and/or the patient's sexual history). Primary syphilis is characterized by an ulcer (chancre), usually with regional lymphadenopathy, and laboratory confirmation involves dark-field examination/the fluorescent antibody method/PCR to detect *T. pallidum* in lesion exudate and/or a reactive serological test to confirm the diagnosis of syphilis. Secondary syphilis is generally characterized by a skin rash, mucocutaneous lesions, and lymphadenopathy, and a reactive serological test is used in the laboratory to confirm the diagnosis of syphilis. Latent syphilis is asymptomatic, with a possible history of infection supported by a reactive serological test and normal cerebrospinal fluid. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are either late latent syphilis or latent syphilis of unknown duration. Tertiary syphilis is defined as syphilis acquired >1 year previously; clinical manifestations (ie, cardiac or gummatous lesions); and a history of primary, secondary, or latent syphilis, in addition to laboratory test confirmation by a reactive serological test.

Data Analysis

The statistical analysis was performed using SPSS software, version 17 for Windows. The Yerushalmi model was used to evaluate the accuracy of 3 syphilis testing algorithms by contrasting with the gold standard (eg, clinical diagnostics, surgical result, histologic examination, image diagnostics) [13–15]. The percentage of agreement and κ coefficient were calculated to

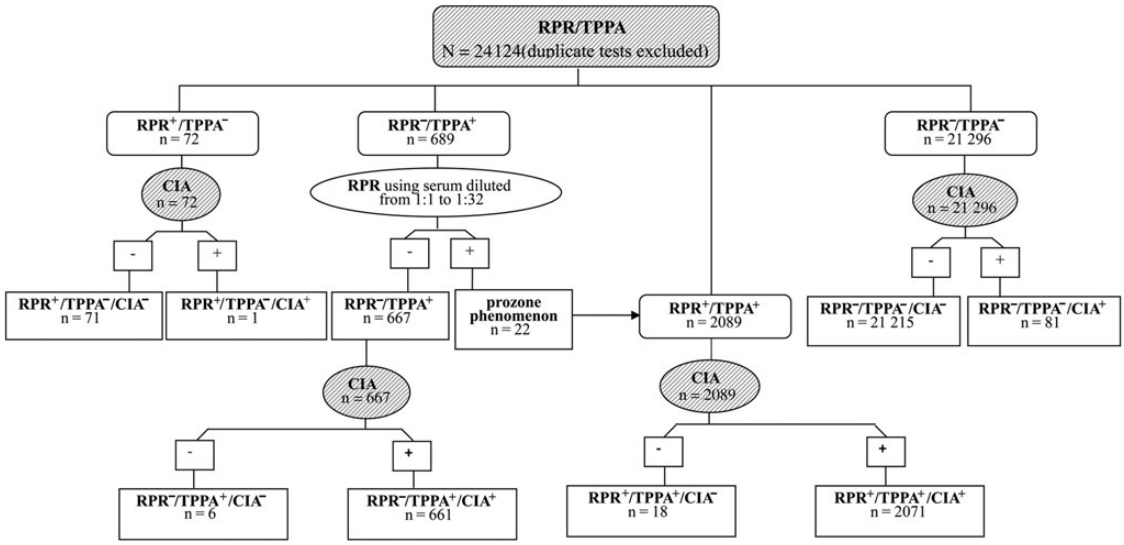

Figure 3. Serologic results and clinical management. Abbreviations: CIA, chemiluminescence immunoassay; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

determine the agreement between the reverse algorithm and the ECDC algorithm. The agreement of the results according to their κ values was categorized as near perfect (0.81–1.0), substantial (0.61–0.8), moderate (0.41–0.6), fair (0.21–0.4), slight (0–0.2), or poor (<0) [16].

RESULTS

Clinical Diagnosis and Management of Syphilis Patients

We performed the RPR, TPPA, and CIA tests on samples from 24 124 subjects between December 2011 and May 2013. The test results are illustrated in Figures 2 and 3. Overall, 2071 subjects had $RPR^+/TPPA^+/CIA^+$ results, and 21 215 subjects had $RPR^-/TPPA^-/CIA^-$ results; 72 subjects were $RPR^+/TPPA^-$. Among these 72 subjects, only 1 was CIA^+, which was discordant with the TPPA test result; all the other 71 subjects were CIA^-, consistent with their TPPA results. These 71 $RPR^+/TPPA^-/CIA^-$ cases were confirmed to have biological false-positive reaction. During our detection process, we found that 689 subjects were $RPR^-/TPPA^+$. The RPR tests of this subgroup were repeated with serum samples diluted from 1:1 to 1:32, and we found that 22 subjects were $RPR^+/TPPA^+/CIA^+$, indicating the presence of the prozone phenomenon. From this subgroup, another 661 subjects were found to be $RPR^-/TPPA^+/CIA^+$, and 6 subjects were $RPR^-/TPPA^+/CIA^-$ (Figure 3). Moreover, as shown in Figure 3, among the 2089 $RPR^+/TPPA^+$ and 21 296 $RPR^-/TPPA^-$ subjects, only 18 had a CIA^- test and 81 had a CIA^+ test, respectively. These data listed above indicated that there had a high degree of consistency between the CIA test and the TPPA test.

In this study, the clinical diagnosis of syphilis was determined by combining serodiagnosis and disease history (including clinical characteristics and/or the patient's sexual history). Ultimately, 2749 patients were diagnosed with syphilis by clinicians. The prevalence of syphilis was thus found to be 11.40% (2749 of 24 124 patients). The clinical information for all 2749 patients with syphilis is listed in Table 1. Asymptomatic and latent syphilis (including subjects with syphilis of unknown duration) were present in 52.0% and 64.6% of the patients, respectively. Primary and secondary syphilis with symptoms were rare, being present in only 0.9% and 13.3% of the 2749 patients, respectively.

Table 1. Clinical Data From 2749 Syphilis Patients

Characteristic	No. (n = 2749)
Sex	
Male	1483 (53.9%)
Female	1266 (46.1%)
Mean age (years): overall, 45.4 (range, 1–90)	
Male	48.5 (range, 2–89)
Female	41.6 (range, 1–90)
Pregnancy status (n = 1266)	
Pregnant	102 (8.1%)
Not pregnant	1164 (91.9%)
Race/ethnicity	
Asian/Han	2746 (99.9%)
Other	3 (0.1%)
Prior history of syphilis	
Yes	1128 (41.0%)
No	1621 (59.0%)
HIV status	
Positive	5 (0.2%)
Negative	1471 (53.5%)
Unknown	1273 (46.3%)
Reason for testing	
Screening (asymptomatic)	1429 (52.0%)
Prenatal/hospitalized	1115 (78.0%)
Patient request	108 (7.6%)
Health examination	149 (10.4%)
Other STD diagnosis	57 (4.0%)
Diagnostic (symptomatic)	192 (7.0%)
Genital ulcer	18 (9.4%)
Rash	103 (53.6%)
Contact with syphilis case	25 (13.0%)
Neurologic symptoms	46 (24.0%)
Monitoring of response to treatment	1128 (41.0%)
Clinical phase	
Primary	24 (0.9%)
Secondary	365 (13.3%)
Tertiary	584 (21.2%)
Early latent	198 (7.2%)
Late latent[a]	1578 (57.4%)
Treatment status	
Untreated	1487 (54.1%)
Treated	1262 (45.9%)

Abbreviations: HIV, human immunodeficiency virus; STD, sexually transmitted disease.

[a] Includes subjects with syphilis of unknown duration.

Evaluation of the Diagnostic Accuracy of the 3 Syphilis Testing Algorithms Compared With Clinical Diagnosis

In this study, with the clinical diagnosis of syphilis as a gold standard, the Yerushalmi model was used to evaluate the accuracy of 3 syphilis testing algorithms. The results indicated that with the traditional syphilis testing algorithm, 2089 of the 24 124 subjects would be diagnosed with syphilis, whereas 665 $RPR^-/TPPA^+$ patients would not be diagnosed (Figure 4). The missed diagnosis rate was 24.2% (665 of 2749 subjects). Furthermore, the sensitivity of the traditional testing algorithm was only 75.81% (95% confidence interval [CI], 74.16%–77.40%), and it had the highest negative likelihood ratio of 0.24 (>0.1) (Table 2). In addition, we further analyzed the 665 cases of missed diagnoses. We found that there were 52 cases of

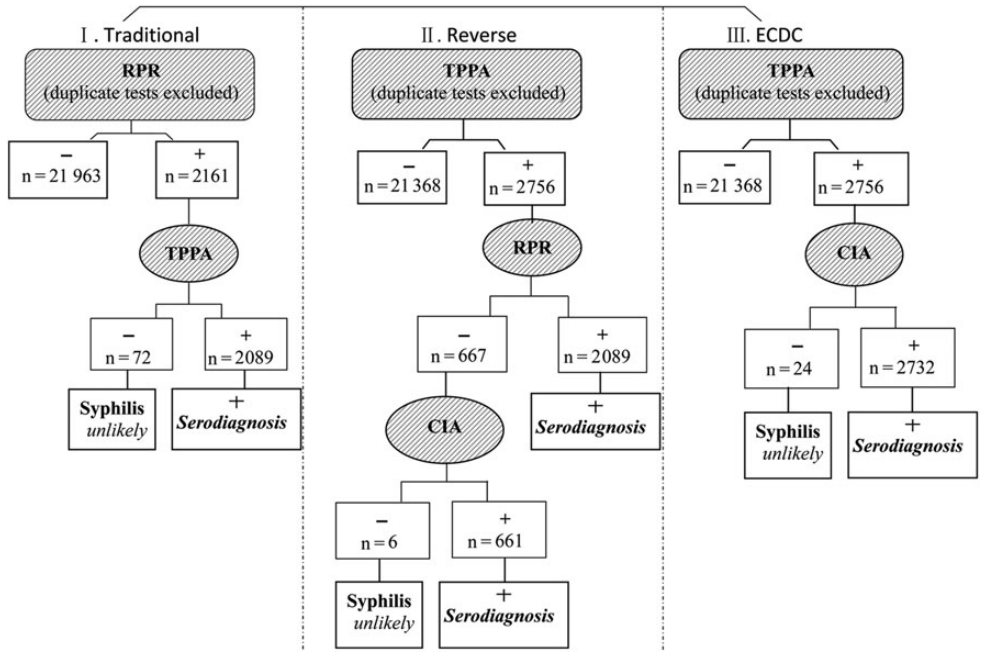

Figure 4. Different testing algorithms for syphilis diagnosis. Abbreviations: CIA, chemiluminescence immunoassay; ECDC, European Centre for Disease Prevention and Control; RPR, rapid plasma reagin; TPPA, *Treponema pallidum* particle agglutination.

early syphilis (including primary, secondary, and early latent syphilis). Moreover, among these 665 cases, 390 patients were being diagnosed with syphilis for the first time, and many patients had received inappropriate treatment (such as the wrong antibiotics or other agents that would not treat syphilis, as well as insufficient course of therapy) by seeking treatment from unlicensed providers and clinics (Table 3).

In comparison, using the reverse algorithm and the ECDC algorithm, 2750 and 2732 subjects, respectively, had a positive serodiagnosis (Figure 4). The sensitivity levels of the reverse and ECDC algorithms were 99.85% (95% CI, 99.63%–99.96%) and 99.38% (95% CI, 99.01%–99.64%), respectively. In addition, the algorithms' specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, and accuracy were 99.98%–100%, 99.82%–100%, 99.92%–99.98%, 4268.78–∞, 0.001–0.006, and 99.93%–99.96%, respectively (Table 2). Both the reverse and ECDC testing algorithms exhibited strong discriminatory power in the serodiagnosis of syphilis.

Comparison of the 3 Serodiagnosis Algorithms at Different Stages of Syphilis

The 2749 cases of syphilis were further classified into different stages of syphilis to evaluate the 3 serological algorithms at the different stages (Table 4). We found that the traditional syphilis testing algorithm had low sensitivity not only for tertiary syphilis (67.81%) but also for primary syphilis (75%). In comparison, the reverse algorithm and the ECDC algorithm both had high sensitivity in the serodiagnosis of different stages of syphilis.

Direct Comparison of the Concordance Between the Reverse and ECDC Syphilis Testing Algorithm

Both the reverse algorithm and the ECDC algorithm had high accuracy in the serodiagnosis of syphilis. However, the ECDC algorithm is slightly different from the reverse algorithm in that the latter involves a nontreponemal assay for diagnosis. Therefore, we directly compared these 2 syphilis testing algorithms using κ coefficient analysis. The result indicated a high degree of consistency between the reverse and the ECDC algorithms, and the overall percentage of agreement and κ value were 99.9% and 0.996, respectively (Table 5).

DISCUSSION

The accurate diagnosis of syphilis continues to elude and perplex many clinicians due to a multitude of test interpretations [17]. In the absence of a reliable gold standard, the diagnosis of syphilis requires evidence of epidemiologic exposure and characteristic symptoms and signs, along with laboratory tests, of which serologic tests are the mainstay. Serologic tests are

Table 2. Comparison of 3 Syphilis Serodiagnosis Algorithms and Clinical Diagnosis[a]

Assay and Result	Clinical Diagnosis (Gold Standard)		Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Accuracy, % (95% CI)
	Positive	Negative							
Traditional testing algorithm									
Positive	2084	5	75.81 (74.16–77.40)	99.98 (99.95–99.99)	99.76 (99.44–99.92)	96.98 (96.75–97.20)	3240.85 (1348.71–7787.55)	0.24 (0.23–0.26)	97.22 (97.01–97.43)
Negative	665	21 370							
Reverse testing algorithm									
Positive	2745	5	99.85 (99.63–99.96)	99.98 (99.95–99.99)	99.82 (99.58–99.94)	99.98 (99.95–99.99)	4268.78 (1776.94–10 255.00)	0.00 (0.00–0.00)	99.96 (99.93–99.98)
Negative	4	21 370							
ECDC testing algorithm									
Positive	2732	0	99.38 (99.01–99.64)	100.00 (99.98–100.00)	100.00 (99.87–100.00)	99.92 (99.87–99.95)	∞ (~)	0.01 (0.00–0.01)	99.93 (99.89–99.96)
Negative	17	21 375							

Abbreviations: CI, confidence interval; ECDC, European Centre for Disease Prevention and Control; NPV, negative predictive value; PPV, positive predictive value.

[a] A total of 24 124 subjects were analyzed.

divided into 2 categories, treponemal and nontreponemal antibody tests. Syphilis-specific immunoglobulin M and immunoglobulin G antibody are generated 2 and 4 weeks after infection, respectively [18], appearing earlier than nontreponemal antibodies. The former type of antibody may persist and does not disappear, even if the patient receives adequate treatment [19, 20]. Moreover, reaginic antibody may be negative in cases of late, latent, or posttreatment syphilis (due to seroreversion) [21]. In the current study, we performed both nontreponemal and treponemal antibody tests for all 24 214 patients. The result indicated that except for biological false-positive reactions, if the RPR test was positive, the TPPA test would certainly be positive; however, the converse was not necessarily true. In other words, if the RPR test was negative, the TPPA test might be positive. In this research, 667 RPR^- subjects had positive TPPA results, and 665 of these patients were diagnosed with syphilis. Moreover, during the detection process, 689 subjects were found to have $RPR^-/TPPA^+$ results. In these cases, the RPR test was repeated with samples diluted 1:1 to 1:32. Last, we identified 22 subjects who displayed the prozone phenomenon. In this research, we also found 71 $RPR^{+/-}/TPPA^-/CIA^-$ cases that were confirmed to be biological false-positive reactions. In summary, our findings once again demonstrate that the treponemal antibody test is more sensitive and more specific for diagnosing syphilis than nontreponemal antibody tests [3, 8], which is consistent with the results of our previous study [3].

The traditional algorithm for the serodiagnosis of syphilis begins with a nontreponemal assay, represented by either the VDRL test or (more commonly) the RPR test. This recommendation is based both on years of experience with the traditional testing algorithm and on a number of studies suggesting that the results of RPR screening may correlate more highly with disease activity than do the results of the reverse testing algorithm [6, 22, 23]. Despite having a proven track record and being suitable for most low-volume clinical laboratories [6], the traditional approach suffers from lower sensitivity and specificity [8]. In the current study, the traditional syphilis testing algorithm led to 2089 patients being diagnosed with syphilis. However, 665 $RPR^-/TPPA^+$ patients were excluded from positive serodiagnosis due to a missed diagnosis rate of 24.2% (665 of 2749 subjects). Of course, the clinical significance of the $RPR^-/TPPA^{+/-}$ cases is still debatable. However, the ECDC has mentioned that a negative RPR/VDRL test does not exclude active infection, although active treponemal disease with a negative RPR/VDRL test is unusual, especially in early syphilis compared with late syphilis [10]. In addition, our data indicated that among the 665 cases of missed diagnoses, there were 52 cases of early syphilis. Moreover, 390 patients were being diagnosed with syphilis for the first time. Thus, attention should be given to missed diagnoses caused by the traditional syphilis testing algorithm.

Table 3. Characteristics of 665 Cases of Missed Diagnoses

Treatment History	Primary (Cases)	Secondary (Cases)	Early Latent (Cases)	Late Latent (Cases)	Tertiary (Cases)
Untreated	6	2	25	236	121
Treated					
Recommended	0	1	6	103	31
Inappropriate treatment[a]	0	0	12	86	36
Total	6	3	43	425	188

[a]Includes subjects with syphilis for whom it was unknown whether the recommended therapy was received.

In addition, using the clinical diagnostic results as the gold standard, the sensitivity of the traditional testing algorithm was only 75.81%. The negative likelihood ratio was 0.24 (>0.1), indicating a high probability of false-negative results. However, both the reverse and the ECDC testing algorithms exhibited strong discriminatory power for the serodiagnosis of syphilis. Most surveillance reports have focused on primary and secondary syphilis cases, which are the best indicator of incident disease and are also more likely to receive timely treatment. Thus, we further analyzed serodiagnosis by the 3 serological algorithms at different stages of syphilis, and especially in early syphilis. We found that the reverse and ECDC syphilis testing algorithms still had high diagnostic significance in early syphilis, as well as the late syphilis. In summary, our results, obtained from a large cohort, support the application of reverse-sequence screening beginning with a treponemal assay for syphilis serology screening in a high-prevalence population (with a syphilis rate of 11.40%).

Many researchers have compared the traditional algorithm and the reverse algorithm before. In a direct comparison of the reverse and traditional algorithms, Binnicker et al reported a higher false-positive rate when using reverse screening [24]. Park et al [5] found that 28% of discordant (CIA reactive, RPR nonreactive) serum samples were negative by the TPPA test, suggesting a false-positive CIA result. Nevertheless, our results using the reverse approach differed dramatically from those described above. In the present study, we found that among the 24 124 samples tested, 2756 were TPPA positive, and 667 of 2756 (24.2%) were subsequently found to be RPR negative. Furthermore, we demonstrated that only 6 of 667 (0.9%) were negative by CIA. Among the 2089 TPPA-reactive, RPR-reactive serum samples, 18 cases were negative by CIA. Together, these results indicate that TPPA and CIA had high consistency. Similarly, Binnicker et al also demonstrated that the overall percentage of agreement and corresponding κ of 7 treponema-specific assays were 95.7%–99.0% and 0.90–0.99, respectively [11].

Table 4. Comparison of the 3 Serodiagnosis Algorithms at Different Stages of Syphilis

Diagnosis	No. of Serum Samples Tested	No. (%) of Serodiagnosis Positive by: Traditional Testing Algorithm	Reverse Testing Algorithm	ECDC Testing Algorithm
Primary	24	18 (75.00)	23 (95.83)	24 (100)
Secondary	365	362 (99.18)	365 (100)	364 (99.73)
Early latent	198	155 (78.28)	198 (100)	195 (98.48)
Late latent	1578	1153 (73.07)	1576 (99.87)	1569 (99.43)
Tertiary	584	396 (67.81)	583 (99.83)	580 (99.31)
Total	2749	2084 (75.8)	2745 (99.85)	2732 (99.38)

Abbreviation: ECDC,European Centre for Disease Prevention and Control.

Table 5. Direct Examination of the Concordance Between the Reverse and the ECDC Syphilis Serodiagnosis Algorithms

Reverse Algorithm	ECDC Algorithm Positive	ECDC Algorithm Negative	Total	Agreement, %	κ Value
Positive	2732	18	2750	99.9	0.996
Negative	0	21 374	21 374		
Total	2732	21 392	24 124		

Abbreviation: ECDC,European Centre for Disease Prevention and Control.

Consistent with recommendations [9, 10], most laboratories currently implement the reverse algorithm for the serodiagnosis of syphilis, but few researchers have mentioned the ECDC syphilis testing algorithm. In fact, the main difference between the algorithms is that the reverse algorithm involves a nontreponemal assay (such as the common RPR test) for syphilis diagnosis. Considering not only that the ECDC algorithm has high sensitivity/specificity and high consistency (in contrast with the reverse algorithm), but also that the RPR test has a long testing window and low sensitivity for latent and late syphilis and is cost effective, we recommend the ECDC algorithm. In our opinion, during the syphilis serodiagnosis procedure, it is unnecessary to use a quantitative nontreponemal assay as a syphilis diagnostic index; rather, this test can be used to detect the serological activity of syphilis and to monitor the serological response.

The limitations of our study include the potential misclassification of patients because of inadequate documentation in the medical record. Some patients used false information (including name and age) to protect their privacy, which made it more difficult to determine their syphilis infection and treatment history. In addition, an important consideration with the new test

algorithm is its positive predictive value and negative predictive value, which depend on the disease's prevalence in the population tested [25]. Our patients were all recruited from Zhongshan Hospital, Xiamen University, which is an area with a high prevalence of syphilis (11.40%); we did not collect data from lower-prevalence areas. Thus, our current study only reflects the characteristics of a high-syphilis-prevalence area. In the future, we will perform similar studies in other hospitals and in low-syphilis-prevalence areas.

Based on our research, we support syphilis screening beginning with a treponemal immunoassay that is followed by a second, different treponemal assay as a confirmatory test in high-prevalence populations [10]. In addition, our results indicate that quantitative nontreponemal assays (eg, the RPR/VDRL test) are unnecessary for syphilis diagnosis, but these tests are recommended for determining the serological activity of syphilis and for monitoring the serological response to treatment. However, each method has limitations, including the potential for false-positive and false-negative results [11]. We believe that to improve the quality of syphilis serology in most areas of the world, a network of independent, specialized laboratories should conduct test evaluations, quality promotion, and interassay standardization of commercially available test kits on a more regular basis. The ongoing participation of laboratories in proficiency testing and the further standardization of tests are strongly recommended to achieve better-quality syphilis serology [4].

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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