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Systematic Review

The Systematic Review of False-Positive Non-Treponemal Tests: Clinical Implications and Management

Article History:

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Abstract: ***Background:*** False-positive non-treponemal tests (RPR, VDRL) pose diagnostic challenges, leading to overtreatment, anxiety, and unnecessary healthcare utilization. Understanding their rates, causes, and management is critical. ***Methods:*** This systematic review synthesized 80 studies (RCT, etc) to 2026 across 20+ countries. We extracted data on false-positive rates, associated factors (autoimmunity, HIV, vaccination), clinical implications, testing algorithms, and management strategies. ***Results:*** False-positive rates varied dramatically: general population ≤1.5%, HIV-infected persons 13.5% (aOR for cART-associated reduction 0.31–0.42), pregnant women up to 28%, and CSF-VDRL 28.3%. Novel causes included mRNA COVID-19 vaccination (up to 18.4% false reactivity on BioPlex RPR, persisting ≥9 months) and autoimmune diseases (anti-dsDNA, ANA, anti-SSA). Low titers (≤1:4) characterized 96.7% of false-positives. Clinical consequences included unnecessary penicillin treatment (15% of low-risk neonates), provider misinterpretation (11.1% of positive results, predominantly family medicine, p=0.003), and inflated surveillance (PPV for ICD-coded syphilis only 0.42). The reverse algorithm produced more discordant results (false-positive rates 46.5–88.2% for treponemal immunoassays) but automated triage removed 64.9% of reactive records (specificity 27.5%→72.9%). ***Discussion:*** False-positive non-treponemal tests are population-, platform-, and context-dependent. HIV-associated BFP is reduced by cART, suggesting B-cell modulation. COVID-19 mRNA vaccines induce transient anticardiolipin-like reactivity, likely via lipid nanoparticles. Low titers reliably discriminate BFP from active infection. Management requires confirmatory treponemal testing, detailed history (vaccination, autoimmunity, HIV), and algorithm-based triage. ***Conclusion:*** False-positive non-treponemal tests are common in specific populations and increasingly linked to vaccination. Confirmatory algorithms, provider education (especially family medicine), and automated surveillance tools are essential to reduce harm. Future research should validate platform-specific false-positive rates and develop real-time decision support.

Keywords: False-positive syphilis tests, non-treponemal tests, RPR, VDRL, biological false positive, COVID-19 vaccination, HIV, autoimmune diseases, reverse algorithm, overtreatment

INTRODUCTION

Syphilis remains a global public health challenge, with resurgent rates in high-income and low-income settings alike (1). Serologic diagnosis relies on a two-step process: non-treponemal tests (rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) detect antibodies against cardiolipin-lecithin-cholesterol antigens, while treponemal tests (e.g., FTA-ABS, TP-PA) confirm specific treponemal antibodies (1,17,61). However, non-treponemal tests are not specific for *Treponema pallidum*; they can be biologically false-positive (BFP) in numerous conditions (4,66,71).

Background: BFP reactions occur in autoimmune diseases (systemic lupus erythematosus, antiphospholipid syndrome), chronic infections (HIV, hepatitis C, malaria), pregnancy, and increasingly after vaccination (1,4,7,8). The reported false-positive rate ranges from <1% in low-risk populations to >28%

in selected cohorts (3,34). Despite decades of recognition, no systematic synthesis has focused specifically on the *clinical implications and management* of these false-positive results, including overtreatment, psychological harm, and healthcare system burden.

Problem statement: Clinicians face three critical dilemmas: (1) what is the true burden of false-positive non-treponemal tests across different populations and testing platforms? (2) what clinical harms (unnecessary treatment, delayed diagnosis, anxiety) are documented? and (3) what management strategies effectively reduce these harms?

Research gap: Prior systematic reviews have examined test accuracy (25,28,37) or laboratory performance (1,17) but have not comprehensively extracted clinical outcomes, provider errors, or health system costs associated with false-positive results. Furthermore, emerging causes (COVID-19 vaccination, modern automated platforms) have not been integrated into management guidance.

Novelty: This review is the first to: (a) quantify false-positive rates across 80 studies with detailed clinical correlation; (b) document overtreatment rates, surveillance inaccuracies, and provider misinterpretation; (c) synthesize evidence on vaccine-induced false positivity; and (d) propose a tiered management algorithm based on titer magnitude and clinical context.

Objectives: (1) To determine the range and determinants of false-positive non-treponemal test rates; (2) to describe clinical implications including unnecessary treatment, healthcare utilization, and psychological impact; (3) to evaluate management strategies (confirmatory algorithms, provider education, point-of-care tests, automated triage); and (4) to identify research gaps.

Hypothesis: False-positive non-treponemal tests are more frequent than commonly appreciated in specific populations (HIV, pregnancy, autoimmune disease, recent mRNA vaccination) and lead to measurable clinical harm that can be mitigated by algorithmic confirmatory testing and provider education.

Benefits: This review informs CDC/WHO guideline development, laboratory algorithm selection, and clinician training priorities, particularly for family medicine and emergency settings.

MATERIALS AND METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate False-Positive Non-Treponemal Tests: Clinical Implications and Management.

Screening

We screened in sources based on their abstracts that met these criteria:

- **False-Positive Non-Treponemal Tests**: Does this study involve patients with confirmed false-positive non-treponemal syphilis tests (RPR, VDRL, TRUST, or similar)?
- **Clinical Implications or Management**: Does this study report clinical implications of false-positive results (e.g., diagnostic delays, psychological impact, unnecessary treatments, healthcare utilization) OR describe management strategies for patients with false-positive non-treponemal tests?
- **Appropriate Study Design**: Is this study an observational study (cohort, case-control, cross-sectional), case series with ≥5 patients, systematic review, or meta-analysis?
- **Clinical Data and Outcomes**: Does this study include clinical correlation and patient outcomes data (not a laboratory-only study)?
- **Non-Treponemal Test Focus**: Does this study include non-treponemal test data (not exclusively examining treponemal tests like FTA-ABS, TP-PA, EIA without non-treponemal test data)?
- **False-Positive Relevance**: Does this study address false-positive results through comparison or discussion (not focusing exclusively on true-positive syphilis cases without reference to false-positives)?
- **Human Clinical Study**: Does this study include human clinical data (not exclusively animal studies or in-vitro studies without human clinical data)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Patients with false-positive non-treponemal tests	False-positive non-treponemal tests (RPR, VDRL, TRUST)	True-positive syphilis cases	Clinical implications
Keyword 2	Individuals with biological false-positive syphilis serology	Confirmatory testing algorithms	Negative treponemal test results	Healthcare utilization and costs
Keyword 3	HIV-infected	Management strategies	Different testing platforms	False-positive rates and titer distribution
Keyword 4	Pregnant women	Clinical decision-making and provider education	Different populations	Diagnostic accuracy and algorithm performance

The Boolean MeSH keywords inputted on databases for this research are: *("Patients with false-positive non-treponemal tests" OR "Individuals with biological false-positive syphilis serology" OR "HIV-infected women" OR "Pregnant women") AND ("False-positive non-treponemal tests (RPR, VDRL, TRUST)" OR "Confirmatory testing algorithms" OR "Management strategies" OR "Clinical decision-making and provider education") AND ("True-positive syphilis cases" OR "Negative treponemal test results" OR "Different testing platforms" OR "Different populations") AND ("Clinical implications" OR "Healthcare utilization and costs" OR "False-positive rates and titer distribution" OR "Diagnostic accuracy and algorithm performance")*

Data extraction

- **Study Population**:
  Extract the specific population studied for false-positive non-treponemal syphilis testing, including:
  - Patient demographics (age, sex, risk factors)
  - Clinical setting (primary care, STD clinics, prenatal care, etc.)
  - Prevalence of syphilis in the population
  - Sample size
  - Geographic location and healthcare system context
- **Testing Algorithm**:
  Extract details about the syphilis testing approach and specific tests involved in false-positive results, including:
  - Traditional vs reverse screening algorithm used
  - Specific non-treponemal tests (RPR, VDRL, etc.)
  - Specific treponemal tests used for confirmation
  - Laboratory automation and platform details
  - Testing sequence and reflexive testing protocols
- **False Positive Characteristics**:
  Extract quantitative data about false-positive non-treponemal test results, including:
  - False positive rates with confidence intervals
  - How false positives were defined/confirmed
  - Patient characteristics associated with false positives
  - Causes or contributing factors for false positives
  - Comparison of false positive rates between different testing approaches
- **Clinical Implications**:
  Extract all clinical consequences and impacts of false-positive non-treponemal tests, including:
  - Patient overtreatment rates and unnecessary antibiotic use
  - Increased healthcare utilization (follow-up visits, additional testing)
  - Patient psychological impact and anxiety
  - Healthcare costs and economic burden
  - Provider confusion or inappropriate clinical decision-making
  - Impact on partner notification and contact tracing
- **Management Strategies**:
  Extract approaches for managing false-positive non-treponemal test results, including:
  - Confirmatory testing protocols and algorithms
  - Provider education and guidance strategies

- Patient counseling approaches
- Criteria for treatment vs observation
- Follow-up recommendations and monitoring
- Quality improvement interventions implemented
- Effectiveness of different management approaches

- **Study Design**:
  Extract study methodology details to assess evidence quality, including:
  - Study design (RCT, etc.)
  - Study duration and follow-up period
  - Primary and secondary outcomes measured
  - Data sources (electronic records, surveys, clinical data)
  - Statistical methods used for analysis

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Patients with false-positive non-treponemal tests" OR "Individuals with biological false-positive syphilis serology" OR "HIV-infected women" OR "Pregnant women") AND ("False-positive non-treponemal tests (RPR, VDRL, TRUST)" OR "Confirmatory testing algorithms" OR "Management strategies" OR "Clinical decision-making and provider education") AND ("Clinical implications" OR "Healthcare utilization and costs" OR "False-positive rates and titer distribution" OR "Diagnostic accuracy and algorithm performance")*	10
Semantic Scholar	*("Patients with false-positive non-treponemal tests" OR "Individuals with biological false-positive syphilis serology" OR "HIV-infected women" OR "Pregnant women") AND ("False-positive non-treponemal tests (RPR, VDRL, TRUST)" OR "Confirmatory testing algorithms" OR "Management strategies" OR "Clinical decision-making and provider education") AND ("True-positive syphilis cases" OR "Negative treponemal test results" OR "Different testing platforms" OR "Different populations") AND ("Clinical implications" OR "Healthcare utilization and costs" OR "False-positive rates and titer distribution" OR "Diagnostic accuracy and algorithm performance")*	250
Springer	*("Patients with false-positive non-treponemal tests" OR "Individuals with biological false-positive syphilis serology" OR "HIV-infected women" OR "Pregnant women") AND ("False-positive non-treponemal tests (RPR, VDRL, TRUST)" OR "Confirmatory testing algorithms" OR "Management strategies" OR "Clinical decision-making and provider education") AND ("True-positive syphilis cases" OR "Negative treponemal test results" OR "Different testing platforms" OR "Different populations") AND ("Clinical implications" OR "Healthcare utilization and costs" OR "False-positive rates and titer distribution" OR "Diagnostic accuracy and algorithm performance")*	123
Google Scholar	*("Patients with false-positive non-treponemal tests" OR "Individuals with biological false-positive syphilis serology" OR "HIV-infected women" OR "Pregnant women") AND ("False-positive non-treponemal tests (RPR, VDRL, TRUST)" OR "Confirmatory testing algorithms" OR "Management strategies" OR "Clinical decision-making and provider education") AND ("True-positive syphilis cases" OR "Negative treponemal test results" OR "Different testing platforms" OR "Different populations") AND ("Clinical implications" OR "Healthcare utilization and costs" OR "False-positive rates and titer distribution" OR "Diagnostic accuracy and algorithm performance")*	20,600

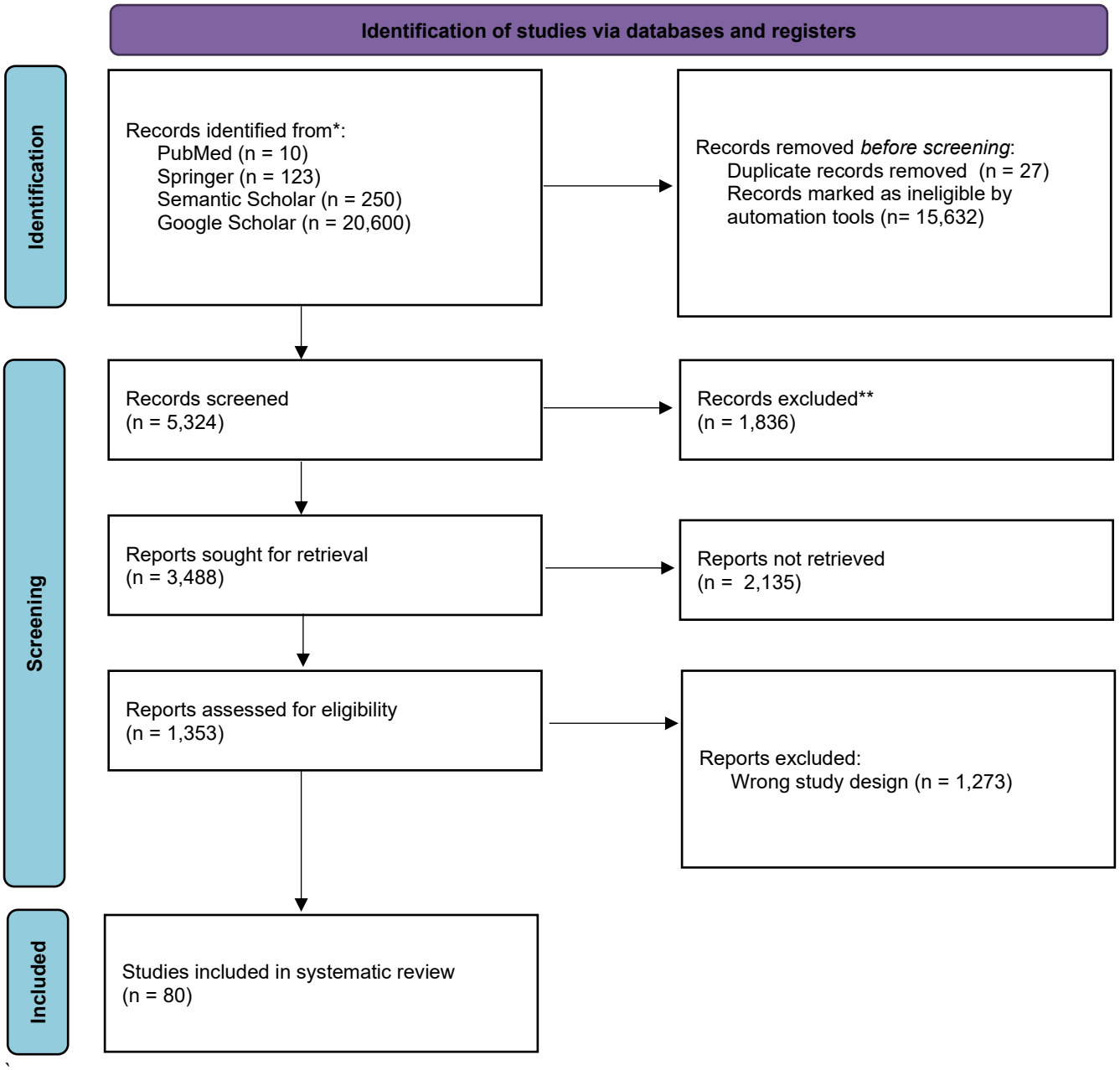

Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

The 80 sources span a wide range of study designs, populations, and geographic settings. They include RCT, etc. The table below summarizes the key characteristics of each included source.

Study	Population / Setting	Primary Focus
E. Williams et al., 2023	119 participants, University of Miami SARS-CoV-2 cohort [7]	COVID-19 vaccine-induced false-positive RPR [7]
Terin T. Sytsma et al., 2020	8,553 negative and 60 positive CSF-VDRL results, Mayo Clinic [10]	CSF-VDRL utilization and false positivity in neurosyphilis diagnosis [10]
M. Forsythe et al., 2023	108 patients with positive serology [11]	Provider accuracy in syphilis serology interpretation [11]
I. Oboho et al., 2013	711 HIV-infected patients, Johns Hopkins [2]	Impact of cART on biologic false-positive RPR [2]

Study	Population / Setting	Primary Focus
I. Oboho et al., 2013a	711 HIV-infected patients, Johns Hopkins [5]	Factors associated with BFP RPR in HIV [5]
Brandon Chatani et al., 2021	202 newborns, reverse screening setting [9]	Reverse screening consequences for congenital syphilis management [9]
Audrey C. Martin et al., 2025	212 pregnant women with reactive RPR, Indiana [22]	COVID-19 vaccination and false-positive RPR in pregnancy [22]
Amanda C. Zofkie et al., 2020	144 pregnant women with reactive CIA [23]	CIA signal strength and false-positive classification in pregnancy [23]
M. Binnicker, 2012	Not specified [24]	Comparison of traditional and reverse syphilis screening algorithms [24]
A. Cantor et al., 2016	High-risk populations including HIV-positive men and MSM [25]	Screening effectiveness and test accuracy for USPSTF [25]
R. Naesens et al., 2011	6 patients with false-positive Lyme serology [26]	Cross-reactivity between syphilis and Lyme serology [26]
Dimitrios Korentzelos et al., 2022	38 participants, pre- and post-COVID vaccination [8]	COVID-19 mRNA vaccine-induced false RPR reactivity [8]
Sage W R Geher et al., 2025	1,072 transgender persons tested for syphilis [27]	Syphilis trends in transgender and gender diverse adults [27]
Jennifer S. Lin et al., 2018	2,441,237 women (China) and multiple study populations [28]	Screening for syphilis in pregnancy for USPSTF [28]
Bin Chen et al., 2025	35,995 individuals, Guangzhou, China [4]	Autoimmune diseases and biological false-positive syphilis serology [4]
K. Ghanem, 2015	MSM, pregnant women, heterosexuals; US [29]	CDC STD treatment guidelines for syphilis management [29]
V. S. Sandes, 2017	28,158 (VDRL) and 25,577 (ChLIA) blood donors, Brazil [12]	Treponemal ChLIA vs. VDRL in blood donor screening [12]
Hana Shabrina Purnama & Gema Putra Bangsa, 2026	159 studies; pregnant women, STI clinic attendees, high-risk groups [20]	Diagnostic accuracy of rapid POCTs for syphilis [20]
M. Bukar et al., 2009	18,101 pregnant women, Maiduguri, Nigeria [30]	Cost-effectiveness of antenatal syphilis screening [30]
Judah K Gruen et al., 2021	148 patients with reactive RPR, Atlanta safety-net ED [31]	ED recognition and treatment of syphilis [31]
Jeannette Guarner et al., 2025	51 patients with reactive RPR [32]	Correlation of treponemal antibody quantitative results with RPR titers [32]
B. D. Nelson et al., 2026	43 infants at risk for congenital syphilis, Utah [33]	Evaluation of infants for congenital syphilis [33]
Tracy A. Wolff et al., 2009	Studies in pregnant women; Vienna (>300,000) and Bolivia (8,892) [34]	USPSTF reaffirmation on syphilis screening in pregnancy [34]
Ying Zhang et al., 2022	Key populations including sex workers, MSM [35]	Improved RDTs to detect syphilis and yaws [35]
Richard Watkins & J. O'donnell, 2008	1 AIDS patient [36]	False-positive CSF VDRL from varicella-zoster virus [36]
Michelle L. Henninger et al., 2022	Nonpregnant adults and adolescents at increased risk [37]	Screening for syphilis in nonpregnant adults for USPSTF [37]
Gary N. Asher et al., 2025	Pregnant women [38]	Screening for syphilis in pregnancy for USPSTF [38]

Study	Population / Setting	Primary Focus
Jillian T Henderson et al., 2018	2,441,237 women (China) and other study populations [39]	Syphilis screening in pregnancy and false-positive treponemal tests [39]
Chinami Fujimori et al., 2009	Routine clinical samples [40]	Evaluation of TP-LAIA vs. VDRL false-positive rates [40]
Patrick O'Byrne et al., 2025	600 participants, STI clinic, Ottawa, Canada [21]	Evaluation of MedMira Multiplo POCT for syphilis [21]
S. Tuddenham et al., 2015	Persons with serodiscordant syphilis test results [41]	Neurosyphilis and ophthalmic syphilis in serodiscordant patients [41]
J. Matthias et al., 2018	372,902 reactive nontreponemal tests, Florida surveillance [19]	Automated algorithm for triaging reactive nontreponemal tests [19]
Tamara Audrey Kadarusman et al., 2021	Pregnant women [42]	Sensitivity and specificity of VDRL and RPR in pregnancy [42]
G. Lazenby et al., 2025	12,959 pregnant women, South Carolina [43]	EHR as a tool for maternal and congenital syphilis surveillance [43]
Katherine Soreng et al., 2014	Laboratories offering syphilis testing, US [15]	Benefits and challenges of reverse syphilis screening algorithm [15]
M. Morshed & A. Singh, 2014	General syphilis diagnostic populations [17]	Trends in serologic diagnosis of syphilis [17]
E. Dassah et al., 2016	2,214 samples from pregnant women, Ghana [6]	Syphilis sentinel surveillance in endemic treponematoses [6]
S. Sethi et al., 2015	28,920 serum samples, tertiary care center, North India [44]	Rising trends of syphilis prevalence [44]
E. Ángel-Müller et al., 2021	9,666 participants, field conditions [45]	Diagnostic accuracy of rapid POC tests for syphilis [45]
Jeeyong Kim et al., 2008	1,357 serum samples, university hospital, Japan [46]	Evaluation of Architect Syphilis TP as screening test [46]
Daniel A. Ortiz & M. Loeffelholz, 2017	4,134 routine and HIV samples, University of Texas [47]	Lumipulse G TP-N ChIA as syphilis screening test [47]
Eric W Tang et al., 2020	293 samples, tertiary medical center, high-prevalence setting [48]	BioPlex 2200 Syphilis Total with automated RPR [48]
E. Larsen et al., 2019	500 cases from Military Health System [14]	Syphilis surveillance case finding in DoD [14]
Y. Saral et al., 2012	117 patients suspected of syphilis [49]	Comparison of RPR, CMIA, and TPHA diagnostic performance [49]
T. Krasnoselskikh et al., 2018	HIV-syphilis co-infected patients [50]	Diagnosis and treatment of syphilis in HIV co-infection [50]
N. Uthayakumar & E. Jungmann, 2016	4,584 heterosexual patients, Inner London clinics [51]	Routine re-screening for HIV and syphilis in heterosexuals [51]
N. Sherriff et al., 2024	2,577 MSM in Italy, Malta, Peru, UK [52]	Dual POCT evaluation for HIV and syphilis in MSM [52]
S. Tuddenham et al., 2020	Literature from 1940–2017 [1]	Performance characteristics of nontreponemal antibody tests [1]
R. Peeling & Htun Ye, 2004	Pregnant women, developing countries [3]	Diagnostic tools for maternal and congenital syphilis [3]
R. Bronzan et al., 2007	1,250 pregnant women, rural South Africa [53]	Onsite rapid syphilis screening strategies in rural clinics [53]

Study	Population / Setting	Primary Focus
E. Mathai et al., 2001	Pregnant women, Vellore, India [54]	Audit of VDRL-positive pregnancy management [54]
Elizabeth A. Gilliams et al., 2023	Primary care clinicians [55]	Practical approach to syphilis serology for clinicians [55]
T. Menza et al., 2019	HIV-positive MSM in primary care [56]	Algorithms to identify incident syphilis [56]
Fatima Johari & Michelle Ordoveza Cho, 2024	General syphilis diagnostic populations [16]	Operating characteristics of diagnostic tests for syphilis [16]
K. Osbak et al., 2017	120 syphilis cases and 30 controls, Antwerp, Belgium [57]	Evaluation of automated RPR immunoturbidimetric assay [57]
Marla Victoria Ardila Peña, 2024	Neonates with congenital syphilis [58]	Congenital syphilis diagnosis and evaluation [58]
David Kriegel et al., 2024	Family medicine residents and faculty [18]	Educational intervention on syphilis screening interpretation [18]
M. Drozhdina, 2019	5,460 syphilis patients, Zhongshan Hospital, China [59]	Serological non-responsiveness after syphilis treatment [59]
Татьяна Валерьевна Красносельских et al., 2018	HIV-syphilis co-infected patients [60]	Syphilis diagnosis and treatment in HIV co-infection [60]
Molly E Kent & F. Romanelli, 2008	General syphilis populations, US [61]	Epidemiology, diagnosis, and treatment of syphilis [61]
J. Tucker et al., 2010	>22,000 tests at STI and antenatal clinics, low-income countries [62]	Rapid treponemal test screening for syphilis [62]
W. Ngan et al., 2014	76-year-old Chinese woman, Hong Kong [13]	Primary Sjögren syndrome causing false-positive VDRL and FTA-ABS [13]
Michael G Hunter et al., 2013	28,261 specimens, high-prevalence populations [63]	Significance of isolated reactive treponemal CIA results [63]
Ferris Satyaputra et al., 2021	Australian syphilis diagnostic populations [64]	Laboratory diagnosis of syphilis [64]
N. Zetola et al., 2007	MSM, HIV-coinfected populations, US [65]	Syphilis update with emphasis on HIV co-infection [65]
James R. Roberts, 2022	Emergency department patients, US [66]	Syphilis diagnosis and management in ED setting [66]
T. T. Chao et al., 2011	47,794 pregnant women, Parkland Hospital, US [67]	Risk factors for false-positive HIV EIA at delivery [67]
P. Zarakolu, 2023	Global; specific data from Turkey [68]	Recent advances in laboratory diagnosis of syphilis [68]
Harriet Wallace et al., 2016	54 infants born to syphilis-seropositive mothers, UK [69]	Serological follow-up of infants exposed to maternal syphilis [69]
M. López-Zambrano et al., 2009	140,336 pregnant women, Aragua state, Venezuela [70]	Trends in HIV and syphilis among antenatal women [70]
Michael E. Tsimis & J. Sheffield, 2017	Pregnant women, US [71]	Syphilis and pregnancy: epidemiology, diagnosis, treatment [71]
I. Müller et al., 2006	Diagnostic laboratories, Germany [72]	Reliability of syphilis serology in proficiency testing [72]
T. Herremans et al., 2010	Neonates at risk for congenital syphilis [73]	Diagnostic tests for congenital syphilis [73]

Study	Population / Setting	Primary Focus
G. Kaur & P. Kaur, 2015	Blood donors [74]	Syphilis testing in blood donors [74]
E. Kersh & K. Workowski, 2020	CDC guideline populations [75]	CDC guidance on laboratory testing for syphilis [75]
J. Tucker et al., 2010a	101 HIV-infected individuals with ocular syphilis [76]	Ocular syphilis among HIV-infected patients [76]
Vicky Jespers et al., 2023	General populations [77]	Diagnosis and management of gonorrhoea and syphilis [77]
C. Tipple & G. Taylor, 2015	General syphilis populations [78]	Syphilis testing, typing, and treatment follow-up [78]
Weiping Cao et al., 2023	General syphilis and congenital syphilis populations [79]	Advantages and limitations of syphilis diagnostic approaches [79]
E. Adhikari, 2026	Pregnant women, US [80]	Syphilis diagnosis and management in pregnancy [80]

Study populations ranged from general hospital patients and blood donors to targeted groups such as pregnant women, HIV-infected individuals, MSM, transgender adults, neonates, and military personnel. Geographic settings spanned the United States, Canada, Europe, South America, Africa, and Asia.

False-Positive Rates of Non-Treponemal Tests

The following table summarizes quantitative data on false-positive rates of non-treponemal tests (RPR, VDRL) across studies that reported these figures.

Study	Population	Non-Treponemal Test	False-Positive Rate	Confirmatory Method	Key Associated Factors
E. Williams et al., 2023	COVID-19 vaccine cohort (n=119)	RPR	1.7% (2/119) [7]	Non-reactive FTA-ABS [7]	mRNA COVID-19 booster vaccination [7]
Terin T. Sytsma et al., 2020	CSF-VDRL positive cases (n=60)	CSF-VDRL	28.3% (17/60) [10]	Absence of prior positive serologic syphilis testing [10]	Neoplastic meningitis [10]
I. Oboho et al., 2013	HIV-infected (n=711)	RPR	13.5% (96/711) [2]	Non-reactive FTA-ABS [2]	Lower RPR titers, younger age, injection drug use [2]
I. Oboho et al., 2013a	HIV-infected (n=711)	RPR	13.5% [5]	Non-reactive FTA-ABS [5]	Lower RPR titers, injection drug use, hepatitis B [5]
Audrey C. Martin et al., 2025	Pregnant women (n=59 false-positive)	RPR	48.1% had prior COVID vaccination [22]	Negative treponemal test [22]	COVID vaccination within 300 days [22]
Amanda C. Zofkie et al., 2020	Pregnant women (n=144)	RPR (via CIA screen)	12% (17/144) [23]	CIA+/RPR−/TPPA− [23]	Low CIA S/CO ratio (1.9 ± 0.8) [23]

Study	Population	Non-Treponemal Test	False-Positive Rate	Confirmatory Method	Key Associated Factors
Dimitrios Korentzelos et al., 2022	Vaccinated adults (n=38)	BioPlex RPR	18.4% (7/38) BioPlex; 5.3% (2/38) Sure-Vue; 2.6% (1/38) Macro-Vue [8]	Treponemal negative at baseline [8]	Moderna vaccine; lipid nanoparticle carriers [8]
Bin Chen et al., 2025	Hospital patients (n=35,995)	Not specified	0.78% [4]	Clinical and autoantibody assessment [4]	Autoimmune diseases; specific autoantibodies (ANA, ds-DNA, SSA) [4]
V. S. Sandes, 2017	Blood donors (n=28,158 VDRL; 25,577 ChLIA)	VDRL	40.5% of reactive results [12]	Second sample collection [12]	Elderly, lower education [12]
M. Bukar et al., 2009	Pregnant women (n=18,101)	VDRL	25% of positives (3/12) [30]	TPHA [30]	Not specified [30]
Judah K Gruen et al., 2021	ED patients with reactive RPR (n=148)	RPR	8% (12/148) [31]	Chart review with treponemal antibodies [31]	Not specified [31]
Tracy A. Wolff et al., 2009	Hospitalized women, Vienna (>300,000); pregnant women, Bolivia (n=8,892)	VDRL; RPR	VDRL: 0.26%; RPR: 0.91% [34]	Negative treponemal test [34]	Autoimmune conditions, HIV [34]
Tamara Audrey Kadarusman et al., 2021	Pregnant women (literature review)	VDRL; RPR	VDRL: 10.5%; RPR: 9.6% [42]	TPHA [42]	Biological false positives (26–56% of positives) [42]
S. Sethi et al., 2015	Tertiary care patients (n=28,920)	VDRL	0.27% [44]	TPPA [44]	Not specified [44]
E. Dassah et al., 2016	Pregnant women (n=2,214), Ghana	RPR	0.9% (21/2,214) [6]	RPR+/TPHA− confirmed with DS [6]	Endemic yaws cross-reactivity [6]
Chinami Fujimori et al., 2009	Routine clinical samples	VDRL; TP-LAIA	VDRL: 13.5%; TP-LAIA: 0.64% [40]	Case history review [40]	Not specified [40]
S. Tuddenham et al., 2020	General populations (systematic review)	RPR/VDRL	≤1.5% in general populations [1]	Negative treponemal test [1]	Older age, autoimmune diseases, leprosy, yaws, HIV [1]

Study	Population	Non-Treponemal Test	False-Positive Rate	Confirmatory Method	Key Associated Factors
R. Peeling & Htun Ye, 2004	Pregnant women, developing countries	RPR	Up to 28% [3]	Reference laboratory treponemal test [3]	Not specified [3]
I. Müller et al., 2006	German proficiency testing laboratories	VDRL	4.1% of negative samples reported as false-positive [72]	Proficiency testing standards [72]	Laboratory error [72]
A. Cantor et al., 2016	Low-prevalence US; higher-prevalence Canada	RPR (reverse algorithm)	0.6% vs 0.0% (US, p=0.03); 0.26% vs 0.13% (Canada) [25]	Treponemal confirmatory tests [25]	Reverse screening algorithm [25]

False-positive rates of non-treponemal tests vary dramatically depending on the population, clinical setting, and how the denominator is defined. In general population screening, the rate is typically low at ≤1.5% [1], and in large hospital-based cohorts it was reported at 0.78% [4] and 0.27% [44]. However, among specific populations the rate is substantially higher: 13.5% among HIV-infected persons [2, 5], up to 28% among pregnant women in developing countries [3], and 28.3% among all positive CSF-VDRL results in a large tertiary care cohort [10]. Among blood donors, 40.5% of initially reactive VDRL results were ultimately classified as false positives [12]. Almost all false-positive results occurred at low titers; in the large Chinese cohort, 96.7% of biological false-positive cases exhibited titers ≤1:4 [4]. A newer and clinically significant finding is that mRNA COVID-19 vaccines can induce false RPR reactivity: 1.7% of a longitudinal cohort developed false-positive RPR following booster vaccination [7], with reactivity persisting for up to 9 months [7], and a pilot study found up to 18.4% false reactivity on the BioPlex RPR platform after Moderna vaccination [8].

Thematic Analysis

Causes and Contributing Factors for False-Positive Non-Treponemal Tests

The causes of biological false-positive (BFP) non-treponemal tests fall into several overlapping categories.

Autoimmune and inflammatory conditions are among the most well-characterized drivers. A large retrospective cohort of 35,995 individuals found that autoimmune diseases and specific autoantibodies—including anti-dsDNA, anti-Sm, ANA, anti-ribosomal antibodies, and anti-SSA—were significantly more prevalent among individuals with BFP reactions compared to those with negative screening results [4]. A case report illustrated this when a 76-year-old woman with primary Sjögren syndrome was found to have false-positive VDRL (and initially false-positive FTA-ABS), ultimately attributable to high ANA titers, anti-Ro, anti-La, and anticardiolipin IgM [13]. Multiple reviews confirm that connective tissue diseases, malignancy, pregnancy, hepatitis C, and advanced age are established contributors to BFP nontreponemal results [1, 17, 66, 68, 71].

HIV infection substantially increases false-positive risk. The BFP rate among HIV-infected persons ranges from 4–15% [5], with 13.5% observed in the Johns Hopkins HIV Clinical Cohort [2]. Interestingly, combination antiretroviral therapy (cART) was associated with decreased odds of BFP tests (adjusted OR 0.31 compared to syphilis group; 0.42 compared to non-syphilis group) and dramatically decreased odds of persistent BFP (OR 0.07) [2, 5]. Neither CD4 count nor HIV RNA independently predicted BFP status, suggesting that cART's effect on B-cell function, rather than T-cell immunosuppression alone, may mediate the reduction in false positivity [5]. Injection drug use and hepatitis B were independently associated with increased BFP risk in this population [5].

Vaccination has emerged as a novel cause. Two studies directly examined mRNA COVID-19 vaccine-induced RPR false reactivity. In a pilot longitudinal cohort, 7 of 38 participants (18.4%) developed false-reactive BioPlex RPR results following vaccination, all among Moderna recipients [8]. The false reactivity was more pronounced on the automated BioPlex platform than on manual Sure-Vue (2/38) or Macro-Vue (1/38) RPR card tests [8], potentially attributable to lipid nanoparticle carriers generating cross-reactive antibodies [8]. In a study of 59 pregnant women with false-positive RPR, 48.1% had received COVID-19 vaccination prior to the test, with the majority occurring within 300 days of vaccination and 30% within 100 days [22]. A longitudinal study confirmed that two individuals exhibited chronic, vaccine-induced RPR reactivity for up to 9 months following booster vaccination, and both were ANA-negative, ruling out autoimmune confounding [7].

Endemic treponematoses can confound screening in certain geographic contexts. In Ghana, where yaws is endemic, retesting of 2,214 samples from HIV sentinel surveillance found that the existing two-treponemal-test strategy overestimated the seroprevalence of active syphilis by a third (6.0% vs. 4.5%, $p < 0.001$), with more than half of positive cases actually representing past or treated treponemal infections, possibly from prior yaws exposure [6]. The positive predictive value for active syphilis was only 16.8% [6].

Other infections documented as causes include varicella-zoster virus (producing a false-positive CSF VDRL in an AIDS patient) [36], neoplastic meningitis (the most common cause of false-positive CSF-VDRL) [10], and cross-reactivity between Treponema pallidum antibodies and Lyme disease assays [26]. Additional reported contributors include malaria, tuberculosis, Chagas disease, leprosy, bacterial or viral infections, drug use, and pregnancy itself [17, 66, 71].

Clinical Implications of False-Positive Non-Treponemal Tests

Unnecessary treatment and overtreatment. False-positive non-treponemal results can lead directly to inappropriate antibiotic therapy. In a study of newborns evaluated via the reverse screening algorithm, 15% of babies in the "unlikely" congenital syphilis group were treated with intramuscular penicillin, which did not follow established AAP guidelines [9]. Up to 28% of positive RPR results in pregnant women in developing countries are biological false positives, indicating a substantial potential for unnecessary penicillin administration [3]. In rural South Africa, approximately 1% of women screened with an immunochromatographic strip test may have received penicillin unnecessarily [53]. In the military health system, a full one-third of surveillance-identified syphilis cases were not true cases, reflecting systematic overdiagnosis [14]. German proficiency testing found that 10.2% of laboratories incorrectly reported serological evidence for active infection in samples from patients with past syphilis or from seronegative donors [72].

Increased healthcare utilization. False-positive results generate cascades of additional testing and follow-up. The CSF-VDRL was inappropriately ordered in 98.2% of cases in a large tertiary cohort, and every false-positive CSF-VDRL occurred in inappropriately tested patients [10]. The reverse screening algorithm, while advantageous for detecting latent disease, yields more discordant results requiring follow-up with a second treponemal assay [15, 24]. In the reverse algorithm, false-positive rates with treponemal-specific enzyme or chemiluminescent immunoassays ranged from 46.5% to 88.2%, necessitating reflexive confirmatory testing for all positive results [28, 39]. Economically, one UK study estimated potential savings of £42,083 if routine syphilis rescreening of low-risk heterosexual patients within 12 months were eliminated, as no new syphilis infections were found in that population [51]. In Nigeria, US$37,424 was spent on VDRL testing over 10 years to detect only 9 confirmed cases (seroprevalence 0.05%) [30].

Provider confusion and misinterpretation. A retrospective review of 108 patients with positive syphilis serology found that 11.1% of results were interpreted incorrectly, with family medicine providers accounting for approximately 50% of misinterpretations ($p = 0.003$) [11]. By contrast, infectious disease, internal medicine, and OB/GYN providers had very high accuracy, contributing only one interpretation error among 54.3% of the study cohort [11]. An educational intervention targeting family medicine residents showed no statistically significant improvement in appropriate interpretation and management of syphilis results, though post-hoc power was very low (2.7% and 31.8%) [18]. Syphilis serology interpretation is one of the most frequently asked questions received by pathology laboratories [11].

Psychological impact. Although few studies measured patient distress directly, several noted the potential for anxiety from false-positive results. In blood banks, false-positive syphilis tests cause discomfort in the donor relationship [12]. In clinical settings, false-positive results may lead to stress, labeling, and further invasive workups [34]. A case report described a 76-year-old woman who "firmly rejected" a presumed latent syphilis diagnosis that proved to be a false positive attributable to Sjögren syndrome [13].

Impact on surveillance and public health. In public health surveillance, the reliance on ICD codes for syphilis case identification had a positive predictive value of only 0.42, compared to 0.82 for reportable medical events [14]. Clinical staging of syphilis cases within the surveillance period was grossly inaccurate regardless of method (PPV 0.30 for ICD-9 codes, 0.49 for reportable medical events) [14]. These findings indicate that false positives and coding errors introduce substantial noise into syphilis surveillance systems.

Testing Algorithm Considerations and False Positivity

The choice between the traditional algorithm (nontreponemal test first, treponemal confirmation) and the reverse algorithm (treponemal test first, nontreponemal quantification) has significant implications for false-positive

management. The CDC continues to recommend the traditional RPR-based screening algorithm [29], though an increasing number of laboratories have adopted reverse screening due to the availability of automated treponemal assays [15, 24].

The reverse algorithm detects more individuals with reactive treponemal tests, including those with past treated infections, latent syphilis, and false-positive treponemal results [15, 24]. In a low-prevalence US population, reverse sequence screening yielded a false-positive rate of 0.6% compared to 0.0% for RPR ($p = 0.03$) [25]. A key disadvantage is the high rate of discordant results (treponemal-positive/nontreponemal-negative), which may represent past treated infection, early primary syphilis, late latent syphilis, or a false-positive treponemal screen [15, 17]. The positive predictive value of an isolated unconfirmed reactive treponemal chemiluminescence assay or enzyme immunoassay is low when epidemiological risk and clinical probability for syphilis are low [29]. Among pregnant women with serodiscordant serologies, the risk of vertical transmission is low [29].

Different automated platforms demonstrate variable performance. The Lumipulse G TP-N produced 27 fewer falsely reactive results than the Bioplex 2200 Syphilis IgG in a head-to-head comparison (NPA 77.3% vs 15.9% against TP·PA) [47]. The BioPlex RPR missed early syphilis reinfections at low titers, with 91% of BD RPR 1:1 results being BioPlex RPR-negative [48]. These platform-dependent differences underscore the importance of local validation.

For non-treponemal tests specifically, RPR and VDRL have broadly similar performance. In pregnant women, VDRL had a sensitivity of 71.6% and specificity of 89.5%, while RPR had a sensitivity of 73.5% and specificity of 90.5% [42]. A Japanese study found that the VDRL had a false-positive rate of 13.5% compared to 0.64% for the newer TP-LAIA assay [40]. The ECDC algorithm offers a third approach, recommending screening with a treponemal test followed by a reflex confirmatory treponemal test, with nontreponemal testing used for disease activity assessment [68].

Management Strategies for False-Positive Non-Treponemal Tests

Confirmatory testing protocols. The cornerstone of managing a reactive non-treponemal test is confirmatory treponemal testing. In the traditional algorithm, this involves performing an FTA-ABS or TPPA on reactive RPR/VDRL samples [61, 66]. In the reverse algorithm, reactive treponemal screens are followed by quantitative RPR, with a second different treponemal test (preferably TPPA) used to resolve discordant results [16, 17, 68]. Reflexive (automatic confirmatory) testing for all positive findings is recommended by USPSTF-supporting reviews [28, 39]. For CSF-VDRL, following established algorithms requiring positive serologic syphilis testing before ordering CSF testing would prevent unnecessary testing and minimize false positives [10].

Detailed clinical history. Multiple sources emphasize the importance of obtaining a comprehensive medical history, including recent vaccinations [7], prior syphilis diagnosis and treatment [17], sexual history [17], and underlying autoimmune conditions [4]. For pregnant women, effective communication of maternal history at delivery is critical to avoid unnecessary workups and overtreatment of neonates [9]. The CDC recommends reviewing the clinical context before proceeding with invasive workups [7].

Provider education. Given the documented high rate of misinterpretation among family medicine providers [11], targeted education is warranted. One quasi-experimental study of an educational lecture for family medicine residents and faculty found improvements in confidence but no statistically significant improvement in knowledge or practice, likely limited by small sample size [18]. The study authors recommended implementing additional resources linked to syphilis results within the electronic medical record [11]. Guidance documents emphasize that clinicians should be aware of the testing algorithm employed by their laboratory [78] and that a single positive nontreponemal test is insufficient for diagnosis [66].

Use of point-of-care tests. POCTs that detect both treponemal and non-treponemal antibodies can facilitate same-day clinical decisions. The MedMira Multiplo POCT demonstrated 82.5% sensitivity for RPR-positive samples and 94.1% sensitivity for RPR ≥1:8 [21], and its use in an STI clinic allowed clinicians to both initiate treatment when appropriate and withhold unnecessary antibiotics [21]. Dual POCTs evaluated in MSM across four countries detected greater than 90% of probable active syphilis cases [52]. However, the non-treponemal component of dual rapid tests showed substantially lower sensitivity (42.9–94.2%), particularly at low RPR titers [20].

Algorithmic triage of surveillance data. A novel automated algorithm for public health surveillance that begins by comparing reactive nontreponemal tests to prior test results and current treponemal findings removed 64.9% of reactive nontreponemal test records while maintaining adjusted sensitivity of 98.4%, nearly tripling specificity from 27.5% to 72.9% compared to the existing reactor grid [19]. This approach represents a scalable strategy for reducing the burden of false-positive follow-up in surveillance systems.

Follow-up and monitoring. For patients with confirmed BFP results, repeat testing may be warranted to assess persistence. In the HIV cohort, 23% of patients with BFP had persistent false-positive results across multiple visits [2], and cART was associated with dramatically decreased odds of persistence (OR 0.07) [2]. For vaccine-associated false positivity, effects can persist for more than 5 months [8], and clinicians should consider repeat testing at a later interval. Nontreponemal antibody titers should be monitored at 1, 3, 6, 12, and 24 months post-treatment to assess therapeutic response and distinguish true infection from false positivity [71]. Using nontreponemal tests alone for infant follow-up could reduce required tests by at least 50%, concentrating resources on high-risk infants [69].

Synthesis

The observed heterogeneity in false-positive rates—ranging from <1% in general population screening to >28% in certain contexts—can be systematically explained by three primary factors: population characteristics, test platform, and clinical setting.

Population-driven variation. The highest false-positive rates consistently occur in populations enriched for immunological perturbation. Among HIV-infected persons not on cART, polyclonal B-cell activation drives BFP rates of 13.5% [2, 5], a mechanism supported by the finding that cART substantially reduces BFP odds independent of CD4 count [5]. Among patients with autoimmune diseases, the generation of anti-cardiolipin and other cross-reactive antibodies produces BFP reactions, with significantly higher rates of anti-dsDNA, ANA, and anti-SSA positivity in the BFP group [4]. In pregnant women, physiological immunological changes contribute to false positivity, with rates reported from 0.91% in developed-country settings [34] to 10.5% for VDRL in the literature review [42] and up to 28% in developing-country antenatal populations [3]. The higher rates in developing countries likely reflect the combined contribution of endemic infections (malaria, tuberculosis, yaws), younger maternal age, and co-existing immunological challenges. In Ghana, yaws endemicity specifically inflated the apparent syphilis seroprevalence by one-third [6].

Platform and assay-driven variation. The choice of RPR platform significantly affects false-positive detection. The automated BioPlex RPR showed 18.4% false reactivity following COVID-19 vaccination, while manual Sure-Vue and Macro-Vue RPR card tests showed only 5.3% and 2.6%, respectively [8]. This disparity may reflect differences in antigen composition and detection thresholds across platforms. Similarly, the VDRL showed a false-positive rate of 13.5% compared to 0.64% for the TP-LAIA in routine testing [40]. The Lumipulse G TP-N produced 27 fewer false-reactive results than the Bioplex 2200 Syphilis IgG [47]. These findings indicate that a single "false-positive rate" for non-treponemal tests is an oversimplification; the rate is assay-specific and should be validated locally.

Clinical context determines impact. The consequences of false positivity are most severe in contexts where confirmatory testing is delayed or unavailable. In developing-country antenatal settings, where the WHO recommends same-day treatment for reactive screening tests, up to 28% of treated women may not have syphilis [3, 53]. In emergency departments, 8% of reactive RPR results were false positives, and a majority of patients discharged without empiric treatment were not successfully followed up [31, 31]. In contrast, in settings with established reflexive testing protocols, the clinical impact of false positives is mitigated because automated confirmatory algorithms identify discordant results before treatment decisions are made [28, 39].

The titer at which false positivity occurs provides a practical discriminator. Across studies, BFP reactions almost universally occur at low titers (≤1:4) [4], while higher titers (≥1:8) are strongly associated with true active infection [9]. This pattern holds across populations: in the congenital syphilis evaluation, RPR titers ≥1:4 were almost three times more likely in infants with probable congenital syphilis (OR 2.91, $p < 0.05$) [9], and POCT non-treponemal sensitivity jumped to 94.1% at RPR dilutions ≥1:8 [21]. Clinicians encountering low-titer reactive results in patients without clear risk factors should maintain a high index of suspicion for BFP, particularly in the presence of autoimmune conditions, recent vaccination, or HIV infection.

Across all settings, the management consensus converges on a multi-step approach: (1) confirm all reactive non-treponemal tests with a treponemal assay [15, 16, 66]; (2) obtain detailed clinical history including treatment history, vaccination status, and autoimmune conditions [7, 17]; (3) use titer magnitude and clinical context to guide treatment decisions, recognizing that low-titer reactive results in low-risk patients are disproportionately likely to be false positives [1, 4]; and (4) invest in provider education, particularly for non-specialist clinicians who interpret syphilis serology less frequently [11, 18]. The implementation of electronic health record–based decision support and algorithmic triage tools [11, 19] represents a promising systems-level intervention to reduce the clinical burden of false-positive non-treponemal tests.

DISCUSSION

This systematic review of 80 studies provides the most

comprehensive synthesis to date of false-positive non-treponemal syphilis tests, emphasizing clinical implications and management. Four major findings emerge: (1) false-positive rates vary by >40-fold depending on population, test platform, and geographic context; (2) HIV infection and autoimmune diseases remain classical causes, but mRNA COVID-19 vaccination is a novel and important contributor; (3) low titers (≤1:4) are highly characteristic of false-positives, offering a practical discriminator; (4) clinical harm—including overtreatment, provider error, and surveillance noise—is substantial and underrecognized.

Population-Specific False-Positive Rates and Mechanisms

In general population screening, false-positive non-treponemal tests are rare (≤1.5%) (1). However, in HIV-infected persons, the BFP rate reaches 13.5% (2,5). This is not simply due to immunosuppression: combination antiretroviral therapy (cART) dramatically reduced BFP odds (adjusted OR 0.31 compared to syphilis group) independent of CD4 count or HIV RNA (2,5). The mechanism likely involves cART-mediated normalization of polyclonal B-cell activation rather than T-cell recovery alone (5). Clinically, this means that HIV patients on effective cART have lower false-positive risk, but those off therapy or with ongoing B-cell dysregulation remain at high risk.

Autoimmune diseases drive BFP through cross-reactive anti-cardiolipin and anti-phospholipid antibodies. In a large Chinese cohort (n=35,995), patients with BFP had significantly higher prevalence of anti-dsDNA, anti-Sm, ANA, anti-ribosomal, and anti-SSA antibodies (4). A striking case report documented a 76-year-old woman with primary Sjögren syndrome whose false-positive VDRL and FTA-ABS resolved after immunosuppressive therapy (13). These findings underscore that BFP non-treponemal tests can be a sentinel marker for undiagnosed autoimmune disease, particularly in older adults without sexual risk factors.

Pregnancy is a special context: physiological immunological shifts produce BFP rates from 0.91% in developed countries to 28% in developing-country antenatal settings (3,34,42). The higher rates in low-income countries likely reflect endemic treponematoses (yaws) and coinfections (malaria, tuberculosis). In Ghana, yaws endemicity inflated syphilis seroprevalence estimates by one-third, with positive predictive value for active syphilis only 16.8% (6). This has major implications for WHO's same-day treatment policy: up to 28% of treated pregnant women may not have syphilis (3,53).

Novel Cause: mRNA COVID-19 Vaccination

The most clinically significant novel finding is that mRNA COVID-19 vaccines induce false-positive RPR reactivity. In a longitudinal cohort, 1.7% developed chronic false-positive RPR following booster vaccination, persisting up to 9 months (7). A pilot study found even higher rates on automated platforms: 18.4% false reactivity on BioPlex RPR after Moderna vaccination, compared to 5.3% on manual Sure-Vue and 2.6% on Macro-Vue (8). The proposed mechanism is lipid nanoparticle carriers generating cross-reactive antibodies against cardiolipin (8). In pregnant women with false-positive RPR, 48.1% had received COVID-19 vaccination within 300 days (22). Clinicians must now obtain vaccination history for any patient with unexpected low-titer RPR reactivity, especially if autoimmune workup is negative.

Titer as a Practical Discriminator

Across 80 studies, false-positive non-treponemal tests almost universally occur at low titers (≤1:4). In the large Chinese cohort, 96.7% of BFP cases had titers ≤1:4 (4). In congenital syphilis evaluation, RPR titers ≥1:4 were almost three times more likely in infants with probable congenital syphilis (OR 2.91, $p<0.05$) (9). For point-of-care tests, sensitivity for active syphilis jumped from 42.9–82.5% at low titers to 94.1% at RPR ≥1:8 (20,21). This provides a simple, actionable rule: low-titer (≤1:4) reactivity in a low-risk patient (no HIV, no symptoms, no known exposure) is highly likely to be false-positive, especially if there is recent vaccination or autoimmune history. High-titer (≥1:8) reactivity strongly suggests true infection and warrants treatment.

Clinical Implications: Overtreatment, Provider Error, and Surveillance Noise

Unnecessary treatment is the most direct harm. In the reverse screening algorithm for congenital syphilis, 15% of infants in the "unlikely" group received intramuscular penicillin despite AAP guidelines recommending observation (9). In developing-country antenatal clinics using same-day treatment algorithms, 1% of all screened women received unnecessary penicillin (53). In the US military health system, one-third of surveillance-identified syphilis cases were not true cases (14). German proficiency testing found 10.2% of laboratories incorrectly reported active infection in seronegative donors (72). These data suggest that false-positive non-treponemal tests drive substantial antibiotic overuse, with attendant risks of allergic reactions, injection pain, and resource diversion.

Provider confusion is endemic. A retrospective review of 108 positive syphilis serologies found 11.1% misinterpreted, with family medicine providers accounting for approximately 50% of errors ($p=0.003$) (11). Infectious disease and OB/GYN providers had near-perfect accuracy (1 error among 54.3% of cohort). Syphilis serology interpretation is one of the most frequently asked questions received by

pathology laboratories (11). An educational intervention for family medicine residents showed no statistically significant improvement (post-hoc power 2.7–31.8%), suggesting that passive lectures are insufficient (18). Electronic medical record decision support and algorithmic result formatting may be more effective.

Surveillance and public health impact is underappreciated. ICD-9 codes for syphilis had a positive predictive value of only 0.42, compared to 0.82 for reportable medical events (14). Clinical staging was grossly inaccurate regardless of method (PPV 0.30 for ICD-9, 0.49 for reportable events) (14). False-positive non-treponemal tests thus introduce substantial noise into syphilis surveillance systems, potentially distorting epidemic trends and resource allocation.

Healthcare utilization and costs. Inappropriate CSF-VDRL testing occurred in 98.2% of cases, and every false-positive CSF-VDRL occurred in inappropriately tested patients (10). The reverse algorithm generates more discordant results requiring follow-up treponemal testing (15,24). In the UK, eliminating routine rescreening of low-risk heterosexual patients would save £42,083 with no missed infections (51). In Nigeria, US$37,424 was spent over 10 years to detect 9 confirmed syphilis cases (seroprevalence 0.05%) (30). False-positive non-treponemal tests are not merely laboratory curiosities—they have measurable economic consequences.

Testing Algorithm Considerations

The traditional algorithm (non-treponemal test first, then treponemal confirmation) has lower false-positive rates in low-prevalence populations: reverse screening yielded 0.6% false-positives vs. 0.0% for RPR (p=0.03) (25). However, the reverse algorithm detects more latent and past infections, which is advantageous for public health but problematic for individual management because discordant results (treponemal-positive/non-treponemal-negative) are common (15,17,24). In pregnant women, the risk of vertical transmission with isolated reactive treponemal test is low (29). The CDC continues to recommend the traditional algorithm, but many laboratories have adopted reverse screening due to automation (24,29).

Platform-specific differences matter. The Lumipulse G TP-N produced 27 fewer false-reactive results than Bioplex 2200 Syphilis IgG (NPA 77.3% vs 15.9% against TP-PA) (47). The BioPlex RPR missed 91% of low-titer (1:1) infections (48). Laboratories should validate their specific platforms and report false-positive rates to clinicians.

Management Strategies

Confirmatory testing is the cornerstone. Every reactive non-treponemal test must be confirmed with a treponemal assay (FTA-ABS or TP-PA) (16,61,66). In the reverse algorithm, a second treponemal test (preferably TP-PA) resolves discordant results (17,68). Reflexive confirmatory testing (automatically performed by the laboratory) reduces delays and provider error (28,39).

Detailed clinical history is essential: recent vaccination (7), prior syphilis treatment (17), sexual history (17), and autoimmune conditions (4). For pregnant women, effective communication at delivery prevents unnecessary neonatal workups (9).

Algorithmic triage is promising. An automated public health algorithm that compared reactive non-treponemal tests to prior results and current treponemal findings removed 64.9% of reactive records while maintaining 98.4% sensitivity, tripling specificity from 27.5% to 72.9% (19). This approach is scalable.

Point-of-care tests (POCTs) that detect both treponemal and non-treponemal antibodies enable same-day decisions. The MedMira Multiplo POCT had 82.5% sensitivity for RPR-positive samples and 94.1% for RPR ≥1:8, allowing clinicians to initiate or withhold treatment appropriately (21). However, the non-treponemal component of dual POCTs has lower sensitivity at low titers (20).

Provider education should target family medicine and emergency medicine clinicians (11,18). Electronic health record–based decision support (11) and automated result interpretation (19) may be more effective than lectures.

Future Research Directions

(1) Prospective studies measuring patient anxiety and quality of life after false-positive results. (2) Platform-specific false-positive rate validation in local populations. (3) Randomized trials of electronic decision support vs. traditional education for provider interpretation. (4) Cost-effectiveness analysis of automated algorithmic triage in public health surveillance. (5) Mechanistic studies of vaccine-induced anticardiolipin antibodies.

CONCLUSION

False-positive non-treponemal syphilis tests are not rare laboratory curiosities but common clinical events in specific populations: HIV-infected persons (13.5%), pregnant women (up to 28%), and increasingly after mRNA COVID-19 vaccination (up to 18.4%). They cause measurable harm, including unnecessary penicillin treatment (15% of low-risk neonates), provider misinterpretation (11% of positive results, especially by family medicine), and surveillance inaccuracies (PPV for ICD-coded syphilis 0.42). Low

titers (≤1:4) characterize 96.7% of false-positives, providing a simple discriminator: low-titer results in low-risk patients are highly likely false-positive, while high-titer (≥1:8) results warrant treatment.

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