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REVIEW

A Systematic Review and Meta-Analysis of Diagnostic Test Accuracy for Human Toxoplasmosis: Performance, Populations, and Validation Gaps

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Background: Accurate and timely diagnosis of toxoplasmosis is crucial for clinical management, particularly in high-risk populations. Despite a diverse diagnostic landscape spanning laboratory-based serology, molecular assays, point-of-care (POC) devices, and emerging technologies, a consolidated quantitative synthesis of their performance and clinical readiness is lacking.

Methods: This systematic review and diagnostic test accuracy meta-analysis employed a dual-method design, integrating evidence mapping and quantitative synthesis. We searched Embase, PubMed, Scopus, IEEE Xplore, and other databases from January 1, 2010, to December 31, 2025, for studies evaluating diagnostic tests for human toxoplasmosis. Evidence mapping classified technologies by target, specimen, and validation stage (Tiers 0–3). Meta-analysis pooled sensitivity and specificity using bivariate random-effects models for subgroups with sufficient data. Risk of bias was assessed using QUADAS-2.

Results: Evidence mapping identified 175 studies yielding 309 diagnostic test evaluations across 37 target groups, 20 clinical populations, and 11 technological categories. Most studies evaluated conventional laboratory assays (75.9%), followed by point-of-care tests (20.9%) and emerging technologies (3.2%). Meta-analysis included 182 test evaluations (42,287 samples) and showed that accuracy differed by detection target, population, and platform. Among targets, IgG+IgM and IgG avidity demonstrated the strongest combined performance (IgG+IgM sensitivity 94.8% [95% CI 89.4–97.5], specificity 96.7% [93.9–98.3]; IgG avidity sensitivity 90.8% [84.9–94.5], specificity 97.1% [91.7–99.0]), whereas DNA assays showed a rule-in profile with lower sensitivity (66.0% [51.9–77.7]) but high specificity (96.2% [94.3–97.5]). Performance varied across clinical populations, with a notable diagnostic gap in other immunocompromised patients (sensitivity 55.7% [33.1–76.2] despite specificity 97.7% [92.3–99.3]). By platform, POCTs had high specificity (97.4% [95.4–98.5]) and good sensitivity (87.7% [80.3–92.6]) compared with conventional assays (84.7% [80.2–88.3]; 95.5% [94.2–96.6]).

Conclusion: Diagnostic accuracy for toxoplasmosis is highly context-dependent. Serology remains central, with IgG avidity (and high-performing IgG+IgM strategies) supporting infection dating, and POCTs offering rapid, high-specificity rule-in utility when embedded in appropriate clinical algorithms. The persistently reduced sensitivity in immunocompromised populations highlights an urgent unmet need for improved diagnostics and more rigorous, standardized real-world validation.

Keywords: toxoplasmosis, diagnostic accuracy, meta-analysis, point-of-care testing, IgG avidity, evidence mapping

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Introduction

Toxoplasmosis, caused by the protozoan parasite *Toxoplasma gondii* (*T. gondii*), remains a globally important infectious disease due to its high prevalence and its potentially severe outcomes in high-risk populations, including pregnant women, fetuses/newborns, and immunocompromised individuals.[1] In these groups, delayed recognition and treatment can lead to substantial clinical burden, including congenital disease and long-term neurological and ocular complications such as ocular toxoplasmosis (OT), a leading cause of infectious posterior uveitis.[2] For this reason, diagnostics are central to clinical decision-making, prevention of vertical transmission, and effective patient management.

Despite long-standing availability of laboratory-based tests, diagnosing toxoplasmosis continues to present practical and methodological challenges. Serology and molecular techniques can provide robust evidence of exposure or active infection; however, they are influenced by various factors including the timing of infection, interpretation of antibody profiles, specimen type, and access to laboratory infrastructure. In ocular toxoplasmosis, for instance, diagnosis in atypical cases is complicated by phenotypic overlap with other retinochoroiditides and often depends on subjective expert interpretation of multimodal imaging, highlighting the limitations of serology alone in complex clinical presentations.[3] In many contexts, testing is limited by cost, turnaround time, availability of trained personnel, and the need for specialized equipment, which can restrict timely diagnosis and delay interventions where rapid decision-making is critical.[4]

In parallel with established laboratory workflows, the diagnostic landscape has expanded to include a broad spectrum of platforms and device-enabled approaches, ranging from rapid immunoassays and portable molecular systems to biosensors, microfluidic devices, and reader-assisted formats. These approaches are increasingly reported across biomedical and engineering literature, resulting in a broad yet fragmented evidence base. Moreover, diagnostic performance claims are not always comparable across studies because evaluations vary in validation maturity, reference standards, specimen matrices, and whether testing is performed in clinical populations or under analytical/contrived conditions.

A key challenge for clinicians, researchers, and implementers is therefore not merely the abundance of technologies but also the lack of consolidated mapping of what has been evaluated, in which settings, using which specimens and targets, and with what level of clinical validity. Without an integrated view, it becomes challenging to judge readiness for clinical adoption, to compare diagnostic classes fairly, and to identify translational gaps where promising approaches remain limited by study design, bias risks, or insufficient field-relevant validation.

Accordingly, this study maps the evidence on toxoplasmosis diagnostics published between 2010 and 2025 across laboratory-based and device-enabled approaches. We classify diagnostic platforms by detection target, specimen matrix, and validation characteristics; summarize reported diagnostic performance using structured evidence mapping and diagnostic accuracy meta-analysis where feasible; and identify evidence gaps that inform future evaluation and implementation. Point-of-care technologies are regarded as an important subset of the overall diagnostic landscape, with their deployment implications emphasized primarily in the Discussion.

Materials and Methods

Study Design and Registration

This study was a systematic review and meta-analysis of diagnostic test accuracy (DTA) for human toxoplasmosis, with the primary aim of synthesizing and comparing the accuracy of available tests. The secondary aims were to analyze performance across key clinical populations and to map the validation maturity of the evidence base, thereby identifying critical gaps. The review was conducted according to the PRISMA-DTA 2020 statement.[5] An internal protocol guided the process, informed by Cochrane and PRISMA-DTA guidelines; the protocol was not prospectively registered.

Information Sources and Search Strategies

A systematic search was performed across biomedical, engineering, and multidisciplinary databases to capture the full spectrum of diagnostic literature, from clinical evaluations to device-development reports. Databases included PubMed, Embase, Scopus, Web of Science Core Collection, ScienceDirect, IEEE Xplore, Engineering Village (Compendex/Inspec), ClinicalTrials.gov, and ProQuest Dissertations & Theses Global.

The search strategy combined core concepts of *Toxoplasma gondii* / toxoplasmosis with terms for diagnostic testing, point-of-care, and device-based detection. Controlled vocabularies (MeSH, Emtree) were used where available, supplemented by extensive free-text synonyms tailored to each database's focus (eg, engineering terminology for IEEE Xplore). Searches were limited to January 1, 2010–December 31, 2025, with no initial language restrictions. One study accepted in 2025 but published online in early 2026 was included after manual screening. The complete search strings are provided in Supplementary Table S1.

Eligibility Criteria

Studies were eligible if they: (1) were original research evaluating a diagnostic test, device, or platform for *T. gondii*; (2) used human specimens or relevant matrices; (3) targeted antibodies (IgG, IgM, avidity), nucleic acids (DNA), antigens, or image-based patterns; (4) reported primary quantitative performance data (eg, 2×2 table, sensitivity/specificity, AUC, LOD); and (5) were published in English. For inclusion in meta-analysis, an acceptable reference standard and complete 2×2 data were required.

Exclusion criteria included: veterinary-only studies, reviews/editorials/case reports without primary data, studies focused on treatment/epidemiology/pathogenesis, insufficient methodological or quantitative data, and publications outside the date/language range.

Study Selection and Data Extraction

Study selection followed the PRISMA 2020 flow diagram (Figure 1). Two reviewers (D.S. and A.S.) independently screened titles/abstracts and full texts against eligibility criteria. Disagreements were resolved by consensus or a third reviewer (L.E.F).

Data were extracted in duplicates using a piloted, standardized form in Microsoft Excel. Extracted items included:

- Bibliographic/Contextual: Author, year, country, study design, clinical population, sample type, sample size.
- Index Test: Technology category (conventional/POCT/emerging), platform, detection target, specimen matrix, time-to-result.
- Reference Standard: Method used for comparison.
- Performance Data: TP, FP, FN, TN counts, sensitivity, specificity, limit of detection (LOD).
- Other: Funding and conflicts of interest.

For this classification, conventional tests were defined as established laboratory-based methods requiring centralized infrastructure and specialized personnel. Point-of-care (POCT) referred to rapid assays designed for use near the patient, while emerging technologies encompassed novel approaches such as biosensors and machine learning-based tools still in early validation stages.

Unit of Analysis and Data Handling

The study (publication) was the primary unit for descriptive analyses and characterization (n=175). Within studies, individual test evaluations (unique index test/cohort combinations) were the unit for accuracy assessment and validation staging. A single study could contribute multiple test evaluations (eg, evaluating both IgG and IgM). From the 175 included studies, 309 test evaluations were extracted.

For the diagnostic test accuracy (DTA) meta-analysis, we included only test evaluations with a complete 2×2 contingency table (true positives, false positives, false negatives, true negatives) derived from an appropriate reference standard. This resulted in 182 test evaluations eligible for quantitative synthesis. This dataset of 182 evaluations forms the basis for all subsequent pooled analyses and subgroup comparisons (by detection target, clinical population, and technology platform), unless otherwise specified (see Subgroup, Heterogeneity, and Sensitivity Analyses for details on the technology subgroup).

Validation Stage Classification (Tiered Framework)

To distinguish analytical feasibility from clinical readiness and to identify validation gaps, each test evaluation was

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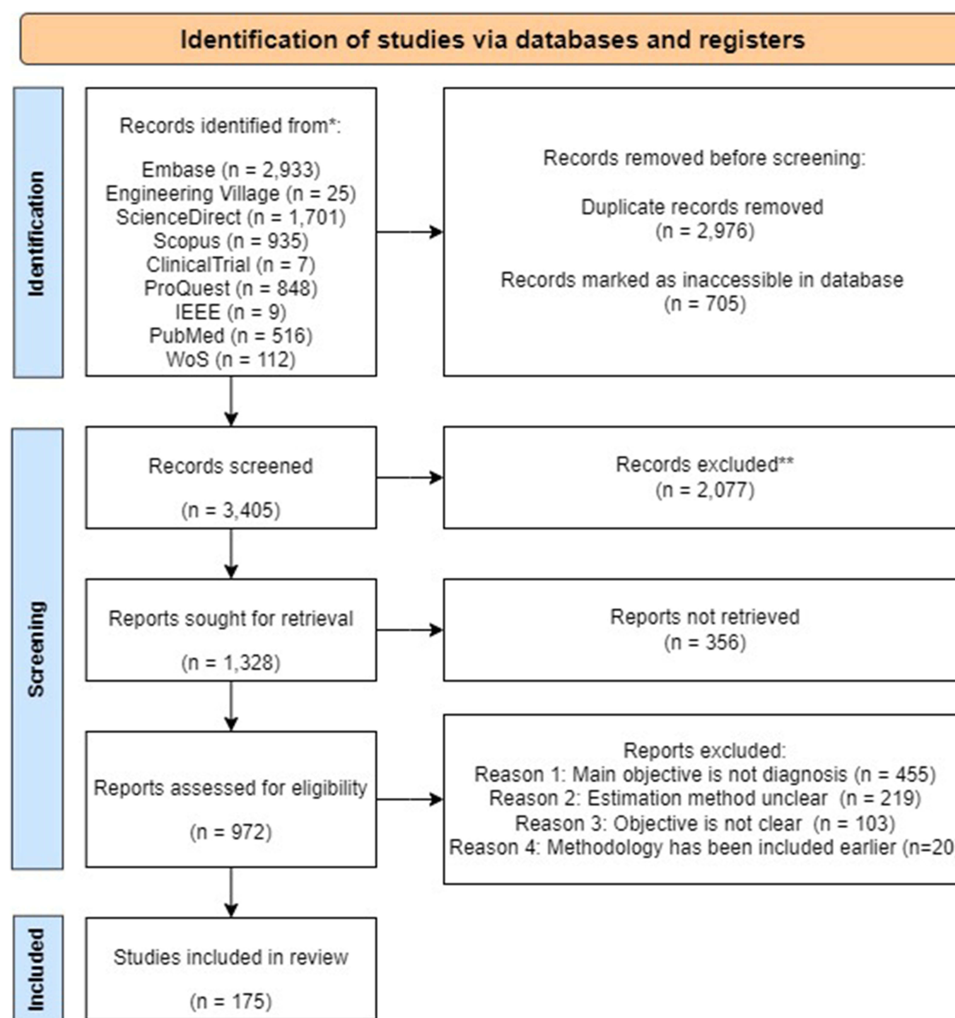

Figure 1 PRISMA flow diagram summarizing the study selection process. Of 7,086 records identified, 972 full-text articles were assessed; 797 reports were excluded (mainly not diagnostic evaluation, unclear estimation method, or unclear primary objective). A total of 175 studies were included in the systematic review, contributing 309 unique diagnostic test evaluations for evidence mapping, of which 182 evaluations with complete 2×2 data were included in the quantitative meta-analysis.

classified into a validation tier:

- Tier 0 (Analytical): Contrived/spiked samples, benchtop feasibility without patient specimens.
- Tier 1 (Clinical-Lab): Human specimens tested under controlled laboratory conditions.
- Tier 2 (Near-Patient Pilot): Limited-site evaluations in workflows approximating intended use.
- Tier 3 (Field Validation): Multi-site deployment under real-world operational conditions.

Classification was based on specimen provenance and workflow description; the minimum defensible tier was assigned if details were unclear.

Risk of Bias Assessment

The methodological quality of studies providing accuracy data was assessed using QUADAS-2 across four domains: Patient Selection, Index Test, Reference Standard, and Flow & Timing. Two reviewers performed assessments independently, with disagreements resolved by consensus. Judgments (Low/High/Unclear risk) were based on pre-defined signaling questions regarding sampling, blinding, threshold pre-specification, the appropriateness of reference standard, timing, and participant flow.

Data Synthesis and Analysis

The synthesis was designed to address the three core aspects of the review: Diagnostic Performance, Population-Specific Analysis, and Evidence/Validation Mapping.

Descriptive Analysis and Evidence Mapping

Descriptive statistics summarized the landscape of evidence, including temporal/geographic trends, technology platforms, detection targets, sample types, operational metrics (time-to-result), and validation maturity (Tier distribution). Where available, reported analytical performance metrics—in particular the limit of detection (LOD)—were also extracted and mapped to characterize the methodological rigor and comparability of test evaluations. This mapping provides context for the quantitative synthesis and highlights key translational and standardization gaps in the evidence base.

Diagnostic Test Accuracy Meta-Analysis (Performance)

The primary quantitative synthesis estimated pooled sensitivity and specificity (with 95% CI) using a bivariate random-effects model (or HSROC model for threshold effects). Between-study heterogeneity was assessed using the bivariate random-effects variance components (τ^2) and the estimated correlation (ρ), alongside visual inspection of study dispersion in ROC space and study-level forest plots.

Subgroup, Heterogeneity, and Sensitivity Analyses

To investigate heterogeneity and address the review's secondary aims regarding population-specific performance, pre-planned analyses were conducted through subgroup meta-analyses, assessment of heterogeneity, sensitivity analyses, and investigation of reporting bias.

Separate bivariate random-effects models were fitted for clinically meaningful subgroups defined by:

- Detection Target (IgG, IgM, IgG Avidity, DNA)
- Clinical Population (pregnant women, immunocompromised patients)
- Technology Platform (conventional laboratory vs point-of-care)

For the technology platform comparison, the analysis focused on conventional versus point-of-care tests. Although the initial evidence mapping classified technologies into three broad categories—Conventional, Point-of-Care (POCT), and Emerging (machine learning, biosensors)—the "Emerging" category was pre-specified for exclusion from pooled subgroup analysis if fewer than 10 evaluations were available. This decision was based on the need for stable estimation and the profound methodological heterogeneity expected within this category.

Heterogeneity within each synthesis was assessed using the bivariate random-effects variance components for sensitivity and specificity (τ^2_sens and τ^2_spec) and their estimated correlation (ρ), alongside visual inspection of dispersion in ROC space and study-level forest plots. Between-subgroup differences were described by comparing pooled estimates and the extent of confidence interval overlap across stratified analyses.

To evaluate the robustness of key findings, sensitivity analyses were planned, including restriction to larger studies (sample size ≥ 50) for the most frequently evaluated target. For meta-analyses containing at least 10 studies, funnel plots were visually inspected to assess potential small-study effects or publication bias.

Software

Data management and evidence mapping used Microsoft Excel (Office 365). Statistical analyses and meta-analyses were conducted in R (v4.5.2) using the "mada" and "metafor" packages. All data and code are archived for reproducibility.

Result

Study Selection

The study selection process is summarized in the PRISMA flow diagram (Figure 1). From 7,086 initial records, 972 full-text articles were assessed. After eligibility screening, 797 reports were excluded, primarily because their main objective

was not diagnostic evaluation (n=455), they had an unclear estimation method (n=219), or an unclear primary objective (n=103). A total of 175 studies met all inclusion criteria and were included in the systematic review.[6–180] These 175 studies contributed 309 unique diagnostic test evaluations (ie, distinct index test/cohort combinations) for evidence mapping. Of these, 182 test evaluations provided complete dichotomous (2x2) data and were included in the quantitative meta-analysis. Further details are available in Supplementary Table S2 for full dataset characteristics.

Characteristics of Included Studies and Test Evaluations

Bibliometric and Temporal Trends

The 175 included studies were published between 2010 and 2025 (with one study accepted in 2025 published online in 2026).[180] Publication output showed progressive growth, increasing from 7 studies in 2010[6–12] to a peak of 20 studies in 2021,[115–134] indicating sustained and increasing research interest (Figure 2A).

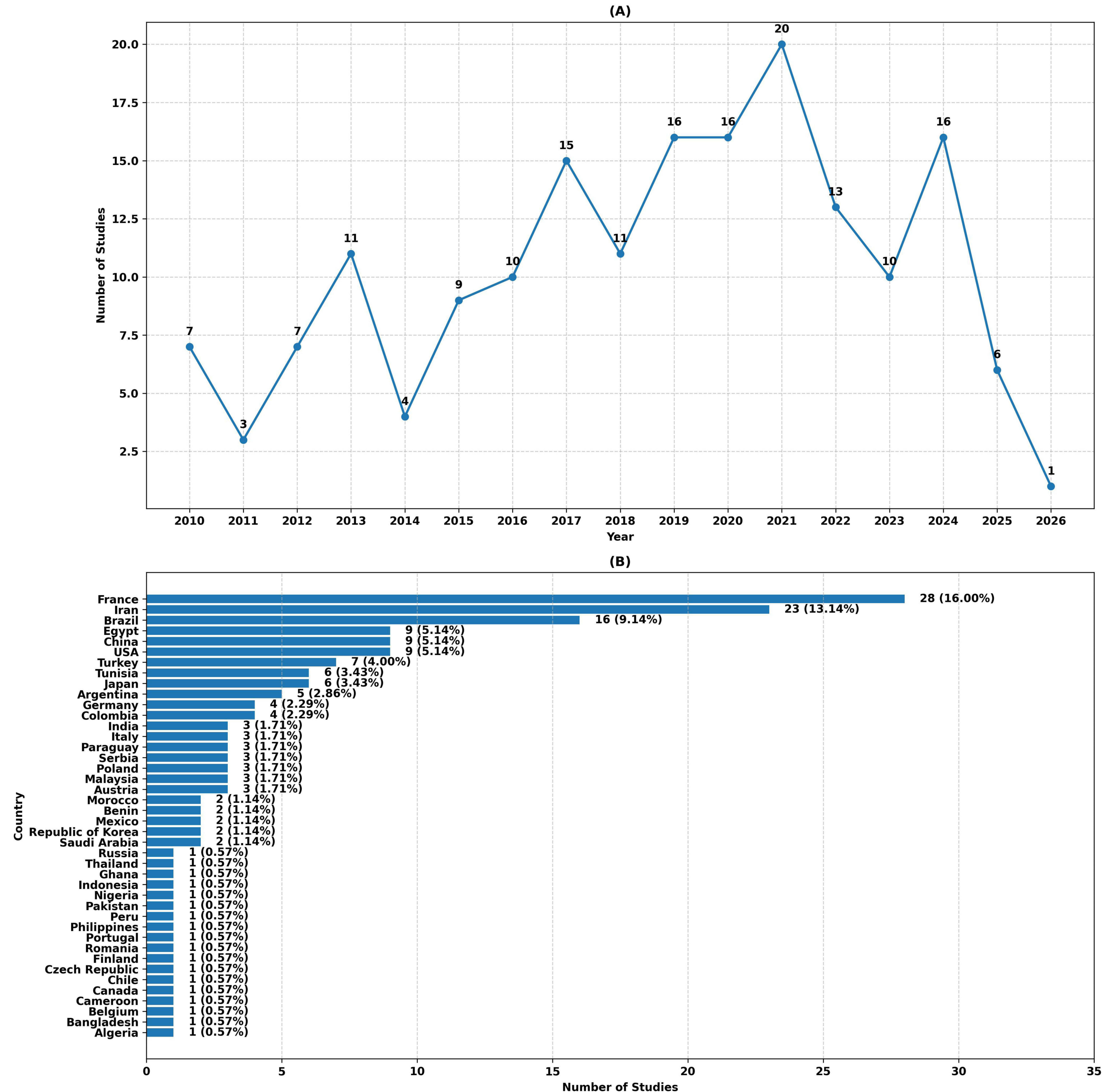

Figure 2 Temporal Trends and Geographic Distribution of Toxoplasmosis Diagnostic Studies (2010–2025). (**A**) Annual publication trend showing increasing research output, with peak activity in 2021. (**B**) Country Contribution to Publications, top 6 contributing countries: France (n=28), Iran (n=23), Brazil (n=16), Egypt (n=9), China (n=9) and USA (n=9).

Table 1 Characteristics of Included Diagnostic Studies (N=175)

Characteristic	Category	n (Studies)	% of 175 Studies
Geographic Distribution	France	28	16.00%
	Iran	23	13.14%
	Brazil	16	9.14%
	Egypt	9	5.14%
	China	9	5.14%
	USA	9	5.14%
	Other (36 countries)	81	46.29%
Study Design	Cross-sectional	40	22.86%
	Retrospective	34	19.43%
	Diagnostic Evaluation	24	13.71%
	Case-control	18	10.29%
	Cohort	17	9.71%
	Method development / analytical validation	11	6.29%
	Prospective	10	5.71%
	Other (Case series)	21	12.00%
Clinical Population	Pregnancy/Antenatal	65	37.14%
	General/Mixed	60	34.29%
	Ocular Toxoplasmosis	19	10.86%
	Congenital/Newborn/Infant	16	9.14%
	HIV/AIDS	8	4.57%
	Other Immunocompromised	7	4.00%

Notes: For multi-country studies, the country of the first author's primary affiliation was used for geographic classification. A complete extraction table is provided in Supplementary Table S2.
Abbreviation: N, total number of studies.

Research contributions were globally distributed across 42 countries. The top contributing countries were France (n=28 studies, 16.0%),[22,30,31,33,37,40,45,57,61,68,76,82,83,86,88,100,102,107,110,111,116,125,135,137,138,141,142,162] Iran (n=23, 13.1%),[12,18,20,47,53,62,63,66,81,87,91,92,94,108,112,119–121,124,127,136,143,154] Brazil (n=16, 9.1%),[10,21,39,43,49,50,58,64,65,70,89,101,103,129,172] and the USA, Egypt, and China (each with n=9, 5.1%) (Table 1 and Figure 2B).

Study Design and Clinical Populations

Cross-sectional design was the most common among the 175 included studies (n=40, 22.9%),[25,28,32,34,36,49,52,55,62,63,69,73,74,84–86,90,91,96,98,99,102,105,106,109,113,114,117–119,121,123,133,134,136,140,144,146,147,152] followed by retrospective (n=34, 19.4%)[13,16,22,29,33,45–49,56,60,62,65,67,68,72,76,78,80,82,83,100,107,110,111,115,125,130,135,137,138,141,142] and diagnostic evaluation studies (n=24, 13.7%)[11,15,19,21,26,27,30,31,39,41,51,54,66,80,90,92,96,105,112,127,139,148,159,168,169,172] (Table 1 and Figure 3A).

The most frequently studied clinical population was pregnant/antenatal women, represented in 65 studies (37.1%),[11,19,25–28,30,31,33–36,38,39,44,46,48,49,51,52,55–58,60–67,70–74,76–84,93,96–98,101,102,106–113,115,117,127,129,132,136,138,141,142,144,146,148–150,152,154,155,158,161,166,171] followed by general/mixed populations (60 studies,34.3%)[6–9,12–14,17,18,20–24,32,34,35,37,40–42,45,47,49,50,53,54,59,68,69,72–75,80,85–90,92,95,97–100,104,105,108–114,118,120–123,126,128,130,131,133–135,138–140,145,147,148,150,151,153,156,157,160,

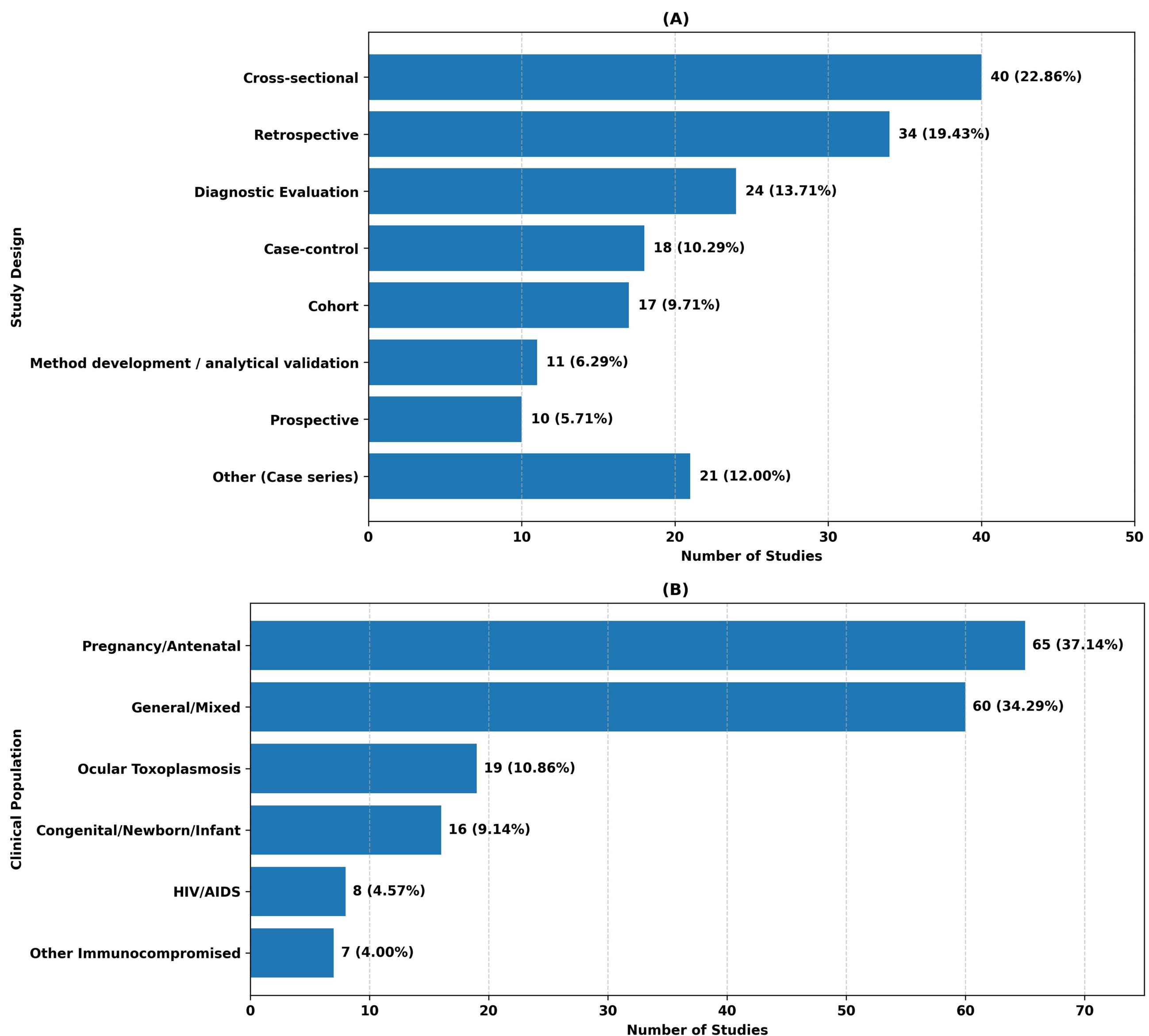

Figure 3 Bibliometric and temporal trends across included studies (N = 175). Panel (**A**) shows the distribution of study designs, and Panel (**B**) shows the distribution of clinical populations represented in the included evidence.

[162,163,165,167,168,170,172,173,176,178,179] and patients with ocular toxoplasmosis (19 studies, 10.9%) (Table 1 and Figure 3B). Studies on immunocompromised populations, particularly non-HIV groups, were less common (7 studies, 4.0%).

Diagnostic Technologies, Targets, and Specimens of Test Evaluations

The majority of the 309 test evaluations were based on conventional laboratory-based methods (245 evaluations; 79.3%).[6–180] Point-of-care (POC) platforms accounted for 56 evaluations (18.1%),[9,29,32,42,54,59,61,64,67,69,72,82,84,87,90,92,95,98,99,104,108,112,114,115,117,121,123,127,128,134,143,146–148,150,155,161,165,168–170,172,173] while emerging technologies (eg, machine learning, biosensors) were represented in only 8 evaluations (2.6%).[13,104,126,128,131,151,160,178]

Regarding detection targets, IgG was the most common (81 evaluations; 26.2%),[6–8,10,12–14,19,21,24–26,28,30,34,35,39,42,47,58,59,68,70,71,73–78,80,81,83,84,86–90,92–180] followed by IgM (40 evaluations; 12.94%),[6,10,18,20,26,30,36,42,53,65,73,77,84,91,113,142,146,162,172] parasite DNA (70 evaluations; 22.7%),[9,15,16,23,29,37,40,41,44,45,48,56,68,69,72,75,76,79,81,82,85,88,94,99,100,107,110,112,113,116,118,119,121,124,125,128,130,131,133–135,137,

[140,143,145,149,150,154,156–158,161,163,164,167,169,172,175,177,179] combined IgG+IgM (52 evaluations; 16.8%),[6,10,11,13,17,22,24,30–32,38,42,43,46,50,52,59,61,63,67,76,77,80,87,89,93,96,98–100,104,107,109–115,117,120,122,123,127,132,134,135,144,146,148,150,152,153,155,159,162,165,166,170,173,176] IgG Avidity (32 evaluations; 10.36%),[7,21,27,33,49,51,54,55,58,60,65–67,70,76,78,91,113,122,129,136,158,171] Antigen (7 evaluations, 2.27%)[73,97,103,116] and others (27 evaluations, 8.74%) encompassing a wide array of diagnostic approaches beyond standard serological and molecular targets. This category included the assessment of IgA antibodies and IgG subclasses for enhanced serological profiling, the evaluation of specific host biomarkers like anti-Hsp70.1 IgG, and the use of machine learning algorithms for the analysis of clinical images. It also captured studies focused on novel antigen-antibody interactions, such as those involving recombinant GRA7 and AMA1 proteins in experimental immunoassays.[15,17,24,30,32,41,43,51,52,63,65,71,77,90,104,112,123,126,131,133,134,140,141,160,163,174]

Serum was the predominant specimen type, used in 214 evaluations (69.3%).[6–180] Other specimen types included unspecified blood (10.7%),[16,43,45,56,63,69,76,77,79,81,82,85,88,94,107,112,119,121,124,125,133,135,137,140,145,156,164,167,169,172,177,179] whole blood (5.2%),[9,65,99,100,107,110,112,119,149,155,161,169] plasma (2.91%)[14,38,42,54,124,152,158] and specialized clinical matrices such as ocular fluid (8,4%),[15,75,103,123,131,140,157,159,160,163,172,175] amniotic fluid (1.94%),[37,40,48,68,132] and urine (1.62%)[73,99,130] (Table 2 and Figure 4).

Operational Readiness and Validation Maturity

Among the 309 test evaluations for which validation stage could be classified, only 71 (23%) reported quantitative time-to-result data.[6,9,11,18,19,21,29,32,33,37,41,44,46,49,53–56,58,59,61,63,65,67–82,84–180] Among this subset of studies, the majority described rapid diagnostic protocols, with 74.7% delivering a result within 30 minutes and nearly half (45.1%) achieving

Table 2 Characteristics of Diagnostic Test Evaluations Included in Evidence Mapping (N = 309)

Characteristic	Category	n (Evaluations)	% of 309 Evaluations
Technology Category	Conventional/Gold Standard	245	79.29%
	Point-of-Care Testing (POCT)	56	18.12%
	Emerging (ML/Biosensors)	8	2.59%
Detection Target	IgG	81	26.21%
	IgM	40	12.94%
	Nucleic Acid (DNA)	70	22.65%
	IgG + IgM (Combined)	52	16.83%
	IgG Avidity	32	10.36%
	Antigen	7	2.27%
	Other	27	8.74%
Sample Type	Serum	214	69.26%
	Blood (Unspecified)	33	10.68%
	Whole Blood	16	5.18%
	Amniotic Fluid	6	1.94%
	Plasma	9	2.91%
	Urine	5	1.62%
	Ocular Fluid / Other	26	8.41%

Notes: The table summarizes the distribution of technology platform, detection target, and specimen/sample type; percentages are calculated using N = 309 evaluations, with each evaluation contributing one count per characteristic category.

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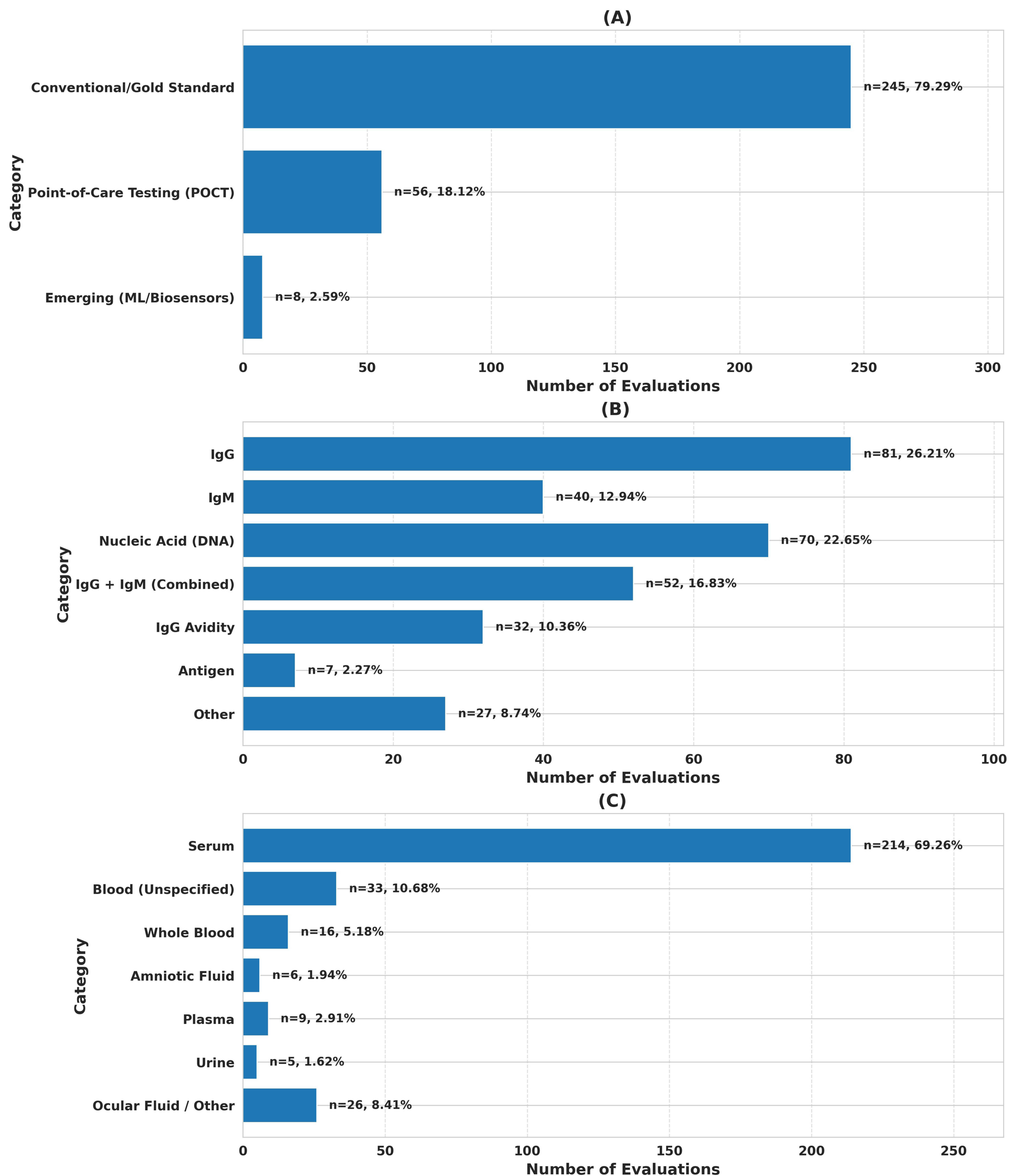

Figure 4 Distribution of diagnostic technologies (**A**), detection targets (**B**), and specimen/sample types (**C**) across included test evaluations (N = 309). Percentages are calculated based on total evaluations.

a result in 10 minutes or less (Table 3). Reported assay times demonstrated substantial variation, ranging from 1 minute to 115 minutes. Further details are available in Supplementary Table S3.

In contrast to the sparse temporal data, information on the validation stage was available for all 309 test evaluations. Analysis using a tiered validation framework revealed that the evidence base is predominantly composed of early-stage

Table 3 Distribution of Time-to-Result Categories Among Evaluations Reporting Quantitative Assay Turnaround Time (n = 71)

Time Category	Count	Percentage (%)
≤10 min (Ultra-rapid)	32	45.1
11-30 min (Rapid)	21	29.6
31-60 min (Moderate)	13	18.3
61-120 min (Extended)	5	7

Notes: Counts and percentages summarize reported time-to-result strata, highlighting the proportion of ultra-rapid (≤10 min) and rapid (11–30 min) diagnostic protocols.

evaluations. A total of 115 evaluations (37.2%) were classified as Tier 0 (analytical/contrived samples only), representing proof-of-concept studies without clinical specimen testing. A further 100 evaluations (32.4%) were classified as Tier 1 (clinical laboratory validation), involving human specimens tested under controlled laboratory conditions. Another 87 evaluations (28.2%) involved general clinical sample testing without broader validation, corresponding to Tier 2 (near-patient pilot). In stark contrast, only 7 evaluations (2.3%) reached Tier 3, defined as large-scale field validation under real-world conditions. This distribution underscores a significant translational gap between initial test development and the generation of implementation-ready evidence.

Risk of Bias Assessment

Methodological quality, assessed using QUADAS-2 for the 175 included studies, revealed substantial concerns (Table 4 and Figure 5). The overall risk of bias was high in 139 studies (79.4%) and unclear in 36 studies (20.6%); no study was rated as low risk.

Consistent with the overall rating, the domain with the highest proportion of high-risk judgments was Patient Selection (103 studies, 58.9%), primarily due to the prevalent use of case-control designs with non-representative controls and non-consecutive sampling.[8,9,13,15,18–24,26,27,29,32–35,40,42,43,45–47,49,52–55,58–68,70,72–180] The Index Test and Reference Standard domains were dominated by unclear risk ratings (85.7% and 82.9%, respectively), reflecting a critical deficit in reporting of pre-specified thresholds, blinding procedures, and reference standard methodology.

Table 4 Summary of Risk of Bias Assessment Using QUADAS-2

QUADAS-2 Domain	High Risk	Unclear Risk	Low Risk	Primary Concerns & Rationale
Patient Selection	103 studies (58.9%)	68 studies (38.9%)	4 studies (2.3%)	Case-control designs with spectrum bias; inadequate sampling; non-representative controls
Index Test	17 studies (9.7%)	150 studies (85.7%)	8 studies (4.6%)	Lack of pre-specified thresholds; insufficient blinding; inadequate test description
Reference Standard	29 studies (16.6%)	145 studies (82.9%)	1 study (0.6%)	Poorly described methodology; inconsistent application; inappropriate reference standards
Flow & Timing	66 studies (37.7%)	84 studies (48.0%)	25 studies (14.3%)	Inappropriate test intervals; partial verification bias; differential verification
Overall Risk	139 studies (79.4%)	36 studies (20.6%)	0 studies (0.0%)	Critical flaws across multiple domains; no studies achieved low risk status

Notes: Risk of bias was assessed for all 175 included studies using QUADAS-2. Percentages are calculated based on the total number of studies assessed in each domain (n=175). Unclear risk ratings were assigned when insufficient information was reported to make a definitive judgment. The overall risk of bias for each study was determined based on ratings across all four domains.

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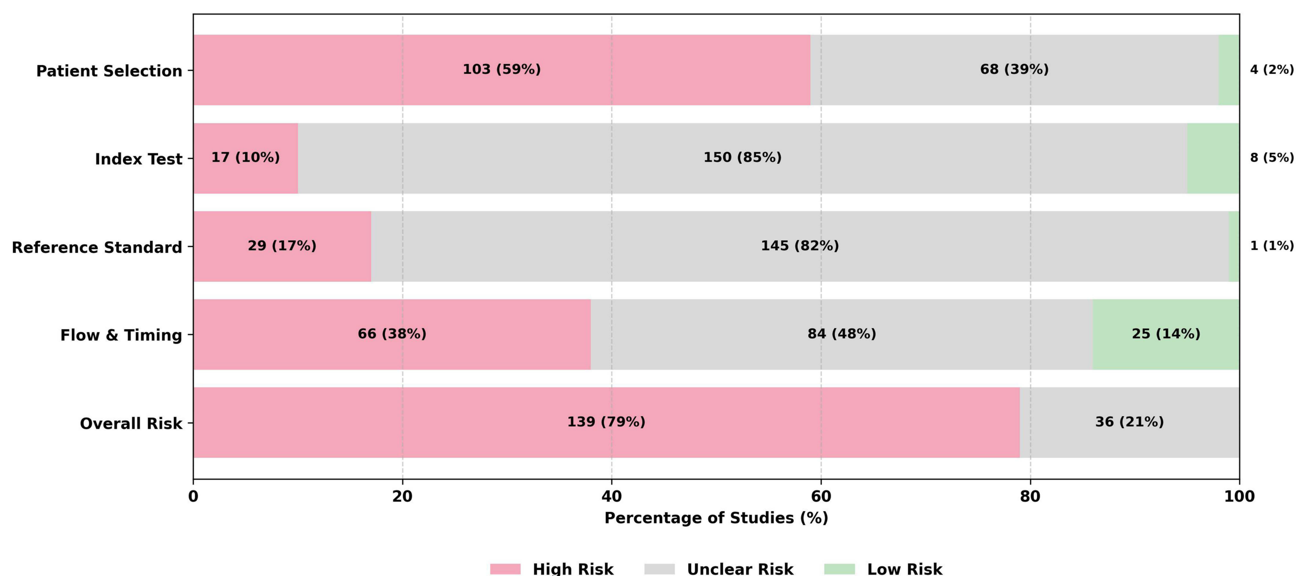

Figure 5 Risk of Bias Assessment Using QUADAS-2 (n=175). Distribution of low, unclear, and high risk judgments across QUADAS-2 domains. Patient Selection had the highest high-risk proportion (58.9%), while Index Test and Reference Standard were dominated by unclear risk ratings (85.7% and 82.9%, respectively). The overall risk of bias was high in 139 studies (79.4%) and unclear in 36 studies (20.6%); no study achieved low risk status.

Meta-Analysis of Diagnostic Accuracy and Associated Heterogeneity

Overall Accuracy by Detection Target

The quantitative synthesis included 182 (58.9%) test evaluations from the 309 identified in evidence mapping, comprising 42,287 total samples. Pooled sensitivity and specificity were estimated using a bivariate random-effects model (Reitsma), which jointly synthesizes sensitivity and specificity while accounting for their correlation across studies and enabling inference in ROC space. To ensure numerical stability in sparse strata with zero cells, a continuity correction (CC) of 0.5 was applied where required for estimation on the logit scale (Table 5).

Across detection targets, pooled accuracy differed markedly (Table 5 and Figure 6). The highest combined performance was observed for IgG+IgM (combined) and IgG avidity, both demonstrating high pooled sensitivity and specificity. Specifically, IgG+IgM achieved pooled sensitivity 94.8% (95% CI: 89.4–97.5) and specificity 96.7% (93.9––98.3), while IgG avidity showed pooled sensitivity 90.8% (84.9–94.5) and specificity 97.1% (91.7–99.0) (Table 5 and Figure 6). In ROC space, IgG+IgM also exhibited substantial dispersion in study operating points, reflected by large bivariate variance components (τ^2_sens = 2.853; τ^2_spec = 1.944) and a strong positive correlation (ρ = 0.854), consistent

Table 5 Pooled Diagnostic Accuracy by Detection Target from the Quantitative Meta-Analysis (n = 182 Evaluations; 42,287 Total Samples)

Target Group	n	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	τ^2_sens	τ^2_spec	ρ	CC Applied?
IgG	61	90.9% (86.6–94.0%)	95.2% (92.4–97.0%)	2.707	2.805	−0.27	Yes
DNA	41	66.0% (51.9–77.7%)	96.2% (94.3–97.5%)	3.149	1.111	0.284	Yes
IgM	29	74.5% (63.4–83.1%)	96.2% (93.2–97.9%)	1.496	2.209	−0.21	Yes
IgG+IgM	22	94.8% (89.4–97.5%)	96.7% (93.9–98.3%)	2.853	1.944	0.854	Yes
IgG Avidity	10	90.8% (84.9–94.5%)	97.1% (91.7–99.0%)	0.513	2.023	−1	Yes
Antigen	5	87.5% (79.5–92.7%)	87.5% (78.4–93.1%)	0.303	0.359	1	No
Other	14	81.2% (65.2–90.9%)	96.4% (92.2–98.4%)	1.794	1.531	0.099	Yes

Notes: Pooled sensitivity and specificity (95% CI) were estimated using the bivariate random-effects (Reitsma) mo between-study heterogeneity is summarized by the variance components (τ^2_sens, τ^2_spec) and the sensitivity–specificity correlation (ρ). A continuity correction (CC = 0.5) was applied where required to handle sparse 2×2 data (zero cells).

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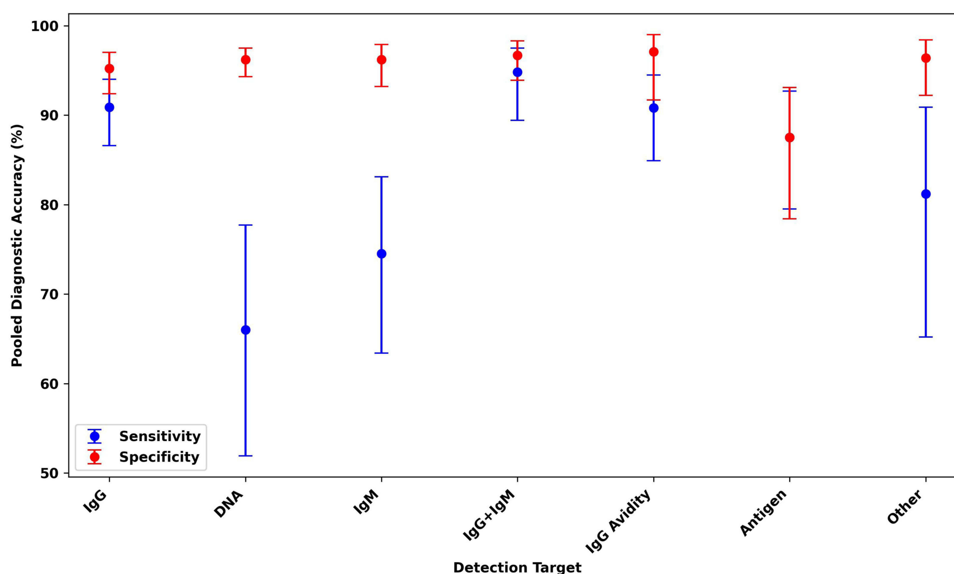

Figure 6 Pooled diagnostic accuracy by detection target, showing sensitivity and specificity with 95% confidence intervals estimated using the bivariate random-effects (Reitsma) model across included evaluations (n = 182; total samples = 42,287).

with meaningful variation in thresholds and implementation across settings (Table 5). This pattern is visually supported by the SROC plot for IgG+IgM (Figure 7), with corresponding study-level dispersion evident in the paired forest plots (Supplementary Figures S1 and S2).

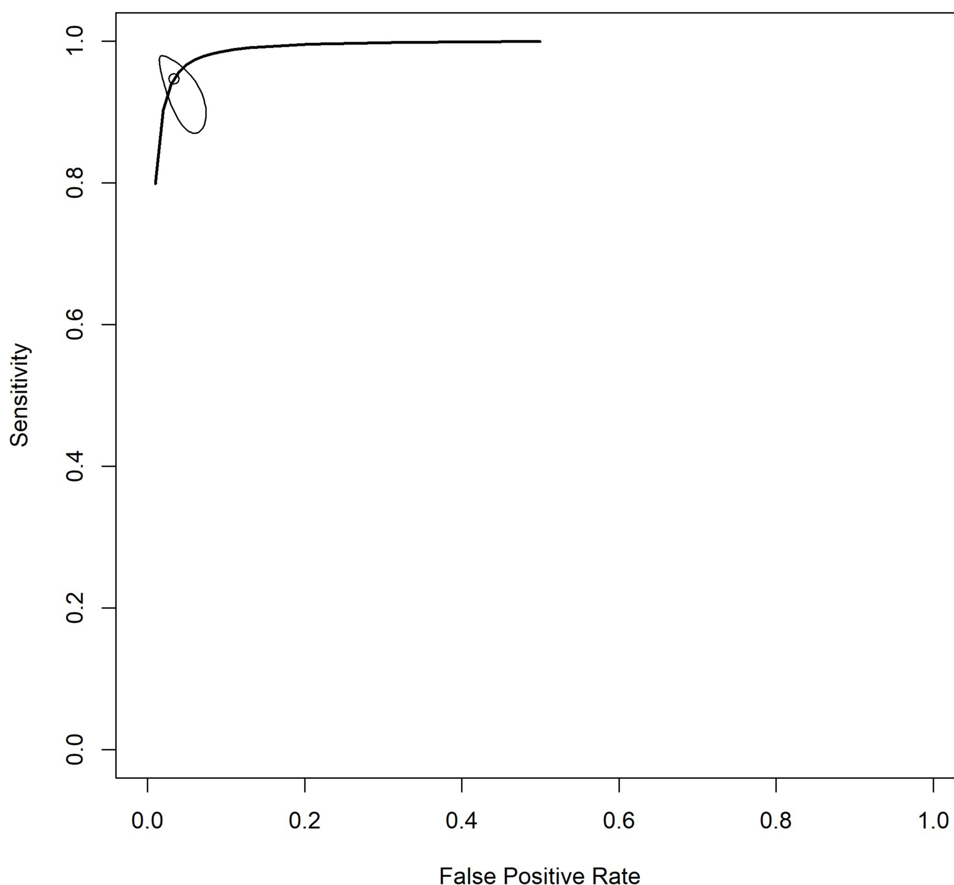

Figure 7 Summary ROC (SROC) plot for the IgG+IgM target group (Reitsma; n = 22 evaluations). Points represent individual study operating sensitivities/specificities, with the summary estimate and confidence region summarizing pooled performance and between-study dispersion.

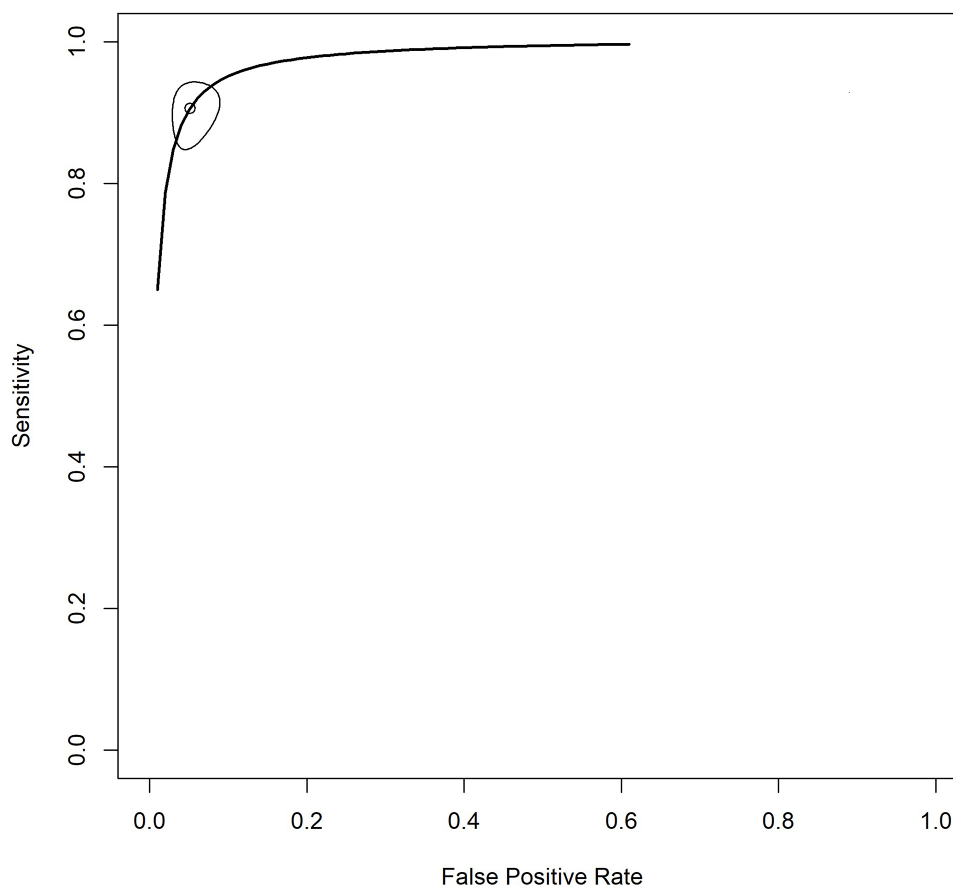

Figure 8 Summary ROC (SROC) plot for the IgG target group (Reitsma; n = 61 evaluations). Study-level operating points are displayed in ROC space, alongside the pooled summary estimate and its uncertainty to illustrate heterogeneity across evaluations.

The most frequently evaluated target, IgG (n = 61), yielded robust pooled estimates—sensitivity 90.9% (86.6–94.0) and specificity 95.2% (92.4–97.0)—but with substantial between-study variability (τ^2_sens = 2.707; τ^2_spec = 2.805) and a modest negative correlation (ρ = −0.27), indicating heterogeneous operating points rather than a single consistent threshold (Table 5). This heterogeneity is apparent on the SROC representation (Figure 8) and is further illustrated by the study-level forest plots (Supplementary Figures S3 and S4).

A clinically informative contrast was observed for DNA-based assays (n = 41), which showed the lowest pooled sensitivity (66.0%, 95% CI: 51.9–77.7) while maintaining high specificity (96.2%, 94.3–97.5), consistent with a “rule-in” profile in which false positives are uncommon, but missed detections remain an important limitation (Table 5 and Figure 6). Heterogeneity in sensitivity was considerable (τ^2_sens = 3.149), while specificity variability was more moderate (τ^2_spec = 1.111), suggesting that differences in assay protocols, specimen matrices, and reference standards may disproportionately affect sensitivity (Table 5). This trade-off and dispersion in ROC space are summarized in the SROC plot Figure 9, with complementary study-level patterns shown in forest plots (Supplementary: Figures S5 and S6).

For IgM (n = 29), pooled sensitivity was lower (74.5%, 63.4–83.1) with high specificity (96.2%, 93.2–97.9), consistent with a confirmatory profile (Table 5 and Figure 6). The negative correlation (ρ = −0.21) and sizeable variance components (τ^2_sens = 1.496; τ^2_spec = 2.209) indicate heterogeneity in operating points that may reflect threshold effects and population spectrum differences across studies (Table 5). These patterns are captured visually in Figure S7 and the corresponding forest plots (Supplementary Figures S8 and S9).

Antigen detection (n = 5) demonstrated balanced pooled accuracy (sensitivity 87.5%, specificity 87.5) with comparatively smaller variance components (τ^2_sens = 0.303; τ^2_spec = 0.359), but inference remains limited by the small number of evaluations; notably, a continuity correction was not applied in this subgroup (Table 5). These findings are best treated as

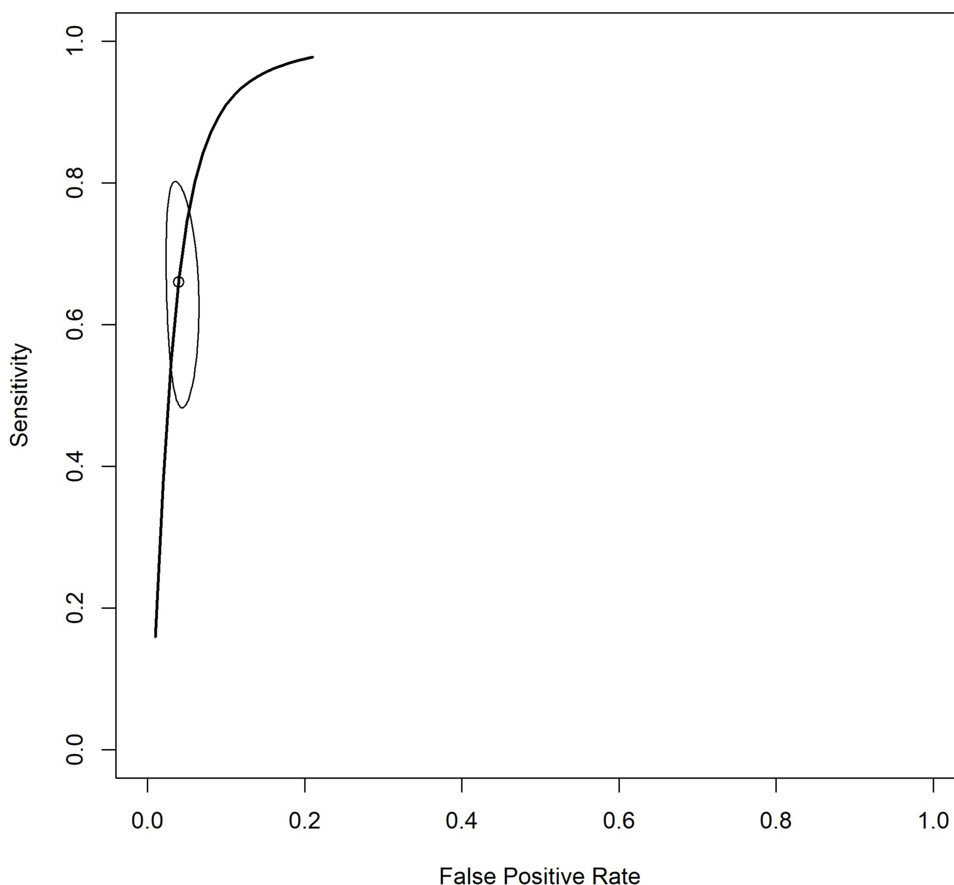

Figure 9 Summary ROC (SROC) plot for the DNA target group (Reitsma; n = 41 evaluations). The plot visualizes the trade-off between sensitivity and specificity across studies and the pooled summary operating point with associated confidence region.

supportive and are presented with full visual context in Figure 10 and paired forest plots (Supplementary: Figures S10 and S11). Finally, the other target category showed intermediate sensitivity (81.2%) with high specificity (96.4%) and notable heterogeneity (τ^2_sens = 1.794; τ^2_spec = 1.531), reflecting the diversity of assays subsumed within this grouping (Table 5). The overall dispersion is summarized in Figure S12 with supporting forest plots (Supplementary: Figures S13 and S14).

Subgroup Analysis by Clinical Population

Performance varied meaningfully across clinical populations (Table 6 and Figure 11). In general/mixed/other populations (n = 58), tests achieved the strongest overall performance with pooled sensitivity 90.6% (95% CI: 87.3–93.2) and specificity 96.6% (94.8–97.8), while heterogeneity remained substantial (τ^2_sens = 1.296; τ^2_spec = 1.951) and the correlation was modestly positive (ρ = 0.206), consistent with dispersion of operating points across heterogeneous real-world cohorts (Figures 11 and 12; Supplementary: Figures S15 and S16).

In pregnancy/antenatal cohorts (n = 74), pooled sensitivity was lower at 85.6% (78.8–90.4) with similarly high specificity 95.7% (93.5–97.1). This subgroup exhibited among the largest bivariate variance components (τ^2_sens = 3.586; τ^2_spec = 2.778) and a negative correlation (ρ = −0.18), indicating wide dispersion in ROC space that is compatible with spectrum effects and differences in testing pathways (screening vs diagnostic work-up) across studies (Figure 11; Supplementary Figures S17, S18 and S32).

Across high-stakes groups, specificity remained consistently high. Congenital/newborn/infant populations (n = 16) showed pooled sensitivity 83.7% (72.7–90.8) and specificity 96.4% (94.2–97.8), with relatively lower specificity heterogeneity (τ^2_spec = 0.360) and near-zero correlation (ρ = −0.05), suggesting more stable specificity across studies (Figure 11). HIV/AIDS populations (n = 10) demonstrated pooled sensitivity 88.5% (61.2–97.4) and specificity 97.0%

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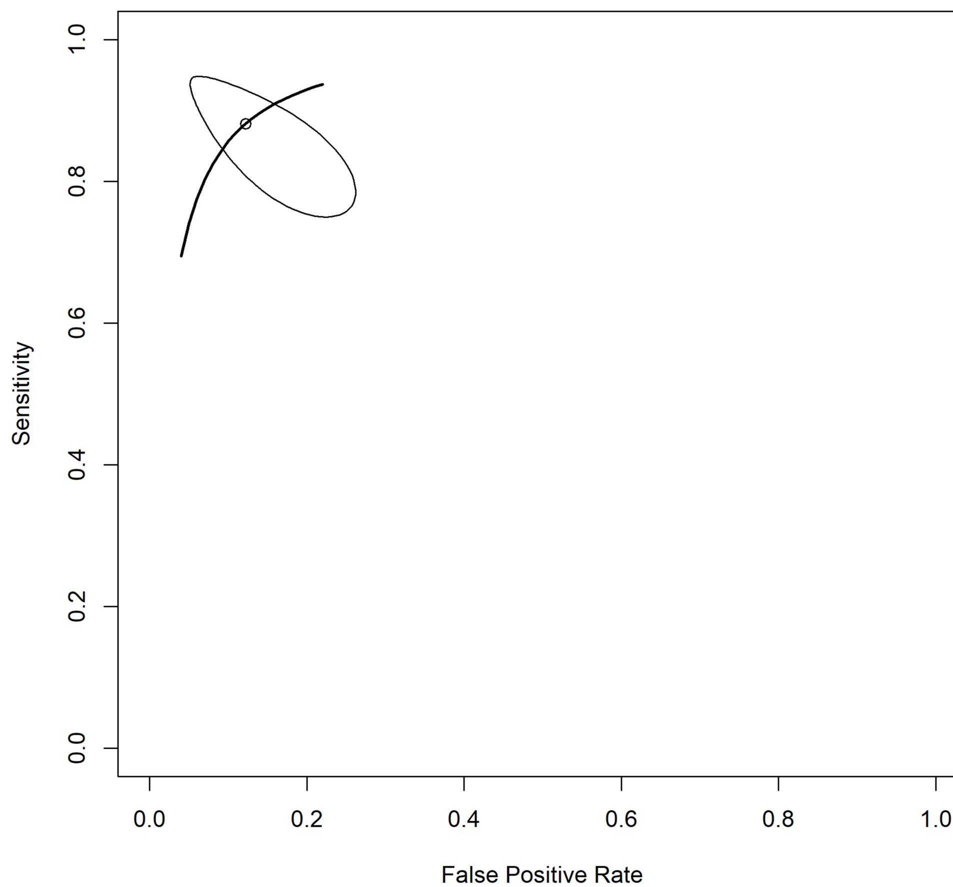

Figure 10 Summary ROC (SROC) plot for the Antigen target group (Reitsma; n = 5 evaluations). Study operating points and the pooled summary estimate are shown; interpretation should consider the limited number of evaluations.

(93.7–98.6); however, the very large sensitivity variance (τ^2_sens = 5.525) indicates substantial instability in operating points, consistent with limited evidence and heterogeneous settings (Figure 11; Supplementary: Figures S19–S22).

Most notably, other immunocompromised populations (n = 12) revealed a pronounced diagnostic gap: pooled sensitivity was markedly reduced at 55.7% (33.1–76.2) despite very high specificity 97.7% (92.3–99.3). Variability was substantial for both components (τ^2_sens = 2.528; τ^2_spec = 4.192), with correlation near zero (ρ = −0.03), implying

Table 6 Subgroup Meta-Analysis of Diagnostic Accuracy by Clinical Population Using the Bivariate Random-Effects (Reitsma) Model

Clinical Population	n	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	τ^2_sens	τ^2_spec	ρ	CC Applied?
Pregnancy/antenatal	74	85.6% (78.8–90.4%)	95.7% (93.5–97.1%)	3.586	2.778	−0.18	Yes
General/mixed / other	58	90.6% (87.3–93.2%)	96.6% (94.8–97.8%)	1.296	1.951	0.206	Yes
Congenital/newborn/infant	16	83.7% (72.7–90.8%)	96.4% (94.2–97.8%)	1.444	0.36	−0.05	Yes
Ocular toxoplasmosis / ophthalmology	12	71.4% (42.4–89.4%)	90.1% (84.1–94.0%)	4.092	0.751	−0.24	Yes
HIV/AIDS	10	88.5% (61.2–97.4%)	97.0% (93.7–98.6%)	5.525	0.496	1	Yes
Other immunocompromised	12	55.7% (33.1–76.2%)	97.7% (92.3–99.3%)	2.528	4.192	−0.03	Yes

Notes: The table reports pooled sensitivity and specificity (95% CI) for each population subgroup, along with between-study heterogeneity (τ^2_sens, τ^2_spec), the sensitivity–specificity correlation (ρ), and whether a continuity correction (CC = 0.5) was applied for sparse 2×2 data.

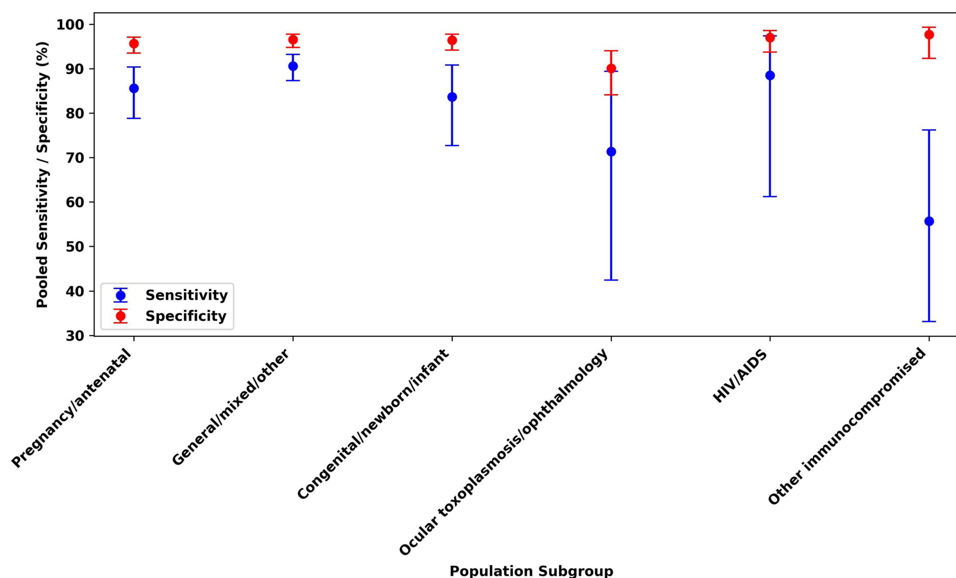

Figure 11 Pooled diagnostic accuracy by clinical population subgroup, showing sensitivity and specificity with 95% confidence intervals estimated using the bivariate random-effects (Reitsma) model. Subgroups are defined by clinical population, and pooled estimates summarize between-study variability in performance across settings.

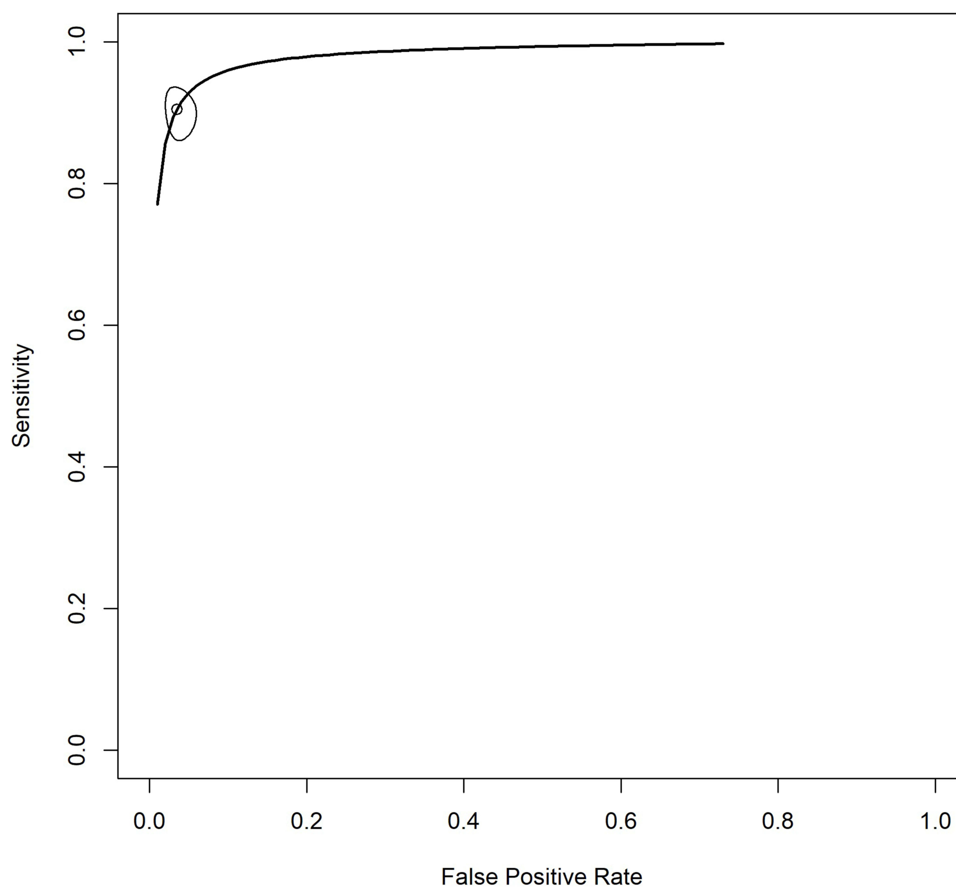

Figure 12 Summary ROC (SROC) plot for the general/mixed/other population subgroup (Reitsma; n = 58 evaluations). Study operating points are displayed in ROC space together with the pooled summary estimate and its uncertainty, illustrating dispersion across heterogeneous real-world cohorts.

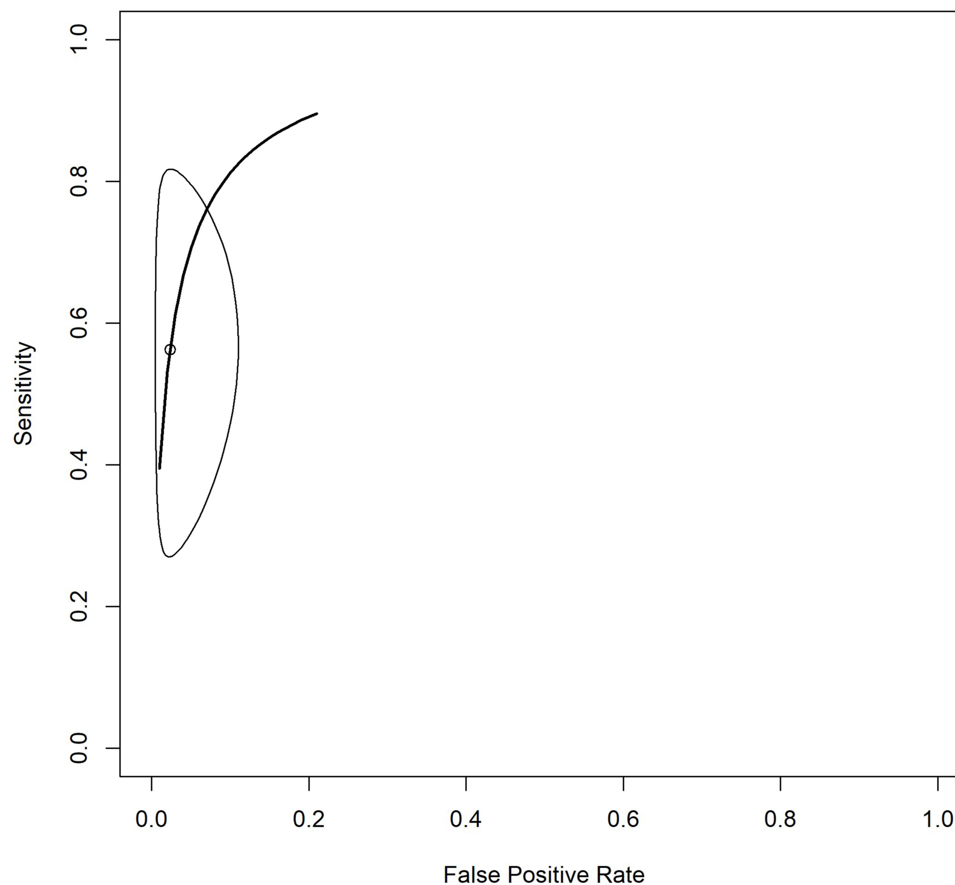

Figure 13 Summary ROC (SROC) plot for the other immunocompromised population subgroup (Reitsma; n = 12 evaluations). The plot visualizes study-level operating points and the pooled summary estimate, highlighting the subgroup's overall pattern of high specificity with reduced sensitivity and substantial heterogeneity.

that sensitivity and specificity varied across studies without a consistent trade-off pattern (Figure 11). Clinically, this pattern is compatible with reduced performance of immune-response–dependent assays in vulnerable hosts, increasing the risk of missed diagnoses (Figure 13; Supplementary: Figures S23 and S24).

For ocular toxoplasmosis/ophthalmology (n = 12), pooled sensitivity 71.4% (42.4–89.4) and specificity 90.1% (84.1–94.0) were accompanied by very large heterogeneity (τ^2_*sens* = 4.092), plausibly reflecting variation in case definitions, ocular specimen matrices, and reference standards (Figure 11; Supplementary: Figures S25–S27).

Subgroup Analysis by Technology Platform

This analysis compared the two major clinically operationalized technology categories (Table 7, Figure 14). Among the 182 evaluations eligible for quantitative synthesis, conventional assays (n = 140) and POCT (n = 40) provided sufficient

Table 7 Subgroup Meta-Analysis of Diagnostic Accuracy by Technology Platform Using the Bivariate Random-Effects (Reitsma) Model

Technology Group	n	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)	τ^2_sens	τ^2_spec	ρ	CC Applied?
Conventional	140	84.7% (80.2–88.3%)	95.5% (94.2–96.6%)	3.111	2.064	−0.04	Yes
POCT	40	87.7% (80.3–92.6%)	97.4% (95.4%–98.5%)	2.587	2.588	0.184	Yes
Emerging	1	Not estimable	Not estimable	—	—	—	—
Other	1	Not estimable	Not estimable	—	—	—	—

Notes: The table presents pooled sensitivity and specificity (95% CI) for Conventional and point-of-care testing (POCT) platforms, with between-study heterogeneity (τ^2_sens, τ^2_spec), the sensitivity–specificity correlation (ρ), and continuity correction status (CC = 0.5). Emerging and Other categories were not pooled because data were too sparse (n = 1 each).

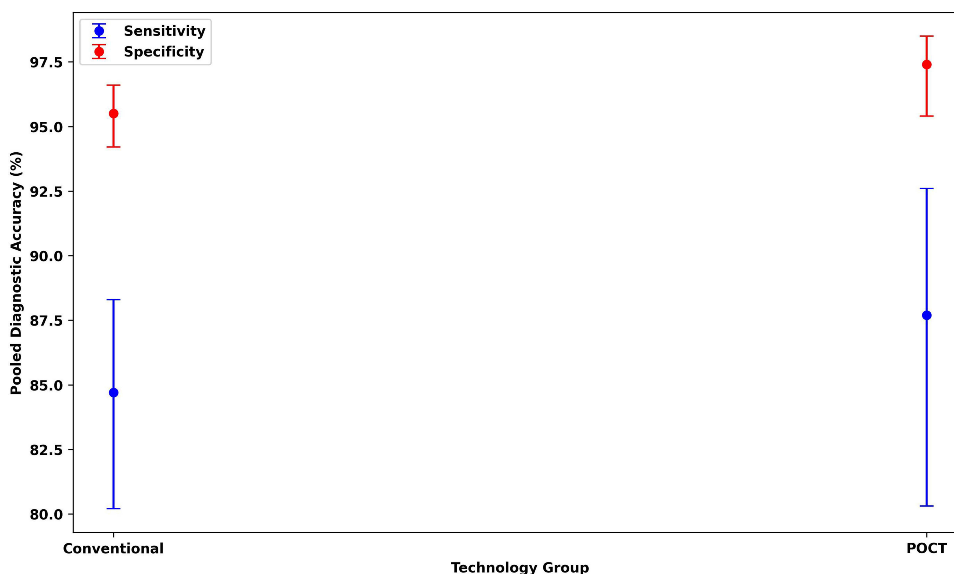

Figure 14 Pooled diagnostic accuracy by technology platform, showing sensitivity and specificity with 95% confidence intervals estimated using the bivariate random-effects (Reitsma) model. Results are presented for Conventional laboratory assays (n = 140) and point-of-care testing (POCT) platforms (n = 40); Emerging and Other categories were not pooled due to insufficient data (n = 1 each).

data for bivariate estimation, whereas Emerging and Other categories were too sparse to pool (n = 1 each) and were therefore not meta-analytically summarized (Table 7).

POCTs (including lateral flow assays and LAMP) demonstrated a favorable accuracy profile, with pooled sensitivity 87.7% (95% CI: 80.3–92.6) and specificity 97.4% (95.4–98.5), while Conventional laboratory assays achieved pooled sensitivity 84.7% (80.2–88.3) and specificity 95.5% (94.2–96.6) (Figures 14–16). Although confidence intervals overlapped, the consistently higher specificity for POCT supports their potential utility as rule-in tools, particularly in settings where rapid turnaround and decentralized testing are operational priorities (Figures 14 and 15).

Heterogeneity remained notable in both groups (Conventional: τ^2_sens = 3.111; τ^2_spec = 2.064; POCT: τ^2_sens = 2.587; τ^2_spec = 2.588), indicating substantial dispersion in study operating points; this dispersion is visually reflected by the breadth of study-level estimates in the technology-stratified forest plots (Supplementary: Figures S28–S31).

Heterogeneity, Sensitivity Analysis, and Visual Synthesis

Between-study heterogeneity was evaluated within the bivariate framework using the random-effects variance components for sensitivity and specificity (τ^2_sens and τ^2_spec) and the estimated correlation (ρ) (Tables 5–7), alongside visual inspection of study dispersion in ROC space. Substantial heterogeneity was evident for multiple targets and subgroups—most notably IgG, DNA, and pregnancy/antenatal cohorts—where large τ^2 values indicate wide variation in study operating points that likely reflects spectrum effects, assay thresholds, specimen types, reference standards, and differences in study conduct (eg, Supplementary: Figures S3–S6, S18 and S32).

Accordingly, robustness was judged primarily from the consistency of pooled estimates across subgroups and from concordance between model-based summaries and the observed dispersion of study operating points in ROC space, with visual support provided by the subgroup-specific forest plots of sensitivity and specificity and the corresponding SROC plots (Supplementary: Figures S7, S12, S17, S19, S20, S25, S33).

Visual synthesis complemented statistical pooling. Forest plots of study-level sensitivity and specificity illustrate the dispersion of estimates within each subgroup, while SROC plots provide an integrated depiction of sensitivity–specificity trade-offs across categories in ROC space. In these visualizations, IgG+IgM and IgG Avidity tend to lie closest to the desirable top-left corner (Figure 7; Supplementary: Figure S33), whereas DNA-based assays cluster in a high-specificity/low-sensitivity region, reinforcing their rule-in profile (Figure 9).

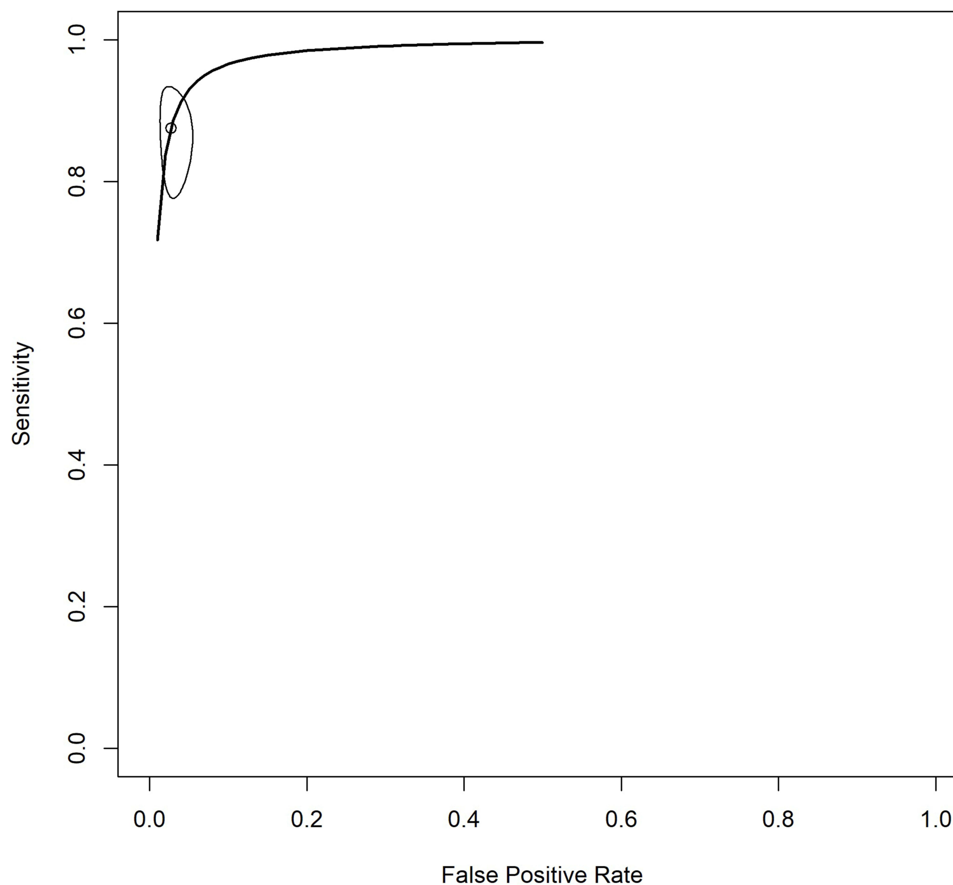

Figure 15 Summary ROC (SROC) plot for POCT platforms (Reitsma; n = 40 evaluations). Points represent individual study operating sensitivities/specificities in ROC space, with the pooled summary estimate and its uncertainty summarizing overall performance and between-study dispersion among point-of-care tests.

Publication bias was explored qualitatively through funnel plots as an assessment of potential small-study effects. Where available, two-panel funnel plots were reviewed for both sensitivity and specificity, but any asymmetry was interpreted cautiously because it may reflect threshold-related variation and clinical heterogeneity rather than selective reporting alone (Supplementary examples Figures S34–S37).

Between-subgroup differences were described by comparing pooled estimates and the extent of confidence interval overlap across stratified analyses (Tables 5–7, Figure 6, Figure 11, Figure 14). These comparisons are intended to support interpretation and hypothesis generation rather than to serve as formal interaction tests.

To complement the pooled bivariate estimates in Tables 5–7, supplementary figures provide full visual support by detection target, clinical population, and technology platform. Specifically, forest plots of study-level sensitivity and specificity (Supplementary Figures S1–S6, S8, S9, S10, S11, S13–S18, S21–S32, S38–S41) depict the spread of operating points contributing to the bivariate random-effects model in each subgroup, while SROC plots summarize the joint sensitivity–specificity trade-off in ROC space (Supplementary: Figures S7, S12, S17, S19, S20, S25, S33). Where the number of evaluations was sufficient, two-panel funnel plots (sensitivity and specificity) were included to explore potential small-study effects (Supplementary: Figures S34–S37, S42–S52), with interpretation tempered by the recognized influence of clinical and threshold-related heterogeneity in diagnostic accuracy meta-analyses.

Systematic Mapping of Analytical Performance Reporting

The reporting of analytical sensitivity, as measured by the Limit of Detection (LOD), was highly heterogeneous across the studies that reported it, presenting a major challenge for comparative evaluation.

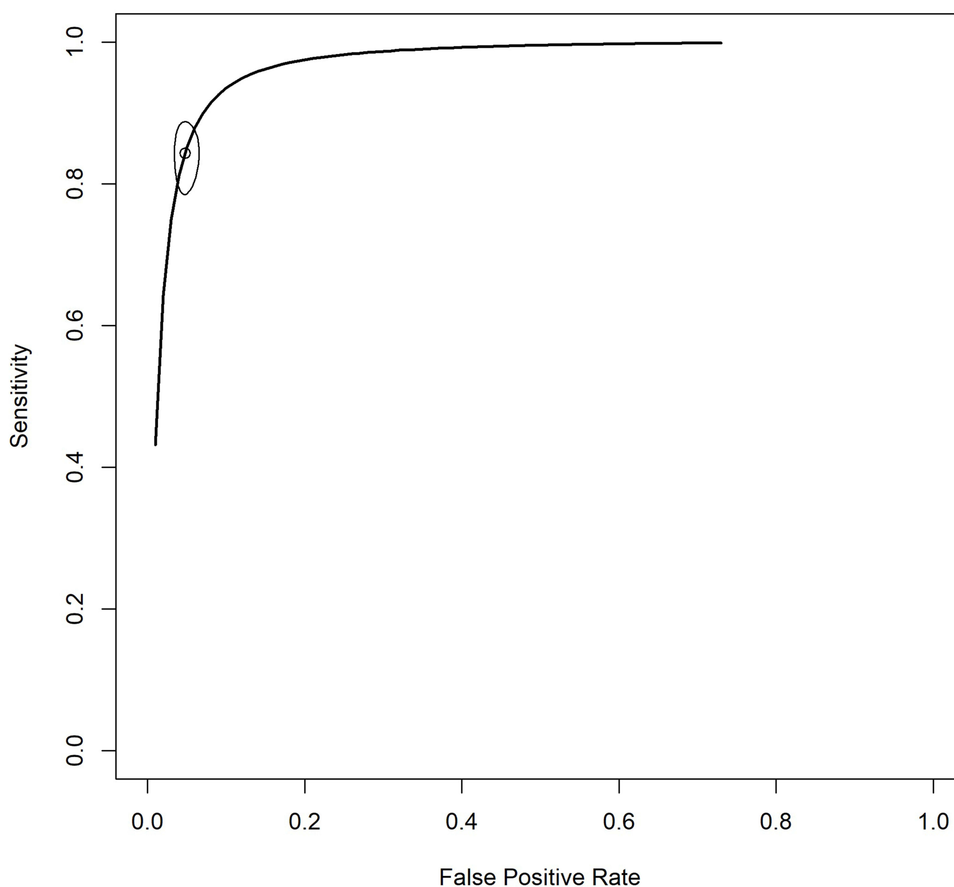

Figure 16 Summary ROC (SROC) plot for Conventional laboratory-based assays (Reitsma; n = 140 evaluations). Study operating points are shown in ROC space together with the pooled summary estimate and confidence region, illustrating heterogeneity and variability in diagnostic performance across conventional platforms.

For nucleic acid amplification tests (NAATs), LOD values were reported with wide variability—spanning over two orders of magnitude—even for the same technology. Values ranged from 0.01–1 parasite or genome equivalent per mL for optimized PCR/qPCR assays[116,137,177] to 5–10 parasites or genome copies per reaction for many LAMP and some PCR protocols.[9,69] This variability was exacerbated by the use of inconsistent and non-comparable units (eg, copies/µL, tachyzoite equivalents, genome equivalents/reaction),[16,69,85] precluding a direct meta-analysis of analytical sensitivity.

For serological assays (IgG/IgM), the quantitative reporting of LOD was exceptionally rare. The field predominantly relied on qualitative cut-offs (eg, IU/mL for ELISA) or reported LOD as "Not Reported/Not Applicable" (NR/NA) or "Not Stated" (N/S)[12,27,28,71] (Figure 8B). This represents a critical standardization gap, as it limits the objective assessment of an assay's ability to detect low antibody titers, a parameter crucial for early infection diagnosis and avidity testing.

Together, these inconsistencies underscore the urgent need for standardized guidelines (eg, following CLSI protocols) for determining and reporting LOD in toxoplasmosis diagnostic studies to enable meaningful cross-assay comparisons.

Discussion

Synthesis of Key Findings

This systematic review and meta-analysis, integrating evidence from 175 studies (309 test evaluations) and over 42,000 samples, provides a definitive, stratified evaluation of diagnostic test accuracy for human toxoplasmosis.[5,181] Our dual-method approach confirms that performance is intrinsically dependent on the diagnostic target, clinical population, and technological platform. Three pivotal findings emerge. First, serological strategies that capture both exposure and infection timing showed the strongest combined accuracy: IgG+IgM (combined) and IgG avidity demonstrated high

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pooled sensitivity and specificity (IgG+IgM: 94.8% and 96.7%; IgG avidity: 90.8% and 97.1%; Table 5), supporting their central role in clinical algorithms where dating infection is critical.[2,182] Second, we identify a clinically important diagnostic blind spot: pooled sensitivity was substantially reduced in other immunocompromised (non-HIV) populations (55.7%) despite very high specificity (97.7%; Table 6), raising concern for missed diagnoses in vulnerable hosts.[183] Third, POCTs demonstrate high specificity (97.4%) with good sensitivity (87.7%; Table 7), supporting rapid rule-in use within defined pathways, while acknowledging ongoing heterogeneity in study operating points.[184]

Interpretation of Dominant Technological Paradigms and Evolution

The evidence landscape remains dominated by conventional laboratory-based methods (79.3% of test evaluations), underscoring their entrenched role as reference standards (Table 2). This aligns with patterns in established infectious diseases, where innovation supplements rather than replaces validated workflows. The substantial representation of both serology (eg, ELISA for IgG/IgM) and molecular methods (eg, PCR for DNA) reflects their complementary roles—assessing immune status and detecting active infection, respectively.

The growth of POCTs to 18.1% of evaluations signals strong research interest in decentralized diagnostics.[184] However, the diversity of platforms (LFIA, LAMP) presents both opportunity and standardization challenges. Emerging technologies (eg, machine learning, biosensors) remain nascent (2.6% of evaluations), primarily integrated with imaging, pointing to a future computational transformation.[3,126,160,170,178]

Most critically, our tiered validation analysis reveals a profound "validation chasm": while 74.7% of assays with timing data are rapid (<30 min), a striking 97.7% of evaluations were limited to laboratory or early clinical validation (Tiers 0-2). Only 2.3% reached Tier 3 (large-scale field validation), highlighting a major translational gap between technological capability and proven real-world impact.[185,186]

Methodological and Analytical Landscape

A clear methodological dichotomy exists. Serological targets (IgG, IgM, Avidity) dominated the evidence base, accounting for the majority of evaluations, and were predominantly performed on serum (69.3% of evaluations). This reflects their well-established and accessible role in routine screening and exposure assessment (Table 2).[25,26,33,53] In contrast, molecular detection of parasite DNA (22.7% of evaluations) was more frequently applied to clinically specialized matrices such as ocular fluid, amniotic fluid, and CSF (collectively categorized as "Ocular Fluid/Other," 8.4% of evaluations) for direct pathogen detection in complex presentations like ocular and congenital toxoplasmosis.[15,40,44,68,75] The substantial evaluation of IgG Avidity (10.4% of evaluations) confirms its recognized clinical importance for dating infection,[30,33,67,129] whereas antigen detection remains a relatively unexplored avenue (2.3% of evaluations) despite its potential for diagnosing acute infection.[73,97,103]

Interpretation in Context of Clinical Scenarios

The clinical utility of a test is context-dependent, a principle starkly illustrated by our subgroup analyses.

Pregnancy: IgG avidity showed high pooled accuracy for infection dating (Table 5) and remains the key adjunct for interpreting serology in prenatal settings.[2,30,33,58,129,182] However, pooled sensitivity in pregnancy/antenatal cohorts was lower than in general/mixed populations (85.6% vs 90.6%; Table 6), consistent with spectrum and pathway effects in screening contexts.

Ocular Toxoplasmosis (OT): Pooled performance was moderate (sensitivity 71.4%; specificity 90.1%; Table 6) with substantial heterogeneity, reaffirming that laboratory testing is often complementary and should be interpreted alongside clinical assessment and imaging, especially in atypical cases.[101,103,123,131,140,157]

Immunocompromised Patients (non-HIV): The reduced pooled sensitivity (55.7% with specificity 97.7%; Table 6) indicates a meaningful diagnostic vulnerability. Current tools may miss reactivation or atypical presentations, supporting the need for improved biomarkers and optimized sampling strategies.[86,119,124,130,143]

Confirmatory Role of Molecular Tests: DNA-based assays showed high specificity (96.2%) but limited sensitivity (66.0%; Table 5), reinforcing their established role as confirmatory tests in selected scenarios (eg, congenital infection work-up, ocular fluid sampling) rather than broad screening.[110,116,137,156,164,177]

The Translational Pathway, Validation Chasm, and Reporting Gaps

Our tiered validation framework maps a concerning pipeline: robust innovation at the analytical (Tier 0) and early clinical (Tier 1) stages, but a dramatic funnel narrowing at the point of real-world implementation.[185] This "validation chasm" is particularly acute for promising POCTs and novel biosensors.[61,98,114,117,146,155] Furthermore, reporting gaps fundamentally undermine evidence quality and comparability. While quantitative time-to-result data were reported in only 29.7% of relevant evaluations, the reporting of analytical sensitivity was critically deficient. As detailed in Systematic Mapping of Analytical Performance Reporting, quantitative Limit of Detection (LOD) data were highly inconsistent for molecular assays[9,16,37,69,85,116,137,169,177] and virtually absent for serological tests,[12,27,28,71] precluding any meaningful cross-assay comparison of analytical performance.

Implications for Clinical Practice and Policy

Beyond performance, fundamental methodological weaknesses plague the evidence base. The QUADAS-2 assessment found no studies rated as low overall risk of bias (high: 79.4%; unclear: 20.6%),[5,181] with prevalent case-control designs and limited reporting of blinding and thresholds. In addition, large bivariate variance components (τ^2) and wide dispersion in ROC space for several key subgroups (eg, IgG, DNA, pregnancy/antenatal, and combined IgG+IgM) limit certainty and suggest meaningful clinical and methodological diversity across studies. Geographic skew (with major contributions from Europe and South America) may also affect generalizability to other regions.[22,34,45,58,132,146]

To address this, we recommend:

1. Test Selection & Algorithms: Prioritize IgG Avidity to support serological dating of infection (Table 5). Use POCTs as rapid rule-in tools given their high specificity (97.4%) and good sensitivity (87.7%) (Table 7), but interpret negative results in clinical context and, where appropriate, follow with conventional laboratory testing or molecular confirmation.[59,61,98,117,146,155]
2. Guideline Update: National and international guidelines should be updated to reflect the established superiority of IgG Avidity over single or combined IgG/IgM tests for serological dating.[2,182]
3. Standardization Mandate: The field must adopt international standards (eg, CLSI, STARD) for analytical validation (LOD, dynamic range) and transparent reporting to enable comparability.[5,181,187–189]

Strengths and Limitations

The primary strengths of this review include its comprehensive, dual-method design integrating evidence mapping (of studies and test evaluations) with diagnostic meta-analysis, rigorous application of PRISMA-DTA/QUADAS-2 guidelines,[5,181] and extensive multi-database searches spanning biomedical and engineering literature. Our tiered validation framework provides novel insights into translational readiness beyond conventional accuracy metrics.[185,186] However, our conclusions are constrained by important limitations in the primary literature: methodological quality was generally poor (high risk of bias in 79.4% of studies), and substantial between-study heterogeneity (large τ^2 estimates and wide dispersion in ROC space) was observed for several key subgroups, reflecting clinical and methodological diversity across studies. Additional limitations include geographical concentration of studies and—as systematically mapped in Systematic Mapping of Analytical Performance Reporting—the extreme heterogeneity and frequent non-reporting of Limit of Detection (LOD) data for molecular assays, precluding a meta-analysis of analytical sensitivity and limiting conclusions about detection at low parasite burdens.[9,12,16,27,28,37,69,71,85,116,137,169,177,188]

Despite these limitations in the primary literature, this review itself was conducted with methodological rigor. Methodologically, this review adhered to its pre-specified analytic framework. All planned subgroup analyses were completed, and pre-defined exclusion criteria for the "Emerging" technology category were applied consistently. Heterogeneity was quantified and contextualized through both statistical parameters (τ^2 and ρ) and visual assessment, supporting the stability of the key conclusions.

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Implications for Future Research

Future efforts must bridge the identified gaps through transformative, implementation-focused science:

1. Prospective, Multi-center Trials: Conduct large-scale, methodologically rigorous (low bias) studies in well-defined cohorts using standardized reference standards.[5,181]
2. Implementation Research: Evaluate the real-world impact, cost-effectiveness, and feasibility of integrating high-accuracy tests (like IgG Avidity) and POCTs into clinical pathways.[155,184,185]
3. Biomarker Discovery: Urgently invest in novel biomarkers to address the diagnostic crisis in non-HIV immunocompromised patients.[86,119,124,130,143]
4. Standardization Initiatives: Develop an international reference panel and consensus protocols for analytical validation and reporting, led by organizations like WHO or FIND.[4,187,189] These protocols must specifically address the severe heterogeneity in LOD determination and reporting documented in this review, mandating the use of standardized units and clinically relevant thresholds.[188]
5. Computational Integration: Further validate and develop machine learning applications, particularly for image analysis in ocular and neurological toxoplasmosis.[3,126,131,160,170,178]

Conclusion

This systematic review and bivariate meta-analysis provide a nuanced, clinically actionable evidence base for toxoplasmosis diagnostics. It highlights that accuracy varies substantially by detection target, clinical population, and technology platform. IgG avidity and combined IgG+IgM strategies demonstrated the strongest combined pooled accuracy for serological assessment and infection dating, while DNA assays showed a high-specificity but lower-sensitivity profile consistent with confirmatory use. POCTs demonstrated high specificity with good sensitivity, supporting rapid rule-in utility when embedded in appropriate algorithms. Critically, performance remained suboptimal in immunocompromised (non-HIV) populations, underscoring an urgent unmet need for improved diagnostics. Across the field, inconsistent reporting and limited large-scale field validation—the identified "validation chasm"—remain key barriers to confident clinical adoption.

Abbreviations

AI, Artificial Intelligence; AUC, Area Under the Curve; CC, Continuity Correction; CI, Confidence Interval; CLSI, Clinical and Laboratory Standards Institute; CSF, Cerebrospinal Fluid; DNA, Deoxyribonucleic Acid; DTA, Diagnostic Test Accuracy; ECDC, European Centre for Disease Prevention and Control; ELFA, Enzyme-Linked Fluorescent Assay; ELISA, Enzyme-Linked Immunosorbent Assay; FIND, Foundation for Innovative New Diagnostics; FN, False Negative; FP, False Positive; GRA, Dense Granule Protein ; HIV, Human Immunodeficiency Virus; HIV/AIDS, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome; HSROC, Hierarchical Summary Receiver Operating Characteristic; Ig, Immunoglobulin; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IHA, Indirect Hemagglutination Assay; IIF, Indirect Immunofluorescence; ISAGA, Immunosorbent Agglutination Assay; LAMP, Loop-Mediated Isothermal Amplification; LFA, Lateral Flow Assay; LFD, Lateral Flow Dipstick; LFIA, Lateral Flow Immunoassay; LOD, Limit of Detection; MeSH, Medical Subject Headings; ML, Machine Learning; NA, Not Applicable; NAAT, Nucleic Acid Amplification Test; NR, Not Reported; N/S, Not Stated; OT, Ocular Toxoplasmosis; PCR, Polymerase Chain Reaction; POC, Point-of-Care; POCT, Point-of-Care Testing; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA-DTA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies; qPCR, Quantitative Polymerase Chain Reaction; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2; RAA, Recombinase-Aided Amplification; RNA, Ribonucleic Acid; ROC, Receiver Operating Characteristic; ROP, Rhoptry Protein; SAG, Surface Antigen; SROC, Summary Receiver Operating Characteristic; STARD, Standards for Reporting Diagnostic Accuracy Studies; TN, True Negative; TP, True Positive; TPP, Target Product Profile; WHO, World Health Organization; ρ, Estimated correlation between logit sensitivity and logit specificity across studies; τ^2, Between-study variance component (random-effects variance) in the bivariate model.

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Ethics Declarations

All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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