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Diagnostic accuracy of salivary immunoglobulin A for early leprosy diagnosis: a systematic review protocol

Sabrina Alberti Nóbrega Oliveira
sabrina.oliveira@fiocruz.br
National Institute for Quality Control in Health (INCQS), Oswaldo Cruz Foundation (Fiocruz)
Helena Pereira da Silva Zamith
National Institute for Quality Control in Health (INCQS), Oswaldo Cruz Foundation (Fiocruz)
Gisele da Rocha Ribeiro
Fundação Oswaldo Cruz
Marisa Coelho Adati
National Institute for Quality Control in Health (INCQS), Oswaldo Cruz Foundation (Fiocruz)

Study protocol

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Abstract

Background

Leprosy remains a significant public health challenge worldwide. Effective disease control depends on early diagnosis and timely treatment to prevent transmission. Because laboratory confirmation lacks an established reference standard, clinicians primarily rely on clinical examination. Serological assays often yield reactive results that require careful interpretation, particularly in asymptomatic individuals and household contacts. Saliva sampling offers a simple, noninvasive, and low-cost approach with minimal contamination risk. This protocol focuses on salivary immunoglobulin A (sIgA) as a supplementary diagnostic marker and aims to evaluate the diagnostic accuracy of sIgA detection in leprosy.

Methods

We will conduct a systematic review guided by the question: “What is the diagnostic accuracy of sIgA detection for the early diagnosis of leprosy?” We will identify studies through electronic databases and reference list screening. We will include diagnostic accuracy studies evaluating IgA in saliva for leprosy screening or diagnosis, regardless of immunoassay format. Studies assessing IgA exclusively in serum, plasma, or other non-salivary specimens will be excluded. Eligible studies will involve leprosy patients, household contacts, or individuals at risk of *Mycobacterium leprae* infection and will report sufficient data to estimate diagnostic performance. Two reviewers will independently conduct study selection, data extraction, and risk-of-bias assessment. We will synthesize results narratively and perform meta-analysis using random-effects models when data permit.

Discussion

This systematic review will assess the diagnostic performance of sIgA-based tests and their potential role in early leprosy detection. The findings may support improved diagnostic strategies, contribute to early case identification, and guide future research on salivary biomarkers for *M. leprae* infection.

Registration

PROSPERO CRD420250557712

BACKGROUND

Leprosy remains a significant public health challenge. The disease persists in more than 120 countries as a neglected condition, with approximately 200,000 new cases reported annually worldwide. India, Indonesia, and Brazil account for nearly 80% of reported cases, representing almost two billion inhabitants, or one quarter of the global population [1, 2]. Leprosy is a chronic infectious disease with diverse clinical manifestations reflecting different immune responses to *M. leprae* [3]. Hansen’s bacillus transmits primarily via the upper respiratory tract after prolonged exposure to untreated individuals, and spreads through the bloodstream and lymphatic system [4, 5]. The disease manifests through dermato-neurological alterations, including reduced thermal, pain, and tactile sensitivity. Although leprosy affects individuals of all ages and sexes and progresses slowly, lack of treatment can cause skin and nerve damage, peripheral neuropathy, anesthesia, and irreversible physical disabilities [6, 7].

Effective leprosy control requires early diagnosis and appropriate treatment to prevent transmission. However, laboratory confirmation absences a reference standard, and clinicians rely mainly on clinical evaluation. Rapid diagnosis remains challenging because some patients do not present typical painless skin lesions [5, 8]. Intradermal smear microscopy offers a fast and inexpensive method but shows low sensitivity and limited availability. Histopathology assists in confirming doubtful cases and classifying clinical forms but requires time-consuming and labor-intensive procedures [9, 10]. Consequently, clinicians often diagnose patients at later stages, when visible lesions and irreversible damage have already developed [5, 11]. Serological diagnostic methods enable rapid screening and monitoring of large sample volumes [12]. Molecular techniques assist in confirming cases, particularly among multibacillary patients, but they show reduced sensitivity in paucibacillary disease and require costly, labor-intensive methodologies that limit routine use in endemic settings [13].

Clinicians commonly use IgM- and IgG-based serological tests to monitor therapeutic response, detect relapse, and identify contacts at higher risk of disease. However, reactive serology may appear in healthy individuals, while confirmed cases - especially paucibacillary (PB) forms - may show negative results. Endemic populations often present higher serological reactivity than populations in low-endemic regions. Therefore, clinicians must interpret reactive results cautiously, particularly in asymptomatic individuals and household contacts [5, 12, 13].

Before systemic immune responses develop, *M. leprae* enters primarily through the nasal mucosa and induces a local humoral response dominated by IgA and IgM antibodies [14, 15, 16]. IgA plays a central role in mucosal defense of the gastrointestinal and respiratory tracts. Although IgA circulates at lower plasma concentrations than IgM and IgG, mucosal fluids contain higher salivary immunoglobulin A (sIgA) levels, where exerts essential protective functions [17]. IgA also contributes to defense against mycobacterial infections by limiting pathogen entry and regulating inflammatory responses [18]. Because saliva collection is simple, noninvasive, low-cost, and minimally prone to contamination, sIgA detection represents a valuable supplementary diagnostic approach [19, 20].

Studies have demonstrated the presence of sIgA from leprosy patients, suggesting that mucosal immunity contributes to protective responses against the disease [21]. Untreated household contacts with continuous exposure show higher sIgA levels than endemic controls, which indicates an activated mucosal immune response [22]. Although some investigations have assessed IgA in serum [23–26], the present review will evaluate only IgA measured in saliva. Studies assessing IgA exclusively in serum, plasma, or other non-salivary specimens will not be eligible. This restriction reflects the review's focus on mucosal immunity and on saliva as a simple, noninvasive specimen for early leprosy detection.

OBJECTIVE

This systematic review aims to evaluate and compare the diagnostic accuracy of sIgA-based tests as a non-invasive, supplementary tool for leprosy detection. Specifically, we will assess test performance in individuals with initial clinical suspicion and household contacts of confirmed cases, accounting for variations in the clinical context of use and the reference standard employed.

METHODS AND DESIGN

We based this study protocol on recommendations of *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* [27]. To ensure transparency, avoid duplicate publication, and minimize bias, we registered the protocol in PROSPERO database (CRD420250557712) in August 2025. We report this protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [28] and complete

checklist is available in Additional file 1. Any relevant protocol amendments will be documented and reported in the final review.

Review question

In individuals with initial clinical suspicion of leprosy or in contacts of confirmed cases, what is the diagnostic accuracy of sIgA tests to identify leprosy?

Eligibility criteria

Population/participants

We will include individuals with clinical suspicion of leprosy or asymptomatic household contacts. We will not restrict eligibility by age, sex, race, education, geographic region, or language. Exclusion criteria will be studies exclusively of therapeutic monitoring, relapse, post-discharge, or leprosy reactions.

Index test

The index test will be sIgA detection using any validated *M. leprae*-related antigen. Studies may use any immunoassay format, including ELISA, CLIA, RIA, or rapid tests, and results may be qualitative or quantitative. Studies assessing IgA exclusively in serum, plasma, or any other non-salivary specimen will be excluded. Eligible studies must report participant numbers, test outcomes (positive and negative), and sufficient data to estimate diagnostic performance.

Studies will be included if leprosy diagnosis and classification were confirmed using a clinical-driven composite reference standard. Clinical evaluation - such as the World Health Organization (WHO) diagnostic criteria – will be mandatory and must be used either alone or in combination with any complementary laboratory test, including slit-smear bacilloscopic, histopathology or polymerase chain reaction (PCR). We will exclude studies where the reference standard was applied inconsistently across participant groups or where leprosy confirmation was ambiguous, unverified, or based solely on self-reported history.

Comparator tests

We will include serum IgA, IgM, IgG and combined antibody assays (irrespective of the antigen utilized); molecular and cellular assays; or other validated diagnostic tools. Robust comparative evidence must be available, preferably from studies employing paired evaluation within the same participant cohort. The absence of a comparator test will not constitute an exclusion criterion for the primary analysis. However, any comparators falling outside these pre-specified criteria will be excluded from secondary analyses.

Outcomes

We will dichotomize sIgA test results as positive or negative. For tests with non-binary outcomes, we will use the threshold specified by each study. Eligible studies must report at least one diagnostic performance measure, such as sensitivity, specificity, accuracy, receiver operating characteristic (ROC) curves, predictive values, likelihood ratios, diagnostic odds ratios, or agreement between tests. Secondary outcomes will include stratified diagnostic accuracy

according to clinical classification (PB and MB disease), study population (household contacts and individuals at risk), salivary collection method, antigen, immunoassay format, and positivity threshold. We will allow any definitions for controls or leprosy diagnostic criteria, but will exclude studies limited to treatment, epidemiology, genetics, or immunology if they are irrelevant to the review scope.

Study design

We will include paired comparative studies, cross-sectional studies, case-control diagnostic studies, cohort studies with diagnostic evaluation, validation studies of diagnostic tests, and field or laboratory evaluations usin0g human samples. Only fully published studies, academic thesis, dissertations, or monographs, will be eligible. We will not include reviews, meta-analyses, conference abstracts, editorials, case reports, letters, clinical trials, or technology development studies.

Setting/location

We will include studies conducted in any geographic region globally, encompassing both endemic and non-endemic countries. Regarding the healthcare setting, studies performed at all levels of care will be eligible, including primary healthcare centers, specialized dermatology or leprosy reference clinics, hospitals, and community-based surveillance or field studies. No restrictions will be applied based on the country's income level or economic development status.

Information sources and search strategy

We plan to start systematic searches in November 2026 in MEDLINE (PubMed), Embase, Web of Science, Scopus, Scientific Electronic Library Online (SciELO), and Latin American and Caribbean Health Sciences Literature (LILACS), along with supplementary sources such as the CAPES (Coordination for Improvement of Higher Education Personnel, Brazil) Periodicals Portal and academic thesis repositories. We will also manually review the reference lists of relevant systematic reviews and eligible studies. We will develop search strategies designed to identify studies evaluating sIgA-based diagnostic methods for leprosy. Each strategy will combine concepts for leprosy, IgA, saliva, and diagnostic performance; we will include terms for comparator methods to support comparative analyses. We will adapt strategies to each database using medical subject headings (MeSH), controlled vocabulary, and free-text terms with Boolean operators. We will impose no language or publication date restrictions. Before the formal search, we will refine the strategies to ensure adequate sensitivity and specificity. The complete database-specific strategies will be reported in tables, and the PubMed strategy is provided in Additional file 2.

Study selection

After completing the searches, we will upload all references to the Rayyan QCRI platform [29] for systematic reference management. One reviewer will identify and eliminate duplicate entries. A pilot test will be conducted before formal screening to improve reviewer selection. Two reviewers will independently and blindly screen titles, keywords and summaries for eligibility, followed by a comprehensive evaluation of full-text articles. Reviewers will resolve discrepancies and disagreements by consensus. We will record the reasons for excluding studies.

Data extraction

After a pilot test, two reviewers will independently extract data from eligible studies into a customized Excel spreadsheet. A standardized registration form will be used to reduce the risk of errors. Reviewers will systematically extract study identification, population characteristics, salivary collection and processing methods, antigen, sIgA

assay characteristics, comparator tests, positivity thresholds, diagnostic accuracy outcomes, and additional notes on key findings and limitations. Relevant outcomes will include diagnostic performance, test applicability, and populations studied.

Data synthesis

Study selection will be presented using a PRISMA flow diagram [28]. Findings will be synthesized narratively, structured by sIgA assay type, antigen, salivary collection method, and study population (PB, MB, and contacts). For each study, we will construct 2×2 contingency tables to estimate sensitivity and specificity, which will be visualized using paired forest plots and receiver operating characteristic (ROC) curves. Study characteristics and accuracy estimates will be tabulated separately by assay type and predefined subgroups. Where studies exhibit sufficient homogeneity in index test, reference standard, and outcome definitions, we will perform meta-analyses using hierarchical models (bivariate or hierarchical summary ROC [HSROC] approaches). Statistical heterogeneity will be evaluated using Cochran's Q test and the I^2 statistic [30, 31]. If data permit, subgroup analyses will explore variations across clinical classifications (PB versus MB), population groups, geographic settings (endemic versus non-endemic), salivary collection methods, antigens, and assay formats. If quantitative synthesis is inappropriate, we will report results narratively. Prevalence and other descriptive measures will be summarized separately and excluded from primary meta-analytic outcomes.

Risk of bias

Two reviewers will independently assess risk of bias and applicability using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool [32], tailored to the specific context of sIgA testing. Tailoring will involve defining signaling questions for each domain: participant selection, index test, reference standard and flow/timing. Domain judgments will be classified as "low", "high", or "unclear" risk of bias and presented graphically. Given expected study heterogeneity, the assessment will particularly consider incorporation bias, the blinding status of index test interpretation, the use of multiple reference standards and applicability variations driven by clinical context and the test's intended role.

DISCUSSION

Leprosy remains highly prevalent in many low- and middle-income countries despite the availability of effective treatments. Delayed diagnosis—due to challenges in symptom recognition and a lack of awareness among both patients and healthcare professionals—continues to hinder disease control and worsen patient outcomes [33]. Salivary IgA testing has the potential to facilitate earlier detection through a noninvasive sampling approach; however, current evidence is inconclusive. By systematically evaluating the diagnostic accuracy and clinical relevance of sIgA, this proposed review may refine diagnostic approaches, identify evidence gaps, and guide future research on mucosal biomarkers in endemic settings.

Abbreviations

CAPES
Coordination for Improvement of Higher Education Personnel (Brazil)
CLIA
Chemiluminescent Microparticle Immunoassay
EMBASE

Excerpta Medica Database
ELISA
Enzyme-Linked Immunosorbent Assay
Ig
Immunoglobulin
LILACS
Latin America and Caribbean Health Sciences Literature
MB
Multibacillary
MeSH
Medical Subject Headings
PB
Paucibacillary
PCR
Polymerase Chain Reaction
PRISMA-P
Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO
Prospective Register of Systematic Reviews
RIA
Radioimmunoassay
ROC
Receiver Operating Characteristic
sIgA
Salivary immunoglobulin A
WHO
World Health Organization.

Declarations

Ethics approval and consent to participate - Not applicable.

Consent for publication - Not applicable.

Availability of data and materials - All data generated or analyzed during this study will be included in the published systematic review and will be available from the corresponding author upon reasonable request.

Competing interests - The authors declare that they have no competing interests.

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Authors' contributions – SANO and HPSZ designed the study. SANO, HPSZ and MCA drafted and critically revised the protocol, and approved the final version. GRR contributed to the structure and revision of the search strategy. SANO and HPSZ are the guarantors of the review.

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