

# Unveiling the Diagnostic Potential of Salivary Biomarkers in Neglected Tropical Diseases: A Comprehensive Review

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## ABSTRACT

Over a billion people with any of these neglected tropical diseases (NTDs) still can't get treatment in poor and neglected areas of the world. This is mostly because the diseases are hard to treat, expensive, and traditional diagnostic methods need a lot of advanced technology to work well. Most importantly, advances in the understanding of salivary biometrics suggest that we can use this convenient and non-invasive sample type to diagnose these types of disorders. <sup>[1]</sup> This review carefully looks at the studies that have been done on different salivary biomarkers for NTD diagnosis, salivary disease pathogens, and immune response indicators. It also talks about the problems that come up when using these biomarkers to come up with new diagnostic strategies that are more accurate and time-effective.

**Keywords:** Saliva, Neglected Tropical disease, Diagnosis

## INTRODUCTION

Neglected tropical diseases (NTDs) are a group of infectious conditions more common in those who live with neurological disorders. Disease and violence against women seem to both cause and result from a cycle of poor health. <sup>[2]</sup> International public health programs largely ignore Neglected tropical disease (NTDs), despite their substantial contribution to the global disease burden. <sup>[3]</sup> Despite advances in diagnosing individual infectious diseases, there are still a number of limitations that arise, especially more so in challenging low-resource settings where traditional diagnostic techniques can be invasive and expensive, along with additional resource-intensive lab infrastructures requiring high capital expenditures. <sup>[4]</sup> <sup>[5]</sup>

Therefore, studies have been conducted to identify alternative point-of-care diagnoses that are more rapid, convenient, less cumbersome, cost-effective, and non-invasive, rather than those that seem a priori flawed. Paradoxically, due to its ease of collection compared to blood samples, saliva has become a preferred diagnostic fluid for identifying potential biomarkers such as proteins and nucleic acids, which represent systemic diseases and immunological responses. <sup>[6]</sup> This paper examines and evaluates the diagnostic accuracy of salivary biomarkers in neglected tropical diseases, focusing on their strengths and limitations. Furthermore, it discusses possible future strategies for improving their clinical utility.

## OBJECTIVES

The goal of this review is to summarize the diagnostic performance and reliability of salivary biomarkers for diagnosis in Neglected Tropical Diseases (NTDs) with their causative agents, as well as the immune responses that follow. This review aims to identify validated saliva biomarkers that serve as valuable diagnostic targets for NTDs, evaluate the suitability of recent progress in disease diagnosis, and explore the potential impact of future directions on the development of accessible point-of-care (POC) oral-based tests in resource-poor environments

## MATERIALS & METHODS

We performed electronic searches of the databases PubMed, Scopus, and Springer Link to identify all relevant studies. We searched for key words such as salivary analysis, neglected tropical disease, chagas disease, and leishmania. We selected studies that demonstrated methodological rigor in terms of sample collection, processing, and analysis procedures, as well as study size, and that reported results relevant to the diagnostic potential of transcriptomics approaches in human NTDs. The study objective for this review was "Are salivary biomarkers suitable diagnostic tools for NTDs?". Three significant studies aimed to determine whether salivary biomarkers might reveal the presence of pathogens and host responses.

### Saliva as a Diagnostic tool

Saliva is an attractive diagnostic fluid due to its non-invasiveness, cost-effectiveness, and easy handling. The least invasive method of saliva collection is particularly interesting for those belonging to the youngest (and older) age groups, as it involves no suffering or pain during the sampling process, unlike when using blood.<sup>[7]</sup> Saliva is a biofluid that can be collected easily and without harm in many places, with little or no special training or equipment needed. It can then be kept at room temperature, which is especially important for testing in places

where labs don't have enough resources to collect higher-complexity nucleic acidified samples. samples difficult.<sup>[6]</sup>

Saliva is dynamically complex with a wide variety of proteins, nucleic acids, hormones, and other molecules that make it an attractive source for molecular diagnostics. The detection of biomarkers in saliva represents mainly local, but occasionally also systemic, infections and is informative about the humoral defense mechanisms deployed by this host tissue.<sup>[8]</sup> However, saliva as a diagnostic material presents several difficulties. Significant fluctuations in saliva composition, caused by factors such as nutrition, hydration status, circadian cycles, or oral hygiene practices, might compromise the accuracy and repeatability of diagnostic results.<sup>[9]</sup> The levels of biomarkers in saliva are often lower than those in blood and necessitate very sensitive techniques to get clinically significant results.<sup>[6]</sup> Additionally, due to the lower levels of these biomarkers in saliva compared to blood, trials may only detect logs less than whole numbers, and the detection range of histograms using first-generation techniques may be restricted. However, to address these limitations and achieve a diagnostic precision comparable to blood tests, we must standardize both the saliva collection mechanisms and the processing and analysis procedures.<sup>[8]</sup>

### Key Findings

#### Study 1: Leishmaniasis and Salivary Biomarkers

The Journal of Tropical Medicine studied the titre of cytokines and some proteins in saliva samples from patients with diagnosed leishmaniasis. Moreover, IL-10 and TNF- $\alpha$  in the infected population have a high level in their blood as compared to normal status.<sup>[11]</sup> Therefore, they constructed a panel of biomarkers using these two features. The study's findings suggest that these markers serve as early infection indicators capable of interfering with leishmaniasis diagnosis and treatment.<sup>[10]</sup>

## Study 2: New Approaches to Diagnosing Chagas Disease

Biomarker potential Researchers at Sao Paulo State University-Brazil examined salivary glycoproteins and published their findings in the American Journal of Tropical Medicine and Hygiene, exploring their potential as biomarkers for Chagas disease.<sup>[16]</sup> This investigation showed the salivary glycoprotein profile in infected individuals, particularly mucin-1, associated with an alternative non-invasive diagnostic of the disease.<sup>[15]</sup> The latter is initiating an increase in opportunities for rapid patient detection, which is essential in areas where there is inadequate healthcare infrastructure.<sup>[12]</sup>

## Study 3: Schistosomiasis Saliva Diagnostics

Published in PLoS Neglected Tropical Diseases, the research sought to evaluate salivary proteomic profiling as a tool for diagnosing schistosomiasis. When infection status was combined, an analysis of the salivary proteome revealed a different pattern—higher levels of calprotectin and lactoferrin.<sup>[14]</sup> Hussein et al.'s study (2023) bolsters the potential usefulness of proteome analysis in schistosomiasis diagnosis and control strategies, facilitating extensive screening programs and epidemiological research endeavors.<sup>[13]</sup>

## RESULT

The essential data on salivary biomarkers, along with the literature review regarding an alternative diagnostic strategy for Neglected Tropical Diseases (NTDs), provide valuable insights. It was clear that certain proteins and cytokines were more abundant in the saliva of people who had leishmaniasis than in the saliva of healthy people.<sup>[10]</sup> This suggests that these proteins and cytokines could be useful for tracking this process. The ability to effectively identify disease-associated salivary glycoproteins emphasizes the potential utility of these biomarkers for accurate diagnosis, especially in resource-poor regions. Equally, the effective identification of salivary glycoproteins associated with Chagas disease highlights a robust diagnostic capability for these biomarkers, particularly in regions with low resources.<sup>[12]</sup> Further studies on salivary proteomic analysis as a method of screening for schistosomiasis in individuals also revealed significant differences between the profiles, indicating that these could potentially be useful additional diagnostic tests.<sup>[13]</sup> Taken together, our results outline associations of particular biomarkers with diseases in novel ways.

**Table 1: Summary of Key Studies on Salivary Biomarkers in NTDs**

Study	NTD	Salivary Biomarkers Identified	Diagnostic Potential	Reference
Sato et al. (2022)	Leishmaniasis	Specific proteins and cytokines	Early diagnosis and treatment monitoring	Sato et al., 2022 <sup>[10]</sup>
Ribeiro & Nunes (2021)	Chagas Disease	Salivary glycoproteins	Non-invasive diagnostic alternative	Ribeiro & Nunes, 2021 <sup>[12]</sup>
Hussein et al. (2023)	Schistosomiasis	Proteomic profiles	Potential for large-scale screening	Hussein et al., 2023 <sup>[13]</sup>
Yoshizawa et al. (2020)	Multiple NTDs	Various proteins, nucleic acids	Wide applicability across different NTDs	Yoshizawa et al., 2020 <sup>[7]</sup>

## DISCUSSION

Saliva diagnostics could be an ideal, low-cost, and non-invasive alternative in areas where traditional diagnostic methods are scarce for diagnosing NTDs. Saliva collection is a facile, cost-effective, and

non-intrusive form of sampling, which makes it an appealing choice in situations with limited resources.<sup>[7]</sup> However, the widespread use of salivary diagnostics requires the elimination of several barriers. Unfailingly necessary is the establishment

of standardized procedures for collection and analysis, as expression levels may change based on extraneous events like nutrient intake, hydration status or oral hygiene.<sup>[9]</sup> Despite the potential high specificity and sensitivity of salivary markers, it is crucial to fully validate them across various populations. It also calls for new research efforts to improve clinical applications and address existing limitations.<sup>[3]</sup>

### **FUTURE DIRECTIONS**

In order to advance salivary diagnostics for neglected tropical disease (NTDs), the whole research effort should validate the results of first investigations in extensive multicenter experiments. The identification of additional salivary biomarkers unique to neglected tropical diseases (NTDs) that can be detected using modern sophisticated diagnostic technologies such as point-of-care testing devices, and their integration with digital health platforms, is imperative.<sup>[6]</sup> A first measure in this regard would be the establishment of uniform procedures for collecting, storing, and analyzing saliva in order to reduce differences and enhance the precision of diagnosis.<sup>[8]</sup> In order to overcome the existing obstacles and achieve salivary diagnostics as an effective supplement to NTD management, it is imperative for researchers, physicians, and policymakers to collaborate actively. This multidisciplinary approach is crucial for the development and future widespread implementation, practicality, and scalability of particularly low-cost (point-of-care) devices tailored for salivary diagnostics in harsh environments.<sup>[11]</sup>

### **CONCLUSION**

Undoubtedly, salivary biomarkers have significant promise as a developing non-invasive biofluid diagnostic tool for neglected tropical illnesses. They provide a convenient and economical means to enhance early detection in communities with limited resources. However, substantial

obstacles provide difficulties for translation into clinical practice, necessitating further verification and standardization, as well as the development of novel diagnostic technologies. Salivary diagnostics have the capacity to become a globally important strategy in global health, providing a revolutionary scale to address these similar issues, particularly when conventional procedures are not accessible and alternative invasive collection techniques are not achievable. Integrating salivary diagnostics into worldwide health initiatives has the potential to change the landscape by reducing the occurrence, frequency, and advancement of diseases caused by neglected tropical disease.<sup>[3]</sup>

### **Declaration by Authors**

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