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Urinary lipoarabinomannan for diagnosis of Tuberculosis in an HIV-negative population: A scoping review

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Background: Tuberculosis (TB) remains a leading cause of mortality in low-resource settings and poses a diagnostic challenge in human immunodeficiency virus (HIV)-negative populations because of limitations in traditional diagnostic methods such as sputum smear microscopy (SSM) and sputum Xpert Ultra. There is a lack of effective, non-invasive diagnostic options for TB diagnosis in HIV-negative populations. This scoping review explores the potential of urinary lipoarabinomannan (ULAM) as a point-of-care diagnostic tool for *Mycobacterium tuberculosis* (MTB) in HIV-negative individuals.

Aim: To evaluate the diagnostic performance of ULAM in detecting TB among HIV-negative populations and assess its feasibility as a rapid, non-invasive diagnostic method.

Method: A systematic search was conducted across PubMed, Google Scholar and Scopus. Articles were selected based on relevance to the topic.

Results: The search yielded 210 articles, with 11 meeting our inclusion criteria. These studies reported varying diagnostic performance metrics for ULAM: sensitivity ranged from 10.0% to 66.7% and specificity from 90.0% to 98.1% among different assays. Notably, the studies demonstrated that the novel assays such as Electrochemiluminescence LAM and the second-generation FujiLAM showed higher sensitivities of 66.7% and 53.2%, respectively. Despite these advancements, the overall effectiveness of ULAM in HIV-negative populations remains limited, with standard assays exhibiting sensitivities as low as 10.0%.

Conclusion: While ULAM holds potential as a diagnostic tool in HIV-associated TB, its application in HIV-negative populations is constrained by low sensitivity of the currently available assays.

Contribution: The development and validation of high-sensitivity assays are crucial for broadening the utility of ULAM in these populations.

Keywords: urinary lipoarabinomannan; tuberculosis; HIV-negative; diagnostic tool; point-of-care; *Mycobacterium tuberculosis*; scoping review.

Introduction

Tuberculosis (TB) is caused by the bacillus *Mycobacterium tuberculosis* (MTB), which is spread when people who are ill with TB expel bacteria into the air (e.g., by coughing). About a quarter of the global population is estimated to have been infected with MTB.[1] Following infection, the risk of developing MTB disease is highest in the first 2 years (approximately 5%), after which it subsequently declines. It is a communicable disease of public health concern that inequitably impacts the most vulnerable populations worldwide.[2] Vulnerable populations are those with high risk for MTB disease and whose disadvantaged or marginalised socioeconomic position limits their access to the health system.[2] Globally, MTB is one of the most prevalent bacterial infections and is a major contributor to mortality in several resource-limited countries.[3]

In 2022, the total number of deaths worldwide on account of MTB was 1.30 million (95% uncertainty interval [UI]: 1.18–1.43 million).[1] Diagnosis of MTB mostly depends on Xpert MTB or RIF Ultra (Xpert Ultra), a polymerase chain reaction (PCR) test for the detection of MTB in sputum, which is affordable, popular and recommended by the World Health Organization (WHO) for use in human immunodeficiency virus (HIV) positive and negative individuals in 2017.[1,4] However, many individuals with presumptive TB do not produce sputum, complicating diagnosis through sputum-based tests.[5,6] A systematic review conducted by Chatla et al.,[4] on the

use of urinary lipoarabinomannan (ULAM) in people living with HIV (PLHIV) observed that ULAM is a useful adjunct to diagnose TB, especially among HIV-positive individuals with CD4 count ≤ 100 cells/μL, in which the specificity ranged from 76% to 100% with a crude average of 92.7% and sensitivity ranged from 8.3% to 93.0% with a crude average of 44.1%.[4]

As of 2024, the Alere Determine TB-LAM Ag test (AlereLAM) is the only commercially available assay and is recommended by the WHO. However, it has unsatisfactory performance, particularly in HIV-negative individuals (sensitivity ~10%).[5,6] The current recommendation is only to assist in TB diagnosis for HIV-positive individuals who exhibit TB signs and symptoms and for severely immunosuppressed patients irrespective of the symptoms.[7] However, these cases cover only a small proportion of new cases (6.7%) and deaths (11.7%), and modelling predicts that morbidity and mortality could be greatly reduced if a ULAM test could be extended to all symptomatic people, including the HIV-negative population.[7] A cross-sectional study on HIV-positive and negative individuals conducted in Uganda evaluated the performance of Xpert Ultra on urine samples and yielded a low sensitivity (17.2%, 95% Confidence Interval [CI] 12.3–23.2), but high specificity (98.1%, 95% CI 94.4–99.6).[5,6] However, to date, no large randomised controlled trials have been conducted and the current evidence does not support this.[5,6] Currently, in HIV-negative individuals, ULAM is not used to diagnose pulmonary TB (PTB). Consequently, diagnosis of Xpert Ultra or smear-negative PTB and extrapulmonary TB (EPTB) remains challenging in such individuals.

An accurate screening test for active PTB is urgently required for patients who are not coinfected with HIV.[7] The early diagnosis of TB can reduce TB-associated morbidity and mortality, as well as transmission.[1] Ideally, a screening test would use a non-invasive body fluid, such as urine, to facilitate utilisation in a low-resource setting.[3] The aim was to summarise the evidence available on the use of urinary LAM as a point of care (POC) diagnostic tool for MTB in an HIV-negative population.

Methods

Study design

Westphaln et al.[8] describe five steps that can assist with such a review: steps one to three involve identifying the research question and identifying the relevant literature with the selection of appropriate studies, and steps four and five are to extract and chart the date, and summarise and report the results.[9] The authors adopted this methodology to produce this scoping review.

This scoping review aims to address the following questions: (1) the use of ULAM as a POC diagnostic tool and (2) use of the current commercial assays in an HIV-negative population.

Search terms and data sources

The search engines employed for this scoping review were PubMed, Google Scholar and Scopus, and the following terms were utilised: urinary lam OR ULAM OR lipoarabinomannan AND HIV negative OR HIV-negative OR HIV negative OR non-HIV OR HIV-negative AND tuberculosis OR TB OR *Mycobacterium tuberculosis* OR MTB AND diagnosis OR diagnostic OR POC OR point of care AND adult. The full form of the acronym HIV – human immunodeficiency virus – was not employed as all articles had the abbreviation mentioned. Any research article that mentioned an association between ULAM as a diagnostic tool for MTB infection in an HIV-negative cohort was included in this scoping review. Moreover, no restriction on the year of publication, language or country of publication was applied to our search. The only filters applied were human studies; all other articles were included.

Data synthesis

On 26 March 2024, a total of 210 articles were identified using the above search terms on three medical search engines (Google Scholar: 44, PubMed: 58, Scopus: 108). Articles were screened by their 'title' to determine if they were relevant to this study. All studies, except case reports, were included, and if the article was deemed suitable for review, then the full 'abstract' was analysed to determine if the article was to be selected. Non-English studies were excluded, and if the article was suitable, it was downloaded and saved by the primary investigator for further analysis in our results. A total of 11 articles were chosen for the review. The article selection process is summarised in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Chart in Figure 1.

Review findings

Demographics of study population

This article provides a comprehensive review of 11 articles which included a total of 842 participants. A summary of the articles appears in Table 1. Majority of these articles were cross-sectional cohorts or prospective studies with all the

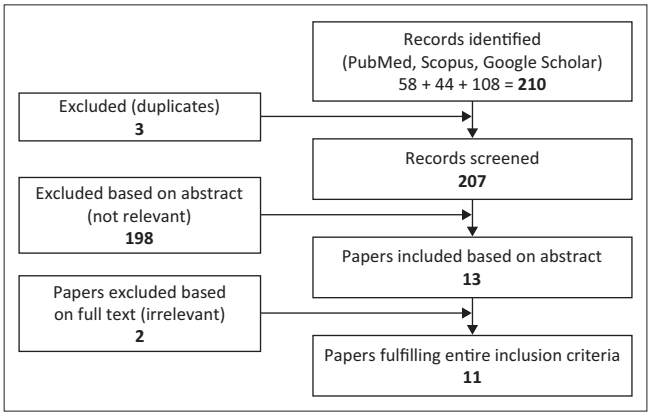

FIGURE 1: PRISMA chart depicting article selection process.

studies being conducted in areas of high TB prevalence. All 11 articles described the diagnostic use of ULAM in an HIV-negative population. All the studies were conducted in lower to middle income countries (LMICs) and were published from various countries covering a wide geographical region with different populations: three articles from South Africa, one from Zimbabwe, one from Uganda, one from Tanzania, one from Peru, one from China, one from India, one from Ethiopia, one from Thailand, and one of the articles was a supplementary article.

Patient cohort

Out of the 11 articles, 8 utilised outpatient cohorts, 2 utilised inpatient cohorts and 1 article was a summary of the current literature. Furthermore, 8 included a comparison between HIV-positive and negative populations, and 3 focussed solely on HIV-negative populations.

Version of urinary lipoarabinomannan used

Since the inception of ULAM to aid in the diagnosis of TB, there have been various assays of ULAM tests available. As described previously, the Alere Determine TB LAM Ag is the only commercially available urine LAM test that has been approved by the WHO.[9] In the 11 selected articles, 2 studies utilised the Chemogen MTB ELISA (1st generation ULAM), 1 utilised the Inverness Clearview ELISA, 1 utilised a mix of the Chemogen and Clearview tests, 4 utilised the Determine ALERE LAM, 1 did not use a commercially available assay and 2 studies utilised both Determine ALERE LAM and the FUJILAM. As of 2024, the use of high-performance probes, such as quantum dot nanobeads (QBs) and Electrochemiluminescence LAM research assays (EclLAM) have been described. These novel tests are still awaiting further testing and validation.

Relationship between HIV status and urinary lipoarabinomannan as a diagnostic tool

Most literature available on ULAM is limited to HIV-positive patients because of poor diagnostic value in HIV-negative patients.[10] A meta-analysis by Minion et al. reported pooled sensitivities of 18% in HIV-negative patients, as opposed to 56% in HIV-positive patients.[11,12,13,14,15] The WHO Updated Guidelines on the use of Lateral Flow LAM (LF-LAM) recommend the test to be used as described: in inpatient settings, WHO strongly recommends using LF-LAM to assist in the diagnosis of active TB in HIV-positive adults, adolescents and children: with signs and symptoms of TB (pulmonary and/or extrapulmonary) (strong recommendation); or with advanced HIV disease or who are seriously ill (strong recommendation); or irrespective of signs and symptoms of TB and with a CD4 count < 200 cells/mm^3 (strong recommendation).[1] Even within an outpatient setting, the use of the ULAM is limited to HIV-positive adults, adolescents and children: with signs and symptoms of TB (pulmonary and/or extrapulmonary) or 'seriously ill patients'; and irrespective of signs and symptoms of TB and with a CD4 count of less than 100 cells/mm^3.[1] The relationship between CD4 count in HIV-positive patients and ULAM positivity is well documented in which an inverse correlation between AlereLAM sensitivity and CD4 count has been identified with increasing sensitivity as patient CD4 count decreased (increased from 16% in patients with CD4 cell count > 200 cells per µL to 24% in patients with CD4 cell count between 101 and 199 cells per µL, to 54% in patients with CD4 ≤ 100 cells per µL).[1]

Discussion

Six studies recommended either the validation or development of novel ULAM tests in an HIV-negative population as the current assays available were not suitable for an HIV-negative population. One study did not observe an association between HIV status or CD4 count and ULAM; however, the sample size in this study was limited and the findings are to be interpreted with caution as this may be a false negative finding. This study further recommended the use of ULAM in patients admitted to intensive care unit (ICU) where TB is likely regardless of the HIV status. One study suggested the possible use of the ULAM test in conjunction with AFB smear and culture in resource-limited countries, to diagnose TB in patients with advanced HIV and in HIV-negative patients with disseminated TB. Three studies recommended against the use of the Chemogen ULAM in HIV-negative individuals.

Overall, the consensus of all studies, except one, recommended against the use of current assays and advocated for the development of new ULAM tests. Minimal disagreement between reviewers existed.

Low and middle-income countries are faced with a large TB burden.[11,12,13,14,15] Healthcare facilities in these settings are inundated with TB cases and function with limited resources, including a shortage of intensive care beds.[11,12,13,14,15] Data suggest that delays in initiation of TB treatment are associated with increased mortality.[11,12,13,14,15] Urinary LAM offers the opportunity to provide a POC diagnosis of TB and has been studied in both outpatient and general hospital settings.[11,12,13,14,15] Furthermore, the use of ULAM may shorten the time to TB diagnosis and diagnose cases of TB that may have been missed with standard testing methods, with the hope that this may improve patient outcomes.

This review provides comprehensive insight into the current literature available on the use of ULAM in an HIV-negative population. All these studies were conducted in areas with a large TB burden. Most of the available data on the use of ULAM is conducted in HIV-positive cohorts. Huang et al. state the current sensitivity of the ULAM in HIV-negative individuals as ~10% as of 2024 for the Alere LAM assay.[7] The WHO requires a minimum sensitivity of 65% to qualify as a biomarker. Consequently, it is evident that the current assay does not meet the criteria to be an approved biomarker for PTB in an HIV-negative population.

TABLE 1: Table depicting a summary of the articles used in the scoping review.

Study year	Author	Type of study	Country	Sample size	Generation of ULAM used	Study population	Main findings in HIV-negative population
2024	Huang et al.[6]	Letter to the Editor	China	169	QBs LAM and Fuji Film LAM and Determine ALERE LAM	Adults with microbiologically confirmed (n = 64) or clinically diagnosed TB (n = 24), other respiratory diseases (n = 56) and healthy donors (n = 25), all HIV negative **Outpatient** cohort	• Combined use of Quantum Dot Nano beads (QBs)-LAM and either Xpert (80%; 95% CI, 69% – 89%) or smear (77%; 95% CI, 66% – 85%) can effectively increase the detection rate • Diagnostic value of urine LAM testing in individuals without HIV • Overall sensitivity of **52%** (95% CI, 41% – 63%) and specificity of 96% (95% CI, 90% – 99%) • Recommend use of novel ULAM
2021	Andama et al.[5]	Cross-sectional	Uganda	357	Determine ALERE LAM	Hospitalised and **outpatient** adults (> 18 years) HIV-positive and HIV-negative who were undergoing sputum-based pulmonary TB evaluation n = 357 participants 166 HIV+; 188 HIV-	• Sensitivity was higher in HIV-positive vs. HIV-negative participants for both urine Xpert Ultra (32.8% vs. **10.1%,** p < 0.001) and Determine TB-LAM (15.6% vs. 4.3%, p = 0.01) • Urine Xpert Ultra continued to have higher sensitivity than Determine TB-LAM among HIV-positive patients (difference 17.2%, 95% CI 4.5–29.8, p = 0.01), without a difference in specificity • Recommend use of novel ULAM
2021	de Vasconcellos et al.[10]	Prospective observational cohort	South Africa	57 HIV+: 29 HIV-: 18 Unknown: 3	Determine ALERE LAM	Critically ill patients **admitted** to a tertiary hospital intensive care unit	• No statistically significant difference in the proportion of positive LAM tests according to HIV status or CD4 count • TB LAM was positive in 8 of 29 (27.6%) HIV-positive patients and 4 of 18 (22.2% HIV-negative patients, p = 0.744 • Sensitivity of urinary LAM for confirmed TB in our study was **50%** • The specificity of TB LAM in the current study was high, ranging from 84.2% to 93.1% • Recommend the use in ICU patients regardless of HIV status where TB is considered likely
2020	Broger et al.[11]	Prospective observational cohort	South Africa Peru	372	Fuji Film LAM and Determine ALERE LAM and Electrochemiluminescence LAM research assay (EclLAM)	HIV-negative adults with symptoms suggestive of pulmonary TB presenting to outpatient health care centres in Peru and South Africa	• Sensitivities of AlereLAM, FujiLAM and EclLAM were 10.8% (95% confidence interval [CI] 6.3% – 18.0%), 53.2% (95% CI 43.9% – 62.1%) and 66.7% (95% CI 57.5% – 74.7%), respectively • The specificities of AlereLAM, FujiLAM and EclLAM were 92.3% (95% CI 88.5% – 95.0%), 98.9% (95% CI 96.7% – 99.6%) and 98.1% (95% CI 95.6% – 99.2%), respectively • Positive likelihood ratios of AlereLAM, FujiLAM and EclLAM were 1.4, 46.2 and 34.8, respectively, and positive predictive values were 37.5%, 95.2% and 93.7%, respectively • Compared with AlereLAM, FujiLAM detected 5 times more patients with TB in HIV-negative participants, had a high positive predictive value and has the potential to improve rapid diagnosis of TB at the point-of-care
2017	Suwanpimolkul et al.[3]	Prospective observational cohort	Thailand	109	Determine ALERE LAM	Group 1: HIV-positive patients with TB (63) Group 2: HIV-negative patients with disseminated TB (20) Group 3: HIV-negative immunocompromised patients with TB (26) Group 4: Patients with diseases other than TB (19) **Outpatient**	• The sensitivity of the test was **20%** in group 2 and **12.5%** in group 3, and the specificity and PPV were 100% for both groups • A positive urine LAM test result was significantly associated with death • The findings from this study suggest the possible use of the ULAM test with AFB smear and culture in resource-limited countries, in the diagnosis of TB in patients with advanced HIV and in HIV negative patients with disseminated TB
2017	Sahle et al.[9]	Cross sectional	Ethiopia	122	Determine ALERE LAM	**Outpatient** adults (≥ 18 years) visiting the health facilities with suspected TB who had one of the signs and symptoms of TB (current cough lasting at least 2 weeks, bloody cough, fever, weight loss, chest pain, fatigue, night sweats, breath shortness). HIV positive (21); HIV negative (101)	• The overall sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of Determine TB LAM (for both HIV-positive and HIV-negative participants) was **37.1%** (95% CI 21.5 – 55.1), 97.7% (95% CI 91.9 – 99.7), 86.7% (95% CI 59.5 – 98.3) and 79.4% (95% CI 70.5 – 86.6) • TB diagnosis in patients who are co-infected with HIV, with advanced immunosuppression
2017	Paris et al.[7]	Cross sectional	Peru	101	Commercial assay not used (copper complex dye within a hydrogel nanocage)	101 subjects (n = 48 microbiologically confirmed TB-positive patients, n = 14 diseased TB-negative patients, and n = 39 healthy volunteers) All HIV negative **Outpatients**	• TB LAM was quantitatively measured in the urine with a sensitivity of **> 95%** and a specificity of **> 80%** (n = 101) in a concentration range of 14–2000 picograms per millilitre, as compared to non-TB, healthy and diseased, age-matched controls 95% confidence interval, 0.9005 – 0.9957 • Urinary LAM was elevated in patients with a higher mycobacterial burden (n = 42), a higher proportion of weight loss (n = 37), or cough (n = 50)

Table 1 continues on the next page →

TABLE 1 (Continues...): Table depicting a summary of the articles used in the scoping review.

Study year	Author	Type of study	Country	Sample size	Generation of ULAM used	Study population	Main findings in HIV-negative population
2011	Achkar et al.[12]	Supplementary article	N/A	N/A	MTB ELISA (Chemogen Inc) and N/A Clearview ELISA (Inverness Medical Innovations)		• Very low sensitivity (**6% – 21%**) for culture-positive TB in HIV-negative patients was a consistent finding among all studies • Specificity was variable in both HIV-positive and negative patients, with three studies from South Africa reporting high specificities of 96% – 100% compared with just 88% – 89% in three other studies from Zimbabwe, Tanzania and India
2009	Shah et al.[13]	Cross sectional	South Africa	499	Clearview ELISA (Inverness Medical Innovations)	**Hospitalised** adults with signs and/or symptoms of active TB were enrolled HIV+: 422 HIV-: 77	• In 47 HIV-negative participants, the LAM test was positive in three, including 2/14 (14%) with confirmed TB and 1/5 (**20%**) indeterminate participants; specificity was **100%** (23/23) in the small number of HIV-negative participants classified as 'not TB' • Low LAM test sensitivity in HIV-negative TB patients may limit this test's utility in settings of low HIV prevalence
2009	Mutetwa et al.[14]	Prospective cohort	Zimbabwe	427	MTB ELISA (Chemogen Inc)	HIV+ and HIV- adults with symptoms suggestive of TB from three hospitals (**outpatients**) HIV-: 99 HIV+: 328	• LAM ELISA sensitivity was **44%** (95% CI 36% – 52%) for culture-confirmed TB (52% in smear positive patients).Specificity was 89% (95% CI: 81% – 94%) • Sensitivity was significantly higher in HIV-related TB (**52%**: 95% CI 43% – 62%, $p < 0.001$) compared to HIV-negative TB (21%: 95% CI 9% – 37%); sensitivity in smear-negative patients was low (**28%**: 95% CI 13% – 43% for combined HIV positive and negative patients) • Greater sensitivity of urine LAM detection for HIV-related TB. However, both sensitivity and specificity were suboptimal, suggesting that this version cannot confirm or exclude TB in either HIV-positive or negative patients
2009	Reither et al.[15]	Prospective cohort	Tanzania	291	MTB ELISA (Chemogen Inc)	HIV+ and HIV- **outpatient** population presenting with symptoms of TB HIV+ :172 HIV- :125	• In HIV-positive individuals, the sensitivity was 62% compared to **21%** in HIV-negative participants ($p = 0.019$) • Overall specificity amounts to 87.8%, being slightly higher in men (93.9%) and HIV-negative participants (**91.1%**) • This commercially available generation of LAM-ELISA does not appear to be useful as an independent diagnostic test for pulmonary TB

Note: Please see the full reference list of the article, Hirachund O, Pillay S. Urinary lipoarabinomannan for diagnosis of Tuberculosis in an HIV-negative population: A scoping review. Afr J Prm Health Care Fam Med. 2024;16(1), a4733. https://doi.org/10.4102/phcfm.v16i1.4733, for more information.

HIV, human immunodeficiency virus; TB, tuberculosis; ULAM, urinary lipoarabinomannan; MTB, *Mycobacterium tuberculosis*; LAM, lipoarabinomannan.

Most articles advocate for the use or validation of a novel test. The enhanced FUJIFILM SILVAMP TB-LAM (FujiLAM) is a second-generation test that utilises high-affinity monoclonal antibodies (mAb) and sliver signal amplification technology, resulting in a much lower limit of detection (LoD) and higher diagnostic sensitivity and appears to show promising results.[7] Broger et al. describe that compared with AlereLAM, FujiLAM detected 5 times more patients with TB in HIV-negative participants, had a high positive predictive value and has the potential to improve rapid diagnosis of TB at the POC.[11,12,13,14,15] However, a more recent study describes that the use is limited because of the relatively complex methodology and subjective naked eye reading when using the FujiLAM resulting in substantial variability and high error rates.[7] Nonetheless, there is a paucity of information surrounding the use of any novel assays in an HIV-negative population.

Vasconcellos and colleagues recommend that ULAM should be considered in critically ill patients admitted to ICU facilities where TB is suspected, regardless of HIV status.[11,12,13,14,15] However, this study provided a small cohort of only 56 patients, of which only 18 (36%) were HIV-negative. These results have not been reproduced in other studies.

This scoping review is subject to certain limitations. Firstly, there was a lack of heterogeneity in the ULAM assays utilised, and secondly, large methodological divergence among the various study designs making comparison between the studies more challenging. Most studies were conducted in African nations or LMICs, and this limits the extrapolation of findings to other regions.

We recommend the continued use of the current commercial assays in HIV-positive individuals; however, we do not recommend that the current assays be utilised in HIV-negative individuals because of the poor sensitivity and specificity. We also encourage further research into: (1) the use of the novel assays in an HIV-negative population (2) the development of novel ULAM or urine based POC diagnostic tests for use in an HIV-negative population, (3) larger prospective clinical trials to be conducted on the use of ULAM in ICU patients.

Conclusion

The use of ULAM as a point of care diagnostic tool for the diagnosis of PTB is a valuable non-invasive test. However, the current commercial assay available, namely, the DETERMINE AlereLAM has a poor sensitivity in an HIV-negative population and is not recommended as a diagnostic tool. Even in critically ill patients who cannot produce sputum, the use is currently not recommended. The FujiLAM and several other assays require more rigorous testing and validation in an HIV-negative population.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

O.H. and S.P. conceptualised and wrote the article entirely. O.H. researched all the articles and conducted the primary search. S.P. assisted with editing and formalisation of the abstract, tables and referencing.

Ethical considerations

This article followed all ethical standards for research without direct contact with human or animal subjects.

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Data availability

The data that support the findings of this study are available from the corresponding author, O.H., upon reasonable request.

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