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Evaluating clinical decision rules and rapid diagnostic tests for the diagnosis of *Streptococcus pyogenes* pharyngitis in Gambian children: A diagnostic accuracy study

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SUMMARY

Objectives: Accurate diagnosis of Streptococcus pyogenes (S. pyogenes) pharyngitis is imperative in high rheumatic heart disease-burden countries. We aimed to assess the diagnostic accuracy of two rapid diagnostic tests and five clinical decision rules (CDRs) in The Gambia.

Methods: Children under 16 years presenting with signs and symptoms of pharyngitis were recruited at Sukuta Health Centre, The Gambia. A rapid antigen detection test (SD Bioline; LFT) and a rapid gene-amplification test (ID NOW™ STREP A2) were assessed for diagnostic accuracy alongside five CDRs against culture and qPCR for S. pyogenes. Logistic regression was used to determine risk factors for S. pyogenes pharyngitis.

Results: Among 376 participants, S. pyogenes positivity was 9·8% (37/376) by culture, 32·4% (122/376) by PCR, 31·6% (119/376) by LFT, and 33·3% (122/366) by ID NOW. The ID NOW had sensitivities and specificities of 94·6% and 73·6% against culture, and 93·5% and 87·6% against PCR. The LFT had sensitivities and specificities of 83·8% and 74·0% against culture and 55·7% and 80·0% against PCR. The Smeesters CDR performed best with an area under the curve (AUC) of 0·694 against culture. S. pyogenes pharyngitis risk increased with age. Recent chest infection/cough (aOR 1·89, 1·08–3·28) and concurrent skin infection (aOR 2·11, 1·21–3·69) were associated with increased S. pyogenes pharyngitis.

Conclusions: The LFT and the CDRs had poor performance in detecting S. pyogenes pharyngitis compared to PCR and culture. Molecular methods detected a higher proportion of S. pyogenes than culture. Affordable

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and sensitive diagnostics are urgently needed to improve S. pyogenes management in resource-limited settings.

Background

Acute pharyngitis in children is one of the most common reasons for primary healthcare consultations worldwide. *Streptococcus pyogenes* (*S. pyogenes*) is responsible for 10–25% of pharyngitis presentations, with a higher proportion in high-income countries (HICs) than low- and middle-income countries (LMICs) (24·3% vs. 17·6%).[1] Data from LMICs including The Gambia are lacking, though a recent study found an incidence rate of 120 cases per 1000 person years (95% CIs 57–252) in children aged 5 to 11 years of *S. pyogenes* pharyngitis, with 16·7% of clinical sore throat episodes positive for Strep A by bacterial culture in that age group.[2,3]

Globally, *S. pyogenes* is implicated in over 500,000 deaths per year, predominantly in LMICs where immune sequelae including acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are common.[4,5] Although most pharyngitis cases are viral in origin, accurate diagnosis of *S. pyogenes* pharyngitis and prompt administration of antibiotics is crucial in RHD-endemic settings.[6] This must be balanced against concerns over antimicrobial resistance and reducing unnecessary antibiotic prescriptions for individuals with viral pharyngitis.[7] In HICs two broad approaches, clinical decision rules (CDRs) and rapid diagnostic tests, have been widely utilised to improve the management of pharyngitis and to guide antibiotic prescribing.

CDRs offer a standardised, pragmatic approach to diagnosis that can aid clinicians, particularly in resource-constrained settings, in making treatment decisions.[8] Although CDRs have been widely implemented for diagnosis of *S. pyogenes* pharyngitis, most were developed and validated in HICs, where demographic characteristics, clinical and molecular epidemiology of *S. pyogenes*, and healthcare systems are substantially different from many African countries.[9,10] The applicability of these CDRs as well as rapid diagnostic tests to LMICs such as The Gambia, is therefore uncertain.

In The Gambia, microbiological culture and rapid diagnostic tests are not available at government health centres. Most outpatient presentations with upper respiratory tract infections are assessed by nurses with limited medical and diagnostic training. Additionally, financial and practical barriers to healthcare-seeking for sore throats exist and patients commonly use local remedies first, only seeking formal healthcare after treatment failure.[11] Collectively, these factors lead to inadequate diagnosis and treatment of *S. pyogenes* pharyngitis, which may contribute to the high burden of RHD. Several rapid diagnostic tests exist for point-of-care diagnosis of *S. pyogenes* pharyngitis within two broad categories: rapid antigen detection tests (RADTs) and rapid nucleic acid (gene-amplification) tests (RNATs). Meta analyses have reported a summary sensitivity for RADTs of 85·6% and a summary specificity of 95·4%, while for RNATs the summary sensitivity is higher at 97·5% and the summary specificity is similar at 95·1%.[12,13] Such tests can offer improved diagnosis over clinical assessment while not requiring laboratories to maintain reagents or consumables. However, there are limited data on their use in low-resource settings such as The Gambia and their use has yet to be shown to be cost-effective over other strategies.[14–16]

We aimed to assess the diagnostic accuracy of two rapid diagnostic tests, one RADT and one RNAT, and five commonly used CDRs for diagnosis of *S. pyogenes* pharyngitis in The Gambia.

Methods

Study design and participants

This prospective diagnostic accuracy study was conducted in children under 16 years of age at Sukuta Health Centre, The Gambia. Children complaining of sore throat in the presence of tonsillopharyngeal erythema, were eligible. Children under five were included if non-specific symptoms were accompanied by tonsillopharyngeal erythema. Participants were identified by recruiting consecutive cases meeting eligibility presenting to the Sukuta Health Centre when study staff were available.

The study was approved by the Gambia Government/MRC joint ethics committee and the LSHTM Research Ethics Committee (LEO17910). Written informed consent was provided by parents or guardians for participants. Participants aged 12 and over provided assent.

Procedures

Clinical assessment

Participants were assessed by a nurse who took a detailed clinical history of the presenting complaint and performed a thorough clinical examination. All clinical information relevant to five clinical decision rules (CDRs) was collected. Three CDRs were originally designed and validated in HICs: the CENTOR score (USA), Modified CENTOR/McIsaac score (Canada), and FeverPAIN (UK), and two in LMIC settings: the Cape Town score (South Africa), the Smeesters score (Brazil) (Supplementary Table S1).[17–21] Socio-demographic data including sex, age, ethnic group, household size, mother's education level, household income, and number of siblings were gathered. Additional exploratory data were collected on potential risk factors for *S. pyogenes* pharyngitis, including recent respiratory symptoms, personal and household history of skin or throat infections, prior antibiotic use, and underlying health conditions.[22,23]

Sample collection

Two swabs were held together to form a dual swab and a sample from the oropharynx was collected using standard techniques. The swabs used were Copan Transystem™ 140C (Copan) and the SD Bioline Group A Streptococcal RADT lateral flow test (LFT) swab (Abbott). The LFT swab was immediately used for the SD Bioline test according to manufacturer's instructions. The Copan swab was placed in its liquid Amies transport medium and transported in a cold box to MRC Unit The Gambia laboratories at Fajara on the same day.

Laboratory procedures

The Copan swab was plated for microbiological culture on Colombia blood agar, and beta-haemolytic colonies underwent latex agglutination testing (Prolex Pro-Lab) for the presence of Group A Streptococci. From the remaining liquid Amies, 200 µl was used for the ID NOW Strep A 2 (Abbott), an RNAT, formerly known as Alere i strep A test, which targets a sequence of the *cep5* gene, encoding the C5a peptidase streptococcal virulence factor.[24,25] The remaining liquid Amies was stored at −70 °C until DNA extraction for PCR. DNA was extracted from 200 µl of Amies using the QIAamp DNA mini kit (Qiagen) according to manufacturer's instructions following incubation with lysostaphin (1 mg/mL) and lysozyme (100 mg/mL).[26]

Sample volume was insufficient for 30 samples, so additional buffer was added to make 200 µl. Quantitative PCR was performed using Bio-Rad CFX 96 Touch Real-Time PCR detection system with primers and probes to detect the highly-conserved *S. pyogenes*-specific gene *speB* (forward: CTAAACCCTTCAGCTCTTGGTACTG; reverse: TTGATGC CTACAACAGCACTTTG; probe: Cy5-CGGCGCAGGCGGCTTCAAC-BHQ2) as previously described.[27,28] Bacterial loads were quantified using standard curves generated by 10-fold serial dilutions of extracted DNA from *S. pyogenes* reference strain H293. The limit of detection (LOD) was determined using curve-fitting models on standard curves generated from eight serial dilutions from 10,000,000 to 1 copy per µl run in 11 replicates. The LOD was defined as the lowest concentration of DNA that could be detected at a 95% detection rate. To optimise throughput, samples were run in a single well. Based on the LOD, we defined a cycle threshold (Ct) of more than 40 to be negative, and less than 36 to be positive. Samples with a Ct between 36 and 40 were repeated to exclude contamination and determined to be positive if an appropriate amplification curve was seen and the Ct was below 40 for both runs. PCR conditions used were 50 °C for 2 min, 95 °C for 10 min, 94 °C for 15 s and 58 °C for 40 s over 45 cycles.

Statistical analysis

A sample size of 385 pharyngitis cases was chosen to detect a *S. pyogenes* pharyngitis proportion of 20% with a precision of 4% and allow us to detect a sensitivity of 95% ± 5% for the CDRs and rapid diagnostic tests versus the index test. The proportion of pharyngitis cases positive for *S. pyogenes* by each test performed was calculated with binomial exact 95% confidence intervals (CIs). Differences in bacterial load by qPCR were assessed by Wilcoxon test with p-values adjusted for multiple testing using a Benjamini and Hochberg correction. For the primary assessment of diagnostic accuracy, microbiological culture was used as the reference standard. Given the limitations of culture,[28] we also performed a secondary analysis using PCR as the reference standard. Performance of the CDRs versus culture and PCR were assessed using the area under the curve (AUC) of receiver operating characteristic (ROC) curves. Unweighted and weighted (60% towards sensitivity) Youden's indices were calculated to identify optimal score thresholds for the CDRs. Logistic regression models were used to explore socio-demographic and other factors associated with PCR-positive *S. pyogenes* pharyngitis in this setting. Unadjusted odds ratios (OR) are reported for univariable models and adjusted odds ratios (aOR) are reported for multivariable models. Marginal probabilities were calculated for each risk factor, and when adjusting age group and sex, assumed age group 5–11 and male sex. P-values <0·05 were considered significant. Data were entered directly into REDCap.

Analysis was performed in R version 4.3.1.

Results

A total of 376 participants were recruited to the study between June 9, 2021, and September 26, 2022. Participants were 55% (208/376) male, with a median age of 4 years (IQR 2–6). Median household size was 5 people (IQR 4–7) (Table 1).

The most reported clinical features were throat pain (364/375, 97·1%), painful swallowing (360/375, 96·0%), a history of fever (353/376, 93·9%) and difficulty swallowing (350/375, 93·3%). The most frequently reported time of onset was less than 12 h ago (130/353, 36·8%). On examination, 374/376 (99·5%) had tonsillar erythema, 364/376 (96·8%) had swollen anterior cervical lymph nodes, 119/376 (31·6%) had tonsillar exudate, and 361/376 (96·0%) had tonsillar swelling (Supplementary Table S2).

Table 1
Socio-demographic and anthropometric characteristics of participants recruited. IQR, interquartile range.

Characteristic	Category	Number (%) n=376
Median age in years (IQR)	-	4 (2–6)
Age group	0–4 years old	256 (68·1)
	5–11 years old	101 (26·9)
	12–15 years old	19 (5·1)
Sex	Male	208 (55·3)
	Female	168 (44·7)
Tribe/ethnic group	Mandinka	172 (45·7)
	Wolof	52 (13·8)
	Fula	73 (19·4)
	Jola	12 (3·2)
	Other	67 (17·8)
Median household size (IQR; range)	-	5 (4–7; 2–20)
Median number of siblings from same mother (IQR)	-	3 (2–5)
Median number of siblings from same father (IQR)	-	4 (2–6)
Mother's education	None	34 (9·0)
	Arabic school only	129 (34·3)
	Primary school only	37 (9·8)
	Middle school	73 (19·4)
	Secondary school	71 (18·9)
	Further/higher education	30 (8·0)
	Don't know/ unwilling to say	1 (0·3)
	Missing	1 (0·3)
Household income per month	GMD <500 (<$10)	184 (48·9)
	GMD 500–999 ($10–20)	7 (1·9)
	GMD 1000–2499 ($20–50)	83 (22·1)
	GMD 2500–4999 ($50–100)	66 (17·6)
	GMD >5000 (>$100)	19 (5·1)
	Unwilling to say	17 (4·5)
Mean height in centimetres (SD)	-	103·3 (22·6)
Mean weight in kilograms (SD)	-	16·5 (8·9)
Mean body mass index-for-age (SD)	-	−0·98 (1·15)

Proportion of participants positive for S. pyogenes

The proportion of participants *S. pyogenes*-positive by culture was 9·8% (37/376; 95% CIs 7·0–13·3). Both rapid tests detected a higher proportion of *S. pyogenes*, with the LFT positive in 31·6% (119/376; 95% CIs 27·0–36·6) and ID NOW positive in 33·3% (122/366; 95% CIs 28·5–38·4) of cases. PCR detected *S. pyogenes* in 32·4% of participants (122/376; 95% CIs 27·7–37·4) (Fig. 1a).

ID NOW results were not available for 10 participants, on five occasions due to machine error, on four occasions due to the test not being done, and on one occasion due to inadequate sample volume due to spillage. Although the overall proportion of positive LFT and ID NOW tests was similar to PCR, the agreement of LFT with PCR was poor, compared to ID NOW (Fig. 1b).

In *S. pyogenes* PCR-positive samples, the bacterial load estimated by quantitative PCR was significantly higher in samples which were culture positive compared to culture negative (p < 0·0001), LFT positive compared to LFT negative (p < 0·0001), and ID NOW positive compared to ID NOW negative (p=0·0025), though the difference was smaller (Fig. 1c).

Diagnostic accuracy of rapid tests

Taking the culture result as the reference standard, the LFT had a sensitivity of 83·8% and a specificity of 74·0%. PCR and the ID NOW

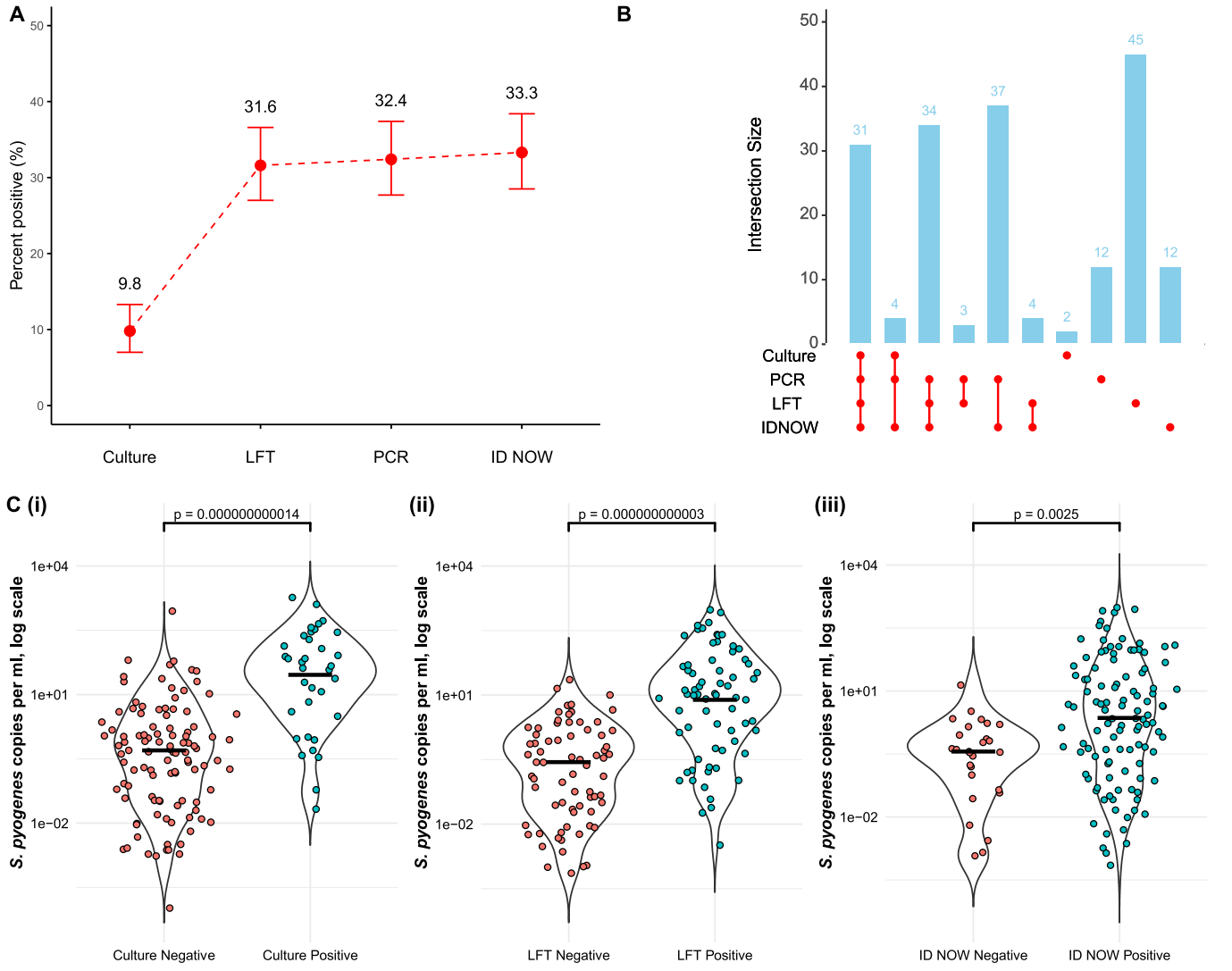

Fig. 1. (A) Chart showing the percentage of participants tested who were positive for *S. pyogenes* by culture, LFT, ID NOW and PCR. (B) UpSet plot showing the number of participants tested who were positive for each test and the agreement between tests. The red lines indicate the combination of positive tests that each blue bar represents. 170 participants were negative for all four tests, and ID NOW was not performed on 10 participants, so these data are excluded from the plot. (C) Violin plots showing bacterial load detected by quantitative PCR in PCR-positive samples by (i) microbiological culture status, (ii) LFT status, and (iii) ID NOW status.

Table 2
Two-by-two tables of LFT and ID NOW test results and of PCR against culture as the reference standard showing the diagnostic accuracy of the two tests. Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.

	Culture +ve	Culture −ve	
LFT +ve	31	88	PPV: 26·1%
LFT −ve	6	251	NPV: 97·7%
	Sens: 83·8%	Spec: 74·0%	
ID NOW +ve	35	87	PPV: 28·7%
ID NOW −ve	2	242	NPV: 99·2%
	Sens: 94·6%	Spec: 73·6%	
PCR +ve	35	87	PPV: 28·7%
PCR −ve	2	252	NPV: 99·2%
	Sens: 94·6%	Spec: 74·3%	

performed similarly, both with a sensitivity of 94·6% and specificities of 73·6% for ID NOW and 74·3% for PCR. The positive and negative predictive values of the ID NOW and PCR were higher than for the LFT (Table 2).

Taking PCR as the reference standard the LFT had a sensitivity of 55·7% and a specificity of 80·0% while the ID NOW had a sensitivity of 87·6% and a specificity of 93·5%. The positive predictive value of both tests was improved when PCR was taken as the reference standard, but the negative predictive value of both tests decreased, though only marginally for ID NOW (Table 3).

Receiver operating characteristic curves of clinical decision rules against PCR

Taking culture as the reference standard, the Smeesters score performed best with an AUC of 0·694, followed by Cape Town with an AUC of 0·617. CENTOR (AUC: 0·584), Modified CENTOR/McIsaac (AUC: 0·496), and FeverPAIN (AUC: 0·600) also performed poorly against culture (Fig. 2). Similarly, with PCR as the reference standard, the performance of all the CDRs were poor (Supplementary Fig. S1). The CENTOR score performed best of the CDRs designed for HICs with an AUC of 0·583, while the Modified CENTOR/McIsaac (AUC

Table 3
Two-by-two tables of LFT and ID NOW test results against PCR as the reference standard showing the diagnostic accuracy of the two tests. Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.

	PCR +ve	PCR −ve	
LFT +ve	68	51	PPV: 57·1%
LFT −ve	54	203	NPV: 79·0%
	Sens: 55·7%	Spec: 80·0%	
ID NOW +ve	106	16	PPV: 86·9%
ID NOW −ve	15	229	NPV: 93·9%
	Sens: 93·5%	Spec: 87·6%	

0·500) performed only as well as a random classifier and FeverPAIN (AUC 0·554) performed only slightly better. Of the two CDRs designed for LMIC settings, the Smeesters score performed better with an AUC of 0·643, while the Cape Town score performed less well (AUC 0·563). Participants exhibited a diversity of score outcomes from all five CDRs tested (Supplementary Fig. S2).

At the optimal weighted threshold, the Cape Town score had the highest combined sensitivity (83·8%) and specificity (34·2%) (Supplementary Table S3). Combining the Cape Town score with the ID NOW into an algorithm where patients with a score above 2·5 undergo an ID NOW test would provide an overall sensitivity of 65·6%, specificity of 94·8%, PPV of 86·0% and NPV of 84·9% whilst preventing 32·4% (122/376) of patients requiring an ID NOW.

Risk factors for S. pyogenes *pharyngitis*

In multivariable logistic regression models, the only socio-demographic characteristic significantly associated with increased odds of PCR-positive *S. pyogenes* pharyngitis was age group (0–4 years, marginal probability [MP] 26·4% compared to 5–11 years, MP 47·5%, aOR 2·52, 95% CIs 1·51–4·23, p=0·0004, and 12–15 years, MP 60·5%, aOR 4·28, 95% CIs 1·50–12·68, p=0·0069) (Supplementary Table S4). In models adjusting for age group and sex, the odds of *S. pyogenes* pharyngitis by PCR were higher in participants presenting with a history of a chest infection/cough in the last two weeks (MP 56·0% vs. 40·3%, aOR 1·89, 95% CIs 1·08–3·28, p=0·024) and with a concurrent skin infection seen (MP 58·8% vs. 40·3%, aOR 2·11, 95% CIs 1·21–3·69, p=0·0087). Clinical presentation features associated with increased odds of *S. pyogenes* were history of fever (MP 44·0% vs. 18·7%, aOR 3·43, 95% CIs 1·18–12·76, p=0·038), difficulty swallowing (MP 43·6% vs. 13·8%, aOR 4·84, 95% CIs 1·38–30·67, p=0·036), pharyngeal erythema (MP 47·7% vs. 34·1%, aOR 1·76, 95% CIs 1·12–2·78, p=0·015) and tonsillar exudate (MP 51·9% vs. 38·0%, aOR 1·76, 95% CIs 1·10–2·81, p=0·019) (Supplementary Table S4–5). No measures of social-mixing were significantly associated with *S. pyogenes* pharyngitis risk (Supplementary Table S6).

Discussion

This study reveals a significant proportion of pharyngitis in Gambian children is caused by *S. pyogenes*, with gene-amplification based diagnosis (PCR and ID NOW) detecting a substantially higher proportion than traditional culture, as might be expected given the higher sensitivity of molecular methods. The LFT appeared to detect a higher proportion as well, but false positives were considerable. Whilst rapid point-of-care tests could be useful tools in LMIC settings, both tests assessed in this study had limitations that would limit their wide-spread implementation. The LFT's low sensitivity and poor positive predictive value would limit its utility in high-RHD risk settings while, although the ID NOW showed high-sensitivity and specificity, its high cost, and requirement for sterile, temperature-controlled, laboratory conditions may limit adoption in low-resource settings. The disparity in diagnostic sensitivity and cost between qPCR, culture, and rapid diagnostic tests like ID NOW and SD Bioline underscores the urgent need to prioritise the

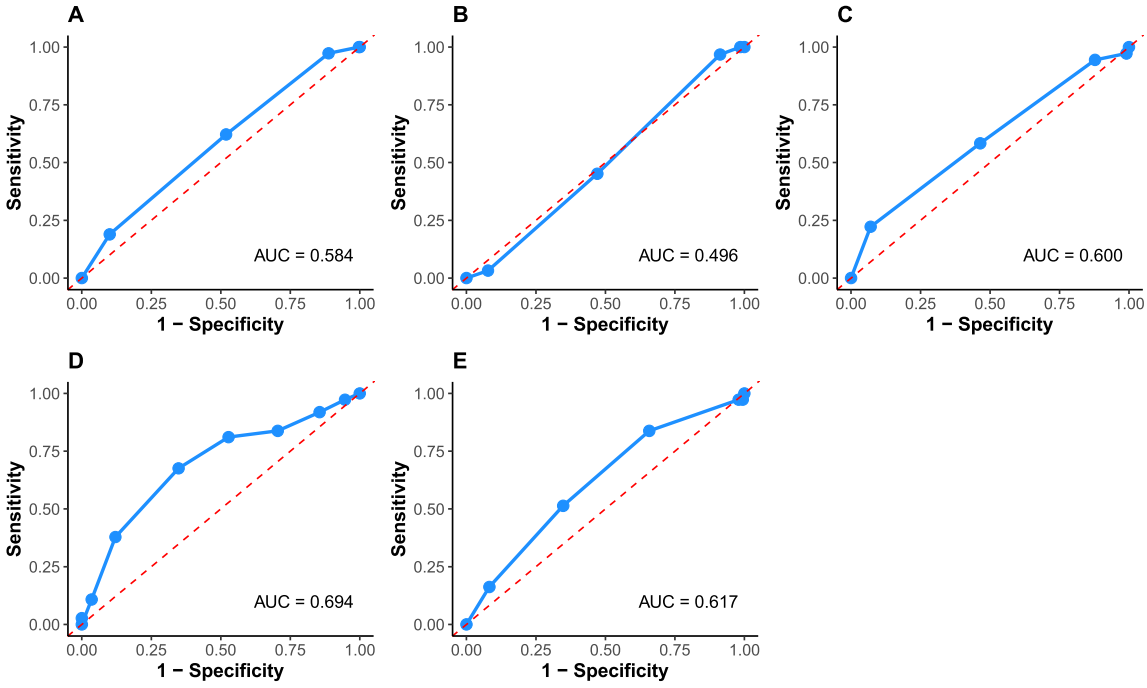

Fig. 2. ROC curves for the five CDRs tested using culture as the reference standard. (A) CENTOR score (1981), (B) Modified CENTOR/McIsaac (note 139 participants excluded due to age < 3), (C) FeverPAIN, (D) Smeesters, (E) Cape Town. The red dashed line indicates how a random classifier test would perform. The area under curve (AUC) is the area under the blue CDR line, a higher AUC suggests a higher diagnostic accuracy.

development and dissemination of cost-effective, high-sensitivity, point-of-care diagnostic tools for *S. pyogenes*, particularly in LMICs.

The stark discrepancy between the PCR and culture results implies a possible underestimation of the global burden of *S. pyogenes* pharyngitis based on traditional microbiological testing. However, the clinical and immunological importance of PCR-positive, culture-negative pharyngitis needs further investigation. In this study, 70·5% (86/122) of PCR-positive cases were negative on culture, and those with a higher bacterial load were more likely to be culture positive. In a region with a high-RHD burden, it is vital to identify and treat symptomatic pharyngitis episodes with evidence of *S. pyogenes* to limit the risk of ARF and RHD.[29] The low positivity of *S. pyogenes* by culture compared to PCR suggests that molecular methods may be preferable to detect *S. pyogenes* in this setting. However, further work is necessary to better understand the cost-effectiveness of molecular and rapid diagnostics in this setting. Such work should consider the direct costs of the tests but also the broader economic impacts of *S. pyogenes* disease and RHD, including healthcare costs, lost productivity, and the societal burden of premature mortality. However, evaluation of potential harms would be needed alongside, including estimates of number needed to treat (NNT), number needed to harm (NNH), and the implications of increased antibiotic use for antimicrobial resistance in using molecular diagnostics. Though the inherent difficulties in capturing the long-term consequences of RHD, coupled with the lack of robust surveillance data from Africa, make such analyses challenging.

While PCR detected substantially more *S. pyogenes* than culture, this likely reflects its higher sensitivity to identify both high-density infections and low-density colonisation (carriage). As PCR cannot distinguish colonisation from symptomatic infection, some PCR-positive cases may not represent true disease. This limitation is important when interpreting test performance and considering treatment implications. Our study did not assess serological responses, or test for alternative causes of pharyngitis, so we cannot be sure that of the aetiology in PCR-positive cases. However, our inclusion criteria align with the SAVAC criteria for a confirmed *S. pyogenes* pharyngitis case.[30] Data on the prevalence of *S. pyogenes* carriage in LMICs, particularly through PCR detection, are limited, but a previous study in The Gambia indicated a *S. pyogenes* pharyngeal carriage rate of 7–13% in children aged 2–4 years.[27] Furthermore, significant anti-*S. pyogenes* serological responses were seen in newly colonised children in that study, raising questions over whether asymptomatic carriage is immunologically silent, or whether it could be contributing to immune priming of RHD.[27] Therefore, while acknowledging the possibility of asymptomatic carriage, in settings with high-RHD risk and substantial barriers to healthcare seeking for pharyngitis, the treatment of all PCR-positive cases could be beneficial and could be considered in future research.[11]

Clinical decision rules (CDRs) have been frequently proposed to optimise the use of limited diagnostic resources. The use of PCR as a reference standard for CDRs must be interpreted with caution, given its inability to differentiate between colonisation and clinical infection and that these CDRs were designed with culture as the diagnostic outcome. However, the low sensitivity of the CDRs assessed compared to both culture and PCR limits their utility in this setting. Many CDRs were designed in HICs, where clinical and molecular epidemiology of *S. pyogenes* is different.[10,31] Combining a CDR with a rapid test into a clinical algorithm could improve specificity while moderating test use but would reduce sensitivity to less than 70%, which may be insufficient in this setting, underscoring the need for novel sensitive diagnostic tools.[32]

This study has several limitations. Firstly, there was potential for selection bias by selecting participants by convenience sampling. We also selected participants only from an outpatient setting, thus missing people less likely to attend health centres. Secondly, the study was conducted in an urban area, which limits its generalisability to rural settings. Thirdly, utilisation of a non-selective culture medium may have contributed to the lower *S. pyogenes* detection by culture than PCR, though our methods were standard. Beyond these limitations, the study's findings highlight the critical gap in our understanding of the clinical presentation of Strep A infections in LMIC.

This study highlights the limitations of current diagnosis of *S. pyogenes* pharyngitis in LMIC settings such as The Gambia. None of the evaluated diagnostic tests nor clinical decision rules appears suitable for adoption in this setting. Identifying and validating alternative diagnostic strategies remains a priority for *S. pyogenes* control globally.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2025.106546.

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