Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines

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Summary

Background Early detection and diagnosis of acute rheumatic fever and rheumatic heart disease are key to preventing progression, and echocardiography has an important diagnostic role. Standard echocardiography might not be feasible in high-prevalence regions due to its high cost, complexity, and time requirement. Handheld echocardiography might be an easy-to-use, low-cost alternative, but its performance in screening for and diagnosing acute rheumatic fever and rheumatic heart disease needs further investigation.

Methods In this systematic review and meta-analysis, we searched Embase, MEDLINE, LILACS, and Conference Proceedings Citation Index—Science up to Feb 9, 2024, for studies on the screening and diagnosis of acute rheumatic fever and rheumatic heart disease using handheld echocardiography (index test) or standard echocardiography or auscultation (reference tests) in high-prevalence areas. We included all studies with useable data in which the diagnostic performance of the index test was assessed against a reference test. Data on test accuracy in diagnosing rheumatic heart disease, acute rheumatic fever, or carditis with acute rheumatic fever (primary outcomes) were extracted from published articles or calculated, with authors contacted as necessary. Quality of evidence was appraised using GRADE and QUADAS-2 criteria. We summarised diagnostic accuracy statistics (including sensitivity and specificity) and estimated 95% CIs using a bivariate random-effects model (or univariate random-effects models for analyses including three or fewer studies). Area under the curve (AUC) was calculated from summary receiver operating characteristic curves. Heterogeneity was assessed by visual inspection of plots. This study was registered with PROSPERO (CRD42022344081).

Findings Out of 4868 records we identified 11 studies, and two additional reports, comprising 15 578 unique participants. Pooled data showed that handheld echocardiography had high sensitivity (0·87 [95% CI 0·76–0·93]), specificity (0·98 [0·71–1·00]), and overall high accuracy (AUC 0·94 [0·84–1·00]) for diagnosing rheumatic heart disease when compared with standard echocardiography (two studies; moderate certainty of evidence), with better performance for diagnosing definite compared with borderline rheumatic heart disease. High sensitivity (0·79 [0·73–0·84]), specificity (0·85 [0·80–0·89]), and overall accuracy (AUC 0·90 [0·85–0·94]) for screening rheumatic heart disease was observed when pooling data of handheld echocardiography versus standard echocardiography (seven studies; high certainty of evidence). Most studies had a low risk of bias overall. Some heterogeneity was observed for sensitivity and specificity across studies, possibly driven by differences in the prevalence and severity of rheumatic heart disease, and level of training or expertise of non-expert operators.

Interpretation Handheld echocardiography has a high accuracy and diagnostic performance when compared with standard echocardiography for diagnosing and screening of rheumatic heart disease in high-prevalence areas.

Funding World Health Organization.

Lancet Glob Health 2024; 12: e983–94

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Introduction

Rheumatic heart disease is a structural and functional change in the heart muscles and valves due to acute rheumatic fever.[1] Single or repeated episodes of acute rheumatic fever can lead to deformity and rigidity of valve cusps, mainly affecting the left-sided cardiac valves. Tricuspid and pulmonary valves can also be involved, but rheumatic heart disease without involvement of the mitral valve is rare.[2]

Despite being preventable, acute rheumatic fever and rheumatic heart disease remain a prevalent public health problem, particularly in low-income and middle-income countries, and can result in disability, low quality of life, early mortality, and financial burden.[3] Globally, acute rheumatic fever has an incidence rate of 8–51 per 100 000 population.[4] In 2019, rheumatic heart disease was estimated to have contributed to 0·31 million deaths (95% uncertainty interval 0·26–0·34), with 40·50 million

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Research in context

Evidence before this study

WHO commissioned an evidence synthesis to clarify the role of handheld echocardiography for: (1) diagnosing acute rheumatic fever and rheumatic heart disease in suspected cases when standard echocardiography is not available; and (2) routine screening for rheumatic heart disease in children in areas of high prevalence. We searched Embase, MEDLINE, LILACS, and Conference Proceedings Citation Index—Science using search terms related to or synonymous with "rheumatic fever", "rheumatic heart disease", and "echocardiography" up to Feb 9, 2024. We identified only one systematic review addressing the role of handheld echocardiography in rheumatic heart disease, which was not up to date, did not include diagnostic test accuracy studies of handheld echocardiography in acute rheumatic fever, provided no data on the diagnostic performance of auscultation, and did not address the two specific questions of the commissioned call by WHO, for which there was still an evidence gap.

Added value of this study

This systematic review provides important insights into the role of handheld echocardiography for screening and diagnosing rheumatic heart disease. 11 diagnostic test accuracy studies were identified, alongside two additional reports of interest, allowing us to address the questions on the role of handheld echocardiography for diagnosing rheumatic heart disease in suspected cases (with moderate degree of certainty) and screening rheumatic heart disease in children in high-prevalence areas (with high certainty of evidence). Our findings suggest that accuracy and diagnostic performance of handheld echocardiography when compared with standard echocardiography is high both for diagnosing and screening of rheumatic heart disease, in contrast to the poor diagnostic performance observed for the alternative, cardiac auscultation. Diagnostic performance seems to be better, with outstanding discrimination, for more advanced forms of disease (ie, definite rheumatic heart disease as defined by the 2012 World Heart Federation). Despite some loss in accuracy when compared with experts, the performance of handheld echocardiography using simplified echocardiography protocols, or by non-experts following a specific and well organised training programme, shows excellent discrimination for cases of rheumatic heart disease (borderline and definite cases). With regard to the diagnosis of carditis and acute rheumatic fever, we found a single diagnostic test accuracy study assessing auscultation versus handheld echocardiography, which showed very low sensitivity of auscultation for diagnosing carditis in children with suspected acute rheumatic fever.

Implications of all the available evidence

This evidence synthesis will provide the basis for the new WHO guideline on the prevention and management of acute rheumatic fever and rheumatic heart disease, and will potentially change the management of patients with these conditions, contributing to better outcomes.

(32·05–50·06) cases and 10·67 million (9·21–12·12) years of healthy life lost due to rheumatic heart disease globally in the same year.[5] In 2010, the cost of deaths due to rheumatic heart disease was estimated to be US$5400 billion globally.[6]

The primary prevention of rheumatic heart disease is through preventing the initial acute rheumatic fever attack, whereas secondary prevention is through protection from recurrent episodes of group A streptococcal infection and acute rheumatic fever by continuous antibiotic chemoprophylaxis. Rheumatic heart disease can remain undetected for many years during its initial stages, thereby hindering the prophylactic administration of penicillin.[3] Around two-thirds of individuals with rheumatic heart disease are school-aged children (aged 5–15 years). If undiagnosed and untreated, these children can face the consequences of the disease in the following decades.[2,7,8] Identifying subclinical rheumatic heart disease is important because asymptomatic individuals can progress to develop complications such as advanced heart failure, pulmonary hypertension, atrial fibrillation, stroke, and infective endocarditis.[9] Antibiotic treatment with injections of benzathine benzylpenicillin prevents recurrent exposure and damage to the heart valves, reducing the risk of disease progression.[10]

Compared with auscultation using a stethoscope, echocardiography has been shown to be a more sensitive and specific diagnostic tool to identify the exact cause of a heart murmur.[11] The 2015 modified Jones criteria for the diagnosis of acute rheumatic fever include the use of echocardiography to assess for cardiac involvement.[12,13]

Larger, stationary echocardiography machines and standard portable echocardiography (standard echocardiography) as diagnostic instruments might not be feasible for diagnosing and screening in regions with a high prevalence of rheumatic heart disease due to their high cost, complexity, and duration of the investigation. Handheld echocardiography done with use of lightweight, highly portable, and easy-to-use devices that can fit into a coat pocket is a low-cost alternative that has gained popularity in recent decades for diagnosing rheumatic heart disease.[14,15] Specific screening criteria for detecting rheumatic heart disease that can be applied in programmes using handheld echocardiography were introduced in the 2023 World Heart Federation (WHF) guidelines.[16]

Investigating the diagnostic accuracy of handheld echocardiography for the diagnosis and screening of rheumatic heart disease or acute rheumatic fever in different settings is of importance as wider use of handheld echocardiography could lead to an increase in

diagnoses and health-care use. A previous systematic review has explored this matter, combining studies in the setting of diagnosis and screening, but did not provide a definitive answer.[17] Accordingly, the WHO Guideline Committee for the clinical practice guidelines on the prevention and management of acute rheumatic fever and rheumatic heart disease decided that an evidence synthesis process was required to separately address two specific questions: (1) among children, adolescents, and adults with suspected acute rheumatic fever or rheumatic heart disease in settings where standard echocardiography is not available, should handheld echocardiography be used by health workers to diagnose acute rheumatic fever or rheumatic heart disease; and (2) in areas with high prevalence of rheumatic heart disease, should handheld echocardiography be recommended for routine screening of rheumatic heart disease among school-aged children and adolescents?

The aim of this systematic review was to investigate the diagnostic accuracy of handheld echocardiography for the diagnosis of rheumatic heart disease or acute rheumatic fever in different settings specific to the two review questions outlined above.

Methods

Overview and study population

We did a systematic review of studies investigating the diagnostic accuracy of handheld echocardiography in comparison with standard echocardiography. The review adhered to PRISMA guidelines, and the protocol was registered with PROSPERO (CRD42022344081).[18]

We defined two populations of interest corresponding to the two review questions: (1) children, adolescents, and adults with suspected acute rheumatic fever or rheumatic heart disease in health-care facilities where standard echocardiography was not available for diagnosis; and (2) school-aged children and adolescents undergoing screening for rheumatic heart disease in areas with a high prevalence of rheumatic heart disease. We used data from Watkins and colleagues[19] to define high-prevalence areas. Additionally, we used data from Noubiap and colleagues, who also assessed the prevalence of rheumatic heart disease in high-prevalence areas by echocardiogram using the WHF and WHO criteria.[20]

Search strategy and selection criteria

On Feb 9, 2024, two authors (FS and FP) searched the following sources from inception up to the search date: Embase via Ovid SP (1974–present), MEDLINE via Ovid SP (1946–present), Latin American and Caribbean Health Sciences Literature (LILACS; 1974–present) and Conference Proceedings Citation Index-Science (CPCI-S; 1990–present). For CPCI-S, the following search terms were used: (Rheumatic Card* or Rheumatic Fever* or Rheumatic Heart or Rheumatoid Fever* or Rheumatic Valv* or Rheumatic Pancarditis or Rheumatic Endocarditis or Rheumatic Myocarditis or Rheumatic Pericarditis or Rheumatoid Pancarditis or Rheumatoid Endocarditis or Rheumatoid Myocarditis or Rheumatoid Pericarditis or Rheumatoid Card* or Rheumatoid Heart or Rheumatoid Valv*) AND (Echocardiogra* or Doppler or Cardiac Echogra* or Cardiac Scan* or Cardial Echogra* or Cardioechogra* or Echo Cardiogra* or Heart Echo Sounding or Heart Echograph* or Heart Scan* or Myocardium Scan* or Ultrasound Cardiogra* or Intra-Cardiac Ultrasound or Intracardiac Echo or Intracardiac Ultrasound or Echo Stress Test or Stress Echo Test or Stress MCE) (Topic). Search strategies for all resources are provided in appendix 8 (pp 2–3).

See Online for appendix 8

We did not search grey literature. Included articles were written in English and no translation was needed; when searching databases such as LILACS, we translated some articles from Portuguese or Spanish, but they did not meet inclusion criteria.

In accordance with the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy*,[21] we included all diagnostic studies with useable data, regardless of being prospective, retrospective, pragmatic, or explanatory. We included studies with simple designs with reference and index tests, studies with multiple groups of participants (including healthy controls), studies with multiple reference tests, and comparative test accuracy studies (randomised and non-randomised).

We excluded studies that did not investigate the diagnostic performance of the index test (ie, those with no available information on index test performance *vs* reference because the reference was not done or was done only in screen-positive cases).

Data extraction is described in detail in appendix 8 (p 4). The following data were extracted from all studies (FZ) and double-checked by an independent reviewer (TK): study characteristics (authors, year of publication, country, study design, sample size, study period, setting, and patient selection [random or consecutive]); patient characteristics (patient type [which patients were selected, and whether known underlying cardiac disease was present], age, sex, and follow-up period); index test details (handheld echocardiography device used, level of experience of the sonographer, and diagnostic criteria used); reference test details; and outcome-related data (sensitivity and specificity as reported in articles [or, if unavailable, calculated from true positives, false positives, true negatives, and false negatives], and secondary outcome data [not reported]). Authors of the studies were contacted as required to obtain the data or information.

Definitions of index, comparator, and outcomes

Handheld echocardiography was the index test, using diagnostic criteria as reported by the authors in their studies.

The comparator was standard echocardiography, the gold standard, with diagnosis of carditis in acute rheumatic fever according to the revised Jones Criteria,[12] and diagnosis of rheumatic heart disease based on 2012

WHF criteria for echocardiographic diagnosis.[3] Data on the diagnostic performance of routine clinical assessment using auscultation were also extracted when reported and used as a comparator, as standard echocardiography was not available in some settings; in such circumstances, the diagnosis is made solely on the basis of clinical grounds. Cardiac auscultation has traditionally been used to screen for rheumatic heart disease.[22] Diagnosis of a primary episode of acute rheumatic fever carditis is based on the presence of significant apical systolic or basal diastolic murmurs, clinical presence of pericarditis, or unexplained congestive heart failure.[23] Precise history taking and evaluation of the patient's clinical status with a thorough physical examination and auscultation are the mainstay of diagnostic evaluation of rheumatic heart disease.[24]

The three primary outcomes of interest were accuracy of diagnosis of carditis with acute rheumatic fever, diagnosis of rheumatic heart disease, and diagnosis of acute rheumatic fever or rheumatic heart disease. Prespecified secondary outcomes were acceptability to provider and patient, adverse events (any), and time to diagnosis (ie, interval from first symptoms to diagnosis) of carditis with acute rheumatic fever or rheumatic heart disease; however, these outcomes were not reported in any of the identified papers.

Studies were classified as diagnostic if a substantial percentage of the sample was known at baseline to have rheumatic heart disease or acute rheumatic fever and healthy controls were included for assessing the diagnostic accuracy of handheld echocardiography. Screening studies were defined as those in which an unselected population was present at a screening site and was screened for cardiac involvement using handheld echocardiography.

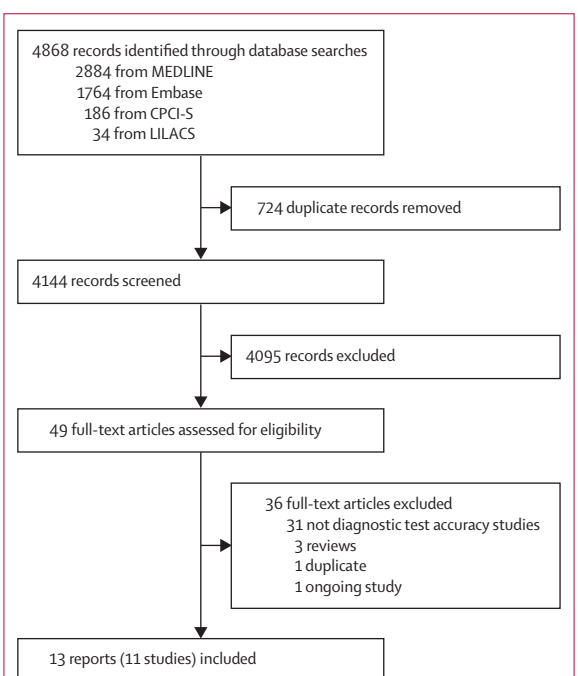


Figure 1: **Study identification and selection**
All records were identified through database searches; none were from other sources. CPCI-S=Conference Proceedings Citation Index—Science. LILACS=Latin American and Caribbean Health Sciences Literature.

Data synthesis and meta-analyses

For the meta-analysis, we summarised diagnostic accuracy statistics (sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio) and estimated 95% CIs by using a bivariate random-effects model through Meta-DiSc 2.0.[25] The bivariate random-effects model is recommended; it jointly models sensitivity and specificity using binomial likelihoods to model within-study variability,[21] and was used whenever enough data were available to fit the model. A univariate random-effects model was used only when the bivariate model could not be fitted (ie, in our case, for analyses including three or fewer studies).[26] Where possible, a summary receiver operating characteristic curve was fitted as described by the Cochrane Collaboration,[21] and we assessed the area under the curve (AUC) using the R package mada.[27] Risk of bias plots were traced using Review Manager 5.4.

The following planned subgroup analyses were done based on the following subgroups: (1) 2012 WHF criteria subcategory (definite rheumatic heart disease [ie, fulfilling WHF criteria for rheumatic heart disease diagnosis] *vs* borderline rheumatic heart disease [ie, having abnormal echocardiographic features but not fulfilling criteria for diagnosis of rheumatic heart disease]); (2) disease stage (subclinical rheumatic heart disease [ie, echocardiographic evidence of rheumatic heart disease discovered while screening patients without signs or symptoms] *vs* symptomatic rheumatic heart disease; and (3) experience level of the sonographer or reader (expert *vs* non-expert, as stated by study authors).

Quality assessment using GRADE and QUADAS-2[28] are described in detail in appendix 8 (pp 12–27). We assessed heterogeneity between studies by visual inspection of forest plots, as recommended for systematic reviews of diagnostic test accuracy.[21]

Role of the funding source

The funder of the study supplied the research questions; defined the population, index test, comparators, and outcomes; and commissioned independent reviewers who commented on the review's protocol and final report several times. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our database searches yielded a total of 4868 records. Following screening, 49 reports were identified for full-text review, of which one was an ongoing study of potential interest,[29] and a further 35 were subsequently excluded due to not being a diagnostic test accuracy study

	Study characteristics						Patient characteristics			
	Country or region	Design and setting	Study period	Sample size	Target population	Index *vs* reference test*	Patient selection	Age, years	Proportion female, n or n/N (%)	RHD or carditis prevalence, n (%), and characteristics
Diagnostic studies: RHD										
Beaton et al (2014)[30]	Uganda	Prospective observational; Uganda Heart Institute, school	Aug to Nov, 2010; Sept, 2012	125 (41 with RHD, 84 healthy controls)	Subclinical RHD	HHE *vs* SE	Children: 41 patients with RHD, 84 healthy controls	Healthy controls mean 10·7, definitive RHD 11·1, borderline RHD 11·1	Healthy controls 44 (52·4%), definitive RHD 15 (60·0%), borderline RHD 10 (62·5%)	RHD 41 (32·8%): 25 definitive, 16 borderline
Zühlke et al (2016)[31]	South Africa (Vanguard, Cape Town)	Case–control observational; community	Aug, 2013 to Sept, 2014	93 (27 asymptomatic with latent RHD, 66 healthy controls)	Asymptomatic latent RHD	(1) HHE *vs* SE; (2) ausc *vs* SE	Children and young adults	Range 10–25; cases median 17 (IQR 14–20), controls 17 (13–21)	Cases 16 (59·2%), controls 48 (73·1%)	RHD 27 (29·0%): 13 definitive, 14 borderline
Diagnostic studies: ARF										
Ali et al (2024)[32]	Sudan (North Kordofan)	Prospective observational; paediatric emergency department	Sept, 2022 to Jan, 2023	400 (126 with definite or possible ARF, 13 with isolated valve, 261 other)	Symptomatic ARF	HHE *vs* ausc	Febrile children with possible ARF	Range 3–18; mean 9·1 (SD 3·6)	180 (45·0%)	Carditis 66 (16·5%): 41 mild, 25 moderate–severe
Screening studies: RHD										
Beaton et al (2015)[15]	Uganda (Gulu)	Prospective observational; 5 schools	Nov, 2013	1420	RHD screening, early diagnosis	HHE *vs* SE	Children and adolescents aged 5–17 years at study sites	Mean 10·8 (SD 2·6)	Healthy 668/1234 (54·1%), definitive RHD 25/47 (53·2%), borderline RHD 64/133 (48·1%)	RHD 180 (12·7%): 47 definitive, 133 borderline
Substudy: Godown et al (2015)[40]	As above	As above	As above	1317	RHD screening, early diagnosis	Ausc *vs* SE	As above	As above	As above	RHD 171 (13·0%): 45 definitive, 126 borderline
Substudy: Lu et al (2015)[41]	As above	As above	As above	1439	RHD screening, early diagnosis	HHE *vs* SE	As above	As above	As above	RHD 180 (12·5%): 47 definitive, 133 borderline
Mirabel et al (2015)[35]	New Caledonia, France (Noumea and suburbs)	Prospective observational; schools	April to Aug, 2013	1217	RHD screening, early diagnosis	HHE *vs* SE	Children aged 9–10 years	Mean 9·6 (SD 0·5)	614 (50·5%)	RHD 49 (4·0%): 15 definitive, 34 borderline
Beaton et al (2016)[33]	Brazil (Belo Horizonte)	Prospective observational and interventional; 5 public schools	May, 2015	397	RHD screening, early diagnosis	HHE *vs* SE	Children and adolescents aged 5–18 years	Mean 13·6 (SD 2·8)	195 (49·1%)	RHD 53 (13·4%): 6 definitive, 47 borderline
Ploutz et al (2016)[36]	Uganda (Gulu)	Prospective observational; 2 schools	June to Aug, 2014	956	RHD screening, early diagnosis	HHE *vs* SE	Children and adolescents aged 5–17 years	Mean 11·1 (SD 2·5)	580 (60·7%)	RHD 43 (4·5%): 11 definitive, 32 borderline
Francis et al (2021)[34]	Australia (Maningrida) and Timor-Leste (Dili and Bobonaro)	Prospective observational; community (public, church, schools, etc)	March to Nov, 2018	2573	RHD screening, early diagnosis	HHE *vs* SE	All children and adolescents aged 5–20 years at screening sites	Median 12 (IQR 10–15)	1497 (58·2%)	RHD 142 (5·5%): 82 definitive, 60 borderline
Voleti et al (2021)[37]	Palau (Koror)	Prospective observational; one elementary school	Aug, 2019	632	RHD screening, early diagnosis	HHE *vs* SE	Children aged 6–15 years	Mean 9·7 (SD 2·6)	311 (49·2%)	RHD 26 (4·1%): 9 definitive, 17 borderline

(Table 1 continues on next page)

	Study characteristics						Patient characteristics			
	Country or region	Design and setting	Study period	Sample size	Target population	Index *vs* reference test*	Patient selection	Age, years	Proportion female, n or n/N (%)	RHD or carditis prevalence, n (%), and characteristics
(Continued from previous page)										
Chillo et al (2023)[39]	Tanzania (Bagamoyo, Kisarawe, Babati, and Kiteto)	Prospective observational; 11 schools	2018–19	4436	RHD screening, early diagnosis	HHE *vs* ausc	Children aged 5–16 years	Mean 10·0 (SD 2·4)	Healthy 2357/4341 (54·3%), RHD 65/95 (68·4%)	RHD 95 (2·1%): 59 definitive, 36 borderline
Francis et al (2023)[38]	Timor-Leste and Australia	Prospective observational; schools and community centres	Aug, 2019 (Timor-Leste), Feb–March, 2020 (Australia)	3329	RHD screening, early diagnosis	HHE *vs* SE	Children and adolescents aged 5–20 years at study sites	Median 12 (IQR 9–15)	Healthy 1670/3196 (52·3%), definitive RHD 32/47 (68·1%), borderline RHD 58/86 (67·4%)	RHD 133 (4·0%): 47 definitive, 86 borderline

Diagnostic studies were those in which a substantial percentage of the sample was known at baseline to have RHD and healthy controls were included for assessing the diagnostic accuracy of HHE. Screening studies were those in which an unselected population was present at a screening site and was screened for cardiac involvement using HHE. Estimated prevalences for any RHD: screening studies 721 (4·8%) of 14 960; diagnostic studies 68 (31·2%) of 218. Estimated prevalences for definite RHD: screening studies 276 (1·8%) of 14 960; diagnostic studies 38 (17·4%) of 218. Estimated prevalences of borderline RHD: screening studies 445 (3·0%) of 14 960; diagnostic studies 30 (13·8%) of 218. ARF=acute rheumatic fever. Ausc=auscultation. HHE=handheld echocardiography. NA=not available. RHD=rheumatic heart disease. SE=standard echocardiography. *Details of diagnostic tests, criteria used, and experience levels are presented in table 2.

Table 1: **Studies investigating the use of HHE for the diagnosis and screening of RHD**

(n=31), including duplicate data (n=1), or being reviews (n=3; appendix 8 pp 9–11; figure 1). Among the excluded studies, there was a relevant systematic review[16] whose reference list was checked for additional studies to add to our review. Finally, 11 studies were included: three addressed our question on handheld echocardiography for diagnosing rheumatic heart disease[30,31] and acute rheumatic fever,[32] and eight studies addressed the use of handheld echocardiography for screening schoolchildren and adolescents[15,33–39] (tables 1, 2). Two additional reports[40,41] of Beaton and colleagues' 2015 study[15] were included with data to inform two additional subanalyses not contemplated in the original publication.

The included studies were conducted between September, 2012 and January, 2023, and all were in areas with a high prevalence of rheumatic heart disease or acute rheumatic fever. Uganda was the dominating geography, with three studies,[15,30,36] and Brazil, Australia, and Timor-Leste were represented twice among the studies. The rest of the countries were mentioned in only one study each: New Caledonia (France), Palau, South Africa, Sudan, and Tanzania.

The studies included 15 578 unique participants in total (excluding those from the two substudies[40,41]), with sample sizes varying from 93 to 4436 participants (table 1). Five studies had a sample size of more than 1000 participants. All studies were prospective observational studies. Beaton and colleagues[30] and Zühlke and colleagues[31] reported studies with a case–control design. Most studies included children and adolescents aged 5–18 years. Zühlke and colleagues[31] included participants aged 10–25 years, and two additional studies[34,38] included participants aged 5–20 years. Nine studies were done in schools, three were conducted or had additional locations in the community (Vanguard communities in the Bonteheuwel and Langa suburbs of Cape Town, South Africa;[31] churches; and community centres[34,38]), and one took place in a paediatric emergency department.[32]

Three studies[30–32] included patients with suspected or known rheumatic heart disease or acute rheumatic fever, and assessed handheld echocardiography in the context of diagnosis. All other studies used handheld echocardiography in the context of rheumatic heart disease screening.[15,33–39] Our analyses were divided accordingly into this grouping (diagnostic studies or screening studies) to address the WHO Guideline Committee's research questions.

For all except two studies, the reference test was standard echocardiography done by experts using the 2012 WHF criteria for diagnosing rheumatic heart disease (table 2).[3] In the remaining two studies,[32,39] auscultation was the reference test. Standard echocardiography was done with portable machines in all studies: Vivid i (GE Healthcare),[34,38] Vivid i/q (GE Healthcare),[15,34,37,38,40,41] Vivid q (GE Healthcare)[33,36] and CX-50 (Philips Healthcare).[15,31,40,41]

Handheld echocardiography was the index test, and was done with the VScan (GE Healthcare) in all studies except one,[38] in which the Lumify S4–1 (Philips Healthcare) was used (table 2). The criteria for diagnosis or positive screen for rheumatic heart disease using handheld echocardiography in four studies[15,30,39,40] were a modified version of the 2012 WHF criteria (because no continuous wave doppler was available in handheld echocardiography, no velocity of the jet could be measured for assessing aortic and mitral regurgitation, and the pansystolic or pandiastolic jets were assessed using colour doppler). The remaining studies opted for simpler echocardiographic

	Index test characteristics			Reference test characteristics		
	Index test	Diagnostic criteria	Experience level	Reference test	Diagnostic criteria	Experience level
Diagnostic studies: RHD						
Beaton et al (2014)[30]	HHE	2012 WHF criteria, modified due to lack of CW Doppler	Expert (paediatric cardiologist, expert reviewer)	SE	2012 WHF criteria	Expert (paediatric cardiologist, expert reviewer)
Zühlke et al (2016)[31]	(1) HHE; (2) ausc	(1) Simplified HHE (single long-axis parasternal view, MR jet length ≥2·0 cm); (2) presence of pathological murmur	Expert (1 expert cardiologist)	SE	2012 WHF criteria	Expert (1 expert cardiologist)
Diagnostic studies: ARF						
Ali et al (2024)[32]	HHE	Simplified (single long-axis parasternal view, MR jet length ≥1·5 cm, any AR, or mitral or aortic morphology)	Acquisition non-expert, reading expert (paediatric resident physician)	Ausc	Murmur	NA
Screening studies: RHD						
Beaton et al (2015)[15]	HHE	2012 WHF criteria, modified due to lack of CW Doppler	Expert (5 paediatric cardiologists, 5 fellows, 3 senior sonographers)	SE	2012 WHF criteria	Expert (5 paediatric cardiologists, 5 fellows, 3 senior sonographers)
Substudy: Godown et al (2015)[40]	Ausc	Non-physiological murmur	Expert (2 expert local physicians)	SE	2012 WHF criteria	Expert (expert imagers, paediatric cardiologists, senior fellows, sonographers)
Substudy: Lu et al (2015)[41]	HHE	Simplified (MR jet length ≥1·5 cm or any AR; also assessed pansystolic AR or MR, and MR in two views or AR)	Expert imagers (paediatric cardiology fellows and sonographer)	SE	2012 WHF criteria	Expert (expert imagers)
Mirabel et al (2015)[35]	HHE	Simplified (MR jet length ≥2·0 cm or any AR)	Non-expert (2 nurses)	SE	2012 WHF criteria	Expert (expert cardiologist)
Beaton et al (2016)[33]	HHE	Simplified (MR jet length ≥1·5 cm or any AR; also assessed cutoff of ≥2·0 cm for MR jet length)	Non-expert (2 nurses, 2 biotechnicians, and 2 medical students, split into 2 teams of 3)	SE	2012 WHF criteria	Expert (2 cardiologists)
Ploutz et al (2016)[36]	HHE	Simplified (MR jet length ≥1·5 cm or any AR)	Non-expert (2 nurses)	SE	2012 WHF criteria	Expert (single physician for SE, 2 cardiologist readers)
Francis et al (2021)[34]	HHE	Simplified (any MR or AR in single parasternal long-axis)	Non-expert (briefly trained non-expert practitioner)	SE	2012 WHF criteria	Expert (cardiologist or sonographer)
Voleti et al (2021)[37]	HHE	Simplified (MR jet length ≥1·5 cm or any AR)	Non-expert (2 nurses, 2 physicians, 1 medical student, 1 patient care technician)	SE	2012 WHF criteria	Expert (4 paediatric cardiologists, 1 senior fellow)
Chillo et al (2023)[39]	HHE	2012 WHF criteria, modified due to lack of CW Doppler	Expert (2 expert cardiologists)	Ausc	Murmur, 4 ausc areas	Non-expert (2 trained final-year medical students)
Francis et al (2023)[38]	HHE	Simplified (any MR or AR in single parasternal long-axis)	Approach 1, non-expert; or approach 2, non-expert sonographer and expert reader (10 physicians, 6 nurses, 6 community health workers)	SE	2012 WHF criteria	Expert (expert paediatric cardiologist and sonographer)

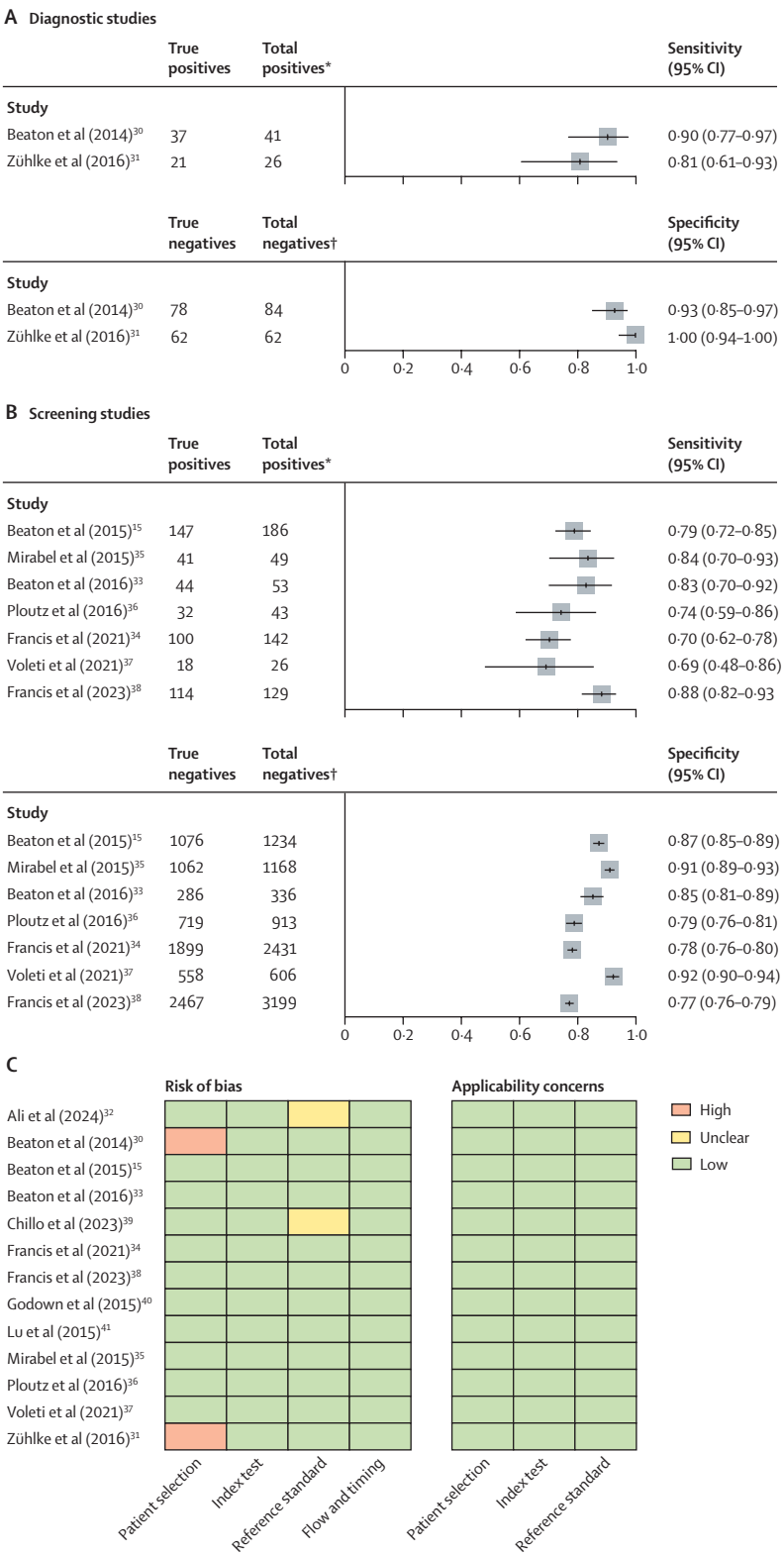
Diagnostic studies were those in which a substantial percentage of the sample was known at baseline to have RHD and healthy controls were included for assessing the diagnostic accuracy of HHE. Screening studies were those in which an unselected population was present at a screening site and was screened for cardiac involvement using HHE. AR=aortic regurgitation. ARF=acute rheumatic fever. Ausc=auscultation. CW=continuous wave. HHE=handheld echocardiography. MR=mitral regurgitation. NA=not available. RHD=rheumatic heart disease. SE=standard echocardiography. WHF=World Heart Federation.

Table 2: **Diagnostic criteria used in studies investigating the use of HHE for the diagnosis and screening of RHD**

criteria for defining a positive test: two studies used a simplified protocol with only one view (parasternal long-axis).[31,34] Zühlke and colleagues[31] used the presence of mitral regurgitation with a 2·0 cm or longer jet as the sole criterion, while Mirabel and colleagues[35] used this mitral regurgitation criterion in addition to the presence of any aortic regurgitation. Four studies[33,36,37,41] used a mitral regurgitation jet length of 1·5 cm or longer or the presence of any aortic regurgitation as the criteria for positivity, whereas Francis and colleagues[34,38] used the presence of any aortic regurgitation or mitral regurgitation in a parasternal long-axis view as the sole criterion. Ali and colleagues[32] defined carditis on handheld echocardiography per the 2015 modified Jones criteria.[12]

Handheld echocardiography was done by experts in four studies[15,30,31,39] (in addition to the two substudies[40,41]) and by non-experts in the remaining studies.[32–38] Information on the training programmes for non-experts can be found in appendix 8 (pp 5–6).

Zühlke and colleagues[31] assessed auscultation and handheld echocardiography versus standard echocardiography for diagnosing rheumatic heart disease; Ali and colleagues[32] assessed auscultation versus handheld echocardiography for diagnosing carditis or acute rheumatic fever; Godown and colleagues[40] assessed auscultation versus standard echocardiography to screen for rheumatic heart disease; and Chillo and colleagues[39] assessed auscultation versus



handheld echocardiography to screen for rheumatic heart disease.

We did a detailed appraisal of the 13 included reports using the QUADAS-2 tool (appendix 8 pp 12–25), including a risk of bias assessment (figure 2). Certainty of evidence was considered moderate for diagnosis (appendix 8 p 26) and high for screening (appendix 8 p 27), according to GRADE criteria.

The pooled data showed that handheld echocardiography had high sensitivity (0·87 [95% CI 0·76–0·93]) and specificity (0·98 [0·71–1·00]) and overall high accuracy (AUC 0·94 [0·84–1·00]) for diagnosing rheumatic heart disease when compared with standard echocardiography (figure 2; appendix 8 p 8). In subanalyses assessing the diagnosis of definite rheumatic heart disease and borderline rheumatic heart disease, handheld echocardiography had high accuracy, with better performance for definite rheumatic heart disease (AUC 0·99 [0·98–1·00]) than for borderline (0·92 [0·79–1·00]; table 3).

Excellent discrimination for screening of rheumatic heart disease was observed for pooled handheld echocardiography versus standard echocardiography data (sensitivity 0·79 [95% CI 0·73–0·84]; specificity 0·85 [0·80–0·89]; AUC 0·90 [0·85–0·94]; figures 2, 3; table 3). In subanalyses, better performance of handheld echocardiography was observed for definite rheumatic heart disease (AUC 0·99 [0·75–1·00]) than for borderline rheumatic heart disease (0·88 [0·80–0·99]; table 3). Six studies[15,33–37] used the VScan (GE Healthcare) and one[38] used the Lumify S4–1 (Philips Healthcare) for screening for any rheumatic heart disease, with minor differences observed in sensitivity (0·77 [0·72–0·82] *vs* 0·88 [0·82–0·93]) and specificity (0·86 [0·81–0·90] *vs* 0·77 [0·76–0·79]).

Combining all nine studies (diagnostic and screening),[15,30,31,33–38] the diagnostic performance of handheld echocardiography versus standard echocardiography for any rheumatic heart disease showed excellent discrimination, with sensitivity of 0·81 (95% CI 0·72–0·85), specificity of 0·88 (0·82–0·92), and an AUC of 0·90 (0·87–0·94).

Extracted positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood

Figure 2: **Sensitivity and specificity of handheld echocardiography versus standard echocardiography for the diagnosis and screening of rheumatic heart disease, and risk of bias summary**

Forest plots show the sensitivity and specificity of handheld echocardiography for diagnosis (A) and screening (B) of rheumatic heart disease in each of the included studies, with standard echocardiography used as the reference test. (C) Summary of risk of bias assessment for all included studies. Beaton et al (2014)[30] and Zühlke et al (2016)[31] had a high risk of bias for patient selection due to their case–control designs. Chillo et al (2023)[39] and Ali et al (2024)[32] had an unclear risk of bias due to insufficient details on the expertise of health professionals performing auscultation. *Sum of true positives and false negatives. †Sum of true negatives and false positives.

	Number of studies	Setting	Reference standard	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Certainty of evidence
Diagnostic studies							
HHE							
Any RHD	2	High prevalence	SE	0·87 (0·76–0·93)	0·98 (0·71–1·00)	0·94 (0·84–1·00)	Moderate
Definite RHD	2	High prevalence	SE	0·97 (0·84–1·00)	0·98 (0·93–0·99)	0·99 (0·98–1·00)	Moderate
Borderline RHD	2	High prevalence	SE	0·72 (0·54–0·86)	0·98 (0·69–1·00)	0·92 (0·79–1·00)	Moderate
Auscultation							
Rheumatic fever	1	High prevalence	HHE	0·17 (0·09–0·28)	0·99 (0·99–1·00)	NA	NA
Any RHD	1	High prevalence	SE	0·19 (0·06–0·38)	0·98 (0·92–1·00)	NA	NA
Definite RHD	1	High prevalence	SE	0·09 (0·01–0·41)	0·95 (0·87–0·99)	NA	NA
Borderline RHD	1	High prevalence	SE	0	0·95 (0·87–0·99)	NA	NA
Screening studies							
HHE							
Any RHD	7	High prevalence	SE	0·79 (0·73–0·84)	0·85 (0·80–0·89)	0·90 (0·85–0·94)	High
Definite RHD	2	High prevalence	SE	0·98 (0·92–0·99)	0·87 (0·85–0·88)	0·99 (0·75–1·00)	High
Borderline RHD	2	High prevalence	SE	0·72 (0·54–0·86)	0·98 (0·69–1·00)	0·88 (0·80–0·99)	High
Simplified HHE							
Any RHD	7	High prevalence	SE with complete diagnostic criteria	0·78 (0·72–0·84)	0·84 (0·79–0·88)	0·88 (0·85–0·92)	High
Expert HHE							
Any RHD	1	High prevalence	Expert SE	0·79 (0·72–0·85)	0·87 (0·85–0·89)	NA	NA
Definite RHD	1	High prevalence	Expert SE	0·98 (0·87–1·00)	0·87 (0·85–0·89)	NA	NA
Borderline RHD	1	High prevalence	Expert SE	0·72 (0·64–0·79)	0·87 (0·85–0·89)	NA	NA
Non-expert HHE							
Any RHD	6	High prevalence	Expert SE	0·79 (0·72–0·85)	0·85 (0·79–0·89)	0·89 (0·84–0·94)	High
Auscultation							
Any RHD	2	High prevalence	SE or HHE	0·11 (0·06–0·21)	0·97 (0·87–0·99)	0·59 (0·54–0·66)	High
Definite RHD	1	High prevalence	SE	0·22 (0·11–0·37)	0·91 (0·89–0·93)	NA	NA

AUC=area under the curve. HHE=handheld echocardiography. NA=not applicable. RHD=rheumatic heart disease. SE=standard echocardiography.

Table 3: **Main results and analyses for diagnostic performance of HHE**

ratio, and pooled values for the same measures are presented in appendix 8 (p 28).

Among screening studies, simplified handheld echocardiography protocols displayed good diagnostic performance for detecting any rheumatic heart disease (pooled sensitivity 0·78 [95% CI 0·72–0·84]; specificity 0·84 [0·79–0·88]; and AUC 0·88 [0·85–0·92]; table 3) compared with standard echocardiography with complete diagnostic criteria. Non-experts also had a good performance (pooled sensitivity 0·79 [0·72–0·85]; specificity 0·85 [0·79–0·89]; AUC 0·89 [0·84–0·94]), similar to that of expert echocardiographers or cardiologists for any rheumatic heart disease (table 3).

Some heterogeneity was observed for sensitivity and specificity across studies, possibly driven by differences in the prevalence and severity of rheumatic heart disease, and level of training or expertise of non-expert operators.

The effects of handheld echocardiography for diagnosing and screening per 1000 patients tested are presented in appendix 8 (p 29 for diagnosis, and pp 30–31 for screening studies).

One diagnostic study assessed auscultation for detecting definite rheumatic heart disease versus standard echocardiography, and showed high specificity (0·95 [95% CI 0·87–0·99]) but very low sensitivity (0·09 [0·01–0·41]).[31] Similar findings were observed for auscultation versus handheld echocardiography for diagnosing carditis with acute rheumatic fever (specificity 0·99 [0·99–1·00]; sensitivity 0·17 [0·09–0·28];[32] figure 3). Two studies[39,40] assessed auscultation for screening of any rheumatic heart disease and showed poor performance versus standard echocardiography or handheld echocardiography (specificity 0·97 [0·87–0·99]; sensitivity 0·11 [0·06–0·21]; AUC 0·59 [0·54–0·66]; table 3).

Information on other outcomes, which were not reported by any of the studies, is presented in appendix 8 (p 7).

Discussion

Our systematic review showed that handheld echocardiography has high sensitivity and specificity and overall high accuracy when compared with standard

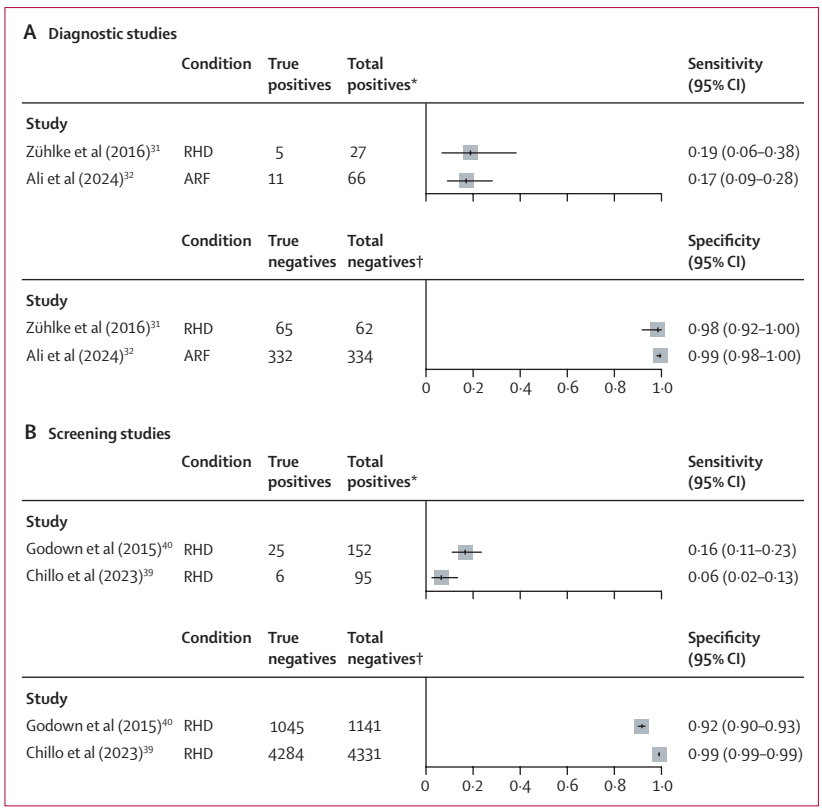


Figure 3: **Sensitivity and specificity of auscultation versus echocardiography (standard echocardiography or handheld echocardiography) for the diagnosis and screening of RHD or ARF**
ARF=acute rheumatic fever. RHD=rheumatic heart disease. *Sum of true positives and false negatives. †Sum of true negatives and false positives.

echocardiography for diagnosing (moderate certainty of evidence) and screening (high certainty of evidence) rheumatic heart disease in high-prevalence areas. By contrast, poor diagnostic performance was observed for cardiac auscultation (good specificity but low sensitivity), suggesting that, when standard echocardiography is not available, handheld echocardiography might constitute a better alternative for screening and diagnosing acute rheumatic fever or rheumatic heart disease. Use of simplified handheld echocardiography or non-experts enrolled in training programmes to conduct handheld echocardiography showed good diagnostic accuracy, despite some loss in sensitivity and specificity.

Ali and colleagues[32] showed that the use of handheld echocardiography versus auscultation led to an increase in diagnosis of carditis, from 2·8% (11 of 400 individuals) to 16·5% (66 of 400),[32] detecting an important fraction of cases that would otherwise be missed. Among these 66 cases, 25 were classified as moderate or severe carditis. The authors reported a high sensitivity and specificity of handheld echocardiography (both 0·88) in a small fraction of 43 patients with cardiac findings who underwent confirmatory standard echocardiography.

Organisation of mass screening programmes for acute rheumatic fever or rheumatic heart disease in high-prevalence areas seems possible, but will require considerable logistic, organisational, and governmental efforts. Use of handheld echocardiography in individuals with suspected disease as an alternative when standard echocardiography is not available might also pose challenges, as handheld echocardiography devices will have to be acquired and staff will need to be trained. However, the studies included in this systematic review show that short training programmes are feasible and allow non-expert operators to perform handheld echocardiography with acceptable diagnostic accuracy. The circumstances of each country should be taken into account during the implementation of any new programme. Cost-effectiveness studies applied to the local reality of the different high-prevalence areas where screening programmes are being planned might be a necessary first step. Previous studies have suggested cost-effectiveness of secondary prevention measures, including portable or stationary echocardiography in India, sub-Saharan Africa, and Fiji,[42–44] and handheld echocardiography in Brazil.[45] False-positive and false-negative cases can potentially add to health-system costs. However, false positives and false negatives might be less of a problem with handheld echocardiography than with cardiac auscultation. Additionally, consideration for follow-up costs and resource use might need to be factored in, as valve surveillance might subsequently be required.

Most of the studies included children or adolescents. It is, therefore, uncertain whether the performance of handheld echocardiography can be extrapolated to older adults, in whom difficult acoustic windows and technical difficulties for acquiring good image quality might be problems in some cases.

Telford and colleagues[17] previously conducted a systematic review on the use of handheld echocardiography, but provided only pooled results combining studies assessing handheld echocardiography for diagnosing and screening rheumatic heart disease. Our up-to-date analyses provide further and separate insight into these two distinct clinical scenarios, and provide information on acute rheumatic fever and carditis, as well as on the performance of auscultation compared with echocardiography, as solicited by the WHO Guideline Committee, with more precision due to a much higher unique patient number (4-times higher participant number).

Seven studies[32–38] included in our meta-analysis trained non-experts to perform handheld echocardiography, but no consensus seems to exist on the core curriculum, training duration, minimum number of hours of practical or supervised training, and minimum number of independent handheld echocardiography examinations for becoming a fully independent and trained individual. These are important aspects to consider for the planning of screening programmes by non-experts, as abbreviated programmes that do not provide the necessary set of

skills to non-expert operators will affect the outcome and success of the programme.

No studies compared handheld echocardiography versus stationary high-end systems (ie, feature-rich devices with cutting-edge technology such as three-dimensional echo or strain, which, despite having wheels, are too heavy or not supposed to be moved).[46] Hence, extrapolation of our findings on the diagnostic and screening accuracy of handheld echocardiography versus portable standard echocardiography to the comparison of handheld echocardiography versus high-end systems relies on the assumption of comparable diagnostic performance of stationary and portable standard echocardiography.

Wider use of handheld echocardiography devices for rheumatic heart disease screening is occurring, with recent studies in Sudan using the VScan (GE Healthcare)[47] and in Ethiopia using the Lumify (Philips).[48]

Some additional limitations need to be highlighted in our review. First, when testing different handheld echocardiography devices, experts have considered some to have better image quality.[49] Furthermore, novel devices such as the PA HD (Clarius) and Kosmos (EchoNous) have pulsed-wave and continuous-wave doppler, respectively. As no head-to-head comparisons of different handheld echocardiography devices are available in the acute rheumatic fever and rheumatic heart disease setting, further studies might be required to ascertain and compare the diagnostic accuracy of different handheld echocardiography devices. Second, we did not include grey literature in our search. This exclusion can artificially affect estimates of treatment effects in reviews of intervention studies,[50] and can potentially affect estimates of diagnostic test accuracy reviews. Third, it is possible that the studies by Beaton and colleagues[30] and Zühlke and colleagues[31] might not fully represent the use of handheld echocardiography in the context of diagnosing cardiac involvement in someone suspected to have rheumatic heart disease, as the rheumatic heart disease cases were composed mainly of patients with subclinical rheumatic heart disease. However, we hypothesise that as most patients with symptomatic rheumatic heart disease will have more advanced disease, handheld echocardiography performance will be better, as we observed for cases of definitive rheumatic heart disease. Fourth, our search strategy was not designed for systematically assessing auscultation for the diagnosis of rheumatic heart disease or acute rheumatic fever. However, we believe we have included all studies assessing handheld echocardiography alongside auscultation, allowing us to better understand the comparative performance of handheld echocardiography and auscultation. Finally, the 2023 WHF guidelines for echocardiographic diagnosis of rheumatic heart disease include screening and confirmatory criteria, weight-based measurements for regurgitant jets, and a classification of rheumatic heart disease in stages (A to D, instead of borderline, definite, and latent).[16] All included studies in our review pre-date this publication. Future research assessing handheld echocardiography for rheumatic heart disease screening and diagnosing individuals in the newly described rheumatic heart disease stages is warranted.

Our findings suggest that handheld echocardiography has a high-accuracy diagnostic performance when compared with standard echocardiography for both diagnosing and screening of rheumatic heart disease in high-prevalence areas, contrasting with the poor diagnostic performance observed for cardiac auscultation. Cost-effectiveness data and longer-term outcome data on the use of handheld echocardiography devices in different high-prevalence regions, and the performance of novel handheld echocardiogram devices (ie, those with pulsed-wave and continuous-wave doppler capability) constitute important areas for future research.

Contributors

RP, GA, FS, FZ, and TK wrote the final draft of the manuscript. FZ, TK, and RP provided methods input. FS and FP provided information specialist expertise. MA, JJHB, EM, MC, MYK, and DSC provided clinical input. All authors revised the first draft of the manuscript and provided comments to improve it and prepare the final version. All authors read and approved the final version of the manuscript, had final responsibility for the decision to submit for publication, and had access to all the data in the study. FZ, TK, FS, and RP accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

All data used for the analyses were extracted from published studies and are included in the Article or appendix 8. No patient-level data were used.

Acknowledgments

This study was funded by WHO, which commissioned this review to support the development of the WHO clinical practice guidelines on the prevention and management of acute rheumatic fever and rheumatic heart disease. We thank Erik von Elm (Cochrane Switzerland, Unisanté Lausanne) and Susan L Norris (WHO Guideline Rapporteur), who independently peer-reviewed this review's protocol and final report.

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Supplementary appendix 1

This translation in Chinese was submitted by the authors and we reproduce it as supplied. It has not been peer reviewed. *The Lancet*'s editorial processes have only been applied to the original in English, which should serve as reference for this manuscript.

此简体中文译文由作者提交，我方按照提供的版本刊登。此译文并未经过同行审阅。医学期刊《柳叶刀》的编辑流程仅适用于英文原稿，英文原稿应作为此手稿的参考。

Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

背景：急性风湿热和风湿性心脏病的早期检测和诊断是防止病情进展的关键，而超声心动图在诊断中起着重要作用。但是，由于其高成本、高复杂度高和时间需求大，在高患病率地区运用标准超声心动图进行检测和诊断可能不太可行。手持式超声心动图作为一种易于使用的、低成本的潜在替代方案，其在筛查和诊断急性风湿热和风湿性心脏病方面的性能还需要进一步研究。

方法：在这项系统综述和荟萃分析中，我们检索了 Embase、MEDLINE、LILACS 和 Conference Proceedings Citation Index—Science 上（截至 2024 年 2 月 9 日）的所有涉及在高患病率地区使用手持式超声心动图（指标检测）或标准超声心动图或听诊器（参考检测）对急性风湿热和风湿性心脏病进行筛查和诊断的研究。我们纳入了所有具有可用数据的研究，用以评估指标检测相较于参考检测的诊断性能。我们提取或计算了已发表文章中关于诊断风湿性心脏病、急性风湿热或急性风湿热性心脏炎（主要结果）的检测准确性数据，并在必要时联系作者。证据质量使用 GRADE 和 QUADAS-2 标准评估。我们使用双变量随机效应模型（或包括三个或更少研究的分析的单变量随机效应模型）总结了诊断准确性统计数据（包括灵敏度和特异度）并估计了 95%的置信区间， 并且计算了总结的接收者操作特征（ROC）曲线下面积（AUC）。异质性通过对图形的视觉检查进行评估。本研究已在 PROSPERO 上注册（CRD42022344081）。

结果：从 4868 份记录中，我们纳入了 11 项研究和两份额外报告，共计 15578 名独特参与者。汇总数据显示，与标准超声心动图相比，手持式超声心动图在诊断风湿性心脏病方面具有较高的灵敏度（0.87 [95% CI 0.76–0.93]）、特异度（0.98 [0.71–1.00]）和高的整体准确性（AUC 0.94 [0.84–1.00]）（两项研究；证据程度中等）； 相较于边缘性风湿性心脏病，其对确定性风湿性心脏病的诊断性能更佳。在汇总手持式超声心动图与标准超声心动图的数据时，其在筛查风湿性心脏病显示出较高的灵敏度（0.79 [0.73–0.84]）、特异度（0.85 [0.80–0.89]）和整体准确性（AUC 0.90 [0.85–0.94]）（七项研究；证据程度高）。大多数研究整体上存在较低的偏倚风险。这些研究在敏感性和特异性上存在一些异质性，可能与风湿性心脏病的患病率和严重程度、以及非专家操作者的培训水平或专业知识水平的差异有关。

解释：在高患病率地区，与标准超声心动图相比，手持式超声心动图在诊断和筛查风湿性心脏病方面具有较高的准确性和诊断性能。

Background Early detection and diagnosis of acute rheumatic fever and rheumatic heart disease are key to preventing progression, and echocardiography has an important diagnostic role. Standard echocardiography might not be feasible in high-prevalence regions due to its high cost, complexity, and time requirement. Handheld echocardiography might be an easy-to-use, low-cost alternative, but its performance in screening for and diagnosing acute rheumatic fever and rheumatic heart disease needs further investigation.

Methods In this systematic review and meta-analysis, we searched Embase, MEDLINE, LILACS, and Conference Proceedings Citation Index—Science up to Feb 9, 2024, for studies on the

screening and diagnosis of acute rheumatic fever and rheumatic heart disease using handheld echocardiography (index test) or standard echocardiography or auscultation (reference tests) in high-prevalence areas. We included all studies with useable data in which the diagnostic performance of the index test was assessed against a reference test. Data on test accuracy in diagnosing rheumatic heart disease, acute rheumatic fever, or carditis with acute rheumatic fever (primary outcomes) were extracted from published articles or calculated, with authors contacted as necessary. Quality of evidence was appraised using GRADE and QUADAS-2 criteria. We summarised diagnostic accuracy statistics (including sensitivity and specificity) and estimated 95% CIs using a bivariate random-effects model (or univariate random-effects models for analyses including three or fewer studies). Area under the curve (AUC) was calculated from summary receiver operating characteristic curves. Heterogeneity was assessed by visual inspection of plots. This study was registered with PROSPERO (CRD42022344081).

Findings Out of 4868 records we identified 11 studies, and two additional reports, comprising 15 578 unique participants. Pooled data showed that handheld echocardiography had high sensitivity (0·87 [95% CI 0·76–0·93]), specificity (0·98 [0·71–1·00]), and overall high accuracy (AUC 0·94 [0·84–1·00]) for diagnosing rheumatic heart disease when compared with standard echocardiography (two studies; moderate certainty of evidence), with better performance for diagnosing definite compared with borderline rheumatic heart disease. High sensitivity (0·79 [0·73–0·84]), specificity (0·85 [0·80–0·89]), and overall accuracy (AUC 0·90 [0·85–0·94]) for screening rheumatic heart disease was observed when pooling data of handheld echocardiography versus standard echocardiography (seven studies; high certainty of evidence). Most studies had a low risk of bias overall. Some heterogeneity was observed for sensitivity and specificity across studies, possibly driven by differences in the prevalence and severity of rheumatic heart disease, and level of training or expertise of non-expert operators.

Interpretation Handheld echocardiography has a high accuracy and diagnostic performance when compared with standard echocardiography for diagnosing and screening of rheumatic heart disease in high-prevalence areas.

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Supplementary appendix 2

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Cette traduction en français a été proposée par les auteurs et nous l'avons reproduite telle quelle. Elle n'a pas été examinée par des pairs. Les processus éditoriaux du *Lancet* n'ont été appliqués qu'à l'original en anglais et c'est cette version qui doit servir de référence pour ce manuscrit.

Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

Contexte : La détection précoce du rhumatisme articulaire aigu et de la cardiopathie rhumatismale sont essentiels pour ainsi prévenir la progression de la maladie. L'échocardiographie joue un rôle clé pour permet un diagnostic précoce mais n'est pas toujours réalisable dans les régions à forte prévalence en raison du coût élevé, de la complexité et de la durée de l'examen. L'échocardiographie portative représente une alternative peu coûteuse et facile à utiliser, mais ses performances pour le dépistage et le diagnostic du rhumatisme articulaire aigu et de la cardiopathie rhumatismale nécessitent d'être davantage étudiés.

Méthodes : Nous avons effectué une recherche dans Embase, MEDLINE, LILACS et le Conference Proceedings Citation Index-Science jusqu'au 9 février 2024, pour identifier les études sur le dépistage et le diagnostic du rhumatisme articulaire aigu et de la cardiopathie rhumatismale en utilisant l'échocardiographie portative (test index) ou l'échocardiographie standard ou l'auscultation (tests de référence) dans les zones à forte prévalence de la maladie.

Nous avons inclus toutes les études avec des données exploitables dans lesquelles les performances diagnostiques du test index ont été évaluées par rapport à un test de référence. Les données sur la précision du test dans le diagnostic de la cardiopathie rhumatismale, de rhumatisme articulaire aigu ou de la cardite avec rhumatisme articulaire aigu (résultats principaux) ont été extraites d'articles publiés ou calculées, les auteurs ayant été contactés au besoin. La qualité des preuves a été évaluée à l'aide des critères GRADE et QUADAS-2. Nous avons résumé les statistiques de précision diagnostique (y compris la sensibilité et la spécificité) et estimé les IC à 95 % à l'aide d'un modèle à effets aléatoires bivarié (ou de modèles à effets aléatoires univariés pour les analyses comprenant trois études ou moins). L'aire sous la courbe (AUC) a été calculée à partir des courbes ROC résumées. L'hétérogénéité a été évaluée par inspection visuelle des graphiques. Cette étude a été enregistrée auprès de PROSPERO (CRD42022344081).

Résultats : Sur 4.868 enregistrements, nous avons identifié 11 études et 2 rapports supplémentaires, comprenant un total de 15.578 participants. Les données combinées ont montré que l'échocardiographie portative présentait une sensibilité élevée (0,87 [IC à 95 % : 0,76–0,93]), une spécificité élevée (0,98 [0,71–1,00]), et une précision globale élevée (AUC 0,94 [0,84–1,00]) pour le diagnostic de la cardiopathie rhumatismale par rapport à l'échocardiographie standard (deux études ; preuve de certitude modérée), avec de meilleures performances pour le diagnostic de la cardiopathie rhumatismale définitive par rapport à la cardiopathie rhumatismale limite. Une sensibilité élevée (0,79 [0,73–0,84]), une spécificité élevée (0,85 [0,80–0,89]), et une précision globale élevée (AUC 0,90 [0,85–0,94]) pour le dépistage de la cardiopathie rhumatismale ont été observées en regroupant les données de l'échocardiographie portative par rapport à l'échocardiographie standard (sept études ; preuve de certitude élevée). La plupart des études présentaient globalement un faible risque de biais. Une certaine hétérogénéité a été observée pour la sensibilité et la spécificité entre les études, peut-être due à des différences dans la prévalence et la gravité de la cardiopathie rhumatismale, ainsi qu'au niveau de formation ou d'expertise des opérateurs non experts.

Interprétation : L'échocardiographie portative présente des performances diagnostiques élevées par rapport à l'échocardiographie transthoracique standard tant pour le diagnostic que pour le dépistage de la cardiopathie rhumatismale dans les zones de forte prévalence.

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Supplementary appendix 3

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Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

Premessa: L’individuazione o la diagnosi precoce della febbre reumatica e della cardiopatia reumatica è fondamentale per prevenirne la progressione, e l'ecocardiografia svolge un ruolo diagnostico importante. L'ecocardiografia standard potrebbe non essere praticabile nelle regioni ad alta prevalenza a causa dei costi elevati, della complessità e della durata dell'indagine. L'ecocardiografia portatile potrebbe rappresentare un'alternativa a basso costo e di facile utilizzo, ma è necessario approfondire ulteriormente la sua efficacia nello screening e nella diagnosi della febbre reumatica e della cardiopatia reumatica.
Metodi: Abbiamo effettuato una ricerca su Embase, MEDLINE, LILACS e ‘Conference Proceedings Citation Index-Science’ fino al 9 febbraio 2024, per studi sull'efficacia dello screening e della diagnosi della RF e della cardiopatia reumatica focalizzati nell’uso della ecocardiografia standard e della ecocardiografia portatile in aree ad alta prevalenza. Abbiamo incluso tutti gli studi con dati utilizzabili in cui le prestazioni diagnostiche del test indice sono state valutate rispetto a un test di riferimento. I dati sull'accuratezza del test nella diagnosi di malattia cardiaca reumatica, febbre reumatica acuta o cardite con febbre reumatica acuta (endpoint primari) sono stati estratti da articoli pubblicati o calcolati, contattando gli autori se necessario. La qualità delle prove è stata valutata utilizzando i criteri GRADE e QUADAS-2. Abbiamo riassunto le statistiche di accuratezza diagnostica (incluse sensibilità e specificità) e abbiamo stimato IC al 95% utilizzando un modello bivariato a effetti casuali (o modelli univariati a effetti casuali per analisi con tre o meno studi). L'area sotto la curva (AUC) è stata calcolata dalle curve sommarie delle caratteristiche operative del ricevitore. L'eterogeneità è stata valutata mediante ispezione visiva dei grafici. Questo studio è stato registrato su PROSPERO (CRD42022344081).
Risultati: Tra i 4.868 documenti emersi dalla ricerca, abbiamo identificato e incluso 11 studi e 2 ulteriori documenti, comprendenti un totale di 15.578 partecipanti. La combinazione statistica di tali dati ha mostrato che l'ecocardiografia portatile registra un alto grado sensibilità, specificità e accuratezza complessiva nella diagnosi della cardiopatia reumatica rispetto alla ecocardiografia standard (sensibilità 0,87, IC del 95% 0,76-0,93; specificità 0,98, IC del 95% 0,71-1,00 e AUC 0,94, IC del 95% 0,84-1,00; 2 studi; certezza moderata delle prove), con prestazioni migliori nella diagnosi della cardiopatia reumatica definita rispetto a quella borderline. Inoltre, è stata osservata un'alta sensibilità, specificità e accuratezza complessiva nello screening della cardiopatia reumatica quando si combinano i dati della ecocardiografia portatile vs l'ecocardiografia standard (sensibilità 0,79, IC del 95% 0,73-0,84; specificità 0,85, IC del 95% 0,80-0,89 e AUC 0,90, IC del 95% 0,85-0,94; 7 studi; certezza elevata). La maggior parte degli studi presentava complessivamente un basso rischio di bias. È stata osservata una certa eterogeneità per sensibilità e specificità tra gli studi, possibilmente influenzata dalle differenze nella prevalenza e gravità della malattia cardiaca reumatica, e dal livello di formazione o esperienza degli operatori non esperti.
Interpretazione: L'ecocardiografia portatile presenta un'alta accuratezza e prestazioni diagnostiche rispetto alla ecocardiografia standard sia per la diagnosi che per lo screening della cardiopatia reumatica in aree ad alta prevalenza.
Finanziamento: Organizzazione Mondiale della Sanità
Protocollo PROSPERO: CRD42022344081

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Supplementary appendix 4

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این ترجمه به زبان فارسی توسط نویسندگان ارسال شده است و ما آن را همانطور که تهیه می شود بازتولید می کنیم .مورد فقط در اصل به زبان انگلیسی اعمال شده است ، که باید به عنوان Lancet بررسی قرار نگرفته است .مراحل تحریریه .مرجع برای این نسخه خطی باشد

Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

زمینه: تشخیص زودهمگام تب روماتیسمی حاد و بیماری روماتیسم قلبی، کلید پیشگیری از پیشرفت آن هاست و اکوکاردیوگرافی نقش مهمی در این تشخیص دارد. با این حال در جاهایی که شیوع این بیماری بالاست، امکان به کارگیری اکوکاردیوگرافی استاندارد به دلیل هزینه بالا، پیچیدگی و زمان لازم برای بررسی، به آسانی ممکن نیست. اکوکاردیوگرافی دستی (Handheld Echocardiography) می تواند جانشینی کم هزینه و آسان از نظر کاربرد برای اکوی استاندارد باشد ولی عملکرد آن برای غربالگری و تشخیص تب روماتیسمی حاد و بیماری روماتیسم قلبی نیازمند بررسی بیشتر است.

روش ها: در این مرور سیستماتیک و متاآنالیز، ما پژوهش هایی که به مقایسه اکوی دستی (تست ایندکس)، اکوی استاندارد و گوشی طبی یا آسکولتیشن (تست های رفرنس) برای غربالگری و تشخیص تب روماتیسمی حاد و بیماری روماتیسم قلبی در مناطق با شیوع بالا می پردازند را با جستجوی امبیس، مدلاین، لایلکس و نمایه چکیده کنفرانس های علمی در 9 فوریه 2024 گردآوری کردیم. مطالعاتی که داده های قابل استفاده ای داشتند و عملکرد تشخیصی تست ایندکس را در برابر تست رفرنس مقایسه می کردند، وارد بررسی ما شدند. داده های دقت تشخیصی در تشخیص تب روماتیسمی حاد، بیماری روماتیسم قلبی، یا التهاب قلب (کاردایتیس) با تب روماتیسمی حاد (پیامدهای اولیه) از مطالعات استخراج یا محاسبه شدند و در صورت نیاز با نویسندگان مقالات تماس گرفته شد. کیفیت و اطمینان شواهد با استفاده از گرید (GRADE) و کواداس-2 (QUADAS-2) بررسی شد. آماره های دقت تشخیصی (شامل حساسیت و ویژگی) را خلاصه و با فاصله اطمینان 95% با استفاده از مدل اثرات تصادفی دومتغیره (یا مدل اثرات تصادفی تک متغیره برای تحلیل هایی که دارای سه مطالعه با کمتر بودند) برآورد کردیم. سطح زیر نمودار (AUC) از خلاصه نمودارهای منحنی مشخصه عملکرد سیستم (ROC) مصاحبه شد. ناهمگنی مطالعات با نگاه به نمودارها بررسی شد. این مطالعه پیش از انجام در رجیستر PROSPERO ثبت شد (CRD42022344081).

یافته ها: با بررسی 4868 رکورد به دست آمده از جستجو، 11 پژوهش و دو گزارش که داده های 15578 شرکت کننده منحصر به فرد را گردآوری کرده بودند، به دست آمد. یافته ها نشان از حساسیت، ویژگی و دقت بالای اکوی دستی در مقایسه با اکوی استاندارد (حساسیت 0.87 با فاصله اطمینان 95% 0.76-0.93، ویژگی 0.98 با فاصله اطمینان 95% 0.71-1.0 و ناحیه زیر نمودار 0.94 با فاصله اطمینان 95% 0.84-1.0؛ بر پایه دو پژوهش؛ اطمینان به این شواهد متوسط است) و عملکرد بهتری برای تشخیص بیماری روماتیسم قلبی قطعی داشت تا برای بیماری روماتیسم قلبی مرزی. اکوی دستی در مقایسه با اکوی استاندارد، حساسیت، ویژگی و دقت بالایی برای غربالگری بیماری روماتیسم قلبی داشت (حساسیت 0.79 با فاصله اطمینان 95% 0.73-0.84، ویژگی 0.85 با فاصله اطمینان 95% 0.80-0.89 و ناحیه زیر نمودار 0.90 با فاصله اطمینان 95% 0.85-0.94؛ بر پایه هفت پژوهش؛ اطمینان به این شواهد بالاست). بیشتر مطالعات خطر سوگیری کلی پایینی داشتند. کمی ناهمگنی برای حساسیت و ویژگی بین مطالعات دیده شد که احتمالا با شیوع و شدت بیماری روماتیسم قلبی، و سطح آموزش و تجربه کاربران غیرمتخصص دستگاه ها مرتبط است.

تفسیر: اکوی دستی دقت و عملکرد تشخیصی بالایی در مقایسه با اکوی استاندارد برای تشخیص و غربالگری بیماری روماتیسم قلبی در مناطق با شیوع بالا دارد.

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Supplementary appendix 5

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Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

Contexto: A deteção precoce ou o diagnóstico da febre reumática aguda e da doença cardíaca reumática é fundamental para evitar a progressão, tendo a ecocardiografia um papel diagnóstico importante. A ecocardiografia padrão pode não ser viável em regiões de alta prevalência devido ao alto custo, complexidade e duração da investigação. A ecocardiografia portátil pode ser uma alternativa de baixo custo e fácil utilização, mas seu desempenho para rastreio e diagnóstico de febre reumática aguda e doença cardíaca reumática necessita ser investigado com maior detalhe.
Métodos: Pesquisamos na Embase, MEDLINE, LILACS e no Índice de Citações de Atas de Conferências-Ciência até 9 de Fevereiro de 2024, estudos sobre triagem e diagnóstico de febre reumática aguda e doença cardíaca reumática usando ecocardiografia portátil (teste índice) ou ecocardiografia padrão ou auscultação (testes de referência) em áreas de alta prevalência.
Incluímos todos os estudos com dados utilizáveis nos quais o desempenho diagnóstico do teste índice foi avaliado em relação a um teste de referência. Os dados sobre a precisão do teste no diagnóstico de doença cardíaca reumática, febre reumática aguda ou cardite com febre reumática aguda (endpoints primários) foram extraídos de artigos publicados ou calculados, tendo os autores sido contatados conforme necessário. A qualidade da evidência foi avaliada usando os critérios GRADE e QUADAS-2. Resumimos estatísticas de precisão diagnóstica (incluindo sensibilidade e especificidade) e estimámos ICs de 95% usando um modelo bivariado de efeitos aleatórios (ou modelos univariados de efeitos aleatórios para análises com três ou menos estudos). A área sob a curva (AUC) foi calculada a partir de curvas resumidas de característica operacional do receptor. A heterogeneidade foi avaliada pela inspeção visual dos gráficos. Este estudo foi registrado no PROSPERO (CRD42022344081).
Resultados: De 4.868 registos, identificámos 11 estudos e 2 relatórios adicionais, totalizando 15.578 participantes únicos. Os dados agrupados mostraram que a ecocardiografia portátil apresentou alta sensibilidade (0,87 [IC 95%: 0,76–0,93]), especificidade (0,98 [0,71–1,00]), e precisão geral alta (AUC 0,94 [0,84–1,00]) para o diagnóstico da doença cardíaca reumática em comparação com a ecocardiografia padrão (dois estudos; nível de certeza moderado), com melhor desempenho para o diagnóstico de doença cardíaca reumática definitiva em comparação com a doença cardíaca reumática borderline. Elevada sensibilidade (0,79 [0,73–0,84]), especificidade (0,85 [0,80–0,89]), e precisão geral (AUC 0,90 [0,85–0,94]) para o rastreamento da doença cardíaca reumática foram observadas ao agrupar dados de ecocardiografia portátil versus ecocardiografia padrão (sete estudos; nível de certeza elevado). A maioria dos estudos apresentou um baixo risco de viés global. Observámos alguma heterogeneidade para sensibilidade e especificidade entre estudos, possivelmente devido a diferenças na prevalência e gravidade da doença cardíaca reumática, e no nível de treino ou expertise dos operadores não especialistas.
Interpretação: A ecocardiografia portátil tem elevada precisão e desempenho diagnóstico quando comparado com a ecocardiografia padrão tanto para diagnóstico quanto para rastreio de doença cardíaca reumática em áreas de alta prevalência.

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Supplementary appendix 6

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Los autores nos proporcionaron esta traducción al español y la reproducimos tal como nos fue entregada. No la hemos revisado. Los procesos editoriales de *The Lancet* se han aplicado únicamente al original en inglés, que debe servir de referencia para este manuscrito.

Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

Antecedentes: La detección temprana o el diagnóstico de la fiebre reumática, (también conocido como reumatismo articular agudo) y la enfermedad reumática del corazón son clave para prevenir la progresión, y la ecocardiografía tiene un papel diagnóstico importante. La ecocardiografía estándar puede no ser factible en regiones de alta prevalencia debido al alto costo, la complejidad y la duración de la investigación. La ecocardiografía portátil puede ser una alternativa de bajo costo fácil de usar, pero su rendimiento para la detección y diagnóstico de fiebre reumática y enfermedad reumática del corazón necesita ser investigado más a fondo.

Métodos: Buscamos en Embase, MEDLINE, LILACS y el Índice de Citas de Actas de Conferencias-Ciencia hasta el 9 de Febrero de 2024, estudios sobre la detección y diagnóstico de fiebre reumática y enfermedad reumática del corazón utilizando ecocardiografía estándar y ecocardiografía portátil en áreas de alta prevalencia.

Incluimos todos los estudios con datos utilizables en los cuales se evaluó el rendimiento diagnóstico de la prueba índice en relación con una prueba de referencia. Los datos sobre la precisión de la prueba en el diagnóstico de enfermedad cardíaca reumática, fiebre reumática aguda o carditis con fiebre reumática aguda (puntos finales primarios) fueron extraídos de artículos publicados o calculados, y se contactó a los autores según fuera necesario. La calidad de la evidencia fue evaluada utilizando los criterios GRADE y QUADAS-2. Resumimos estadísticas de precisión diagnóstica (incluyendo sensibilidad y especificidad) y estimamos intervalos de confianza del 95% utilizando un modelo bivariado de efectos aleatorios (o modelos univariados de efectos aleatorios para análisis con tres o menos estudios). El área bajo la curva (AUC) fue calculada a partir de curvas resumidas de característica operativa del receptor. La heterogeneidad fue evaluada mediante inspección visual de gráficos. Este estudio fue registrado en PROSPERO (CRD42022344081).

Hallazgos: De 4,868 registros identificamos 11 estudios y 2 informes adicionales, que comprenden un total de 15,578 participantes únicos. Los datos agrupados mostraron que ecocardiografía portátil tiene una alta sensibilidad, especificidad y precisión general para diagnosticar enfermedad reumática del corazón en comparación con ecocardiografía estándar (sensibilidad 0.87, 95% CI 0.76-0.93, especificidad 0.98 95% CI 0.71-1.00 & AUC 0.94, 95% CI 0.84-1.00; 2 estudios; certeza de evidencia moderada), con un mejor rendimiento para diagnosticar enfermedad reumática del corazón definitiva que enfermedad reumática del corazón borderline. Se observó una alta sensibilidad, especificidad y precisión general para rastrear enfermedad reumática del corazón al agrupar datos de ecocardiografía portátil vs ecocardiografía estándar (sensibilidad 0.79, 95% CI 0.73-0.84, especificidad 0.85, 95% CI 0.80-0.89 & AUC 0.90, 95% CI 0.85-0.94; 7 estudios; certeza alta). La mayoría de los estudios tuvieron un bajo riesgo de sesgo en general. Se observó cierta heterogeneidad en la sensibilidad y especificidad entre los estudios, posiblemente impulsada por diferencias en la prevalencia y gravedad de la enfermedad reumática del corazón, y el nivel de capacitación o experiencia de los operadores no expertos.

Interpretación: La ecocardiografía portátil tiene una alta precisión y rendimiento diagnóstico en comparación con ecocardiografía estándar tanto para diagnosticar como para la rastrear enfermedad reumática del corazón en áreas de alta prevalencia.

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Supplementary appendix 7

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اردو میں یہ ترجمہ مصنفین کے ذریعہ پیش کیا گیا تھا اور ہم اس کی ہو بہو دوبارہ تخلیق کرتے ہیں۔ اس کا ہم مرتبہ ماہروں کے ذریعہ جائزہ نہیں لیا گیا ہے۔ *لانسیٹ* کے ادارتی عمل کا اطلاق صرف انگریزی کے اصل پر ہوا ہے، جو اس نسخے کے حوالہ کے طور پر کام کرے گا

Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

پس منظر

شدید ریومیٹک بخار اور ریومیٹک دل کی بیماری کی جلد تشخیص اور تعین کلیدی ہوتی ہے تاکہ بیماری کی پیش قدمی کو روکا جا سکے، اور ایکوکارڈیوگرافی کا تشخیصی کردار اہم ہے۔ معیاری ایکوکارڈیوگرافی اعلی وقوع پذیر علاقوں میں ممکن نہیں ہو سکتی کیونکہ اس کی زیادہ لاگت، پیچیدگی، اور وقت کی ضرورت ہوتی ہے۔ ہاتھ سے پکڑنے والی ایکوکارڈیوگرافی ایک آسان، کم لاگت کا متبادل ہو سکتی ہے، لیکن شدید ریومیٹک بخار اور ریومیٹک دل کی بیماری کی تشخیص اور اسکریننگ کے لیے اس کی کارکردگی کی مزید تحقیق کی ضرورت ہے۔

طریقہ کار

اس نظامتی جائزہ اور میٹا-تجزیہ میں، ہم نے ایمبیس، میڈلائن، لیلاکس، اور کانفرنس پروسیڈنگز سائٹیشن انڈیکس—سائنس میں ۹ فروری ۲۰۲۴ تک، ہاتھ سے پکڑنے والی ایکوکارڈیوگرافی (انڈیکس ٹیسٹ) یا معیاری ایکوکارڈیوگرافی یا آسکلٹیشن (حوالہ ٹیسٹ) کا استعمال کرتے ہوئے شدید ریومیٹک بخار اور ریومیٹک دل کی بیماری کی اسکریننگ اور تشخیص کے مطالعات کے لیے تلاش کیا۔ ہم نے ان تمام مطالعات کو شامل کیا جن میں استعمال ہونے والا ڈیٹا تھا جس میں انڈیکس ٹیسٹ کی تشخیصی کارکردگی کا حوالہ ٹیسٹ کے خلاف جائزہ لیا گیا تھا۔ ریومیٹک دل کی بیماری، شدید ریومیٹک بخار، یا شدید ریومیٹک بخار کے ساتھ کارڈیٹس (اولین نتائج) کی تشخیص میں ٹیسٹ کی صحت کے ڈیٹا کو شائع شدہ مقالات سے نکالا گیا یا حساب لگایا گیا، ضرورت پڑنے پر مصنفین سے رابطہ کیا گیا۔ شواہد کی معیار کا جائزہ GRADE اور QUADAS-۲ معیارات کا استعمال کرکے لیا گیا۔ ہم نے تشخیصی صحت کے اعداد و شمار (بشمول حساسیت اور خصوصیت) کو خلاصہ کیا اور ۹۵% CIs کا تخمینہ دو متغیری بے ترتیب اثرات ماڈل (یا تین یا کم مطالعات کے تجزیات کے لیے یک متغیری بے ترتیب اثرات ماڈل) کا استعمال کرکے لگایا۔ ایریا انڈر دی کرو (AUC) کو خلاصہ ریسیور آپریٹنگ خصوصیت منحنیوں سے حساب کیا گیا۔ اس مطالعہ کو PROSPERO (CRD۴۲۰۲۲۳۴۴۰۸۱) کے ساتھ رجسٹر کیا گیا تھا۔

نتائج

۴۸۶۸ ریکارڈز میں سے ہم نے ۱۱ مطالعات، اور دو اضافی رپورٹس کی شناخت کی، جس میں ۱۵,۵۷۸ منفرد شرکاء شامل تھے۔ پول ڈیٹا نے دکھایا کہ ہاتھ سے پکڑنے والی ایکوکارڈیوگرافی کی حساسیت اعلی (.۸۷ [۹۵% ۰.۹۳–۰.۷۶ CI]), خصوصیت (.۹۸ [۹۵% ۱.۰۰–۰.۷۱ CI]), اور کل اعلی صحت (۱.۰۰–۰.۸۴ CI ۹۵%] ۰.۹۴ AUC]) ریومیٹک دل کی بیماری کی تشخیص کے لیے معیاری ایکوکارڈیوگرافی کے مقابلے میں دکھائی گئی (دو مطالعات؛ معتدل یقین دہانی کے ساتھ شواہد), یکساں ریومیٹک دل کی بیماری کی تشخیص کے مقابلے میں بہتر کارکردگی دکھائی۔ حساسیت کی اعلی درجہ (.۷۹ [۹۵% ۰.۸۴–۰.۷۳ CI]), خصوصیت (.۸۵ [۹۵% ۰.۸۹–۰.۸۰ CI]), اور کل صحت (CI ۹۵%] ۰.۹۰ AUC ۰.۹۴–۰.۸۵]) ریومیٹک دل کی بیماری کی اسکریننگ کے لیے دیکھی گئی جب ہاتھ سے پکڑنے والی ایکوکارڈیوگرافی کا ڈیٹا معیاری ایکوکارڈیوگرافی کے مقابلے میں پول کیا گیا (سات مطالعات؛ اعلی یقین دہانی کے ساتھ شواہد).زیادہ تر مطالعات میں مجموعی طور پر تعصب کا خطرہ کم تھا۔ کچھ ہم آہنگی مختلف مطالعات میں حساسیت اور تخصص کے لحاظ سے دیکھی گئی، جو شاید ریومیٹک دل کی بیماری کی موجودگی اور شدت، اور غیر ماہر آپریٹرز کی تربیت یا مہارت کی سطح میں اختلافات کی وجہ سے تھی۔

تفسیر

ہاتھ سے پکڑنے والی ایکوکارڈیوگرافی کی تشخیصی اور اسکریننگ کارکردگی اعلی ہے جب اسے معیاری ایکوکارڈیوگرافی کے ساتھ موازنہ کیا جاتا ہے، خصوصاً ریومیٹک دل کی بیماری کی تشخیص اور اسکریننگ کے لیے اعلی وقوع پذیر علاقوں میں۔

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Supplementary appendix 8

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Supplement to: Providência R, Aali G, Zhu F, et al. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. *Lancet Glob Health* 2024; **12:** e983–94.

Supplementary Material – Appendix 8

Rui Providencia, Ghazaleh Aali, Fang Zhu, Thomas Katairo, Mahmood Ahmad, Jonathan J H Bray, Ferruccio Pelone, Mohammed Y Khanji, Eloi Marijon, Miryan Cassandra, David S Celermajer, Farhad Shokraneh. Handheld echocardiography for the screening and diagnosis of rheumatic heart disease: a systematic review to inform WHO guidelines. Lancet Global Health. 2024

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Search Strategies

Search strategies were developed by consulting the clinicians, controlled vocabularies (Medical Subject Headings=MeSH and Excerpta Medica Tree=Emtree), literature review, and test search results. Based on the recommendations from the 2nd edition of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks 2022), the searches were balanced between sensitivity and specificity of the search results without applying a methodological search filter. Furthermore, the search was not limited to publication date, publication language, publication status, or document type.

The search strategies were peer-reviewed by a second Information Specialist (FP) before the final run. The searches were run, documented, and reported by a senior information scientist (FS).

The search results were imported into EndNote 20. After removal of duplicates, the remaining records were imported into Rayyan for double-blind screening by two reviewers (TK, FZ). The blinding was inactivated when the screening was finished to resolve the conflicts by a third reviewer (FS).

Database: Embase <1974 to 2024 February 9>

1 Rheumatic Fever/ or (Rheumatic Fever* or Rheumatoid Fever*).mp. (10135)
2 exp *Echocardiography/ or exp *Doppler Echocardiography/ or *Color Doppler Echocardiography/ or *Pulsed Doppler Echocardiography/ or exp *Speckle Tracking Echocardiography/ or exp *Stress Echocardiography/ or *Contrast Echocardiography/ or *Four Dimensional Echocardiography/ or *Intracardiac Echocardiography/ or *M Mode Echocardiography/ or *Three Dimensional Echocardiography/ or *Tissue Doppler Imaging/ or *Transesophageal Echocardiography/ or *Transthoracic Echocardiography/ or *Two Dimensional Echocardiography/ or *Three Dimensional Speckle Tracking Echocardiography/ or *Two Dimensional Speckle Tracking Echocardiography/ or *Dobutamine Stress Echocardiography/ or *Exercise Stress Echocardiography/ or (Echocardiogra* or Doppler or Cardiac Echogra* or Cardiac Scan* or Cardial Echogra* or Cardioechogra* or Echo Cardiogra* or Heart Echo Sounding or Heart Echograph* or Heart Scan* or Myocardium Scan* or Ultrasound Cardiogra* or Intra-Cardiac Ultrasound or Intracardiac Echo or Intracardiac Ultrasound or Echo Stress Test or Stress Echo Test or Stress MCE).mp. (672591)
3 1 and 2 (1770)
4 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1240111)
5 Animal experiment/ not (human experiment/ or human/) (2606142)
6 4 or 5 (2677577)
7 3 not 6 (1764)

Database: Ovid MEDLINE(R) ALL <1946 to February 9, 2024>

1 Rheumatic Heart Disease/ or exp Rheumatic Fever/ or (Rheumatic Card* or Rheumatic Fever* or Rheumatic Heart or Rheumatoid Fever* or Rheumatic Valv* or Rheumatic Pancarditis or Rheumatic Endocarditis or Rheumatic Myocarditis or Rheumatic Pericarditis or Rheumatoid Pancarditis or Rheumatoid Endocarditis or Rheumatoid Myocarditis or Rheumatoid Pericarditis or Rheumatoid Card* or Rheumatoid Heart or Rheumatoid Valv*).mp. (26562)
2 exp Echocardiography/ or exp Echocardiography, Doppler/ or Echocardiography, Three-Dimensional/ or Echocardiography, Doppler, Color/ or Echocardiography, Doppler, Pulsedor/ or Echocardiography, Stress/ or Echocardiography, Four-Dimensional/ or Echocardiography, Transesophageal/ or (Echocardiogra* or Doppler or Cardiac Echogra* or Cardiac Scan* or Cardial Echogra* or Cardioechogra* or Echo Cardiogra* or Heart Echo Sounding or Heart Echograph* or Heart Scan* or Myocardium Scan* or Ultrasound Cardiogra* or Intra-Cardiac Ultrasound or Intracardiac Echo or Intracardiac Ultrasound or Echo Stress Test or Stress Echo Test or Stress MCE).mp. (343170)
3 1 and 2 (2887)
4 exp Animals/ not Humans.sh. (5194870)
5 3 not 4 (2884)

Conference Proceedings Citation Index-Science (CPCI-S; 1990 - to February 9, 2024)

(Rheumatic Card* or Rheumatic Fever* or Rheumatic Heart or Rheumatoid Fever* or Rheumatic Valv* or Rheumatic Pancarditis or Rheumatic Endocarditis or Rheumatic Myocarditis or Rheumatic Pericarditis or Rheumatoid Pancarditis or Rheumatoid Endocarditis or Rheumatoid Myocarditis or Rheumatoid Pericarditis or Rheumatoid Card* or Rheumatoid Heart or Rheumatoid Valv*) AND (Echocardiogra* or Doppler or Cardiac Echogra* or Cardiac Scan* or Cardial Echogra* or Cardioechogra* or Echo Cardiogra* or Heart Echo Sounding or Heart Echograph* or Heart Scan* or Myocardium Scan* or Ultrasound Cardiogra* or Intra-Cardiac Ultrasound or Intracardiac Echo or Intracardiac Ultrasound or Echo Stress Test or Stress Echo Test or Stress MCE) (Topic)

Latin American and Caribbean Health Sciences Literature (LILAC; 1990 - to January 2024)

("febre reumatica" OR "cardite reumatica" OR "cardiopatia reumatica" OR "pancardite reumatica" OR "miocardite reumatica" OR "endocardite reumatica") AND ("ecocardiogra*" OR "Doppler" OR "ultrasso*") AND (db:("LILACS")) (Título, resumo, assunto) 34

Data extraction & Quality assessment

Data extraction

The following data were extracted from all studies (FZ) and double-checked by an independent reviewer (TK).

- Study characteristics: authors, year of publication, country, study design, sample size, study period, setting, patient selection (random/ consecutive);
- Patient characteristics: patient type, age, gender, follow-up period;
- Index test details: HHE device used (i.e., VScan, Sonoheart, Optigo, Acuson P10, Lumify etc.), level of experience of the sonographer, diagnostic criteria etc;
- Reference test details: reference test (clinical/SE);
- Outcome-related data: sensitivity and specificity directly from papers (if not available, this was calculated from the true positives, false positives, true negatives, and false negatives in the 2 × 2 tables), any adverse event (deaths, complication), time to diagnosis (mean and standard deviation – SD), acceptability to provider and patient

Authors of the studies were contacted on an as-required basis to obtain the data or information.

Quality assessment

The methodological quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [1]. The QUADAS-2 checklist consists of four domains: (i) patient selection, (ii) index test, (iii) reference standard and (iv) flow and timing, each of which is further divided into sub-items. Each domain was scored as 'yes' (positive assessment, high quality), 'no' (negative assessment, low quality), or 'unclear'. Disagreements between the two appraisers (RP & JB) were resolved by consensus or via a third party (MA).

GRADE methodology

The certainty of the evidence was rated using the GRADE methodology for diagnostic tests [2-4]. We used GRADEpro to create this table for the diagnostic question. The five domains (risk of bias, indirectness, inconsistency, imprecision, and publication bias) were judged as without concerns, with serious concerns, or with very serious concerns. The reason for each of the five domains was judged as not serious, serious (downgraded by one level), or very serious (downgraded by two levels) were documented.

References:

1. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MMG, Sterne JAC, Bossuyt PMM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Internal Med. 2011;155:529-536.
2. GRADEpro, G. (2015). GRADEpro GDT: GRADEpro Guideline Development Tool (Software). McMaster University, 2015 (developed by Evidence Prime, Inc.).
3. Schünemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, Williams Jr JW, Kunz R, Craig J, Montori VM, Bossuyt P, Guyatt GH; GRADE Working Group. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ. 2008;336:1106-1110.
4. Singh S, Chang SM, Matchar DB, Bass EB. Chapter 7: Grading a body of evidence on diagnostic tests. J Gen Intern Med. 2012;27(Suppl 1):S47-55.

Training of Non-Experts

Beaton 2016

Non-Experts: Six nonexperts with a variety of health care backgrounds (2 nurses, 2 biotechnicians, and 2 medical students) and practical experience obtaining echocardiographic images (4 with 6 weeks and 2 with 1 year) participated in the study.

Educational Training and content: A previously published simplified RHD screening protocol was taught, and participants performed limited echocardiograms and interpreted them as screen positive or negative.

The 3-week self-directed educational period was followed by field-testing of school-based echocardiographic screening using HHE. The educational program focused on self-directed, computer-based modules translated into Portuguese that could be completed asynchronously at the participants' convenience without support from expert staff. Lessons were assigned for 3 consecutive weeks. Midweek, participants received a personalized quiz link through their email, including 25 to 50 multiple choice and true/false questions generated using the survey feature of REDCap, an electronic data capture tool hosted at Children's National Health System. Participants received scores through their email within 24 hours of quiz completion, and if they scored <85%, they were asked to recomplete the week's educational module.

During week 1, Six of the WiRED International Echocardiographic Diagnosis of RHD "Nurse Training Modules" (freely available at https://www.wiredhealthresources.net/EchoProject/index.html) were used for teaching on the background of RHD screening, the 2012 WHF criteria, and measurement of mitral and aortic regurgitation.

Education during weeks 2 and 3 used self-guided PowerPoint presentations and an image library, a file of HHE studies through cloud image sharing and access to proprietary software program (General Electric Gateway, Milwaukee, Wisconsin) that allowed them to interact with the images to freeze, play, scroll, and perform measurements.

Practical Training: Observational and hands-on training on acquiring echocardiographic images with approximately 60 hours of training over 6 weeks. This training did not include image interpretation or field experience.

Francis 2021

Non-Experts: Eighteen people were offered training: six paediatric doctor trainees, four nurses and eight community workers. Non-expert practitioners were identified from Timor-Leste and the Northern territories, with emphasis on selecting people from the communities that would be involved in the study.

Educational Training and content: Participants were required to complete 10 modules of an online course in the echocardiographic diagnosis of RHD prior to face-to-face training.

Participants were encouraged to to attend a five-day face-to-face course of intensive training at Menzies School of Health Research and NT Cardiac in Darwin, Australia

Practical Training: Face-to-face practical training delivered over 6 days by cardiac sonographers and cardiologists with expertise in the diagnosis of RHD. Most participants spoke English as a second language and were taught single parasternal-long-axis view with a sweep of the heart (SPLASH) echocardiography, and to identify any mitral regurgitation and/or aortic regurgitation as being abnormal. They were not taught to identify other pathological valvular changes, associated with RHD.

To successfully complete training, nonexpert practitioners had to perform a minimum of 50 supervised SPLASH studies, which included volunteers with normal hearts and with RHD, and pass written and practical assessments.

Mirabel 2015

Non-Experts: Two nurses with no previous experience in echocardiography underwent focused training for the recognition of left-sided valve abnormalities.

Educational Training and content: Theoretical lectures for 3 days to allow the non-experts to a) acquire basic knowledge in cardiovascular physiology and cardiac anatomy; b) recognize the long and short axis parasternal, and all 3 apical transthoracic views, name the four chambers and the four cardiac valves; c) acquire the views in grey scale and use Color Doppler; d) recognize morphological changes of the mitral valve (thickening of the anterior leaflet and of the chordae, restriction of the posterior and anterior leaflet, prolapse of the tip of the mitral leaflet); e) detect the presence of MR or AR; f) measure the maximum MR length using the caliper function on the device.

Practical Training: 30 hours of 2-to-1 hands-on sessions (normal volunteers + patients) at the echocardiography unit, Centre Hospitalier Territorial de Nouvelle Calédonie, Nouméa, New Caledonia. Nurses reviewed a set of 50 of their scans with an experienced reader and undertook 12-hours practical of sessions (one to one sessions) addressing the pitfalls of each nurse (acquisition, interpretation).

Ploutz 2016

Non-Experts: Two Ugandan nurses with 6 months' experience in obtaining a limited echocardiography protocol for RHD using SE. Already competent in obtaining 2D and colour images in the standard parasternal long, parasternal short,

and apical four-chamber views, but without any previous experience in identification of morphological or functional abnormalities of left-sided valves.
Educational Training and content: Training included approximately 4h of physician-directed teaching, using a combination of computer-based training modules (WiRED International Echocardiographic Diagnosis of RHD "Nurse Training Modules"), didactics and case studies, including information on the use of HHE equipment and on the simplified screening approach. Training focused on basic left-sided cardiac anatomy, recognising MR and AR, use of the HHE equipment and correct measurement of regurgitant jets using the built-in calliper on the HHE equipment.
Practical Training: Two-day hands-on session with patients at a RHD clinic. Each nurse performed and interpreted a minimum of 50 studies using HHE over these 2 days with 1:1 or 2:1 supervision.

Voleti 2021

Non-Experts: Six novice users from various health-care backgrounds (two nurses, two physicians, one medical student, one patient care technician) with no prior echocardiographic experience.
Educational Training and content: Two weeks before beginning the school health screening programme, all learners completed the Wired International 'Nurse Training Modules'. After the completion of these modules, they took a pre-designed quiz to assess knowledge acquisition from the modules. Follow-up complementary didactics included review of the quiz answers was provided. A 2-day session comprising a total of 8 h was held prior to the first day of the school screening programme, during which the Wired Module quizzes, RHD background, diagnosis and pathophysiology were reviewed again.
Practical Training: Two hands-on sessions (1.5 h each) with a local internist, who reviewed practical echocardiography skills, adequate probe positioning to acquire necessary images, and interpretation of scans demonstrating MR and AR. During the final 2-day session further practical hands-on training with the HHE machines containing the novel application was completed. The total time spent in face-to-face, hands-on learner training was approximately 11 h.

Francis 2023

Non-Experts: Twenty-two people (10 nonspecialist doctors, 6 nurses and 6 community health workers) participated in SPLASH echocardiography training after being selected and recommended to the study team by their health service; 13 were from Timor-Leste and 9 from Australia. Four were Aboriginal Australians. Eighteen had no previous echocardiography experience and 4 had participated in Francis 2021.
Educational Training and content: Participants were required to complete online modules course in the echocardiographic diagnosis of RHD prior to face-to-face training.
Face-to-face training included lectures and practical training delivered over 10 days time period.
Practical Training: Practical training involved a minimum of 100 supervised SPLASH studies.
The final assessment included a written examination (21 short-answer questions) and an evaluation of practical skills (3 supervised SPLASH echocardiograms assessed as competent, with at least one involving a known RHD patient).

Ali 2024

Non-Expert: Pediatric resident who had undergone study specific training.
Educational Training and content: N/A
Practical Training: N/A

Other Outcomes & Sub-group analyses

Non-reported outcomes

Time to diagnosis was not reported for any of the studies.
There were no properly designed diagnostic test accuracy studies assessing HHE vs SE for diagnosing ARF, or reporting on adverse events, acceptability to provider and patient, or prevention of complications or death.

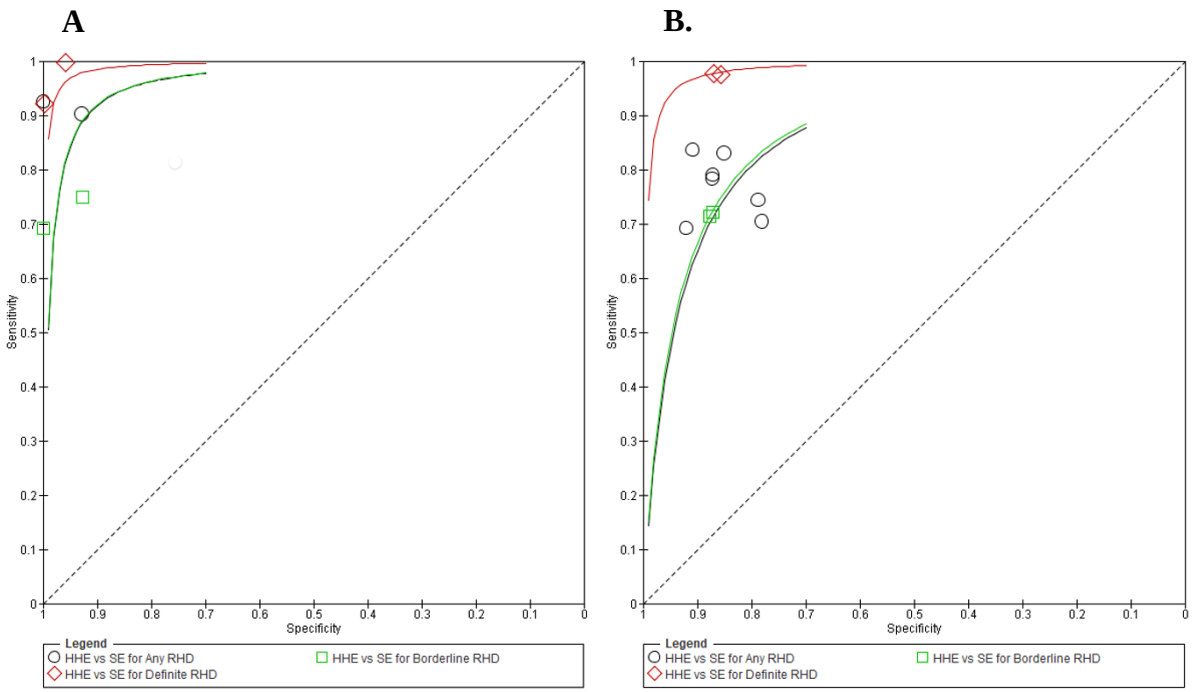
Average Time per Scan

Beaton et al. 2015 reported that their investigation was conducted over 5 days, comprising 4,773 SE and 1,420 HHE.
Mirabel et al. 2015 reported the mean scanning time as 5.9 (SD=1.7) minutes and 7.0 (SD=1.9) minutes for two nurses.
Ploutz et al. 2016 mentioned that each nurse performed and interpreted a minimum of 50 studies using HHE over 2 days (assuming 8 hours of work per day, 9.6 minutes per study can be inferred).
Zuhlke et al. 2016 reported average time to record the images using the HHE as 117 (SD=22) seconds.

Non-reported subgroup analyses

No additional pre-specified subgroup analyses were possible due to lack of data or all studies falling within the same category (i.e. all in high prevalence areas and no studies were randomized controlled trials).

Figure S-1: SROC curve for diagnosis (panel A) and screening studies (panel B), HHE vs. SE, for any RHD, definite RHD and borderline RHD



Legend: Panel A - Legend: AUC for diagnosis studies for any RHD = 0.94 (95%CI 0.84-1.00); AUC for diagnosis studies for definite RHD = 0.99 (95%CI 0.98-1.00); AUC for diagnosis studies for borderline RHD = 0.92 (95%CI 0.79-1.00). Panel B - AUC for screening studies for any RHD = 0.90 (95%CI 0.85-0.94), AUC for screening studies for definite RHD = 0.99 (95%CI 0.75-1.00), AUC for screening studies for borderline RHD = 0.88 (0.80-0.99).

Table S-1: Table of excluded studies

Study name	Reason for exclusion
Agnes C. 2023	Not diagnostic test accuracy study. Additional: Abstract; no information on screening method.
Ali et al. 2018a	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Ali et al. 2018b	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Amade et al. 2023	Not diagnostic test accuracy study. Additional: HHE was used, but no information on SE usage and results, hence no info on TP, TN, FP and FN.
Bastian Junior et al. 1989	Not diagnostic test accuracy study. Additional: not HHE.
Bechtlufft et al. 2020	Not diagnostic test accuracy study. Additional: study assessed a score that predicted progression of borderline RHD.
Bhavnani et al. 2018	Not diagnostic test accuracy study. Additional: RCT assessing HHE vs standard of care in rheumatic and structural heart disease clinics in resource-limited areas.
Brown et al. 2024	Not diagnostic test accuracy study. Additional: study assessing the use of artificial intelligence to improve echocardiographic screening of RHD.
Diamantino et al. 2018	Duplicate data from 4 studies already included in the review.
Elazrag et al. 2023	Not diagnostic test accuracy study. Additional: HHE was used, but apparently no subsequent SE was performed, hence no info on TP, TN, FP and FN.
Fareed et al. 2023	Not diagnostic test accuracy study. Additional: not HHE.
Franco et al. 2022	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Hosseini et al. 2022	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Hunter et al. 2021	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Kaltenborn et al. 2023	Not diagnostic test accuracy study. Additional: HHE was used, but only the number of screen positive results with HHE and prior to HHE introduction was compared, hence no info on TP, TN, FP and FN.
Kazahura et al. 2021	Not diagnostic test accuracy study. Additional: not HHE.
Mapelli et al. 2022	Not diagnostic test accuracy study. Additional: not HHE.
Meira et al. 2005	Not diagnostic test accuracy study. Additional: not HHE.
Meira et al. 2006	Not diagnostic test accuracy study. Additional: not HHE.
Miranda et al. 2014	Not diagnostic test accuracy study. Additional: not HHE.
Musuku et al. 2018	Not diagnostic test accuracy study. Additional: : HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Nascimento et al. 2021a	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Nascimento et al. 2021b	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Njathi et al. 2023	Not diagnostic test accuracy study. Additional: study assessing the use of artificial intelligence to improve echocardiographic screening of RHD.
Peck et al. 2023	Not diagnostic test accuracy study. Additional: study assessing the use of artificial intelligence to improve echocardiographic screening of RHD.
Regmi et al. 2023	Not diagnostic test accuracy study. Additional: not HHE.
Roshanitabrizi et al. 2022	Not diagnostic test accuracy study. Additional: study assessing the use of artificial intelligence to improve echocardiographic screening of RHD.
Roshanitabrizi et al. 2023	Not diagnostic test accuracy study. Additional: study assessing the use of artificial intelligence to improve echocardiographic screening of RHD.
Scheel et al. 2019	Not diagnostic test accuracy study. Additional: HHE was used, but SE was used only for assessing screen positive patients, hence no accurate info on TP, TN, FP and FN.
Telford et al. 2018	Protocol for Systematic Review. Telford et al. 2020
Telford et al. 2020	Systematic Review. Included studies were checked.
Topçu et al. 2023	Review paper
Ubels et al. 2020	Not diagnostic test accuracy study. Additional: Modelling study for assessing cost-effectiveness of HHE in Brazil.
Webb et al. 2023	Not diagnostic test accuracy study. Additional: not HHE.
Wegener et al. 2022	Not diagnostic test accuracy study. Additional: not HHE.

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Table S-2: Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool

Diagnostic Studies			
Study	Domain		
Beaton et al. 2014	Domain 1. Patient selection	Patient Sampling	Studies recorded during a 2-week period in September 2012 included 60 patients presenting for follow-up as part of a registry and 65 asymptomatic Ugandan schoolchildren who took part in an echocardiography-based screening program.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	No
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	One pediatric cardiologist performed all scans. One expert reviewer interpreted all echocardiographic images. – HHE and SE.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	Yes. 2012 WHF criteria. Modification for assessing MR and AR as no continous wave Doppler can be used with HHE.
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	Same pediatric cardiologist performed the scans.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Zühlke et al. 2016	Domain 1. Patient selection	Patient Sampling	Original sample from a screening of 2720 scholars from the Vanguard communities of Cape Town, was then processed into nested case–control study for assessing HHE's performance for diagnosing subclinical

			RHD. Inclusion from August, 2013 to September 2014.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	No
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	A single experienced cardiologist performed and interpreted all scans.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	Yes. MR jet length ≥2cm was considered positive.
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	Same cardiologist performed the scans. The 2012 WHF criteria were used to diagnose RHD.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Screening Studies			
Study	Domain		
Beaton et al. 2015	Domain 1. Patient selection	Patient Sampling	Studies conducted over a 5 day period in 5 schools in Uganda.
		Was a consecutive or random sample of patients enrolled?	Yes. Ten percent were randomly preselected (through study ID number) to undergo HHE as well as SE.
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Unclear
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	Five attending paediatric cardiologists, four paediatric cardiology fellows, and three senior echocardiography technicians performed the scans. Those acquiring HHE images did so in a separate

			area and were blinded to the results of SE. An 11-image standardized acquisition protocol was used, which was identical to the longer SE protocol with the exception of spectral Doppler.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	Yes. 2012 WHF criteria. Modification for assessing MR and AR as no continous wave Doppler can be used with HHE
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	Same team. A 7-image acquisition protocol that focused on left-sided valve pathology and function was used for studies not pre-assigned for a paired HHE. An extension protocol of five additional images was added to this standardized acquisition protocol, including the addition of parasternal short images and continuous-wave Doppler across the mitral inflow and aortic outflow for studies pre-assigned to the paired HHE study, and in any study with evidence of MR or AR. Images interpreted by 6 experienced cardiologists in the US. Reviewers were blinded to the paired SE study and the reason for HHE.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Yes
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Godonow et al. 2015	Domain 1. Patient selection	Patient Sampling	Children aged 5 to 17 years who attended 5 different schools in Uganda. A random

(sub-study of Beaton 2015)			subset (10%) was preselected by a unique identification number to undergo HHE. In addition, any subject with detectable MS, MR, AS, or AR, was referred for HHE.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	Performed by experienced imagers (attending pediatric cardiologists, senior cardiology fellows, or sonographers) blinded to SE findings. Same echo protocol as SE, with the omission of continuous wave Doppler. Interpreted by the same cardiologists that interpreted SE using modified 2012 WHF criteria.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	Modified 2012 WHF criteria
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	All subjects underwent a focused SE examination. SE performed by experienced imagers (attending pediatric cardiologists, senior cardiology fellows, or sonographers). Focused echocardiogram to evaluate aortic and mitral valves.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	All blindly reviewed by experienced cardiologists using the 2012 WHF criteria. A second reader confirmed any study with borderline or definite RHD, with any disagreements adjudicated by a third reader.
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Lu et al. 2015 (sub-study of Beaton 2015)	Domain 1. Patient selection	Patient Sampling	Children aged 5 to 17 years from 5 primary schools in Uganda. A random subset (10%) was preselected by a unique identification number to undergo HHE. In addition, any subject with detectable MS, MR, AS, or AR, was referred for HHE.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	Performed by experienced imagers (pediatric cardiologists, fellows, and sonographers) blinded to SE findings/isolated from SE stations. Same echo protocol as SE, with the omission of continuous wave Doppler. Interpreted by the same cardiologists that interpreted SE using modified 2012 WHF criteria.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	Individual HHE parameters were pre-specified and the best combination was then chosen: MR≥1.5cm & or any AR
		Could the conduct or interpretation of the index test have introduced bias?	Unclear
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	All subjects underwent SE examination consisting of 13 clips: parasternal long-axis view through the mitral and aortic valves, color Doppler over the mitral valve, color Doppler over the aortic valve, apical four-chamber view, apical four-chamber view with color Doppler over the mitral valve, apical five-chamber or three-chamber view, color Doppler over the aortic valve, continuous-wave Doppler of any MR or AI, parasternal short-axis view at the levels of the mitral and aortic valves, and color Doppler across the mitral and aortic valves. SE was performed by experienced imagers (attending pediatric cardiologists, senior

			cardiology fellows, or sonographers). All images were read by six experienced pediatric cardiologists using 2012 WHF criteria.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	All blindly reviewed by experienced cardiologists using the 2012 WHF criteria. A second reader confirmed any study with borderline or definite RHD, with any disagreements adjudicated by a third reader.
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Mirabel et al. 2015	Domain 1. Patient selection	Patient Sampling	School children aged 9–10 years in New Caledonia from April to August 2013. Each participant underwent 3 echocardiograms the same day in a randomly allocated order, blinded to the child's diagnosis and to the other sonographer's findings.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	HHE performed by two nurses trained specifically for this. Grayscale and color Doppler parasternal long axis and parasternal short axis, apical 4-, 2-, and 3-chamber views were acquired. Distances were measured with the caliper.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	The utilized simplified criteria consisted of combination of of MR jet length ≥2.0 cm or any AR and

			was defined in the first part of the study
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	An experienced cardiologist performed SE. Parasternal long axis and parasternal short axis, apical 4-, 2-, and 3-chamber views were acquired and settings optimized: grayscale without harmonics were recorded in the parasternal long-axis view for subsequent measurements of the anterior mitral leaflet, color Doppler was used in all views, continuous wave Doppler was applied to systematically measure the mean transmitral gradient and if a mitral or aortic regurgitant jet was seen on color Doppler.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	All blindly reviewed by an experienced reader using the 2012 WHF criteria.
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Beaton et al. 2016	Domain 1. Patient selection	Patient Sampling	Studies recorded in 5 schools in Brazil during a 4-day period.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	6 non-experts: 2 nurses, 2 biotechnicians, and 2 medical students) and practical experience obtaining echocardiographic images (4 with 6 weeks and 2 with 1 year) and interpreting them. Divided into 2 teams of 3,

			and paired with 2 cardiologists at parallel sites
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	Yes. MR ≥1.5 cm and/ or the presence of any AR was considered screen positive
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	Two cardiologists cardiologist obtaining images with a SE and interpreting according to the WHF 2012 criteria.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	All patients received the reference test. 25% normal scans were randomly selected for HHE and all abnormal scans were also screened with HHE. Non-experts were blinded to which group patients belonged to.
		Was there an appropriate interval between index test(s) and reference standard?	Yes
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Ploutz et al. 2016	Domain 1. Patient selection	Patient Sampling	June to August 2014 in two schools from Uganda. Each participant underwent 2 echocardiograms the same day with operators blinded to each others findings.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	HHE performed by two non-experts (nurses). This included 2D and colour Doppler in the parasternal long-axis and apical four-chamber and five-chamber views, with a total of 11–13 recorded images per examination. Measurements done with caliper.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes. Operators were blinded to each other's findings.

		If a threshold was used, was it pre-specified?	A combination of of MR jet length ≥1.5 cm or any AR was considered a positive screen.
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	SE performed by Senior Pediatric Cardiology fellow.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	Off-line independent interpretation by two cardiologists with expertise in RHD using the 2012 WHF criteria. Any disagreement between the two reviewers was adjudicated by a third paediatric cardiologist.
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Yes
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Francis et al. 2021	Domain 1. Patient selection	Patient Sampling	All participants aged 5 to 20 presenting to the screening sites in Timor-Leste and Australia on the day of screening.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	Non-experts performing HHE to identify presence or absence of any MR or AR in a single parasternal long-axis view.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	positive index test was defined as any MR and/or AR
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3.	Describe the reference standard and how it was conducted and interpreted:	SE performed by cardiologist of sonographer with

	Reference Standard		experience in diagnosis of RHD. WHF diagnosis criteria were used. All abnormal cases were reviewed in real time by a panel of 3 expert echo- cardiographers including at least one cardiologist to determine a consensus diagnosis
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Voleti et al. 2021	Domain 1. Patient selection	Patient Sampling	Elementary school in Palau screening over a 9 day period in 2 independent rooms.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	HHE performed by six novice users from various health-care backgrounds (two nurses, two physicians, one medical student, one patient care technician) without previous echocardiography experience. HHE was performed to 100% of RHD cases diagnosed by experts and 25% of children without RHD by expert scan. Assignement to non-experts was random, and these ere blinded to the reason for the referral.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes. Operators were blinded to each other's findings.
		If a threshold was used, was it pre-specified?	A combination of of MR jet length ≥1.5 cm or any AR was considered a positive screen.
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk

	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	SE performed by five expert screeners (four paediatric cardiologists and one senior paediatric cardiology fellow). A detailed protocol incorporating 2D, colour and continuous wave Doppler to allow usage of the 2012 WHF echocardiographic diagnostic criteria for RHD was followed.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	All positive studies identified by a first expert reader, along with 20 randomly selected negative studies, were compiled into a scrambled, de-identified list and sent to a blinded second expert for a second read. Cases of non-agreement were referred to an external paediatric cardiologist.
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Yes
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Chillo et al. 2023	Domain 1. Patient selection	Patient Sampling	A multi-stage sampling procedure was utilized to identify schools and districts in Tanzania. At each selected school all children aged 5–16 years were invited to participate through letters distributed to their parents/guardians, with written consent from parents and children verbal consent required for participation.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	Two expert cardiologists performed HHE in a quiet room or outside under enclosed space.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Not specified

		If a threshold was used, was it pre-specified?	Yes. 2012 WHF criteria. Modification for assessing MR and AR as no continous wave Doppler can be used with HHE.
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	Auscultation was done in a quiet room or outside in an enclosed screen with participants having bear-chest and rested in a 450 inclined examination bed. This was done by two trained last year Medical students. All 4 auscultatory areas (mitral, tricuspid, aortic and pulmonary area) were assessed. Abnormal sounds were considered a positive finding, and murmurs were then classified as systolic or diastolic.
		Is the reference standard likely to correctly classify the target condition?	Unclear
		Were the reference standard results interpreted without knowledge of the results of the index test?	Yes
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Yes
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Francis et al. 2023	Domain 1. Patient selection	Patient Sampling	All patients aged 5 to 20 presenting to the screening sites in Timor-Lest and Australia on the day of screening.
		Was a consecutive or random sample of patients enrolled?	Yes
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	Non-experts performing HHE to identify presence or absence of any MR or AR in a single parasternal long-axis view.
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes

		If a threshold was used, was it pre-specified?	positive index test was defined as any MR and/or AR
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk
	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	SE performed by expert cardiologist of sonographer with experience in diagnosis of RHD. All abnormal cases were reviewed on site by a panel of 3 experts to determine a consensus diagnosis on the basis of WHF diagnosis criteria.
		Is the reference standard likely to correctly classify the target condition?	Yes
		Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Low risk
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Unclear
		Could the patient flow have introduced bias?	Low Risk

Study	Domain		
Ali et al. 2024	Domain 1. Patient selection	Patient Sampling	Febrile children aged 3 to 18 presenting to a Pediatric Emergency in Sudan with possible acute rheumatic fever
		Was a consecutive or random sample of patients enrolled?	Unclear
		Was a case-control design avoided?	Yes
		Did the study avoid inappropriate exclusions?	Yes
		Could the selection of patients have introduced bias?	Low risk
		Are there concerns that the included patients do not match the review question?	Low risk
	Domain 2. Index Test	Describe the index test and how it was conducted and interpreted	Non-expert performing HHE, 2D + Colour Doppler on a single parasternal long-axis view. Interpreted with the aid of an Expert cardiologist
		Were the index test results interpreted without knowledge of the results of the reference standard?	Yes
		If a threshold was used, was it pre-specified?	positive index test was defined as MR≥1.5cm, or presence of any AR or mitral/aortic valve changes consistent with ARF/RHD in
		Could the conduct or interpretation of the index test have introduced bias?	Low risk
		Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low risk

	Domain 3. Reference Standard	Describe the reference standard and how it was conducted and interpreted:	Auscultation by unspecified physician – presence of murmur
		Is the reference standard likely to correctly classify the target condition?	Unclear
		Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear
		Could the reference standard, its conduct, or its interpretation have introduced bias?	Unclear
		Are there concerns that the target condition as defined by the reference standard does not match the review question?	Low risk
	Domain 4. Flow and Timing	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard:	Unclear
		Was there an appropriate interval between index test(s) and reference standard?	Unclear
		Did all patients receive a reference standard?	Yes
		Did all patients receive the same reference standard?	Yes
		Were all patients included in the analysis?	Yes
		Could the patient flow have introduced bias?	Low Risk

Table S-3: Evidence Table for Diagnostic Studies

Sensitivity	0.87 (95% CI: 0.76 to 0.93)	Effect per	1,000		
Specificity	0.98 (95% CI: 0.71 to 1.00)	Prevalences	0.444%	2.61%	1.13%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 0.444%	pre-test probability of 2.61%	pre-test probability of 1.13%	
True positives (patients with Acute Rheumatic Fever or Rheumatic Heart Disease)	2 studies 68 patients	case-control type accuracy study	serious [a]	not serious	not serious	not serious	none	4 (3 to 4)	23 (20 to 24)	10 (9 to 11)	⨁⨁⨁◯ Moderate
False negatives (patients incorrectly classified as not having Acute Rheumatic Fever or Rheumatic Heart Disease)								0 (0 to 1)	3 (2 to 6)	1 (0 to 2)	
True negatives (patients without Acute Rheumatic Fever or Rheumatic Heart Disease)	2 studies 150 patients	case-control type accuracy study	serious [a]	not serious	not serious	not serious	none	976 (707 to 996)	954 (691 to 974)	969 (702 to 989)	⨁⨁⨁◯ Moderate
False positives (patients incorrectly classified as having Acute Rheumatic Fever or Rheumatic Heart Disease)								20 (0 to 289)	20 (0 to 283)	20 (0 to 287)	

a. The two studies were case-controls. Decision was downgrade by 1 level as cases were asymptomatic and not severe, and hence not likely to inflate test performance too much.

Pre-test probabilities – 0.444% from Watkins 2017 (defined as “RHD identified by a clinician, with or without echocardiographic confirmation”) for high-prevalence areas, and 2.61% and 1.13% from Noubiap 2019 based on echocardiographic studies using WHF and WHO criteria, respectively.
Pooled results for:
- PPV 16.7%, 53.4% and 33.3% for pre-test probabilities of 0.444%, 2.61% and 1.13%, respectively.
- NPV 100%, 99.7% and 99.9% for pre-test probabilities of 0.444%, 2.61% and 1.13%, respectively.
- LR+ = 43.5
- LR- = 0.1
Using the estimated prevalence of any RHD across the two studies used included in our systematic review (i.e. 68/218 = 31.22%), the effect per 1,000 patient tested would be: TP = 272, FN = 40, TN = 674 & FP = 14.

Table S-4: Evidence Table for HHE Screening Studies

Sensitivity	0.78 (95% CI: 0.72 to 0.84)	Effect per	1,000		
Specificity	0.84 (95% CI: 0.79 to 0.88)	Prevalences	0.444%	2.61%	1.13%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE	
			Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	pre-test probability of 0.444%	pre-test probability of 2.61%	pre-test probability of 1.13%		
True positives (patients with Acute Rheumatic Fever or Rheumatic Heart Disease)	7 studies 626 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	3 (3 to 4)	20 (19 to 22)	9 (8 to 9)	⨁⨁⨁⨁ High	
False negatives (patients incorrectly classified as not having Acute Rheumatic Fever or Rheumatic Heart Disease)								1 (0 to 1)	6 (4 to 7)	2 (2 to 3)		
True negatives (patients without Acute Rheumatic Fever or Rheumatic Heart Disease)	7 studies 9898 patients	cross-sectional (cohort type accuracy study)	not serious	not serious	not serious	not serious	none	836 (786 to 876)	818 (769 to 857)	831 (781 to 870)	⨁⨁⨁⨁ High	
False positives (patients incorrectly classified as having Acute Rheumatic Fever or Rheumatic Heart Disease)								160 (120 to 210)	156 (117 to 205)	158 (119 to 208)		

Pre-test probabilities – 0.444% from Watkins 2017 (defined as "RHD identified by a clinician, with or without echocardiographic confirmation") for high-prevalence areas, and 2.61% and 1.13% from Noubiap 2019 based on echocardiographic studies using WHF and WHO criteria, respectively.
Pooled results for:
- PPV 2.1%, 6.1% and 12.8% for pre-test probabilities of 0.444%, 2.61% and 1.13%, respectively.
- NPV 99.9%, 99.3% and 99.8% for pre-test probabilities of 0.444%, 2.61% and 1.13%, respectively.
- LR+ = 5.5
- LR- = 0.3

Using the estimated prevalence of any RHD across the two studies used included in our systematic review (i.e. 721/14,960 = 4.82%), the effect per 1,000 patient tested would be: TP = 38, FN = 10, TN = 800 & FP = 152.

Table S-5: Positive and Negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-) for definite or borderline rheumatic heart disease

Study	PPV, 95%CI	NPV, 95%CI	LR+, 95%CI	LR-, 95%CI
Diagnostic studies (Handheld echocardiogram vs. Standard echocardiogram)				
Beaton et al. 2014	86.0% 73.9-93.1	95.1% 88.5-98.0	12.6 5.8-27.5	0.1 0.04-0.3
Zhülke et al. 2016	100% 83.9-100.0	92.7% 85.2-96.6	43*	0.08*
Screening studies (Handheld echocardiogram vs. Standard echocardiogram)				
Beaton et al. 2015	47.2% 43.1-51.3	96.5% 95.4-97.3	6.1 5.2-7.2	0.3 0.2-0.3
Godown et al. 2015	19.0% 16.9-21.3	96.9% 95.2-98.6	1.7 1.5-2.0	0.2 0.1-0.4
Beaton et al. 2016	45.8% 38.2-53.5	96.8% 92.6-98.7	5.5 4.0-7.5	0.2 0.1-0.5
Ploutz et al. 2016	14.2% 11.7-17.0	98.5% 97.5-99.1	3.5 2.8-4.3	0.3 0.2-0.5
Francis et al. 2021	15.8% 13.1-18.9	97.8% 97.1-98.4	3.2 2.8-3.7	0.4 0.3-0.5
Francis et al. 2023 (approach 1)	8.53% 7.9-9.2	99.1% 98.6-99.4	2.2 2.1-2.4	0.2 0.1-0.3
Francis et al. 2023 (approach 2)	14.0% 13.0-15.1	99.4% 99.0-99.6	3.9 3.5-4.2	0.2 0.1-0.2
Diagnostic studies (Auscultation vs. Standard echocardiogram)				
Zhülke et al. 2016	83.3 % 37.9-97.6	74.7% 71.1-78.0	12.2 1.5-99.8	0.8 0.7-1.0
Diagnostic studies (Auscultation vs. Handheld Echocardiogram)				
Ali et al. 2024	84.6% 54.5-97.3	85.8% 84.8-86.2	27.8 6.1-180.8	0.8 0.8-0.9
Screening studies (Auscultation vs. Standard echocardiogram)				
Godown et al. 2015	27.7% 20.9-35.7	89.9% 88.9-90.8%	2.8 1.9-4.1	0.8 0.7-0.9
Screening studies (Auscultation vs. Handheld Echocardiogram)				
Chillo et al. 2023	11.3% 5.3-22.6	98.0% 97.9-98.1%	5.8 2.6-13.3	1.0 0.9-1.0

*values provided by authors as per contingency tables adjusted for 0 values according to Glas et al. J Clin Epidemiol 2003; 56: 1129–1135.

Table S-6: Effects per 1,000 patients tested for the different sub-analyses on RHD Diagnosis or Carditis/ARF.

Index test (no. of studies)	**Reference standard**	**Population**	**Prevalence**	**TP** 95%CI	**FN** 95%CI	**TN** 95%CI	**FP** 95%CI
HHE (2)	SE	Definite RHD	WHF : 1.14%	11 10-11	0 0-1	969 919-979	20 10-70
			WHO : 0.64%	6 5-6	0 0-1	974 924-984	20 10-70
			Syst.Review: 17.43%	169 146-174	5 0-28	809 768-817	17 9-58
HHE (2)	SE	Borderline RHD	WHF: 1.52%	11 8-13	4 2-7	965 680-985	20 0-305
			WHO: 0.56%	4 3-5	2 1-3	975 686-994	19 0-308
			Syst.Review: 13.76%	99 74-118	39 20-64	845 595-862	17 0-267
Auscultation (1)	SE	Definite RHD	WHF : 1.14%	1 0-5	10 6-11	939 860-879	50 10-129
			WHO : 0.64%	1 0-3	5 3-6	944 864-984	50 10-130
			Syst.Review: 17.43%	16 0-71	158 103-174	784 718-817	42 9-108
Auscultation (1)	SE	Borderline RHD	WHF: 1.52%	0 0-0	15 15-15	936 857-975	49 10-128
			WHO: 0.56%	0 0-0	6 6-6	945 865-984	49 10-129
			Syst.Review: 13.76%	0 0-0	138 138-138	819 750-854	43 8-112
Auscultation (1)	HHE	Carditis/ARF	Sub-clinical: 18.10%	31 16-51	150 130-165	811 803-819	8 0-16
			Syst.Review: 16.50%	28 15-46	137 119-150	827 818-835	8 0-17

Pre-test probabilities from Noubiap 2019 based on echocardiographic studies using WHF and WHO criteria, respectively, and sub-clinical carditis as per Tubridy-Clark et al. Int J Cardiol. 2007;119:54-58. Estimated probabilities from our systematic review: any RHD: 68/218 = 31.22%; definite RHD: 38/218 = 17.43%, borderline RHD: 30/218 = 13.76%, and Carditis: 66/400 = 16.50%.

Table S-7: Effects per 1,000 patients tested for the different sub-analyses on RHD Screening.

Index test (no. of studies)	**Reference standard**	**Population**	**Prevalence**	**TP** 95%CI	**FN** 95%CI	**TN** 95%CI	**FP** 95%CI
HHE (2)	SE	Definite RHD	WHF : 1.14%	11 10-11	0 0-1	860 840-870	129 119-149
			WHO : 0.64%	6 6-6	0 0-1	864 845-874	130 120-149
			Syst.Review: 1.84%	18 17-18	0 0-1	854 834-864	128 118-148
HHE (2)	SE	Borderline RHD	WHF: 1.52%	11 8-13	4 2-7	965 680-985	20 0-305
			WHO: 0.56%	4 3-5	2 1-3	975 686-994	19 0-308
			Syst.Review: 2.97%	21 16-26	9 4-14	951 670-970	19 0-300
Simplified HHE / Non-expert (7)	SE with complete diagnostic criteria	Any RHD	Clinical: 0.44%	3 3-4	1 0-1	836 787-876	160 120-209
			WHF: 2.61%	20 19-22	6 4-7	818 769-857	156 117-205
			WHO: 1.13%	9 8-9	2 2-3	831 781-870	158 119-208
			Syst.Review: 4.82%	38 35-40	10 8-13	800 752-838	152 114-200
Expert HHE (1)	Expert SE	Any RHD	Clinical: 0.44%	3 3-4	1 0-1	866 846-	130 110-150
			WHF: 2.61%	21 19-22	5 4-7	847 828-867	127 107-146
			WHO: 1.13%	9 8-10	2 1-3	860 840-880	129 109-149
			Syst.Review: 4.82%	38 35-41	10 7-13	828 809-847	124 105-143
Expert HHE (1)	Expert SE	Definite RHD	WHF : 1.14%	11 10-11	0 0-1	860 840-880	129 109-149
			WHO : 0.64%	6 6-6	0 0-0	864 845-884	130 110-149
			Syst.Review: 1.84%	18 16-18	0 0-2	854 834-874	128 108-148
Expert HHE (1)	Expert SE	Borderline RHD	WHF: 1.52%	11 10-12	4 3-5	857 837-876	128 109-148
			WHO: 0.56%	4 4-4	2 2-2	865 845-885	129 109-149

			Syst.Review: 2.97%	21 19-23	9 7-11	844 825-864	126 106-145
Auscultation (2)	SE / HHE	Any RHD	Clinical: 0.44%	0 0-1	4 3-4	966 866-986	30 10-130
			WHF: 2.61%	3 2-5	23 21-24	945 847-964	29 10-127
			WHO: 1.13%	1 1-2	10 9-10	959 860-979	30 10-129
			Syst.Review: 4.82%	5 3-10	43 38-45	923 828-942	29 10-124
Auscultation (1)	SE	Definite RHD	WHF : 1.14%	3 1-4	8 7-10	900 880-919	89 70-109
			WHO : 0.64%	1 1-2	5 4-5	904 884-924	90 70-110
			Syst.Review: 1.84%	4 2-7	14 11-16	893 874-913	89 69-108

Pre-test probabilities from Watkins 2017 (clinical diagnosis) and from Noubiap 2019 based on echocardiographic studies using WHF and WHO criteria, respectively, for high-prevalence areas. Estimated probabilities from our systematic review for: any RHD: 721/14,960 = 4.82%; definite RHD: 276/14,960 = 1.84%; and borderline RHD: 445/14,960 = 2.97%.