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Standard Echocardiography versus Handheld Echocardiography for the Detection of Subclinical Rheumatic Heart Disease: A Systematic Review

University of Cape Town

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ABSTRACT

The research undertaken for this MPH dissertation compares the accuracy of handheld echocardiography for the detection of rheumatic heart disease to the reference standard using systematic review methods.

PART A is a research protocol which describes the background and process of the proposed review. This section details the quantitative methods to be used in the systematic review and meta-analysis of studies which assess the diagnostic accuracy of handheld echocardiography for rheumatic heart disease detection in children and adolescents. The proposed systematic review methods are based on those of the Cochrane Collaboration.

PART B is an extended literature review which expands on some of the topics raised in the background section of the protocol. A more in depth insight into the context surrounding the proposed research is offered and its importance highlighted. By reviewing the current body of evidence, this literature review aimed to both describe and contextualise the global burden of rheumatic heart disease whilst providing a rationale for further research into better screening modalities. Similarly, it also sought to describe the importance of understanding rheumatic heart disease epidemiology so that future research and screening programmes may be targeted accordingly.

PART C is a full systematic review of diagnostic test accuracy studies presented as a journal 'ready' manuscript in a format suitable for submission to PLoS ONE. The background to the systematic review is briefly summarised after which the results are then presented and discussed. The main findings, from seven included studies, provide some evidence for the potential of handheld echocardiography to increase access to echocardiographic screening for rheumatic heart disease. Lastly and in conclusion, implications arising from the findings of the review are posited and suggestions for future research offered.

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PART A: Protocol

ABBREVIATIONS AND DEFINITIONS

Abbreviations

ARF	Acute Rheumatic Fever
AR	Aortic Regurgitation
AV	Aortic Valve
CVD	Cardiovascular Disease
DALYs	Disability Adjusted Life Years
ECG	Electrocardiogram
GAS	Group A Streptococcus
HAND	Handheld Echocardiography
HCU	Hand Carried Ultrasound
HHCU	Hand-Held Cardiac Ultrasound
LMICs	Low and Middle Income Countries
MR	Mitral Regurgitation
MS	Mitral Stenosis
MV	Mitral Valve
RHD	Rheumatic Heart Disease
STAND	Standard Echocardiography
WHF	World Heart Federation
WHO	World Health Organisation

Definitions

Asymptomatic	*A health condition which does not display any clinical signs or symptoms.*
Aetiology	*The cause or set of causes or manner of causation of a disease or condition.*
Endemic	*Usual pervasiveness of a disease or condition among certain populations or within a geographic area.[1]*
Epidemiology	*Burden (incidence/prevalence), distribution and possible control of diseases.*
Morphology	*The structure and form of a specific organ, tissue, organism or cell.*
Pathogenesis	*The manner of origination and development of a disease.*
Pathological	*Altered or caused by disease (i.e. pathological changes in the body) / indicative of disease (i.e. pathological symptoms).*
Pathophysiology	*The disordered processes associated with disease or injury / the functional changes that accompany a particular disease.*
Physiological	*Relating to physiology / characteristic of or appropriate to an organism's healthy or normal functioning / differing in, involving or affecting physiological factors.*
Regurgitation	*The abnormal backward flowing of blood through a heart valve.*
Sequelae	*A condition that is the result of a preceding disease or injury.*
Stenosis	*The narrowing or constriction of an opening such as a heart valve.*
Symptomatic	*A health condition which displays clinical signs or symptoms.*
Valve	*An opening between two chambers of the heart or between a chamber of the heart and a blood vessel which is covered in membrane flaps.*

1. BACKGROUND

Rheumatic heart disease (RHD) is a permanent heart valve condition resulting from an abnormal immune reaction to group A streptococcal infection typically occurring in childhood.[2] If left untreated, disease progression can result in irreversible heart valve damage, cardiac failure, stroke and premature death.[3,4] Significantly, RHD is a preventable and treatable chronic condition which mostly affects disadvantaged populations across the world.[3] Even though the disease has mostly been eradicated in North America and Europe, barring a few indigent pockets, it remains prolific in areas of the Middle East, the South Pacific, Africa as well as Central and South Asia.[3]

The continued persistence of RHD contributes to considerable amounts of preventable morbidity and mortality, particularly among adolescents and young adults.[5] This adds additional strain to what are often already overburdened health systems, with endemic regions, which are typically poorly resourced, bearing the brunt of the disease.[2,6] Furthermore the accurate detection of subclinical RHD in children and adolescents remains hampered by the cost of diagnostic machinery and scarcity of trained personnel.[7]

Echocardiography has been demonstrated to significantly enhance screening programmes for the detection of RHD over auscultation alone.[5,8] However, the cost of standard portable echocardiographic machines is prohibitive in many RHD-endemic areas and the training and expertise required to conduct a full-screening echocardiogram according to the 2012 World Heart Federation (WHF) criteria restricts its wide scale use.[5,9] Alternative RHD screening tests, which are both accurate and affordable, are therefore needed in many endemic areas.

Recently, handheld echocardiography has become widely available with a variety of clinical uses.[10] Similarly, diagnostic accuracy has already been demonstrated in a number of studies assessing its value as a screening tool, despite some limitations such as lack of Doppler capabilities.[7] Due to the non-invasive, safe, portable and relatively inexpensive nature of handheld echocardiography, the device has been presented in recent publications as a promising alternative to standard echocardiography in resource-limited and remote settings.[8–11]

1.1 Rationale

Incorporating handheld echocardiography into screening programmes could provide the potential for significantly more cases of subclinical RHD to be detected, thereby reducing the time to commencement of secondary prophylaxis and thus, in turn, improving long term outcomes.[13] However, in order to test the assertion that HAND could provide a promising alternative to STAND in endemic areas, the diagnostic accuracy of handheld echocardiography needs to be evaluated using a systematic approach. This review, therefore, proposes to evaluate the accuracy of handheld echocardiography for the detection of RHD in children and adolescents within a screening setting.

We anticipate the findings of this review will generate new quantitative evidence whilst also highlighting any critical gaps in research. It is envisaged that this review will assist clinicians by prompting guideline developers to establish new evidence-based guidelines for diagnosing RHD with handheld echocardiography. Ultimately, this will improve the management of patients with RHD, as effective treatment of subclinical RHD requires accurate and timely diagnosis.

2. OBJECTIVES

2.1 Primary Objective

To identify, evaluate and synthesise existing literature reporting on the diagnostic accuracy of handheld echocardiography compared to standard echocardiography (2D, continuous-wave, and colour-Doppler echocardiography) performed by an experienced imager in conjunction with the 2012 WHF criteria for the detection of any RHD in children and adolescents.

2.2 Secondary Objective

To investigate potential sources of variation in relation to age, gender, geographical location, echocardiographic criteria and echocardiographer expertise in detecting subclinical RHD with handheld echocardiography.

3. REVIEW QUESTION

What is the accuracy of handheld echocardiography for the detection of RHD in children and adolescents worldwide?

4. METHODS

The protocol was prepared according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines.[14]

4.1 Study Selection Criteria

4.1.1 Types of studies

We will include all primary observational studies which compare the diagnostic accuracy of handheld echocardiography to the reference standard; standard echocardiography

performed by an experienced imager and in conjunction with the 2012 WHF criteria. Eligible studies can be of a cross-sectional, cohort or diagnostic case-control design, provided both cases and controls have been sampled from the same population. Descriptive studies such as case studies/series will be excluded from this review.

4.1.2 Types of participants

We will consider all studies in which samples of study participants are either, a randomly, or consecutively selected series of individuals from populations in which RHD is prevalent worldwide for inclusion. For the purposes of this review, children and adolescents will be defined as being between the ages of 5 and 17 years. More specifically, participants will be considered children if they are between 5 and 9 years of age and adolescents if they are between 10 and 17 years of age.

4.1.3 Types of diagnostic methods

We will include studies evaluating the accuracy of handheld echocardiography for RHD detection. There will be no restrictions regarding the type of handheld device used or the aptitude of person performing the cardiac ultrasound, however these data will be recorded and analysed accordingly. Studies will be deemed eligible for inclusion if the reference standard constituted the interpretation of echocardiographic findings using the 2012 WHF criteria when echocardiographic assessment by 2D, continuous-wave, and colour-Doppler echocardiography was performed by a cardiologist or cardiac sonographer.

We will exclude all studies published before 2012 in order to omit any study which does not use standard echocardiography in conjunction with the 2012 WHF criteria as the reference standard. We will consider all studies which evaluate any RHD (definite and borderline) as the condition of interest for inclusion in this review. All case definitions will be consistent with the 2012 WHF criteria.[15]

4.1.4 Types of outcome measures

Studies which report on, or contain the data necessary to extract information on the proportions of true positives (TP), false positives (FP), true negatives (TN) and false negatives (FN) will be included. Studies which enrolled only those with a confirmed RHD diagnosis will be excluded on account of the potential for overestimation of sensitivity. Studies in which we are unable to generate two-by-two tables, as well as different studies which report on duplicate data will not be considered for inclusion in this review. In instances where studies report on the same data, the most recent and complete version will be used.

Table 1. Eligibility criteria

	Inclusion	**Exclusion**
Study Design	Primary observational studies (cross-sectional, cohort or diagnostic case-control) evaluating the diagnostic accuracy of handheld echocardiography	Descriptive studies such as case studies and case series.
Study Participants	Children and adolescents between the ages of 5 and 17 years from RHD prevalent populations worldwide.	Participants with a confirmed RHD diagnosis.
Target Condition	Borderline or definite RHD consistent with case definitions as defined by the 2012 WHF criteria.	Case definitions which are not consistent with the 2012 WHF criteria.
Index Test	Any handheld device with no restrictions in terms of the interpreter's expertise.	Non-handheld devices
Reference Test	Standard echocardiography (2D, continuous-wave, and colour-Doppler echocardiography) performed and interpreted by an expert cardiologist or cardiac sonographer and in conjunction with the 2012 WHF criteria.	Diagnostic criteria other than the 2012 WHF criteria.
Outcome Measures	Proportions of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN).	Insufficient data to generate 2x2 tables. Studies reporting on the same data.

4.2 Search Methods

4.2.1 Electronic searches

A comprehensive electronic literature search of PubMed, Scopus, Web of Science and EBSCOhost will be conducted to identify relevant literature. No restrictions in terms of language will be applied during the search. Searches will however be limited to only include articles published from 2012 up until the present as a proxy for studies conducted from 2012 onwards. All sources will be systematically searched using a combination, where relevant, of both free text words and Medical Subject Heading (MeSH) terms. Search strategies will be tailored to meet the requirements of each electronic database as in *table 2* below. Search terms will include synonyms for 'rheumatic heart disease', 'echocardiography' and ‘handheld’. A list of all articles identified through the literature search will be compiled and references managed using Mendeley software.

4.2.2 Additional searches

In addition, a manual search of all eligible articles' reference lists, articles citing eligible articles as well as relevant review articles will be carried out in order to identify any additional literature not identified by the comprehensive electronic literature search. Abstracts from any relevant conference proceedings will also be searched for among appropriate websites and followed up on if eligibility requirements are sufficiently met. Finally, experts in the field will be contacted for additional information if necessary.

Table 2. Search strategy

Database	Search Terms	Limits
PubMed	((((((((((((((Hand-held) OR handheld) OR hand held) OR hand-carried) OR hand carried) OR HAND) OR HCU) OR HHCU) OR pocket size) OR pocket sized) OR portable) OR miniaturization) OR miniaturized) OR focused) OR focus)) AND ((((("Echocardiography"[Mesh]) OR echocardiography) OR echocardiographic) OR cardiac ultrasound)) AND (((("Rheumatic Heart Disease"[Mesh]) OR rheumatic heart disease) OR RHD) MeSH terms will be exploded during the search	Limited to 2012-2017
Scopus	**1.** Hand-held OR handheld OR hand held OR hand-carried OR hand carried OR HAND OR HCU OR HHCU OR pocket size* OR portable OR miniatur* OR focus* **2.** Echocardiograph* OR cardiac ultrasound **3.** Rheumatic Heart Disease OR RHD **#1 AND #2 AND #3**	Limited to 2012-2017
ISI Web of Science	**1.** Hand-held OR handheld OR hand held OR hand-carried OR hand carried OR HAND OR HCU OR HHCU OR pocket size OR pocket sized OR portable OR Miniaturization OR Miniaturized OR focused OR focus **2.** Echocardiography OR Echocardiographic OR cardiac ultrasound **3.** Rheumatic Heart Disease OR RHD **Combine #1 AND #2 AND #3**	Limited to 2012–2017 and filtering out MEDLINE
EBSCOHost	**S1.** Hand-held OR handheld OR hand held OR hand-carried OR hand carried OR HAND OR HCU OR HHCU OR pocket size OR pocket sized OR portable OR Miniaturization OR Miniaturized OR focused OR focus **S2.** Echocardiography OR Echocardiographic OR cardiac ultrasound **S3.** Rheumatic Heart Disease OR RHD **S1 AND S2 AND S3**	Limited to 2012-2017

4.3 Selection of Studies for Inclusion

The titles and/or abstracts of all articles identified by the literature search will be screened independently by two reviewers (LT and LA). Based on the predefined inclusion and exclusion criteria any clearly ineligible studies will be excluded. Following this, LT and LA will then review the full text versions of all potentially eligible studies in order to assess their eligibility. Any discrepancies regarding eligibility will be resolved through discussion and consensus with a third reviewer (ME).

5. DATA EXTRACTION AND MANAGEMENT

Using a predefined data extraction form, LT and LA will independently extract the following information from all studies meeting the criteria for inclusion;

- Study identifiers: Author(s), year of publication, journal
- Study characteristics: Study design, study country/setting/context, study population/participants, sample size, participant recruitment procedures, participant demographics and RHD prevalence (pre-test probability)
- Reference standard and index test details;
    - General: test positive or negative
    - Specific: individual findings on cardiac ultrasound
    - Expertise of person(s) performing and/or interpreting tests: expert vs non-expert
    - Diagnostic criteria: test threshold(s)
    - Number of missing or unavailable test results
- Diagnostic test outcome measures: Sensitivity, specificity, positive and negative predictive values, number of TP, FP, TN and FN

If necessary any disagreements will be resolved through discussion with a third reviewer (ME) until a consensus is reached. Any data missing from the reports of included studies will be requested from study authors by LT. In cases where studies have used different diagnostic criteria for handheld echocardiography, attempts will be made to standardise them to mirror the 2012 WHF criteria as closely as possible. The information garnered through the data extraction process will be used to determine each study's quality as well as for synthesising evidence.

6. RISK OF BIAS AND QUALITY ASSESSMENT

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (see *table 3*) will be used to assess the risk of bias and concerns regarding applicability of all included studies.[16] The tool encompasses four domains which have been tailored to meet the specific requirements of the review. Two reviewers will independently assess the risk of bias in all included studies according to the revised QUADAS-2 criteria. Any discrepancies will be resolved through discussion until consensus is reached and with the assistance of a third reviewer if necessary. Both text and graphics will be used to demonstrate the results.

Table 3. Design-specific QUADAS-2 criteria to assess methodological quality

CATEGORIES	DOMAINS			
	1. Patient Selection	**2. Index Test** (IT)	**3. Reference Standard** (RS)	**4. Flow & Timing**
Description	Briefly describe the methods of patient selection:	Describe the IT (HAND), how it was conducted and interpreted:	Describe the RS (STAND) how it was conducted and interpreted:	Describe patients that did not receive HAND, &/or STAND or who were excluded from the 2X2 table: Describe the time interval & any interventions between the HAND & STAND:
Indicator Questions (yes, no, unclear)	Was a consecutive or random sample of patients enrolled? Was a case-control design avoided? Did the study avoid inappropriate exclusions?	Were the HAND results interpreted without knowledge of the results of STAND? Was a pre-specified threshold used?	Was STAND likely to correctly classify the target condition? Were the STAND results interpreted without knowledge of the HAND results?	Was there an appropriate time interval between HAND & STAND? Did all patients receive STAND & was it the same RS? Were all patients included in the analysis?
***Risk of Bias** (low, high, unclear)	Based on the indicator questions, could the selection of patients have introduced bias?	Based on the indicator questions, could the conduct or interpretation of HAND have introduced bias?	Based on the indicator questions, could STAND, its conduct, or its interpretation have introduced bias?	Based on the indicator questions, could the patient flow and timing have introduced bias?
Concerns Regarding Applicability (low, high, unclear)	Describe included patients (prior testing, presentation, intended use of HAND and setting): Based on the description of included patients, are there concerns that the included patients do not match the review question?	Are there concerns that HAND, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by STAND does not match the review question?	

* Criteria for Grading Risk of Bias:
- If all indicator questions for a single domain are answered “yes” then the risk of bias will be judged as being “low”
- If any indicator question is answered “no” then the potential for bias will be flagged and the review authors will be required to judge the risk of bias with the assistance of the senior author (ME)
- If all or most indicator questions were answered "no" then the risk of bias will be judged as being "high"
- Indicator questions are can only be answered as “unclear” when the data are insufficient to allow for the formulation of a judgment

**Adapted from Whiting et al.[16]

7. DATA ANALYSIS AND SYNTHESIS

7.1 Subgroup and Sensitivity Analyses

7.1.1 Subgroup analysis

Subgroup analysis may be performed, considering specific characteristics of the studies, such as echocardiography protocol, training background of the examiner, age and geographical location.

7.1.2 Sensitivity analysis

We will conduct a sensitivity analysis to investigate the effect of variations in criteria on the overall accuracy of diagnosis. In addition we will explore the effect of excluding studies with a high risk of bias on the accuracy of summary estimates, sensitivity and specificity. We will not investigate publication bias.

7.2 Statistical Analysis and Data Synthesis

7.2.1 Statistical analysis

We will first analyse data descriptively by plotting the sensitivity and specificity (including 95% confidence intervals) of all included studies in both forest plots and Receiver Operating Characteristic (ROC) space. These plots will be generated using the Review Manager software package.[17]

7.2.2 Data synthesis

If there are sufficient data, we will conduct a meta-analysis to produce summary results of sensitivity and specificity. Because we anticipate that studies will have different positivity

thresholds due to the use of different sets of diagnostic criteria, we will pool the results using the Hierarchical Summary Receiver Operating Characteristic (HSROC) method.

Meta-analysis will be performed using SAS/STAT® software.[18] We will also explore, through meta-regression, the relationship of test accuracy with categorical or continuous covariates such as test threshold.[19]

7.2.3 Assessment of heterogeneity

Investigations of heterogeneity will initially begin by visually examining the forest and ROC plots for heterogeneity in sensitivity and specificity. We will then analyse the possible sources of heterogeneity as covariates in the statistical models. Potential sources of heterogeneity to be investigated as categorical variables include; age (children vs adolescents), sex (male vs female), geographical location (high vs low and middle income countries), diagnostic criteria (single vs multiple views and different thresholds) and echocardiographer expertise (expert vs non-expert).

7.3 Presenting and Reporting of Results

The study selection process will be summarised in the form of a flow diagram detailing the reasoning behind all exclusions. Results will be reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20]

8. FUNDING STATEMENT

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

9. ETHICS

Ethics approval is not required for this systematic review of previously published literature.

10. DISSEMINATION

The planned review will provide a summary of the diagnostic accuracy of handheld echocardiography. Results may feed into evidence-based guidelines and will therefore be disseminated to members of the WHF criteria working group. Should the findings of this review warrant a change in clinical practice, a summary report will be circulated amongst leading clinicians and healthcare professionals in the field.

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PART B: Literature Review

1. INTRODUCTION

1.1 Objectives

This literature review examines the current state of knowledge on rheumatic heart disease (RHD) epidemiology, aetiology, pathogenesis, diagnosis and screening. Through an evaluation of the existing body of evidence, this literature review will both describe and contextualise the global burden and distribution of RHD in relation to the history and development of various diagnostic and screening modalities. A synthesis and summary of relevant literature provides context and rationale for the succeeding systematic review.

1.2 Methods

An exploratory approach involving iterative methods was employed for the collection and synthesis of relevant evidence. The most recent and seminal works on RHD were first searched for in PubMed and Google Scholar using a broad search strategy which included a variety of search terms for RHD, epidemiology, screening and diagnosis. Thereafter, further pertinent literature was identified through hand searching the bibliographies of initially identified works as well as by following up on articles cited by relevant sources.

The scope of this literature review is broad and begins with a brief history of RHD in order to situate current global agendas. Thereafter, the epidemiology of RHD is outlined and the aetiology and pathogenesis of the disease is summarised. A précis of the history and development of diagnostic modalities then follows providing context for the concluding discussion on the current importance and possible future role of echocardiographic screening for RHD.

2. BACKGOUND

2.1 Historical Context

RHD has largely been eradicated in North America and Europe, barring a few indigent pockets within some developed countries. [1] This trend can mainly be attributed to improvements in living circumstances, access to health care and the use and availability of high-quality penicillin.[1,2] Yet while the incidence and prevalence of both acute rheumatic fever (ARF) and RHD has been steadily decreasing in developed countries since the early 1990s, rates continue to remain constant or increase in many developing countries.[3]

Contributing to considerable amounts of preventable morbidity and mortality, particularly among adolescents and young adults, the disease adds additional strain to what are often already overburdened health systems.[4–6] What's more, endemic regions are typically poorly resourced and often lack the capability to treat advanced RHD which requires expensive surgical procedures.[1]

2.2 Current Global Agenda

An unfortunate result of the declining rates of ARF and RHD in developed countries was a corresponding drop in associated research.[7] Additionally, while the pathogenesis of the condition is indeed better understood now, advances in the treatment and management of the disease have largely revolved around what are often inaccessible and expensive solutions for advanced RHD.[8] Recently, a resurgence in ARF/RHD awareness within global health contexts has occurred as recognition of the disease's continued persistence in many low and middle-income countries (LMICs) has grown.[7,9]

RHD is increasingly receiving more prominence in global agendas where advocacy for its eradication has been spearheaded by organisations such as the World Heart Federation (WHF), who in 2012 set the ambitious goal of achieving "25 x 25 < 25".[10,11] This goal seeks to see a 25% reduction in premature deaths resulting from RHD in those younger than 25 years of age by the year 2025.[4,8] With efforts such as those espoused by the 2017 WHF roadmap for improved RHD prevention and control, the actualisation of this goal has become a real possibility.[13]

Likewise, numerous calls to action emphasising research priorities and agendas have been publicised in recent years.[14–19] On June 1st, 2017 these calls were finally answered when the World Health Organisation (WHO) announced that a resolution to eradicate ARF and RHD will be presented for adoption at the World Health Assembly in 2018. This will mark the first time in recent history where RHD has been recognised as a global health priority at this level and will institute a worldwide commitment to the prioritisation of ARF and RHD prevention, management and control strategies in endemic areas.[20]

3. EPIDEMIOLOGY

Establishing the real burden of RHD and understanding the distribution of ARF/RHD both between and within populations is crucial for the formulation and effective implementation of preventive, diagnostic and management programmes.[2]

3.1 Global Burden

3.1.1 Acute rheumatic fever

Up until 100 years ago, ARF was second only to tuberculosis as the leading cause of death among young adults in the United States and the principal cause of mortality among

American school-children.[7] Likely due to improvements in hygiene, living conditions and sanitation,[7] the annual incidence of ARF in the United States decreased to around 4-6 cases per 100 000 children during the latter half of the 1900s.[21] The same cannot be said of many LMICs where a vastly dissimilar pattern mirroring that of the early developed world still exists.[22]

A 2005 report commissioned by the WHO analysed population-based data on ARF and RHD spanning 20 years and found that 471, 000 cases of ARF occur annually worldwide,[4] with approximately 60% of those living in endemic areas going on to develop RHD.[23] The same report also found that the number of new cases in children between 5 and 15 years of age ranged from 10 cases per 100, 000 in developed countries, to 374 cases per 100, 000 in the Pacific area.[4] These figures highlight the discrepancies in disease burden between the developed world and LMICs.

3.1.2 Rheumatic heart disease

Findings from the 2015 Global Burden of Disease study showed that the worldwide estimate for RHD prevalence has risen to nearly 34 million cases,[24] while an estimated 80 million people might also be living with subclinical RHD.[7] Furthermore, it was reported that as many as 319, 400 premature deaths were attributable to the disease in 2015.[25] Although, these estimates are likely to be an underestimate due to the widespread scarcity of good quality epidemiologic data on the disease, particularly from developing countries.[4,26]

The prevalence of RHD progressively increases as age increases,[27] with the disease peaking in adults aged between 25 and 34 years of age.[26] Significantly, RHD remains the most commonly occurring acquired cardiovascular disease (CVD) among people under the age of 25, thereby affecting those afflicted during their most productive years.[28]

A recent systematic review of the burden of RHD among children and adolescents in endemic areas calculated the pooled prevalence of clinical RHD to be 2.7 per 1000 people (95% CI: 1.6 – 4.4). In comparison the pooled prevalence of subclinical RHD was estimated at 21.1 per 1000 people (95% CI: 14.1 – 31.4), which the author's note is around seven to eight times greater than that of clinically manifest RHD.[27]

Differentiating between clinical and subclinical disease is therefore particularly important as it would appear that a much larger proportion of all RHD cases are subclinical. However, where clinical or definite RHD, defined as "structural and functional changes on echocardiography consistent with RHD in the presence of a pathological murmur"[29] is relatively easy to detect and diagnose, a diagnosis of subclinical or borderline RHD defined as "RHD detected on echocardiography without an associated clinically pathological murmur"[30] is more challenging and can be unreliable due to the subjectivity involved in assessing some morphological features.[31]

3.2 Global Distribution

3.2.1 Between populations

The burden of RHD is disproportionally distributed both within and between countries with the global poor bearing the brunt of disease as can be seen in the figure below.[11,32] According to 2013 estimates, the disease remains prolific in areas within Africa, the Middle East, the South Pacific, as well as Central and South Asia.[12,28] Notably, while the global North has experienced a significant decrease in the prevalence of RHD since 1990, parts of Africa, the Middle East, Central and South America as well as the Pacific region have seen increases in disease rates of up to 20% or more.

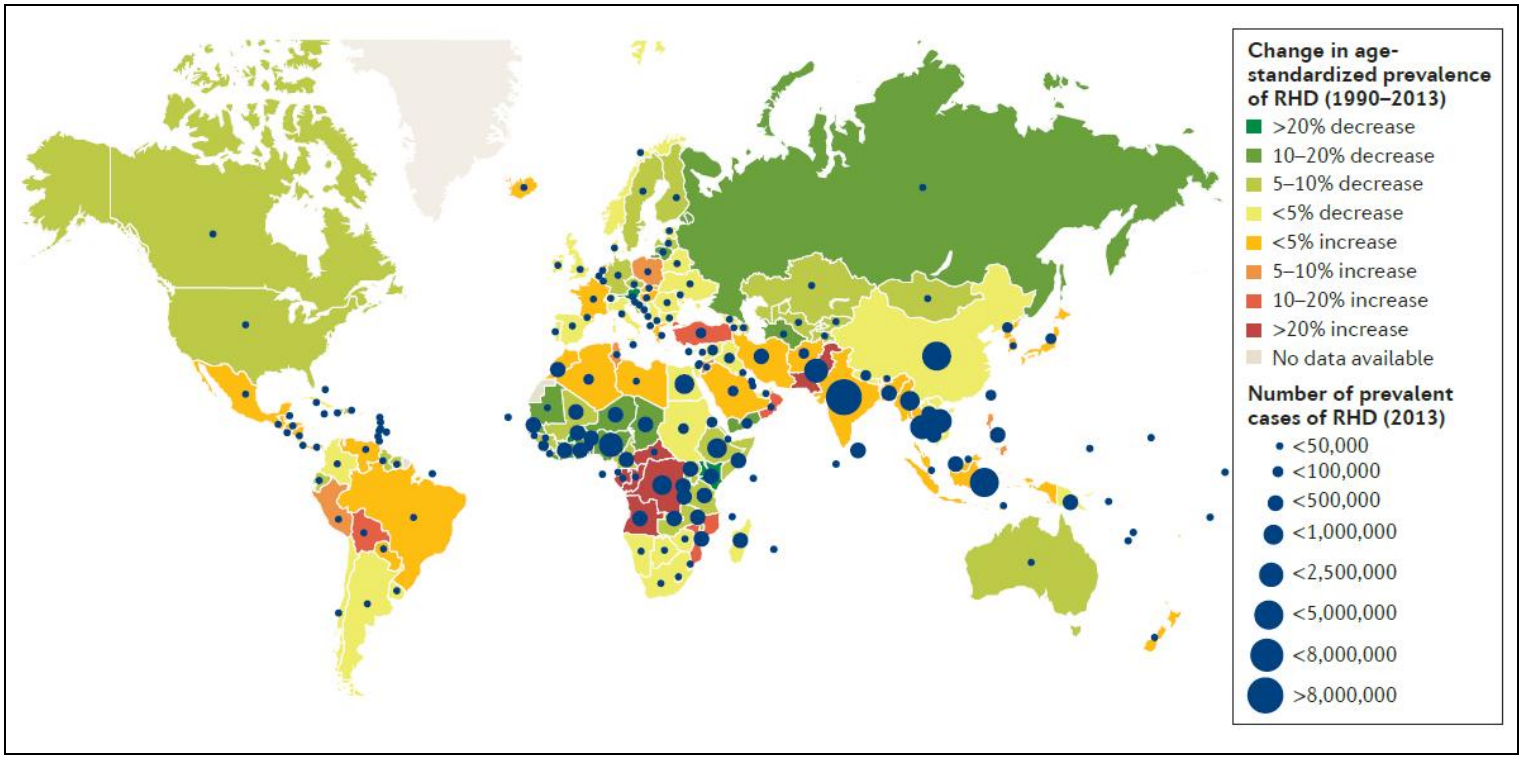

Figure 1. Global burden of rheumatic heart disease by country based on 2013 estimates (source: Carapetis et al., 2016) [32]

3.2.2 Within populations

Whilst the occurrence of ARF is similar in both males and females, the risk of developing RHD is 1.6 to 2 times greater in women compared to men.[32] Although a number of reasons for this trend have been hypothesised, the exact cause remains unclear. Suggested explanations include the possibility of innate susceptibility, hormonal factors, limited access to preventive medical services, greater exposure to the bacterial pathogen; *streptococcus pyogenes* and the worsening of existing subclinical RHD in pregnancy, oftentimes leading to initial diagnosis.[23,26]

Additionally while an association with ethnic origin has yet to be established, there is some evidence that points to an underlying proportion of between 3 and 6% of any population being genetically susceptible to ARF.[26] In essence, both the burden and distribution of ARF and RHD are determined by a multitude of often intersecting environmental, social, behavioural and biological factors.[21]

4. AETIOLOGY

Risk factors associated with the development of ARF and the subsequent outcome RHD are both numerous and varied, with environmental factors being arguably the most significant determinants of disease distribution.[33] Associated risk factors can be broadly categorised as being biological, behavioural or environmental in nature.

4.1 Biological Risk Factors

Broadly speaking, biological risk factors for the development of RHD include genetic predisposition, older age, being female and a history of ARF.[26]

4.2 Behavioural Risk Factors

Behavioural factors associated with increased risk of developing RHD include poor adherence to treatment, lack of secondary prophylaxis and limited knowledge about the condition.[26] Importantly insufficient awareness and knowledge regarding the symptoms, treatment and consequences of streptococcal pharyngitis within communities has major implications for the expression of ARF and RHD within populations.[33]

4.3 Environmental Risk Factors

The indirect yet imperative role that both environmental and socio-economic factors play in determining the amount and severity of ARF and RHD within populations has been well established.[33] Socio-environmental risk factors associated with the aetiology of RHD include low socio-economic status (SES), substandard living conditions, overcrowding, shortage of resources for health care, insufficient access to medical care and inadequately trained health care providers.[33] Consequently a combination of biological, behavioural and environmental risk factors will result in the pathogenic development of RHD.

5. PATHOGENESIS

5.1 Pathogenic Pathway

The pathogenesis of RHD (see *figure 2*) is a complex process involving genetic as well as other factors.[34] While the molecular pathways between GAS infection and ARF remain insufficiently understood, it has been definitively established that ARF is caused by an abnormal autoimmune reaction to particular bacterial epitopes in genetically susceptible individuals.[23,26]

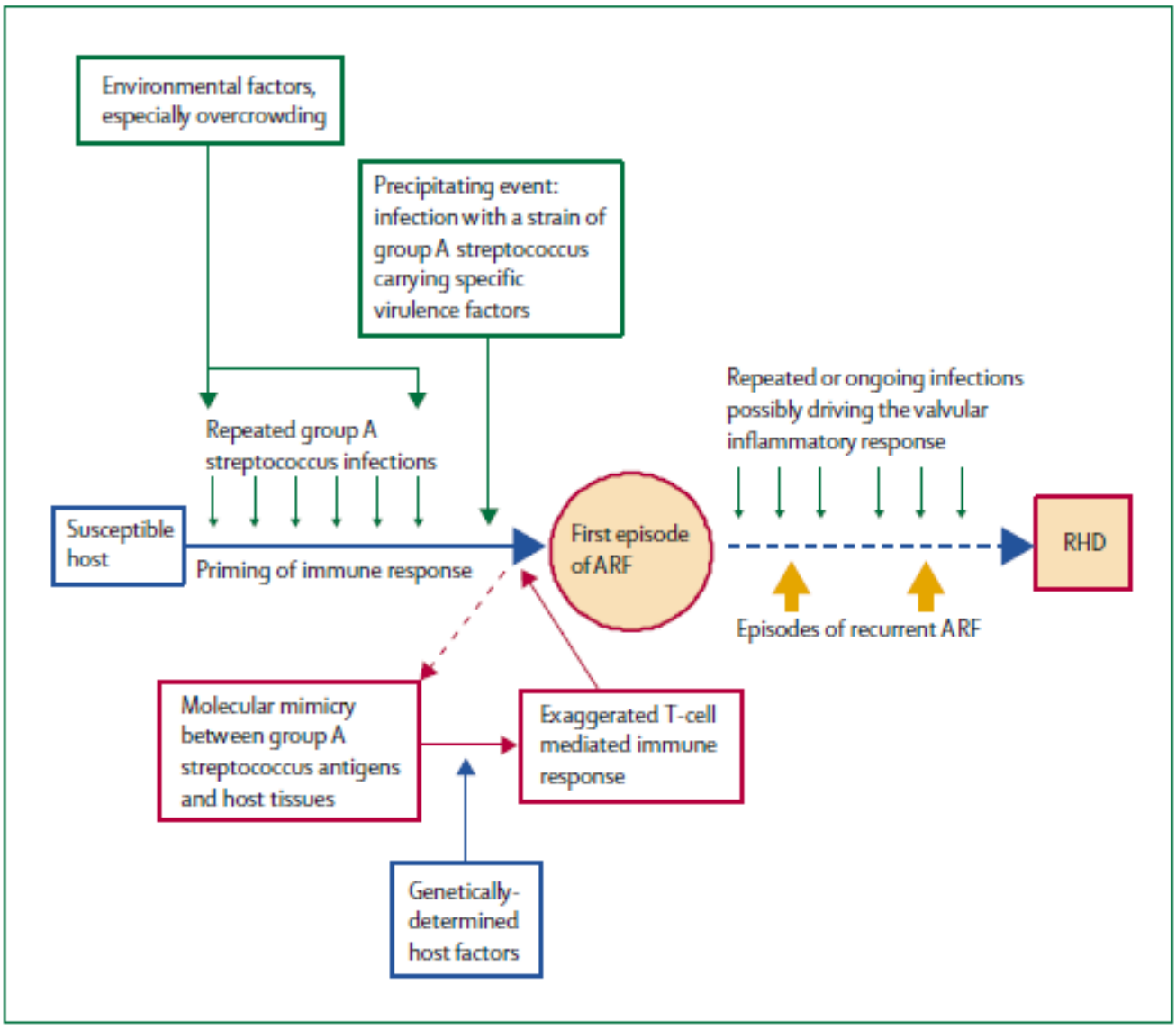

Figure 2. An illustrated pathogenic pathway of ARF and RHD (source: Carapetis et al., 2005) [26]

In essence the pathogenic pathway of RHD begins with the recurrence of streptococcal infections in predisposed hosts. If left untreated the onset of ARF then follows which inevitably leads to the development of RHD if insufficient secondary preventive measures are taken.[1] Consequently, RHD most often occurs as a result of the cumulative damaging effects of repeated ARF episodes, although an initial episode can also lead directly to RHD.[26]

Chronic RHD is a disease characterised by progressive and irreversible valvular lesions.[34] Heart valve damage resulting from RHD can lead to congestive heart failure, pulmonary hypertension, endocarditis, stroke, atrial fibrillation and premature death.[3,35,36] While there are a number of clinical signs and symptoms indicating manifest disease at each stage along the pathogenic pathway, patients may remain largely asymptomatic or else be unaware of their symptoms until the advanced stages.[35]

6. CLINICAL MANIFESTATION

6.1 Signs and Symptoms

Clinical signs and symptoms due to GAS infections as well as their non-suppurative sequelae have been well documented over the years (see *table 1* below). ARF presents with one or more of a constellation of symptoms called the “Jones Criteria” while symptomatic RHD is manifest by heart palpitations, angina, syncope, exertional dyspnoea and fatigue amongst other symptoms.[37]

Table 1. Main clinical signs and symptoms of GAS, ARF and RHD* [38]

Condition	Signs and/or symptoms
Pharyngitis	Sore throat, fever, malaise
Acute Rheumatic Fever	Polyarthritis, carditis, rapid and jerky movements, rash, subcutaneous nodules
Rheumatic Heart Disease	Mitral and/or aortic regurgitation with potential stenosis over time presenting as: cardiac murmur, angina, syncope, fatigue, exertional dyspnoea

*Adapted from Walker et al., 2014: p.266
Abbreviations: GAS, Group A Streptococcus; ARF, Acute Rheumatic Fever; RHD, Rheumatic Heart Disease

Significantly, asymptomatic cases are not uncommon and misdiagnosis or failure to detect both pharyngitis and ARF often occurs.[29] This is evidenced by the fact that approximately 40% of all individuals presenting with established RHD cannot recall a recognisable episode of ARF.[29,35]

7. DIAGNOSIS

A variety of different methods, each with their own advantages and disadvantages, are employed by physicians for the detection and definitive diagnosis of RHD. Typically a combination of various techniques will yield a confirmed diagnosis by an experienced cardiologist, with the current gold standard test being a clinical examination in conjunction with a detailed echocardiographic assessment.[29] In those without a clear history of ARF, a diagnosis is made in one of two ways; either as a result of a confirmatory diagnosis following a positive screening test or if cardiac symptoms are present usually indicating advanced disease.[29] It should be noted that a diagnosis made in absence of a confirmed preceding ARF episode can be uncertain.[29]

7.1 Diagnostic Tests

7.1.1 Cardiac auscultation

Cardiac auscultation for the detection of RHD refers to the action of listening to the heart sounds with a stethoscope in order to detect a heart murmur in patients with or without a history of ARF prior to echocardiographic confirmation.[30,39] Up until recently, this method has been the only non-invasive diagnostic device available to physicians in remote and resource-limited settings.[30] Whilst cardiac auscultation is undoubtedly a simple, cost effective and accessible tool it remains inherently subjective and a progressively challenging clinical skill to master.[40]

7.1.2 Cardiac ultrasound

Cardiac ultrasound has been credited as being the most significant development in diagnostic cardiology since the invention of X-Rays.[41] The first echocardiograms of the heart using reflected sound waves were produced in 1953 by Drs Inge Elder and Helmuth Hertz, [41,42] who detailed its value for evaluating mitral-valve disease.[43] The use of M-mode echocardiography (echo) for assessing left-ventricular dimensions in clinical practice was then standardised by Dr Harvey Feigenbaum during the 1960s.[43] Subsequently, the 1970s saw the advent of two-dimensional (2D) and pulsed Doppler echocardiography followed by colour Doppler in the 1980s.[43] As a result new methods for routine bedside assessment of cardiac structure and hemodynamics came into being.[43]

7.1.3 Standard echocardiography

Standard echocardiography (2D, continuous-wave, and colour-Doppler echocardiography) or STAND is a highly sensitive and specific method used to screen for the presence of RHD in

suspected cases.[5,23] It is widely accepted as the best non-invasive reference or gold standard test currently available for the detection of RHD when performed by a trained cardiologist.[5]

Echocardiography allows clinicians to rapidly obtain vital information about the size, structure and function of the heart through the application of its high frequency ultrasound capabilities whilst colour-Doppler is used to assess hemodynamics.[44,45] In the context of RHD, echocardiographic assessment permits the grading of regurgitation severity through a combination of techniques which make use of the machine's 2D and colour-flow imaging abilities.[23] Furthermore, echocardiographic images can be evaluated immediately thereby enabling speedy diagnosis within an array of different settings.[44]

To date no studies comparing echocardiographic with post-mortem findings exist. Similarly, there is currently no alternative gold standard test for the detection of RHD. This makes the estimation of the machine's inherent diagnostic accuracy challenging. Moreover, whilst the technical competency of this diagnostic modality is impressive, its accuracy is entirely reliant on the proficiency of the person(s) performing, analysing and interpreting images.[44] This has led researchers to adopt an evolving consensus which assumes sensitivity on echo to be between 95 and 100% with specificity varying in range accordingly.[46]

Nevertheless, since its introduction into clinical practice during the 1970s, [45] echocardiography has been shown to have the ability to detect significantly more cases of early RHD compared to clinical examination alone [36] with reports indicating moderate to excellent inter-observer agreement.[48,49]

7.2 Diagnostic Criteria

In 2009 under the patronage of the WHF, a number of experts in echocardiographic screening for RHD from across the world assembled to form an international advisory board.[50] Together these 21 experts developed evidence-based guidelines for the echocardiographic detection of RHD.[30] The guidelines were specifically developed with the intention of defining the minimum echocardiographic criteria for RHD diagnosis in asymptomatic patients without a clear history of ARF.[30,50] Officially released in 2012, the diagnostic guidelines were formulated for use in clinical practice as well as in screening programs. Soon thereafter they became accepted as the gold standard for screening on echo.[50]

The 2012 WHF criteria for the echocardiographic diagnosis of RHD [30] (see *table 2* below) require assessment using 2D, continuous-wave and colour Doppler echocardiography. Valvular features identified by echocardiography assigns individuals into one of three main categories; 'normal', 'borderline RHD' or 'definite RHD'. Specific findings are then used to further classify individuals according to subcategories of which there are three under 'borderline RHD' and four under 'definite RHD'.[30] The 2012 report also stressed that results from echocardiographic screening should always be interpreted together with the patient's clinical findings and history as well as in conjunction with their pre-test probability of RHD, which differs according to ethnicity, living conditions and geographical location.[30]

Table 2. 2012 WHF criteria for echocardiographic diagnosis of RHD [30]

Echocardiographic criteria for individuals aged ≤ 20 years
1. Definite RHD (either A, B, C or D): A) Pathological MR and at least two morphological features of RHD of the MV B) MS mean gradient ≥ 4 mmHg* C) Pathological AR and at least two morphological features of RHD of the AV‡ D) Borderline disease of both the AV and MV§
2. Borderline RHD (either A, B or C) A) At least two morphological features of RHD of the MV without pathological MR or MS B) Pathological MR C) Pathological AR
3. Normal echocardiographic findings (all of A, B, C and D) A) MR that does not meet all four Doppler echocardiographic criteria (physiological MR) B) AR that does not meet all four Doppler echocardiographic criteria (physiological AR) C) An isolated morphological feature of RHD of the MV (for example, valvular thickening) without any associated pathological stenosis or regurgitation D) Morphological features of RHD of the AV (for example, valvular thickening) without any associated pathological stenosis or regurgitation
Echocardiographic criteria for individuals aged > 20 years
Definite RHD (either A, B, C or D) A) Pathological MR and at least two morphological features of RHD of the MV B) MS mean gradient ≥ 4 mmHg* C) Pathological AR and at least two morphological features of RHD of the AV, only in individuals aged < 35 years‡ D) Pathological AR and at least two morphological features of RHD of the MV
*Congenital MV anomalies must be excluded. Furthermore, inflow obstruction due to non-rheumatic mitral annular calcification must be excluded in adults. ‡Bicuspid AV, dilated aortic root, and hypertension must be excluded. §Combined AR and MR in high prevalence regions and in the absence of congenital heart disease is regarded as rheumatic.
Abbreviations: Aortic regurgitation (AR), aortic valve (AV), mitral regurgitation (MR), mitral stenosis (MS), mitral valve (MV), rheumatic heart disease (RHD), World Heart Federation (WHF)

Use of different criteria to define RHD on echocardiography essentially render the comparison of epidemiological studies invalid.[50] The 2012 WHF criteria by virtue of being a standardised set of diagnostic criteria have since enabled the comparability, consistency, and reproducibility of findings.[51] In turn standardisation has increased specificity for definite RHD diagnosis as well as raised the threshold for borderline RHD thereby reducing the false positive rate.[50]

Regardless of the use and availability of increasingly accurate diagnostic tools, many people still present in the advanced stages of disease and without an associated history of ARF. In such situations, reliance on a preceding diagnosis of ARF in all at risk individuals will inevitably result in a failure to detect a considerable number of people who might otherwise profit from secondary prophylaxis.[52] For this reason early screening remains an essential tool in the cardiologist's arsenal against the continued persistence of RHD.

8. SCREENING

The primary purpose of screening is to identify the presence of disease or a preceding condition in seemingly well individuals.[29] Five disease specific criteria need to be satisfied before population level screening can be considered a suitable preventive measure. First; there needs to be clear evidence of a significant disease burden, second; the condition in question needs to present with an initial latent stage, third; the latent stage of the condition needs to be detectable by appropriate tests, fourth; the latent stage must be able to be treated with adequate therapy, and finally; there must be clear evidence that early intervention at the latent stage improves prognostic outcomes.[39,51,53]

At first glance, echocardiographic screening for RHD appears to meet the first two criteria unequivocally. There is an obvious burden of disease, particularly in the developing world and RHD does have a well-documented latent stage often referred to as subclinical, clinically silent or borderline disease.[51,53] The remaining criteria, however, remain insufficiently met due to gaps in knowledge.[35] In this regard it has been argued that a number of issues still need to be addressed prior to the endorsement of wide scale echocardiographic screening.[50]

These include amongst others the continued obscurity of the natural history of both borderline RHD and definite RHD without a clear history of ARF.[52] While they are both variants of the disease it remains unclear as to whether secondary prophylaxis using long acting penicillin injections would slow disease progression as is the case with conventionally diagnosed RHD.[32,52]

While the WHO has recommended screening for RHD in endemic areas since 2004 [6], researchers caution that prior to implementing wide scale echocardiographic screening programs, the impact on both heath care systems and populations alike must be carefully considered.[52] False positive diagnoses prompting the unwarranted initiation of long-term prophylaxis would add additional strain to health care systems as well as detrimentally impact on individuals. Moreover, there is little value in screening for RHD if insufficient resources and systems exist to provide the necessary follow-up and treatment.[52]

8.1 Role and Value

An unfortunate reality is that most people only present to care when their disease becomes symptomatic.[54] One of the reasons for this is the latent nature of RHD during the initial stages preceding the clinical period.[54,55] Screening for subclinical RHD is therefore directed at diagnosing RHD during its asymptomatic phase in order to initiate prophylaxis and potentially slow progression to overt clinical RHD.[32,56] However, in order to increase rates of early diagnosis more active surveillance systems and large scale screening programmes are needed in endemic areas.[35]

Programmes reviewing secondary prophylaxis in mild ARF have demonstrated regression of valve lesions within 5-10 years.[57] Initiating secondary prophylaxis in early-stage RHD patients through targeted screening programmes thus has the potential of preventing,

stopping or even regressing further valve damage.[35] The value of screening for RHD is that cases of subclinical RHD might be detected early on thereby reducing the time to secondary prophylaxis and thus improving long term outcomes by effecting a delay in disease progression.[35,52] Furthermore, early disease detection has the potential to prevent many of the unwanted consequences associated with advanced RHD including the need for costly surgical interventions.[58]

Historically cardiac auscultation has been the basis of screening for RHD in many developing countries.[59,60] However, the revelation that a large amount of subclinical RHD remains undetected when using cardiac auscultation alone has had major implications for this practice going forward.[5,30] Regrettably, the use of standard echocardiography for wide scale RHD screening in endemic areas continues to be restricted primarily as a result of the high costs involved and scarcity of trained personnel.[5,58,61]

8.2 Handheld Echocardiography

Recently handheld echocardiography or HAND, shown in *figure 3* below, has become widely available with a variety of clinical uses.[6] Similar diagnostic accuracy has already been demonstrated in a number of studies assessing the value of HAND as a screening tool and the device has been shown to significantly improve the detection of RHD over auscultation alone in preliminary studies.[5,6] On this basis it been suggested that these handheld devices could provide a more affordable and accessible alternative to standard echocardiography in screening for RHD.[51,52]

These new echocardiographic machines are light-weight, pocket-sized and able to fit in the palm of a hand making them highly portable and easily carried.[62] The devices are battery operated and offer real time imaging as well as the capacity to store and transfer information digitally.[63] An ability to accurately assess left ventricular function, visualise chamber size and rheumatic valves as well as rule out pericardial effusions [23] is demonstrative of their diagnostic potential for identifying significant cardiac pathologies.[63,64]

Figure 3. Image of an ultra-portable hand held ultrasound device [65]

8.3.1 Advantages

The average cost of a handheld device is $5, 920 which is considerably less than larger machines such as the GE Vivid-I, GE Vivid-q and Philips CX50, which can cost upwards of $29, 200 and as much as $42, 000.[65] In addition the handheld devices are light-weight and battery operated making them more portable than the standard machines which are heavy and require wired electricity.[66] Decreased costs coupled with increased portability provide opportunities for the decentralisation of echocardiographic based screening as well as other clinical applications, such as point-of-care use in intensive care and emergency settings.[23]

8.3.2 Limitations

The handheld devices are not without their limitations and a number of technical challenges impede their true value for screening. They were designed for sporadic rather than continuous use and run the risk of overheating if used uninterruptedly. Similarly, their relatively short battery life necessitates the availability and frequent replacement of batteries.[64] This is particularly limiting with respect to large screening programmes where lengthy use of the device could be required.

Other limiting factors include the inability to manually enter patient information, poorer resolution, lack of spectral Doppler capabilities and fixed colour Doppler settings.[64] Specifically, a complete assessment of the left ventricle is impeded by the lack of spectral Doppler [63] whilst a tendency to overestimate valvular regurgitant jet lengths is an upshot of the unadjustable colour Doppler settings.[64] Overall these technical shortfalls limit the usefulness of handheld echocardiographic devices in terms of screening.[51]

Due to these limited technical capacities, handheld devices are currently not endorsed as a substitute for standard echocardiography.[63] It is therefore also recommended that screen positive cases detected on HAND be re-examined with STAND for confirmatory diagnosis.[52] In light of this, researchers have urged that the utility of HAND for both screening and clinical practice should remain a topic of research.[52]

8.3.3 Opportunities for future research and further development

Researchers have suggested that further improvements to incorporate spectral Doppler capabilities in handheld devices would expand the device's suitability for screening purposes.[51,58] Additional developments to improve the functionality of handheld devices

include better battery life, frequency shifting abilities and manual entry of patient data.[64] It has also been suggested that a modification of the WHF criteria for use with HAND may increase accuracy for the detection of RHD.[58]

Increasingly, the role of echocardiographic screening has passed to non-experts using a simplified set of diagnostic criteria specific to HAND. [64] It is clear that the feasibility of wide scale screening using echocardiography depends on the success of task-shifting.[58] For task-shifting to succeed, standardised training programs for non-experts will need to be developed, tested and validated.[58,64] Whilst handheld echocardiography signifies encouraging progress, it is clear that more research is required before advocating its use in wide scale echocardiographic screening programs.[64]

9. CONCLUSION

The enduring challenge of RHD is not due to a lack of understanding of how to control and prevent the disease. Rather it is a result of the failure to effectively implement wide scale prevention and treatment strategies.[21] Screening for asymptomatic disease is one of the methods employed for early detection and treatment, despite some uncertainty regarding long-term effects on prognosis and disease progression. Yet, the accurate detection of subclinical RHD in children and adolescents remains hampered by the cost of diagnostic machinery and scarcity of trained personnel in many endemic areas.[67] Alternative RHD screening tests which are accurate, affordable and user-friendly are therefore needed.

Handheld echocardiography is a non-invasive, safe, portable and relatively inexpensive device which has been presented in recent publications to be a promising alternative to standard echocardiography as a first line screening test.[5,6] Due to diminished cost and

ease of transportation, the use of HAND over STAND has the potential to increase the accessibility of echocardiographic screening in LMICs where the disease remains endemic.[5] However, for HAND to be considered as a suitable replacement for STAND in the context of RHD screening, the device's accuracy needs to be at least similar to that of STAND. A systematic review of the diagnostic accuracy of handheld echocardiography for the detection of subclinical RHD is therefore proposed.

Findings from the proposed review could provide insight into targeted screening-based intervention strategies as well as open up avenues for further research. The generation of new quantitative evidence will allow clinicians and guideline developers to establish a set of evidence-based criteria for diagnosing RHD using handheld echocardiography. Ultimately, this will improve the management of patients with the disease, as effective treatment of subclinical RHD requires accurate and timely diagnosis.

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PART C: Journal Manuscript

[Diagnostic Test Accuracy Review]

Standard Echocardiography versus Handheld Echocardiography for the Detection of Subclinical Rheumatic Heart Disease: A Systematic Review

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ABSTRACT

Background

Handheld echocardiography presents an opportunity to address the need for more cost-effective methods of detecting rheumatic heart disease (RHD) in resource-limited and remote settings. This systematic review, therefore, sought to summarise the accuracy of handheld echocardiography which, if shown to be sufficiently similar to that of the current gold standard, could usher in a new age of RHD screening in endemic areas.

Methods

A search of the electronic sources; PubMed, Scopus, Web of Science and EBSCOhost without language restriction was performed to identify studies published from 2012 onwards. We included all studies assessing the accuracy of handheld echocardiography for RHD detection in children and adolescents living in RHD endemic areas when the reference standard constituted standard echocardiography performed by an experienced cardiologist in conjunction with the 2012 World Heart Federation (WHF) criteria.

Data collection and analysis

Two authors independently assessed the methodological validity and quality of included studies against review specific QUADAS-2 criteria and extracted information on metrics of diagnostic accuracy. A meta-analysis was conducted to produce summary results of sensitivity and specificity using the HSROC method. Forest plots of sensitivity and specificity as well as scatter plots in Receiver Operating Characteristic (ROC) space in combination with subgroup analyses were used to investigate heterogeneity for the categorical covariates; geographic location, echocardiographer expertise and HAND protocol. Publication bias was not investigated.

Main findings

We included seven studies, five of which were from African countries. The average prevalence of any RHD (definite or borderline) for six of the seven included studies was 12% (95% CI: 7% - 18%). Handheld echocardiography was most accurate in detecting definite RHD only but demonstrated poor accuracy for the detection of borderline RHD only. Nevertheless, the main findings, from seven included studies, provide some evidence for the potential of handheld echocardiography to increase access to echocardiographic screening for RHD in resource limited and remote settings.

Strengths and limitations

We have evaluated and summarised the accuracy of handheld echocardiography for the detection of RHD in endemic areas, making the review relevant to current global agendas. The results of this review are also highly applicable for use in endemic areas for which screening programmes are frequently targeted. Overall methods of study design and conduct were insufficiently reported according to current standards which limited the scope of this review by restricting the number of subgroup and sensitivity analyses able to be performed.

Author's conclusions

This review provides a summary of the accuracy of handheld echocardiography for the detection of RHD in children and adolescents. Among the three disease categories, handheld echocardiography was most accurate in detecting definite RHD only. The device proved less accurate in detecting any RHD (definite or borderline) and demonstrated poor accuracy for the detection of borderline RHD alone.

Keywords Rheumatic heart disease, echocardiography, screening, diagnostic accuracy

1. BACKGROUND

Rheumatic heart disease (RHD) is an acquired permanent heart valve condition which results from an atypical immune reaction to group A streptococcal (GAS) infection typically occurring in childhood.[1,2] Disease progression leading to chronic RHD can result in irreversible heart valve damage, cardiac failure, stroke and premature death.[3,4] RHD is, however, a preventable and treatable chronic condition which mostly affects disadvantaged populations.[3,5]

Significantly, ARF may go undiagnosed and RHD can remain asymptomatic for many years, particularly during the initial stages thereby hindering the timely implementation of penicillin prophylaxis.[6] Echocardiographic screening in order to identify those with subclinical disease has been advocated as a means to support secondary prevention and potentially slow disease progression to overt clinical RHD.[7,8] Yet the feasibility of wide scale echocardiographic screening remains hindered by high costs and the dearth of trained personnel.[9] Alternative screening tests for RHD which are both accurate and affordable are therefore needed in many endemic areas.

Handheld echocardiography (HAND) is a non-invasive, safe, highly portable and comparatively less expensive device which has been presented in recent publications to be a promising alternative to standard echocardiography (STAND) despite some limitations such as the lack of spectral Doppler capabilities.[10,11] For HAND to be considered a suitable replacement for standard echocardiography, the device's accuracy needs to be similar to that of STAND. However, a slightly lower accuracy would still be acceptable if the device can be unequivocally shown to be less costly, more portable, and easier to use and interpret as well as logistically less demanding overall.

We conducted a systematic review and meta-analysis of studies assessing the diagnostic accuracy of handheld echocardiography for the detection of RHD in children and adolescents. The findings of this review may offer direction to guideline developers as well as assist with the identification of gaps in diagnostic testing for RHD in endemic areas.

2. METHODS

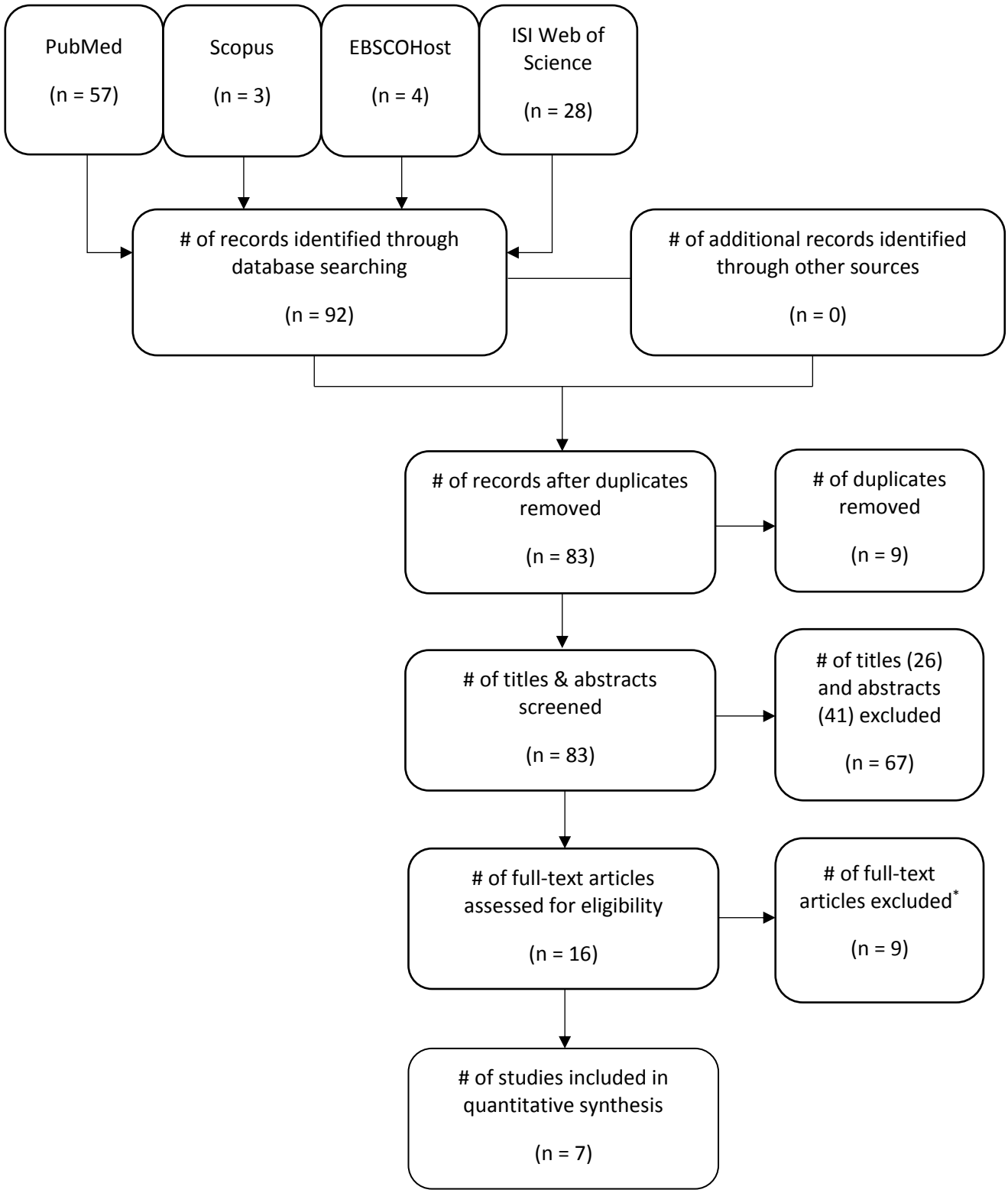
This systematic review was prepared according to the Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies (PRISMA-DTA) guidelines (see Appendix 5 for the Checklist).[12] The protocol for this review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42016051261 and is currently in press with BMJ Open. Section 4 in Part A describes the methods used in this review in detail.

3. RESULTS

3.1 Results of the Search

Results of the literature search are reported in accordance with the PRISMA Statement and the study selection process is illustrated in f*igure 1* below.[13] The search strategy yielded a total of ninety two records, of which nine were duplicates. Of the remaining eighty three records, a total of sixty seven were excluded based on title or abstract leaving sixteen articles for full-text review. Nine of the sixteen remaining studies were then excluded on the basis of a full-text review. Seven studies which met the predefined eligibility criteria were included in this review.

Figure 1. Study flow diagram



*Reasons for exclusion on full-text review can be found in the table of excluded studies

3.1.1 Included studies

A summary of notable characteristics of all included studies [10,14–19] is shown in *table 1* below. One study did not avoid a case-control design, however cases and controls were sampled from the same population. Research has shown that case-control studies which use alternative diagnosis controls, controls from non-endemic areas or confirmed disease-free (healthy) controls tend to overestimate specificity.[20] Significantly, all but two studies were conducted in Africa. Screening was performed in RHD endemic areas among children and adolescents with most studies being school-based. Combined, all seven studies included a total of 5525 participants of which 54% were female. The pooled mean age of participant's was 10.8 years (SD: ±2.1).

Table 1. Summary of characteristics of included studies [ordered alphabetically by study author]

Study	Study Design	City, Country (Classification¤)	Recruitment Site/Setting	Method of Participant Selection	Inclusion Criteria	Sample Size (N)	% Female	Mean Age (years)	SD
Beaton, 2014[15]	Spiked cohort	Kampala, Uganda (Low income)	A School and the Mulago Hospital Complex	Unclear	"Half (n=65) of the cohort were asymptomatic Ugandan school children who took part in an echo based screening study at their school. The other half (n=60) were patients presenting for follow up as part of the Ugandan RHD registry project."[15]	125	55.2	10.8¥	-
Beaton, 2015[19]	Cross-sectional	Gulu, Uganda (Low income)	5 public schools	A random 10% subset of the entire sample plus any child with mitral or aortic regurgitation were preselected to receive HAND	"Government schools in Gulu, Uganda, were evaluated and five were selected to ensure adequate population numbers."[19]	1420	53	10.8	±2.6
Beaton, 2016[17]	Cross-sectional	Belo Horizonte, Brazil (Upper-middle income)	2 primary and 3 secondary public schools	A subset of the sample containing all STAND abnormals plus a random 25% of all STAND normals were preselected for HAND	"The study was conducted in the context of an existing school-based RHD screening program-PROVAR. The PROVAR study selection criteria were asymptomatic children aged between 5 and 18 years old attending public schools of underserved areas in the State of Minas Gerais. This study included 5 schools from Belo Horizonte as testing sites."[17]	397	49.1	13.9	±2.6
Godown, 2015[10]	Cross-sectional	Gulu, Uganda (Low income)	5 public schools	A random 10% subset of the entire sample were preselected to receive both HAND and auscultation	"Children attending 5 different schools in Gulu, Uganda were eligible for inclusion."[10]	1317	53.9	10.8	±2.6
Mirabel, 2015[16]	Cross-sectional	Nouméa, New Caledonia (High income)	Primary schools	Consecutive	"All fourth grade (aged 9-10 years) children attending local primary schools in Nouméa, the capital city and its suburbs were eligible."[16]	1217	50.5	9.6	±0.5
Ploutz, 2016[18]	Cross-sectional	Gulu, Uganda (Low income)	2 primary schools	Consecutive	"All students attending 2 public primary schools in Gulu, Uganda were eligible for inclusion."[18]	956	60.7	11.1	±2.5
Zühlke, 2016[14]	Nested case-control	Cape Town, South Africa (Upper-middle income)	Schools	Unclear	"Cases were scholars previously diagnosed with asymptomatic RHD on screening echocardiography with persistent disease. Controls were normal healthy scholars previously enrolled in the original screening study who were matched for age, school grade, and residential area."[14]	93	68.8	17¥†	-
Total						5525	54	10.8	±2.1

¤ According to the World Bank's economic classification system
¥ excluded from pooled mean & SD calculations (incomplete or incomparable data)
† median age (mean age not available)

A summary of index test details is included in *table 2* below. All seven included studies used the same make of handheld device; the Vscan machine (General Electric, Medical Systems, Milwaukee, Wisconsin, USA) paired with a 1.7 - 3.4 MHz transducer. These machines provide both two-dimensional (2D) and colour imaging on an integrated 8.9cm display.[16,19] Frame rates range from 25 to 30 Hz for greyscale imaging and 12 to 16 Hz for colour Doppler.[15,18] Vscan machines are however limited by a lack of spectral Doppler capabilities.[19] The majority of included studies evaluated the accuracy of handheld echocardiography when performed and interpreted by experts whereas only three studies assessed the device's performance in the hands of briefly trained non-experts.

Table 2. Summary of index test details

Study	Diagnostic Equipment	HAND Interpreter Expertise	Time of Interpretation	Primary Test Threshold
Beaton, 2014[15]	GE Vscan handheld device paired with a 1.7 - 3.4 MHz transducer	expert	later/offline‡	MR > 2cm & AR > 1cm
Beaton, 2015[19]		expert	later/offline‡	MR ≥ 2cm, AR ≥ 1cm & thickness of anterior mitral leaflet ≥ 3mm
Beaton, 2016[17]		non-expert	on-site§	MR ≥ 1.5cm &/or any AR
Godown, 2015[10]		expert	unclear	MR > 2cm & AR > 1cm
Mirabel, 2015[16]		non-expert	on-site§	MR ≥ 1.5cm &/or any AR
Ploutz, 2016[18]		non-expert	on-site§	MR ≥ 1.5cm &/or any AR
Zühlke, 2016[14]		expert	on-site§	MR ≥ 2cm

§ on-site: refers to interpreting images at the time of screening / evaluation
‡ later/offline: refers to the use of Vscan Gateway software to interpret images post screening

3.1.2 Excluded studies

Nine studies [9,21–28] were excluded during the full-text screening phase as shown in *figure 1*. Reasons for exclusion are listed in *table 3* with the most common being abstract only publication and the use of ineligible reference or index tests. One study was excluded on account of using duplicate data from four other included studies whilst another was not a study of diagnostic accuracy.

Table 3. Characteristics of excluded studies [ordered by year of study]

Study	Reason for Exclusion
Mirabel, 2012[21]	Ineligible reference standard (2012 WHF criteria not used)
Colquhoun, 2013[22]	Ineligible reference standard (2012 WHF criteria not used)
Godown, 2014[23]	Published as an abstract ahead of full-text publication in 2015
Lu, 2014[24]	Published as an abstract ahead of full-text publication in 2015
Lu, 2015[9]	Test threshold(s) not specified a-priori
Engelman, 2016[25]	Ineligible index test and test threshold(s) not specified a-priori
Hardie, 2016[26]	Published as an abstract on a poster only with no full-text available
Lopes, 2016[27]	Not a test accuracy study
Diamantino, 2017[28]	Uses duplicate data

3.2 Methodological Quality of Included Studies

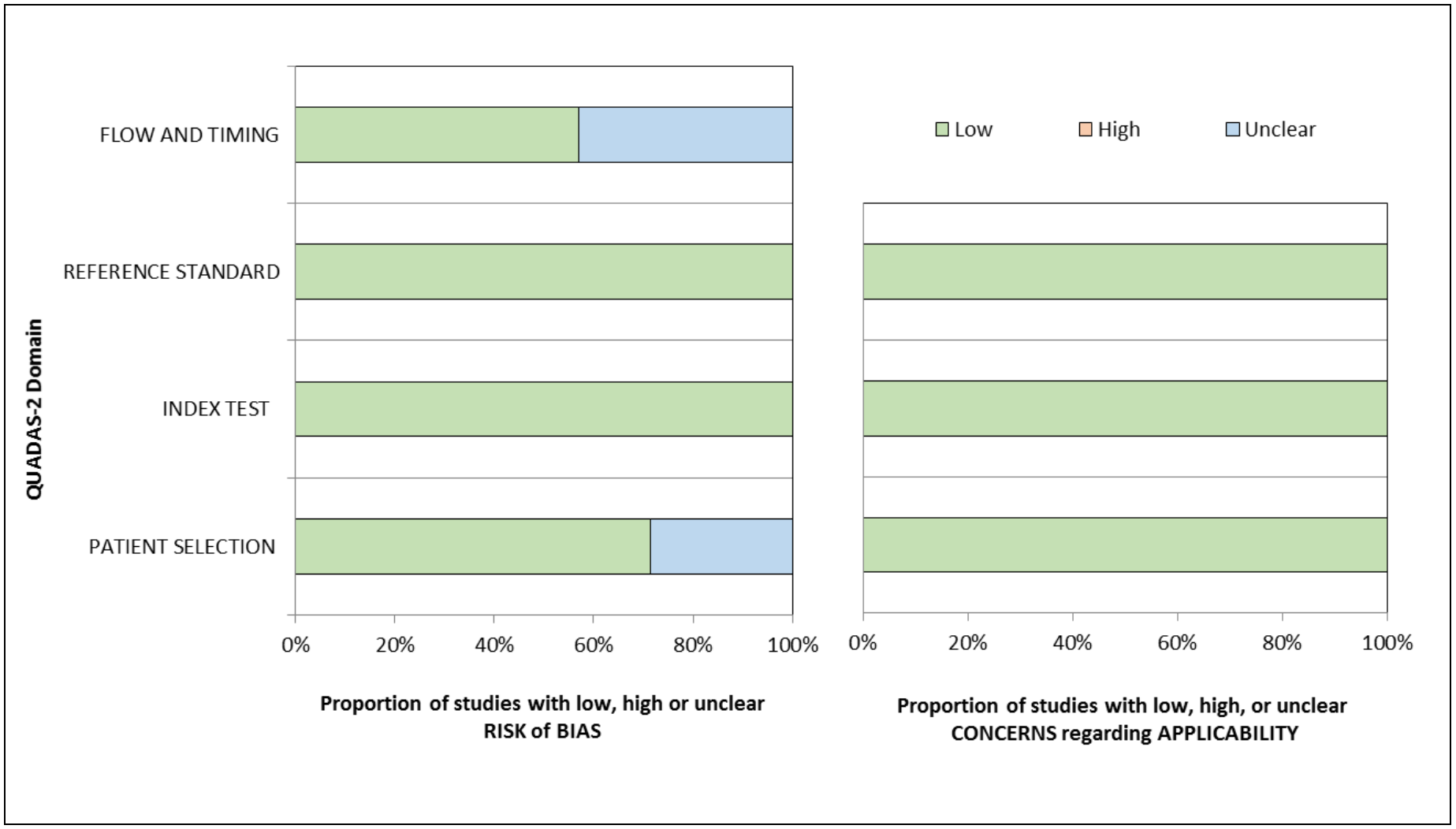
A summary of the assessment of methodological quality of all included studies is illustrated in t*able 4* and *figure 2* below. Overall only two of the seven included studies were assessed as having a low risk of bias while the risk of bias in the remaining five was unclear. Two studies had participant selection bias concerns. Of these both failed to adequately describe participant enrolment methods whilst one study also did not avoid a case-control design.

The risk of bias in terms of flow and timing was unclear in three studies. Of these, two did not include all participants in the analysis while the time interval between the index and reference test was unclear in one study. Of the two studies which did not include all participants in the analysis, not all participants received an index or reference test in one whilst technical difficulties precluded the inclusion of all participants in the analysis of the other study. Overall, time intervals between index and reference standard tests were poorly described. Likewise, reporting of quality control of the index test was uniformly poor across all included studies. Concerns regarding applicability were low in all seven studies.

Table 4. Summary of quality appraisal of included studies

	Risk of BIAS					Concerns about APPLICABILITY				
Study	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Overall**	**Study**	**Patient selection**	**Index test**	**Reference standard**	**Overall**
Beaton, 2014[15]	Unclear	Low	Low	Low	**Unclear**	Beaton, 2014[15]	Low	Low	Low	**Low**
Beaton, 2015[19]	Low	Low	Low	Unclear	**Unclear**	Beaton, 2015[19]	Low	Low	Low	**Low**
Beaton, 2016[17]	Low	Low	Low	Low	**Low**	Beaton, 2016[17]	Low	Low	Low	**Low**
Godown, 2015[10]	Low	Low	Low	Unclear	**Unclear**	Godown, 2015[10]	Low	Low	Low	**Low**
Mirabel, 2015[16]	Low	Low	Low	Low	**Low**	Mirabel, 2015[16]	Low	Low	Low	**Low**
Ploutz, 2016[18]	Low	Low	Low	Unclear	**Unclear**	Ploutz, 2016[18]	Low	Low	Low	**Low**
Zühlke, 2016[14]	Unclear	Low	Low	Low	**Unclear**	Zühlke, 2016[14]	Low	Low	Low	**Low**

Figure 2. Risk of bias and applicability concerns graph



3.3 Findings

We evaluated the accuracy of handheld echocardiography according to three disease categories; any RHD (borderline or definite), definite RHD only and borderline RHD only. The any RHD category was considered the main meta-analysis as it had the most complete data. We were unable to extract metrics of diagnostic accuracy for the definite and borderline RHD only categories from Beaton, 2016 and therefore excluded this study from these meta-analyses. We chose to use Nurse A's results for Mirabel, 2015 since Nurse A and Nurse B both interpreted the same HAND images thereby preventing the pooling of data.

Data from Zühlke, 2016 were included in the analysis and synthesis of data even though the age range of participants fell outside the predefined range for eligibility. It was determined that this study should be included, regardless, since the data overall were quite few and the variation in age was not significant enough to warrant exclusion. However, data from Zühlke, 2016 were excluded from all summary estimates of disease prevalence since this study used a nested case-control design which predetermines disease prevalence by design.

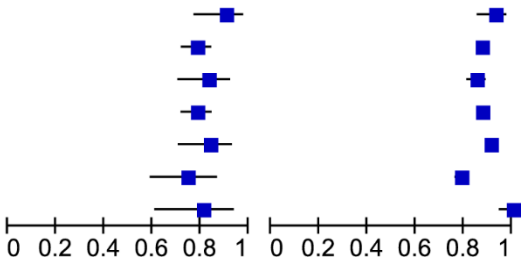
The Hierarchical Summary Receiver Operating Characteristic (HSROC) model was used for meta-analysis as it accounts for variations in test thresholds. We were only able to examine relationships between test accuracy and the categorical covariates; echocardiographer expertise, HAND protocol and geographic location. We were unable to perform meta-regression for the covariates; age and sex due to insufficient data.[29] Heterogeneity was examined for the main meta-analysis only. All plots were generated using the Review Manager (RevMan) software package, version 5.3.[30] Meta-analysis was performed using SAS® software, version 9.4.[31] The overall findings for each of the three disease categories are presented in detail below and a summary of the key findings can be found in *table 7*.

3.3.1 For any RHD

A total of seven evaluations of handheld echocardiography for any RHD were performed with data from seven studies and a total of 5506 participants. Pooled prevalence of any RHD (definite or borderline) from six included studies was 12% (95% CI: 7% - 18%). The forest plot (*figure 3*) reveals little variation in estimates of sensitivity and specificity. The HSROC plot (*figure 4*) reveals moderate accuracy of the test as most study points lie close to the upper left corner of the plot. Meta-analytical sensitivity and specificity (95% confidence interval (CI)) of data at mixed thresholds were 81% (76% to 85%) and 89% (85% to 93%) respectively.

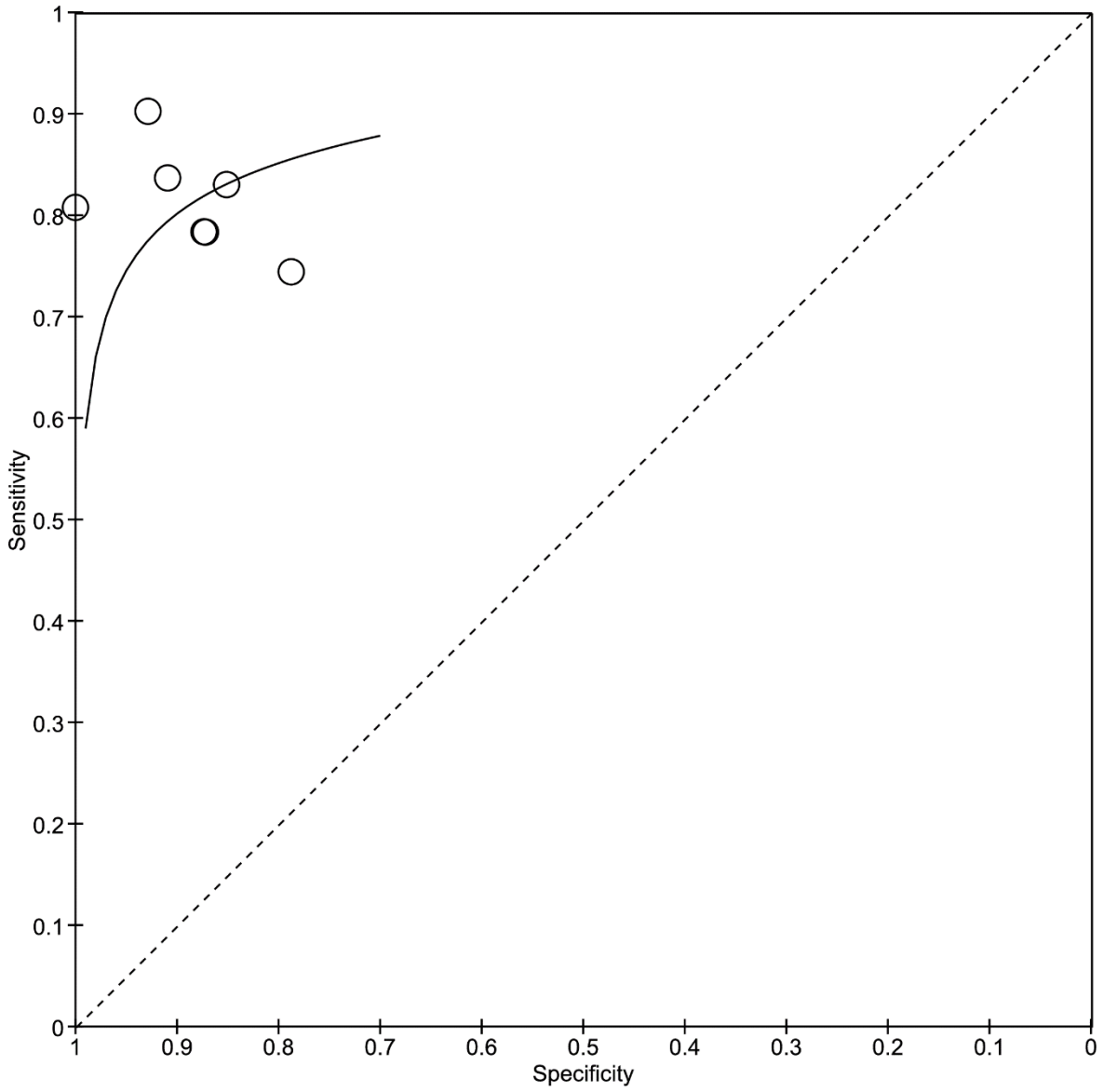
Figure 3. Forest plot of sensitivity and specificity of handheld echocardiography for any RHD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Beaton (2014)	37	6	4	78	0.90 [0.77, 0.97]	0.93 [0.85, 0.97]
Beaton (2015)	141	158	39	1076	0.78 [0.72, 0.84]	0.87 [0.85, 0.89]
Beaton (2016)	44	50	9	286	0.83 [0.70, 0.92]	0.85 [0.81, 0.89]
Godown (2015)	134	145	37	1001	0.78 [0.71, 0.84]	0.87 [0.85, 0.89]
Mirabel (2015)	41	106	8	1062	0.84 [0.70, 0.93]	0.91 [0.89, 0.93]
Ploutz (2016)	32	194	11	719	0.74 [0.59, 0.86]	0.79 [0.76, 0.81]
Zuhlke (2016)	21	0	5	62	0.81 [0.61, 0.93]	1.00 [0.94, 1.00]



The blue squares represent the sensitivity and specificity of each study and the black line its corresponding 95% confidence interval.

Figure 4. Summary ROC plot of sensitivity versus specificity of handheld echocardiography for any RHD. The size of the points is proportional to the sample size. The solid line indicates the summary ROC curve.



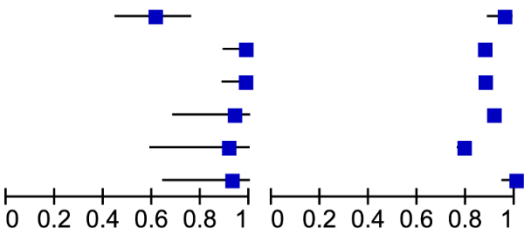
Abbreviations: ROC, Receiver Operating Characteristic; HSROC, Hierarchical Summary ROC

3.3.2 For definite RHD

A total of six evaluations of handheld echocardiography for definite RHD were performed with data from six studies and a total of 4779 participants. Pooled prevalence of definite RHD from five included studies was 5% (95% CI: 2% - 10%). The forest plot (*figure 5*) reveals some variation in estimates of specificity while estimates of sensitivity are largely homogenous with the exception of a single outlier. The HSROC plot (*figure 6*) reveals good accuracy of the test as most study points lie in the upper left corner of the plot. Meta-analytical sensitivity and specificity (95% CI) of data at mixed thresholds were 93% (85% to 100%) and 91% (86% to 96%) respectively.

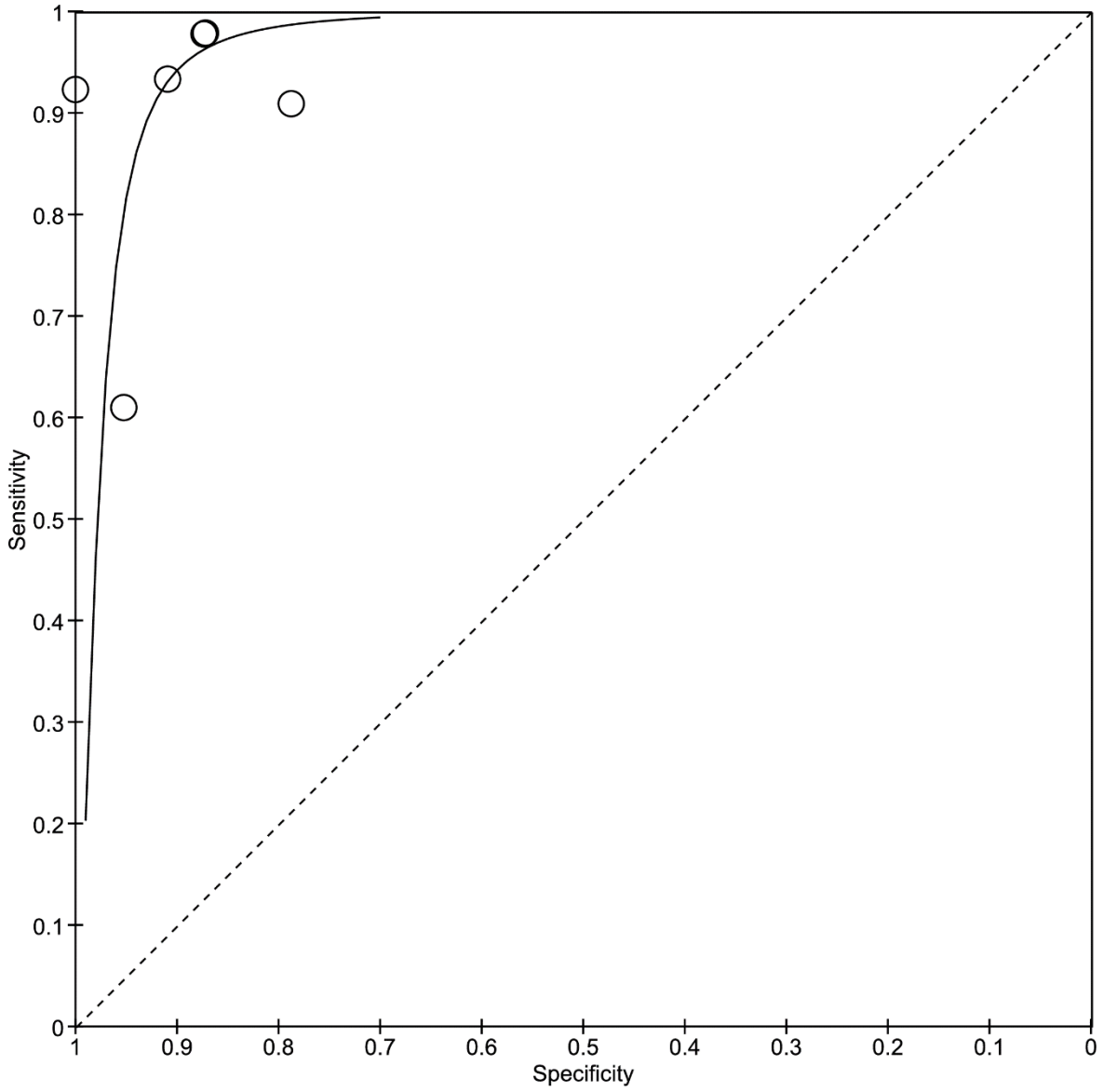
Figure 5. Forest plot of sensitivity and specificity of handheld echocardiography for definite RHD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Beaton (2014)	25	4	16	80	0.61 [0.45, 0.76]	0.95 [0.88, 0.99]
Beaton (2015)	46	158	1	1076	0.98 [0.89, 1.00]	0.87 [0.85, 0.89]
Godown (2015)	44	145	1	1001	0.98 [0.88, 1.00]	0.87 [0.85, 0.89]
Mirabel (2015)	14	106	1	1062	0.93 [0.68, 1.00]	0.91 [0.89, 0.93]
Ploutz (2016)	10	194	1	719	0.91 [0.59, 1.00]	0.79 [0.76, 0.81]
Zuhlke (2016)	12	0	1	62	0.92 [0.64, 1.00]	1.00 [0.94, 1.00]



The blue squares represent the sensitivity and specificity of each study and the black line its corresponding 95% confidence interval.

Figure 6. Summary ROC plot of sensitivity versus specificity of handheld echocardiography for definite RHD. The size of the points is proportional to the sample size. The solid line indicates the summary ROC curve.



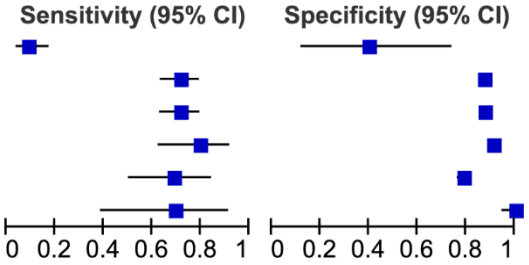
Abbreviations: ROC, Receiver Operating Characteristic; HSROC, Hierarchical Summary ROC

3.3.3 For borderline RHD

A total of six evaluations of handheld echocardiography for borderline RHD were performed with data from six studies and a total of 4957 participants. Pooled prevalence of borderline RHD from five included studies was 18% (95% CI: 7% - 31%). The forest plot (*figure 7*) reveals some variation in estimates of specificity while estimates of sensitivity are largely homogenous with the exception of a single outlier. The HSROC plot (*figure 8*) reveals poor accuracy of the test as most study points lie close to the diagonal line. Meta-analytical sensitivity and specificity (95% CI) of data at mixed thresholds were 64% (40% to 88%) and 83% (70% to 97%) respectively.

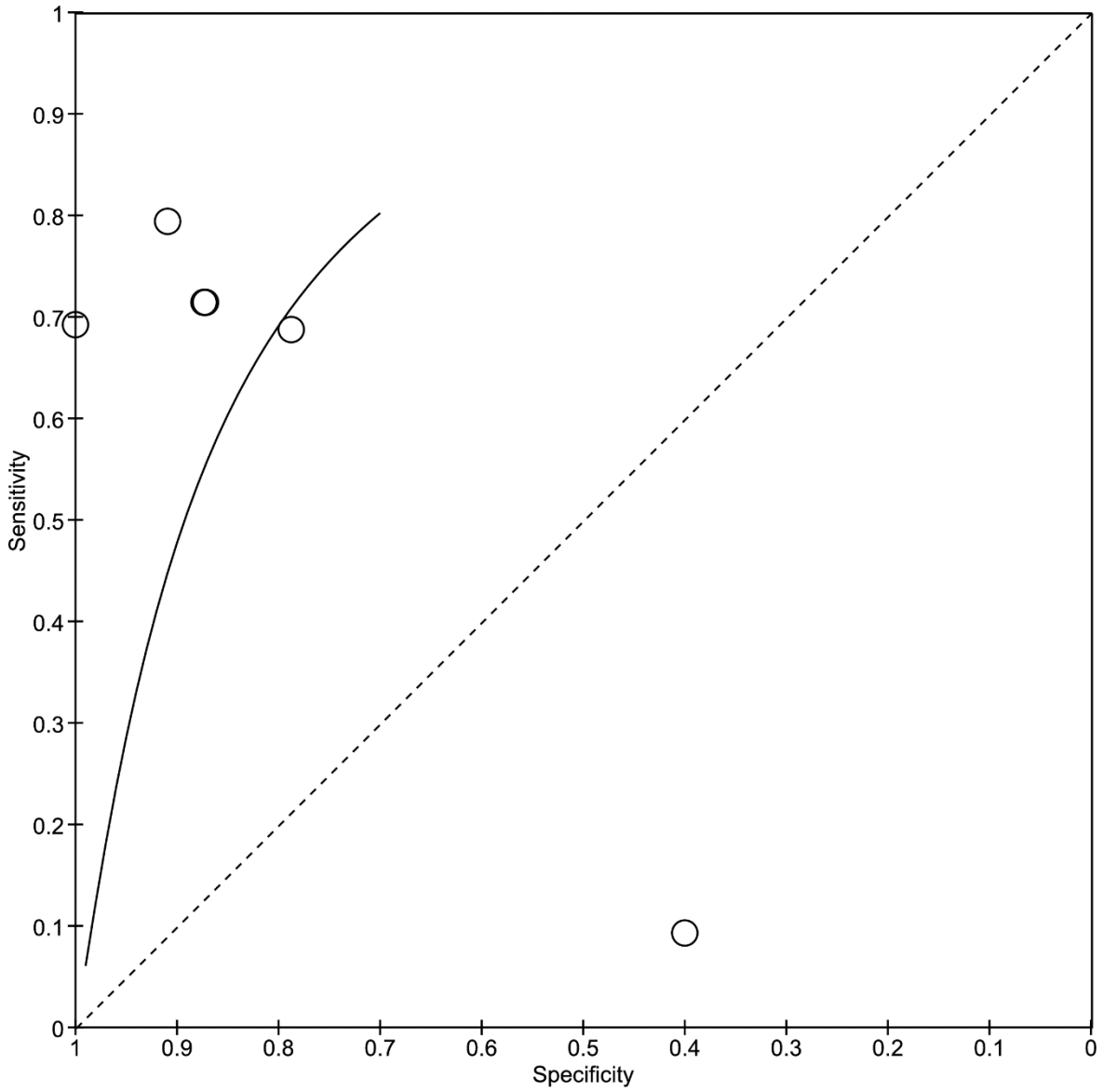
Figure 7. Forest plot of sensitivity and specificity of handheld echocardiography for borderline RHD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Beaton (2014)	8	6	78	4	0.09 [0.04, 0.18]	0.40 [0.12, 0.74]
Beaton (2015)	95	158	38	1076	0.71 [0.63, 0.79]	0.87 [0.85, 0.89]
Godown (2015)	90	145	36	1001	0.71 [0.63, 0.79]	0.87 [0.85, 0.89]
Mirabel (2015)	27	106	7	1062	0.79 [0.62, 0.91]	0.91 [0.89, 0.93]
Ploutz (2016)	22	194	10	719	0.69 [0.50, 0.84]	0.79 [0.76, 0.81]
Zuhlke (2016)	9	0	4	62	0.69 [0.39, 0.91]	1.00 [0.94, 1.00]



The blue squares represent the sensitivity and specificity of each study and the black line its corresponding 95% confidence interval.

Figure 8. Summary ROC plot of sensitivity versus specificity of handheld echocardiography for borderline RHD. The size of the points is proportional to the sample size. The solid line indicates the summary ROC curve.



Abbreviations: ROC, Receiver Operating Characteristic; HSROC, Hierarchical Summary ROC

We evaluated the accuracy handheld echocardiography for three distinct disease categories and found that, overall, the test was most accurate for detecting definite RHD only, moderately accurate for detecting any RHD (definite or borderline) and least accurate for detecting borderline RHD. A summary of the accuracy estimates produced by meta-analysis using the HSROC method is shown in *table 5* below.

Table 5. Overall meta-analysis

Test	**N**	**Sensitivity** (95% CrI)	**Specificity** (95% CrI)
Any RHD	7	80.79% (76.39 – 85.19)	89.1% (84.78 – 93.41)
Definite RHD	6	93.23% (85.41 – 100)	90.82% (85.5 – 96.14)
Borderline RHD	6	63.61% (38.82 – 88.39)	83.34% (70.02 – 96.65)

Abbreviations: N, number of studies; CrI, credible interval

3.4 Investigations of Heterogeneity

Heterogeneity or variation between studies was investigated both visually as well as through subgroup and sensitivity analysis for the main meta-analysis (any RHD) only.

3.4.1 Co-variates in the models

We were only able to use three of the five pre-specified covariates to investigate heterogeneity due to insufficient data. Pre-identified potential sources of heterogeneity which were investigated included the categorical covariates; HAND echocardiographer expertise (expert vs non-expert), geographic location (high vs low and middle income countries) and HAND protocol (single vs multiple views).

For the covariate; geographic location and in terms of the World Bank's economic classification system South Africa and Brazil are classed as upper middle income countries whereas Uganda is classified as a low income country and New Caledonia a high income

country. Of the seven included studies, six were conducted in either low or middle income countries while only one was conducted in a high income country.

For the covariate; echocardiographer expertise, only three studies evaluated the accuracy of handheld echocardiography when performed and interpreted by trained non-experts while the remaining four assessed its accuracy in the hands of experts. For the covariate; HAND protocol, only one of the seven included studies used a single view protocol whereas the rest used multiple view protocols.

3.4.2 Subgroup and sensitivity analyses

A subgroup analysis was performed to investigate potential sources of heterogeneity. We were only able to perform this analysis for the any RHD category as the data were too few to enable model convergence for the definite and borderline RHD only categories. Since no studies were found to have a high risk of bias we did not explore the effect of excluding such studies on the accuracy of summary estimates; sensitivity and specificity**.** We did not investigate publication bias as methods of assessing publication bias for studies of diagnostic accuracy are still being developed. While the Deeks test has been suggested for use in diagnostic accuracy studies, the test has low power for detecting asymmetry in funnel plots, particularly when a large amount of heterogeneity is present.[32]

Modelling the effects of the covariates on overall sensitivity and specificity in the statistical models revealed a general increase in sensitivity and a decrease in specificity for the covariates; geographic location, echocardiographer expertise and HAND protocol, as shown in *table 6*. More specifically, in the low and middle income subgroup, sensitivity (80.41% vs 83.31%) was lower and specificity (89.09% vs 88.12%) higher compared to the overall

analysis. Both sensitivity (81.8% vs 80.76%) and specificity (92.11% vs 85.71%) were higher for any RHD detection using handheld echocardiography when tests were performed and interpreted by experts compared to non-experts. In the multiple view protocol subgroup, both sensitivity (80.12% vs 83.99%) and specificity (87.38% vs 88.79%) were lower compared to the overall analysis.

Table 6. Sources of heterogeneity for handheld echocardiography for any RHD

Group	**Covariate**	**Subgroup**	**n** (N=7)	**Median Pooled Sensitivity** (95% CrI)	**Median Pooled Specificity** (95% CrI)
Overall			7	**80.79% (76.39 – 85.19)**	**89.1% (84.78 – 93.41)**
Subgroup Analysis	Geographic Location	Overall		83.31% (71.36 – 95.26)	88.12% (83.74 – 92.51)
		High income countries*	1	-	-
		Low and middle income countries	6	80.41% (75.7 – 85.11)	89.09% (83.5 – 94.69)
	HAND Interpreter Expertise	Overall		85.23% (70.31 – 100)	85.01% (78.42 – 91.59)
		Expert	4	81.8% (75.32 – 88.28)	92.11% (85.98 – 98.25)
		Non-expert	3	80.76% (73.18 – 88.33)	85.71% (79.91 – 91.51)
	HAND Protocol	Overall		83.99% (79.57 – 88.41)	88.79% (84.57 – 93)
		Single view studies	1	-	-
		Multiple view studies	6	80.12% (75.53 – 84.71)	87.38% (83.94 – 90.82)

Abbreviations: HAND, handheld echocardiography; CrI, credible interval; n, number of studies; N, total number of included studies
*There was insufficient data to pool results for high income countries

4. DISCUSSION

4.1 Summary of Main Findings

Data from seven studies involving a total of 5525 participants overall were used in this review. Six of the seven studies were conducted in low or middle income countries and all with the exception of one were based in field settings (schools and communities).

All studies were conducted in RHD endemic areas and all studies used the Vscan machine paired with a 1.7 – 3.4 MHz transducer as the index test. The main findings, including average accuracy estimates for each of the three disease categories, are reported in *table 7* below.

Briefly, our findings suggest that if handheld echocardiography is used for the detection of definite RHD only, 93% of truly diseased individuals will screen positive, whilst 91% of individuals without definite RHD will be correctly screened as normal. If handheld echocardiography is used to screen for any RHD, only 81% of those with definite or borderline disease will be correctly identified as such by the screening test whereas 89% of truly disease free individuals will test negative. In contrast, if handheld echocardiography is used to screen for borderline RHD only, the test will only correctly identify 64% of those with borderline RHD as such while 83% of individuals without borderline RHD will be correctly identified as normal by the screening test. We then applied the summary estimates to a hypothetical cohort of 1000 patients and discuss the findings in detail following the summary of findings table.

Table 7. Summary of findings

What is the diagnostic accuracy of handheld echocardiography in detecting any rheumatic heart disease (definite or borderline)?	
Patients/Population	People residing in areas endemic for rheumatic heart disease (7 out of 7 studies)
Prior testing with echo	Yes (2 studies), No (5 studies)
Settings	6 out of 7 screening studies were field setting (communities and schools) based while 1 study was half registry follow-up, half school based. 5 of the 7 studies were conducted in Africa with 4 of the 5 from Uganda.
Index test(s)	General Electric (GE) Vscan handheld machine (7 out of 7 studies)
Reference standard	Standard echocardiography (2D, continuous-wave, and colour-Doppler echocardiography) performed by an experienced imager and in conjunction with the 2012 WHF criteria (7 out of 7 studies). Machine brands included; GE Vivid-I ultrasound machine (2 out of 7 studies) GE Vivid-Q ultrasound machine (2 out of 7 studies) Philips CX-50 ultrasound machine (1 out of 7 studies) Either a GE Vivid-I or Q or Philips CX-50 ultrasound machine (2 out of 7 studies)
Importance	This test is being used as first line replacement for standard echocardiography in disease screening programmes for RHD, as it is comparably inexpensive, quick, user friendly, easy to interpret, and may have similar sensitivity to standard echocardiography.
Studies	Cross-sectional (n = 5), spiked cohort (n = 1) and nested case-control (n = 1) studies. More than half (n = 4) of all included studies did not explicitly state the study design used and were thus assigned a study design based on other reported characteristics and participant enrolment methods used.
Quality concerns	Poor reporting of study design, participant characteristics and pre-test probability were common concerns. For the majority of studies the risk of bias assessment was unclear in terms of the QUADAS domains 'patient selection' and 'flow and timing'. Concerns regarding applicability were low in all included studies.

Test types	**Number of participants*** (N)	**Summary Estimates** (95% credible CI)	**Test result**	**Prevalence in 1000 people tested**		
				2.5%	**5%**	**10%**
Handheld echocardiography for **any RHD**	5506 (7)	Sensitivity; 80.79% (76.39 – 85.19) Specificity; 89.1% (84.78 – 93.41)	All cases (TPs + FNs)	25	50	100
			Missed cases (FNs)	5	10	19
			False positives (FPs)	106	104	81
			All positives (TPs + FPs)	126	144	179
Handheld echocardiography for **definite RHD**	4779 (6)	Sensitivity; 93.23% (85.41 – 100) Specificity; 90.82% (85.5 – 96.14)	All cases (TPs + FNs)	25	50	100
			Missed cases (FNs)	2	3	7
			False positives (FPs)	90	87	83
			All positives (TPs + FPs)	113	134	176
Handheld echocardiography for **borderline RHD**	4957 (6)	Sensitivity; 63.61% (38.82 – 88.39) Specificity; 83.34% (70.02 – 96.65)	All cases (TPs + FNs)	25	50	100
			Missed cases (FNs)	9	18	36
			False positives (FPs)	162	158	150
			All positives (TPs + FPs)	178	190	214

Abbreviations: CI, confidence interval; N, number of studies; TPs, true-positives; FPs, false-positives; TNs, true-negatives; FNs, false-negatives

* Excluding participants with other diagnoses on STAND

For any RHD diagnosis in apparently healthy children and adolescents the pooled sensitivity and specificity (95% CrI) of handheld echocardiography were 81% (76% to 85%) and 89% (85% to 93%) respectively. Given these estimates and in hypothetical cohort of 1000 children and adolescents with a prevalence of 5%, handheld echocardiography will correctly detect any RHD in 40 people, fail to detect ten cases while 104 people would receive unnecessary treatment or be needlessly referred for further testing.

For definite RHD diagnosis in apparently health children and adolescents the pooled sensitivity and specificity (95% CrI) of handheld echocardiography were 93% (85% – 100%) and 91% (86% to 96%). Given these estimates and in a hypothetical cohort of 1000 children and adolescents with a pre-test probability of 5%, handheld echocardiography will correctly detect definite RHD in 47 people, while only three will miss treatment and 87 people will receive unnecessary treatment or be needlessly referred or further testing.

For borderline RHD diagnosis in apparently healthy children and adolescents the pooled sensitivity and specificity (95% CrI) of handheld echocardiography were 64% (39% to 88%) and 83% (70% to 97%). Given these estimates and in a hypothetical cohort of 1000 children and adolescents with a pre-test probability of 5%, handheld echocardiography will correctly detect borderline RHD in 32 people, while eighteen people will miss treatment and 158 people will receive unnecessary treatment or be needlessly referred for further testing.

While only seven additional cases would be missed if HAND was used to screen for any RHD as opposed to definite RHD only, an extra seventeen healthy people would be incorrectly classified and another seven people would be missed by the test. However, given the implicit value of identifying borderline cases in order to initiate prophylaxis, this trade off could be considered acceptable.

4.2 Strengths and Weaknesses of this Review

4.2.1 Strengths

We have evaluated and summarised the accuracy of handheld echocardiography for the detection of RHD in endemic areas, making the review relevant to current global agendas. This review also serves to highlight the existing gaps in evidence for which further research could be beneficial. We did not impose a search filter or any limits in terms of language during the literature search so as to minimise the chance of missing studies. Data extraction was performed by two independent reviewer authors thereby reducing the risk of bias.

4.2.2 Weaknesses

There were a number of shortcomings of this review which include the following.

Eligibility

We were unable to include studies which used STAND in conjunction with criteria other than the 2012 WHF criteria as the reference standard which limited the number of studies eligible for inclusion.

Quality of included studies

Insufficient reporting of participant characteristics and study methods including study design, participant selection and test timing restricted our ability to adequately assess risk of bias and investigate potential sources of heterogeneity.

Paucity of data

Insufficient data as well as the presentation of aggregate data limited the scope of our investigations of heterogeneity and the small number of included studies prevented us from

performing meta-regression. Overall, the findings from this review may lack power due to the small sample size.

4.3 Applicability of Findings to the Review Question

Concerns regarding the applicability of included studies to the review question were assessed as being low according to review-specific QUADAS-2 criteria. Since all but one study were conducted in low or middle income countries, and all studies but one were conducted in field settings, the results of this review are applicable for use in endemic areas for which screening programmes are frequently targeted. However, our limited assessment of risk of bias and investigations into sources of heterogeneity such as age and gender due to insufficient and unreliable reporting may lessen the applicability of findings to the review question.

In the context of disease control programmes, being able to demonstrate variation in test accuracy associated with factors such as age and gender would be beneficial for policy makers. Fully understanding included studies' risk of bias would also assist in objectively assessing the strength of evidence. For these reasons, prospective authors of diagnostic test accuracy studies are urged to make use of the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines [33] when reporting methods of study design and conduct.

5. CONCLUSION

This review provides a summary of the accuracy of handheld echocardiography for the detection of RHD. In populations of children and adolescents living in RHD endemic areas, handheld echocardiography is both sensitive and specific for detecting definite RHD. The

device is less accurate in detecting any RHD (definite or borderline) and demonstrates substandard accuracy for the detection of borderline RHD only. Nonetheless, this test may hold value as a replacement in terms of first line screening due to its high sensitivity for definite RHD detection and adequate accuracy for any RHD detection.

5.1 Implications for Practice

Handheld echocardiography demonstrates sufficient accuracy for any RHD detection and good accuracy for definite RHD detection when used as a screening tool, however, the device's potential value in terms of diagnostics has yet to be established. We therefore posit that handheld echocardiography could be recommended as an acceptable replacement test for first line screening in endemic areas provided a standardised set of device specific diagnostic criteria are developed.

Another key consideration is the applicability of these findings for recommendations for integrating screening into routine clinical practice. A recent publication has reviewed the cost-effectiveness of screening in high-risk populations [34] and determined that screening all indigenous Australian 5 to 12 year-olds in half of their communities in alternate years was found to be cost-effective (incremental cost-effectiveness ratio less than AU$50 000 per disability-adjusted life-year averted), if RHD can be detected at least two years earlier; however, this result was sensitive to a number of assumptions, including the local costs and context.

Other cost-effectiveness models have also suggested modestly improved outcomes at lower cost.[35] Neither of these studies included the significant cost-reduction using HAND instead of STAND, hence, we highly recommend adding a cost-effectiveness analysis into proposed

new screening studies. In addition, these studies focused on small pockets within endemic countries, recommendations for wide scale population screening, despite the demonstrated diagnostic accuracy in our study, needs detailed further investigation.

Finally, our findings demonstrate comparable results by non-experts, this has also been demonstrated in several other reports [22,36], but again there are no detailed cost-effectiveness analyses using non-experts and HAND.

5.2 Implications for Research

The findings of this review highlight the need for a new set of evidence-based guidelines tailored to the capabilities of handheld echocardiography in order to maximise the device's diagnostic potential. Further studies assessing the diagnostic accuracy of HAND when using a standardised protocol are needed as is further research into the feasibility, cost-effectiveness and consequences of implementing wide scale RHD screening programs. Furthermore, the development of standardised training programs for non-experts is recommended as screening for RHD in endemic areas inevitably rests on the success of task shifting.[18]

We conclude that while handheld echocardiography has been shown to be sufficiently accurate for the detection of RHD there is still a need for further research before its' wide scale use can be endorsed.

6. ACKNOWLEDGEMENTS

6.1 Contributions of Authors

Conception of the review: Liesl Zühlke, Mark Engel

Writing of first drafts of the protocol, literature review and manuscript: Lisa Telford

Methodological advice: Eleanor Ochodo, Mary Shelton (expert librarian)

Content advice: Liesl Zühlke, Mark Engel

Data collection: Lisa Telford, Leila Abdullahi

Data analysis: Eleanor Ochodo, Lisa Telford

Contributions to editing subsequent versions of the protocol and manuscript: All authors

Contributions to editing subsequent versions of the literature review: Liesl Zühlke

6.2 Declarations of Interest

The authors report no conflicts of interest

6.3 Sources of Support

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PART D: Appendices

APPENDIX 1: DATA EXTRACTION FORM

Reviewer Name:		Date Form Completed: (dd/mm/yyyy)	

1. General Information

Publication Type: (e.g. full report, abstract)			
Journal:			
Article Title:			
First Author:		Publication Year:	
Author Contact Details:			
References of Potentially Eligible Studies: (from the bibliography hand search)			

1a. Is this a study that examines the accuracy of tests for rheumatic heart disease (RHD)?	☐ Yes	
	☐ No	**Exclude paper!**
	☐ Unclear	Comment:
1b. If 'No' at item 1a., please describe the type of article		

2. Target Condition **Page(s):**

2. Rheumatic heart disease (RHD)	☐ Definite ☐ Borderline ☐ Mixed definite & borderline	
	☐ No RHD in study	**Exclude paper!**
	Comment:	

3. Study Population **Page(s):**

3a. Country of study	Please state the country or countries in which the study took place:		
3b. What is the estimated prevalence of RHD in the study area prior to the study?	Prevalence / Pre-test probability:		☐ Not reported
3c. Age of participants	Mean/Median Age:	SD/Range:	☐ Not reported
3d. Total number of participants included in study (sample size)	No. of participants: No. of samples:		☐ Not reported

3e. Proportion or number of participants by sex	Male:	Female:	☐ Sex not specified

FOR THE QUESTIONS 4 & 5, DRAWING A FLOW DIAGRAM OF THE STUDY MAY BE HELPFUL
(space is provided on page 6 of this data extraction form)

4. Patient Selection **Page(s):**

4a. Please cite the patient selection criteria	Inclusion Criteria:	Exclusion Criteria:
	☐ Not reported	☐ Unclear Comment:
4b. What was the stage of disease at enrolment?	☐ Asymptomatic ☐ Symptomatic ☐ Both asymptomatic & symptomatic ☐ Unclear Comment:	
4c. What was the study design?	☐ Cross-sectional study ☐ Cohort study ☐ Case-control (cases & controls from the same population/nested) ☐ Case-control (with healthy controls) EXCLUDE! ☐ Case-control (with alternative diagnosis controls) EXCLUDE! ☐ Case-control (with controls from non-endemic areas) EXCLUDE! ☐ Randomized trial ☐ Not stated ☐ Unclear Comment:	
4d. Was a case-control design avoided?	☐ Yes ☐ No ☐ Unclear	
4e. Was either a consecutive or random sample of patients enrolled? (please specify which)	☐ Yes ☐ No ☐ Unclear	
	Comment:	
4f. Did the study avoid inappropriate exclusions?	☐ Yes ☐ No ☐ Unclear	
4g. Could the selection of patients have introduced bias? (Please indicate the level of risk)	☐ Low risk of bias (if questions 4d and 4e were both answered 'yes') ☐ High risk of bias (if both question 4d and 4e were answered 'no') ☐ Unclear (any other combination of answers)	

4h. Is there concern that the included patients do not match the review question? (Please indicate the level of concern)	☐ Low concern (participants from endemic areas) ☐ High concern (tourists, non endemic areas) ☐ Unclear concern Comment:

5. Patient Flow and Timing **Page(s):**

5a. Was there an appropriate interval between the index test and reference standard?	☐ Yes	☐ No	☐ Unclear
5b. Did all patients receive a reference standard test? (Focus on 2*2 table)	☐ Yes	☐ No	☐ Unclear
5c. Did all patients receive the same reference standard test?	☐ Yes	☐ No	☐ Unclear
5d. Were all patients included in the analysis?	☐ Yes	☐ No	☐ Unclear
5e. Could the patient flow have introduced bias? (Please indicate the level of risk of bias)	☐ Low (if questions 5a-d were all answered 'yes', or at least three were answered 'yes' and the other 'unclear') ☐ High (if two or more of questions 5a-d were answered 'no') ☐ Unclear (any other combination of answers)		

6. Index Test **Page(s):**

6a. Please state index test's name (i.e. brand name/manufacturer) and the person(s) performing and interpreting the test as well as the time at which interpretation occurred (i.e. on-site/at time of screening or later/offline)	Test name:		☐ Not stated
	Performed by:		
	Interpreted by:		
	Time of interpretation:		
6b. Was a pre-specified set of diagnostic criteria or protocol used?	☐ Yes ☐ No ☐ Unclear ☐ Not stated		Comment:
6c. Was the HAND interpreter trained to use the protocol? If the HAND interpreter has prior experience/skill/expertise and training was not necessary please also select 'Yes'.	☐ Yes ☐ No ☐ Unclear ☐ Not stated		Comment:
6d. What was the initial level of expertise of the HAND interpreter?		☐ Not stated	Comment:
6e. Was quality control done? (e.g. 10% of samples cross checked by another person)	☐ Yes ☐ No ☐ Unclear ☐ Not stated		Comment:
6f. Were the index test results interpreted without knowledge of the results of the reference standard?	☐ Yes ☐ No ☐ Unclear ☐ Not stated		Comment:

6g. If a diagnostic threshold was used was it pre-specified?	☐ Yes ☐ No ☐ Unclear ☐ Not stated	Comment:
6h. Could the conduct or interpretation of the index test have introduced bias?	☐ Low risk of bias (if questions 6b-g were all answered 'yes') ☐ High risk of bias (if two or more of questions 6b-g were answered 'no') ☐ Unclear (any other combination of answers)	

7. Reference Test **Page(s):**

7a. Please state reference test's name (i.e. brand name / manufacturer) and the person(s) performing and interpreting the test as well as the time at which interpretation occurred (i.e. on-site / at time of screening or later / offline)	☐ 2D, continuous-wave, & colour-Doppler echocardiography	☐ Other	**Exclude paper!**
	Test Name:		
	Performed by:		
	Interpreted by:		
	Time of interpretation:		
7b. Number of reference test images examined per patient		☐ Unclear	☐ Not stated
7c. Was quality control done? (e.g. were 10% of samples cross checked by another person)	☐ Yes ☐ No ☐ Unclear ☐ Not stated		Comment:
7d. Is the reference standard likely to classify the target condition?	☐ Yes ☐ No ☐ Unclear		Comment:
7e. Were the reference standard results interpreted without knowledge of the results of the index test?	☐ Yes ☐ No ☐ Unclear ☐ Not stated		Comment:
7f. Could the reference standard, its conduct, or its interpretation have introduced bias?	☐ Low risk of bias (if questions 7c-e were all answered 'yes') ☐ High risk of bias (if one or more of questions 7c-e were answered 'no') ☐ Unclear (any other combination of answers)		

8. Test Results **Page(s):**

8a. Prevalence of disease based on STAND results: Please state mean and range/confidence intervals *(for all who were screened with STAND irrespective of HAND)*	Mean:	
	Range:	
	CI:	
	☐ Not stated	Comment:
8b. Severity of disease: Please state the disease severity according to assessment by STAND *(only for those who received both HAND & STAND)*		☐ Not stated
8c. Missing Data:	☐ Yes ☐ Not that I noticed Please explain:	

Were there missing, uninterpretable or unavailable results of the reference standard?	
Were there missing, uninterpretable or unavailable results of the index test?	☐ Yes ☐ Not that I noticed Please explain:

8d. Accuracy Results

- Please calculate and list results of the *index test* below: TP,TN, FP, FN, Sens, Spec.
- Please also indicate the *main test threshold* used to calculate the results.
- If *multiple thresholds* have been used please indicate so in the comments box.

Table A

Test	Test Threshold	TP	FP	FN	TN	Sens	Spec

Comments:

Flow Diagram

For questions **4** and **5**, drawing a flow diagram of the study may be helpful. Flow diagrams of patient selection, flow and timing illustrate the number of patients who were eligible for the study, how many were actually recruited, the proportion of which received the index test as well as the proportion of which received the reference standard etc. In addition, the number of true and false positives and true and false negatives are also displayed. If necessary please draw a flow diagram for the primary study to aid your understanding**.**

APPENDIX 2: BACKGROUND DOCUMENT TO THE DATA EXTRACTION FORM

***NB:** At the beginning of each section please write the page number(s) on which the majority of the information pertaining to that section was found. A space is provided next to the section heading for this.

(1) GENERAL INFORMATION

Publication type: Describe the type of publication, i.e.: full report, abstract, conference proceeding etc.

Journal: Name of the journal in which the article is published (if published)

Article title: Enter the title of the article

First author: Enter the full name of first author

Publication year: Enter the year in which the article was published

Author contact details: Record the contact details of the corresponding author for future reference in instances where additional data needs to be obtained or questions clarified

The following questions have activated checkboxes next to the responses. Please make your selection by clicking the appropriate checkbox.

1a. Is this a primary study that examines the accuracy of tests for rheumatic heart disease (RHD)?
Tick the appropriate box. If answered 'no', EXCLUDE the paper. This item is meant to enable the quick distinction between potentially relevant articles and articles that clearly have a different scope. If the article does not clearly evaluate the accuracy of tests as a primary or secondary objective you can tick 'no' and stop the data extraction exercise. If you are unsure please tick 'unclear', comment on why you are unsure and then proceed with the data extraction exercise.

1b. If the article does not evaluate accuracy tests for RHD, please describe what kind of article it is?
Please describe what type of publication it is (e.g. narrative overview article, a purely prevalence study etc.)

(2) TARGET CONDITION BEING EVALUATED

2. Please indicate the target condition being evaluated in the study.
[All studies should evaluate both borderline and definite in accordance with the 2012 WHF criteria]

Please tick the appropriate box to indicate if the study evaluates either definite or borderline RHD or both as the condition of interest. If it doesn't evaluate definite or borderline RHD but rather another condition; EXCLUDE the paper and add an explanation in the comment in the box provided.

(3) STUDY POPULATION

3a. Country of study

Some studies may be carried out in one country or in multiple countries. Please state the country or countries in which the study was conducted.

3b. What is the estimated prevalence of RHD in the study area prior to the study?

Prior to the study commencing, the authors may state the estimated prevalence of RHD in the area or country of study. This estimated prevalence may be based on previous reports or other studies. If it is not reported please tick the box 'Not reported'.

3c. Age of participants

Please indicate the mean or median and SD or range of the age of the study participants included in the study. Please state the measures that are reported in the study. If no measures were reported in the study, please tick the box 'Not reported'. Some studies may describe a subset of the larger cohort as receiving both the index test and reference standard and the entire cohort separately – in this instance please only report the age of participants who received both tests.

3d. Number of participants

Please write in the box provided the number of participants and/or the number of samples included in the study. Some studies may describe a subset of the larger cohort who received both the index test and reference standard and the entire cohort separately – in this instance please report only the number of participants who received both tests (i.e. the subset of participants who received both HAND and STAND). You may also state that the study consisted of a large cohort with a subset within that cohort in the space provided for 'number of samples'.

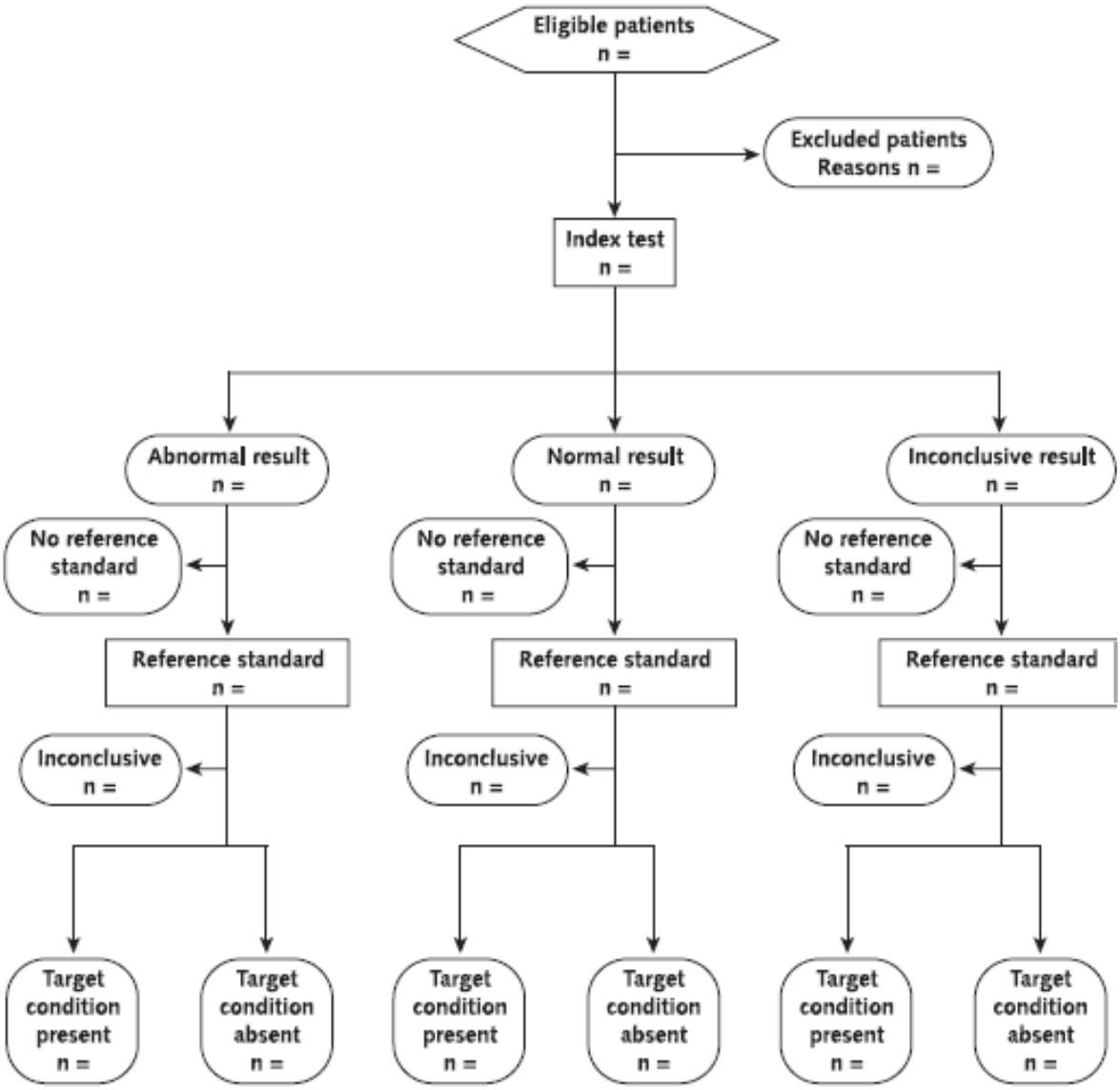
3e. Proportion or number of participants by gender

Please write in the box provided the proportion/percentage or number of participants per sex of those who received both tests (i.e. those that received both HAND and STAND). For example; 50% of participants were female or 590 females were in the study. This information can usually be found in the results section but if the sex of participants was not specified please tick the box 'Sex not specified'.

Flow diagram

For questions **4** and **5**, drawing a flow diagram of the study may be helpful. Flow diagrams of participant selection, flow and timing illustrate the number of participants who were eligible for the study, how many were actually recruited, the proportion of which received the index test as well as the proportion of which received the reference standard etc. In addition, the number of true and false positives and true and false negatives are also displayed. If necessary please draw a flow diagram for the primary study in the space provided on page 6 of the data extraction form**.**

An example of a flow diagram is as shown below.



(4) PARTICIPANT SELECTION

These questions have been designed to help assess the risks of bias in the study.

4a. Please cite here the selection criteria

Please list the inclusion and exclusion criteria which were applied when recruiting study participants in the spaces provided. Inclusion criteria might also include the characteristics of included participants. For example "all children attending primary schools in the area were eligible for inclusion". If no criteria were reported, please tick 'Not reported' and if the criteria were unclear please tick "Unclear" and explain your answer.

4b. Stage of disease

Participants recruited into the study may be with or without symptoms. Please indicate the disease stage of participants at the time of enrolment by ticking the appropriate box. If the study does not clearly report the clinical status of participants, please tick the box marked 'unclear' and comment in the space provided.

4c. What was the study design?

Please indicate the design of the study by ticking one of the choices provided.
We will not include case-control studies which include healthy controls, alternative diagnosis controls or controls from non-endemic areas. Research has shown that these types of studies have a tendency to overestimate accuracy measures. Healthy controls are those who have been confirmed as being disease-free, alternative diagnosis controls are controls that have similar symptoms to those of the disease under study but do not have the condition of interest and controls from non-endemic areas are those from areas in which the condition of interest is not highly prevalent. If the study design is not reported or is unclear please tick the appropriate box and if necessary add a comment.

4d. Was a case-control design avoided?

- **Yes:** If the authors report using any study design apart from a case-control one.
- **No:** If the authors report using a case-control study design.
- **Unclear:** If the authors do not explicitly report the study design used.

4e. Was a consecutive or random sample of participants enrolled?

- **Yes:** If the authors report random sampling or consecutive enrolment of participants.
- **No:** If participants were selected, for example based on previous (reference or index) test results.
- **Unclear:** There appears to be no problem, but the authors do not explicitly state that participants were enrolled randomly or consecutively.

4f. Did the study avoid inappropriate exclusions?

- **Yes:** If no participants were excluded after inclusion/enrolment.
- **No:** If, for example, participants with mild disease severity were excluded, because they are more difficult to detect.
- **Unclear:** If not reported or insufficient information given to make a decision.

4g. Could the selection of participants have introduced bias?

- **Low:** If both questions 4d and 4e were answered 'yes' or if at most one was answered 'unclear'.
- **High:** If one or more of questions 4d and 4e were answered 'no'.
- **Unclear:** Any other combination of answers, for example if both questions 4d and 4e were answered 'unclear'.

4h. Is there a concern that the included participants do not match the review question?

- **Low concern:** If study participants reside within RHD endemic areas as they will include those at risk of infection, those who are infected but asymptomatic as well as those who are infected and have symptoms.
- **High concern:** If study participants don't reside in endemic areas. For example; tourists, healthy controls or controls with alternative diagnoses.
- **Unclear:** If there is insufficient information to make a decision.

(5) PARTICIPANT FLOW AND TIMING

5a. Was there an appropriate interval between index test and reference standard?

- **Yes:** If the participants were examined using both the reference standard and index test at the same time or within a two week time period.
- **No:** If the time period between index and reference standard was more than two weeks.
- **Unclear:** If there is no or insufficient information on time period.

5b. Did all participants receive a reference standard? (Focus on participants included in the 2*2 table)

- **Yes:** If the whole study sample or a random selection of the sample or a selection of the sample with consecutive series receive verification using the reference standard.
- **No:** If a part of the study sample that is non-randomly or non-consecutively selected receives verification using the reference standard.
- **Unclear:** If there is no or insufficient information to ascertain whether the whole sample or a random selection of the sample received verification using the reference standard.

5c. Did participants receive the same reference standard?

- **Yes:** If study participants are tested with the same reference standard (2D, continuous-wave, and colour Doppler echocardiography) regardless of index test result.
- **No:** If 2D, continuous-wave, and colour Doppler echocardiography is used with different techniques depending on the results of the index test.
- **Unclear:** If there is no or insufficient information on the reference standard used.

5d. Were all participants included in the analysis?

- **Yes:** If all the participants that were included in the study, were also included in the analysis.
- **No:** If some participants / results are missing in the analysis.
- **Unclear:** If there is no or insufficient information to make a decision.

5e. Could the conduct or interpretation of participant flow & timing have introduced bias?

- **Low:** If all questions were answered 'yes' or at least three were answered 'yes' and the other 'unclear'.
- **High:** If two or more of questions 5a - 5d were answered 'no'.
- **Unclear:** Any other combination of answers. For example if all questions were answered 'unclear' or if three were 'unclear' and one was 'yes'.

(6) INDEX TEST

6a. Please state the name and specifications of the index test under evaluation in the study.
Please state the name/label of the index test as well as any additional specifications. The label is the brand name of the test or the manufacturer who made the device. Additional specifications might include the type of transducer/probe attached to the device. If the brand name or label is not reported please tick the box 'Not reported'. Please also describe the person(s) performing and interpreting the test as well as the time at which interpretation occurred. In some instances the person(s) performing the index test might be different from the person(s) interpreting the test results – please describe both. Please also describe the time at which the index test results were interpreted, for example on-site at the time of screening/evaluation or later/offline.

6b. Was a pre-specified set of diagnostic criteria or protocol used?

- **Yes:** If a pre-specified modified diagnostic protocol or set of diagnostic criteria for HAND was used.
- **No:** If no pre-specified set of diagnostic criteria or diagnostic protocol was used or if criteria were not modified to suit the capabilities of HAND.
- **Unclear:** If there is insufficient information to make a judgment.
- **Not reported:** If there is no information reported on this item.

6c. Was the HAND interpreter trained to use the diagnostic protocol?

- **Yes:** If the person who conducted the echocardiographic screening using the handheld device was trained on how to interpret results using the pre-specified diagnostic protocol or if the person interpreting the HAND results is described as an expert/experienced reviewer/imager/reader. For example this might include any of the following; paediatric cardiologists, paediatric cardiology fellows, echocardiography imagers/technicians & sonographers.
- **No:** If the person who conducted echocardiographic screening using the handheld device does not have any prior experience or expertise in interpreting echocardiographic images and was not given any training with regards to interpreting results using a pre-specified diagnostic protocol.
- **Unclear:** If there is insufficient information to make a judgment.
- **Not reported:** If there is no information reported on this item.

6d. What was the initial level of expertise of the HAND interpreter?

Please state the HAND interpreter's initial level of clinical expertise. For example were they a clinician, nurse or community health worker etc. If not reported please tick the appropriate box and if necessary comment in the space provided.

6e. Was quality control done?

To ensure reliability or good quality of results a sub-set of the sample population may be cross-checked by a second person or an expert in echocardiographic imaging. Please indicate if this was done in the study. If the information is insufficient or if the information given is unclear please tick the box 'unclear'. If not reported, tick the box 'Not reported' and if necessary, comment in the box provided.

6f. Were the index test results interpreted without knowledge of the results of the reference standard?

- **Yes:** If results of the index test are interpreted without knowledge of reference test results or if the index test is performed prior to administering the reference standard.
- **No:** If results of the index test are interpreted with knowledge of the reference standard test results.
- **Unclear:** If there is insufficient information on when the index and reference tests were interpreted.
- **Not reported:** If no information was reported with regards to the timing and interpretation of tests.

6g. If a threshold was used, was it pre-specified?

- **Yes:** If the authors report the use of a primary, pre-specified, cut-off value or threshold. A pre-specified threshold also includes statements such as "the test was scored according to manufacturer's instructions".
- **No:** If multiple cut-off values were tested and the best one chosen afterwards.
- **Unclear:** If only one cut-off value was used, but this was not explicitly reported in the methods section.
- **Not reported:** If no information was reported on this item.

6h. Could the conduct or interpretation of the index test have introduced bias?

- **Low:** If questions 6b – 6g were all answered 'yes'.
- **High:** If one or more of questions 6b – 6g were answered 'no'.
- **Unclear:** Any other combination of answers. For example if one or more questions were answered 'unclear'.

(7) REFERENCE TEST

The reference test for RHD that this review will evaluate is 2D continuous-wave, and colour Doppler echocardiography with results interpreted in accordance with the 2012 WHF criteria.

7a. Please indicate the reference test applied in the study

For RHD, if the reference test used was not 2D, continuous-wave, and colour Doppler echocardiography tick 'other' and EXCLUDE the paper.

Please state the name/label of the reference standard machine as well as any additional specifications. The label is the brand name of the test or the manufacturer who made the device. Additional specifications might include the type of transducer/probe attached to the machine. If the brand name or label is not reported please tick the box 'Not reported'. Please also describe the person(s) performing and interpreting the test as well as the time at which interpretation occurred. In some instances the person(s) performing the index test might be different from the person(s) interpreting the test results – please describe both. Please also describe the time at which the index test results were interpreted, for example on-site at the time of screening/evaluation or later/offline.

7b. Number of reference test images examined per participant

Please state the number of images recorded and examined per participant using 2D, continuous-wave, and colour Doppler echocardiography. If a different number of images were examined per participant or if the information is insufficient please tick the box marked 'unclear'. If no information is reported please tick the box 'Not reported'.

The following questions (7c-7f) are part of the QUADAS-2 tool and will be used to assess the risk of bias in how the reference test was conducted.

7c. Was quality control done?

To ensure reliability the test results for a subset of the sample population may be cross checked by a second person or an expert in echocardiographic imaging. Please indicate if this was done in the study. This might include all suspected cases (definite or borderline) on STAND being independently reviewed by a second reader with conflicts adjudicated by a third reader if necessary. If information is insufficient to make a judgment please tick the box 'unclear'. If no information is reported please tick the box 'Not reported' and if necessary, comment in the box provided.

7d. Is the reference standard likely to correctly classify the target condition?

- **Yes:** If measures to increase sensitivity are used e.g. multiple angles/images examined per patient and machine settings optimised.
- **No:** If for example only ill children are sampled for testing using the reference standard.
- **Unclear:** If there is insufficient information on the reference standard used or echo imaging technique used to make a judgment.

7e. Were the reference standard results interpreted without knowledge of the results of the index test?

- **Yes:** If results of the reference standard are interpreted without knowledge of index test results in cases when the reference test was used before the index test.
- **No:** If results of the reference test are interpreted with knowledge of the index test results in cases when the index test is performed before the reference test.
- **Unclear:** If there is insufficient information on when the index and reference tests were interpreted.
- **Not reported:** If no information was reported on this item.

7f. Could the conduct or interpretation of the reference standard have introduced bias?

- **Low:** If questions 7c – 7e were all answered 'yes'.
- **High:** If one or more of questions 7c – 7e were answered 'no'.
- **Unclear:** Any other combination of answers.

(8) TEST RESULTS

8a. Prevalence of disease based on STAND results

[For those who received the reference test regardless of whether or not they also received the index test]

Please state the reported prevalence estimates for rheumatic heart disease based on the reference standard test results. Report these measures in terms of the mean, 95% confidence interval and range. Please report the results for all participants in the study who were screened for RHD using standard echocardiography. In some instances this indicates the larger cohort of participants who were all screened for RHD using STAND but of which some did not receive the index test as well. This is fine as long as all participants screened received the same reference standard test. If this information is not given or cannot be extracted from the results provided please tick the box 'Not reported' and add a comment in the space provided if necessary.

8b. Severity of disease

[Only for those who received both the index and reference test]

Please indicate the range of disease severity for the participants included in the study who received both the index test (HAND) and the reference test (STAND) according to assessment by standard echocardiography. For example state the number or proportion of participants who were diagnosed as having definite RHD, borderline RHD or normal echocardiographic findings according to assessment by standard echocardiography. If no information is given please tick the box 'Not reported'.

8c. Missing data

Please indicate if there were missing, uninterpretable or unavailable results for both the reference standard and index tests by ticking the appropriate boxes. These may or may not be reported by the authors. Please explain your answers in the comment boxes provided citing the number of missing / uninterpretable / unavailable test results.

To understand the following section better please refer to the paper by van Stralen K et al (2009). 'Diagnostic Methods I: sensitivity, specificity, and other measures of accuracy'. Kidney International, 75; 1257-1263.

8d. Accuracy results

Please ONLY report accuracy results for handheld echocardiography (HAND). Do not report results for auscultation or any other tests.

- Please extract the required data into the 2 by 2 table by listing the results in the spaces provided using the following format: True Positives (TP), True Negatives (TN), False Positives (FP), False Negatives (FN), Sensitivity (Sens), Specificity (Spec), Positive Predictive Value (PPV) and Negative Predictive Value (NPV). Please also extract 95% confidence intervals for measures of sensitivity, specificity, PPV and NPV if and when reported by study authors.

- In the first column (**Test**) please specify whether the results refer to any RHD (definite or borderline) or to definite RHD only. Please also further specify, where applicable, whether the results are pooled/combined (i.e. for all experts/non-experts/nurses etc.) or if the results are for different individuals (i.e. Nurse A or Nurse B). Please report all permutations thereof, for instance report the results for nurse A, then for Nurse B and lastly both of their results combined.

- Please specify the threshold or cut-off value in terms of mitral regurgitation (MR) &/or aortic regurgitation (AR) in the second column (**Threshold**). If multiple different thresholds were used, please report the results for each threshold separately (i.e. each one on a different row).

General comments

At the end of the data extraction form a comment box has been provided for general comments about the paper you have evaluated. Please use this box when and if necessary.

APPENDIX 3: ETHICS WAIVER

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338
Email: lamees.emjedi@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 October 2017

A/Prof M Engel
Medicine
J Floor
OMB

Dear A/Prof Engel

Project Title: Standard Echocardiography versus Handheld Echocardiography for the Detection of Subclinical Rheumatic Heart Disease

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that the proposed study is a systematic review.

As the systematic review involves published literature available through publically accessible electronic databases, research ethics review and approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: "*Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research.*"

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015).

The HREC acknowledge that the student Lisa H Telford will also be involved in this project.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

APPENDIX 4: PLOS ONE INSTRUCTIONS FOR AUTHORS

PLOS ONE Submission Guidelines

STYLE AND FORMAT	
File Format	Manuscript files can be in the following formats: DOC, DOCX, or RTF. Microsoft Word documents should not be locked or protected.
Length	Manuscripts can be any length and there are no restrictions on word count, number of figures, or amount of supporting information. We encourage you to present and discuss your findings concisely.
Font	Use a standard font size and any standard font, except for the font named "Symbol". To add symbols to the manuscript, use the Insert → Symbol function in your word processor or paste in the appropriate Unicode character.
Headings	Limit manuscript sections and sub-sections to 3 heading levels. Make sure heading levels are clearly indicated in the manuscript text.
Layout & Spacing	Manuscript text should be double-spaced. Do not format text in multiple columns.
Page & Line Numbers	Include page numbers and line numbers in the manuscript file. Use continuous line numbers (do not restart the numbering on each page).
Footnotes	Footnotes are not permitted. If your manuscript contains footnotes, move the information into the main text or the reference list, depending on the content.
Language	Manuscripts must be submitted in English.
Abbreviations	Define abbreviations upon first appearance in the text. Do not use non-standard abbreviations unless they appear at least three times in the text. Keep abbreviations to a minimum.
Reference Style	PLOS uses "Vancouver" style
Nomenclature	Use correct and established nomenclature wherever possible.
MANUSCRIPT ORGANISATION	
Beginning Section	*The following elements are required, in order:* • Title page: List title, authors, and affiliations as first page of manuscript • Abstract • Introduction
Middle Section	*The following elements can be renamed as needed and presented in any order:* • Materials and Methods • Results • Discussion • Conclusions (optional)
Ending Section	*The following elements are required, in order:* • Acknowledgments • References • Supporting information captions (if applicable)
Other Elements	• Figure captions are inserted immediately after the first paragraph in which the figure is cited. Figure files are uploaded separately. • Tables are inserted immediately after the first paragraph in which they are cited. • Supporting information files are uploaded separately.

If your article is a systematic review or a meta-analysis you should:

- State this in your cover letter
- Select "Research Article" as your article type when submitting
- Include the PRISMA flow diagram as Fig 1 (required where applicable)
- Include the PRISMA checklist as supporting information

APPENDIX 5: PRISMA-DTA 2018 CHECKLIST

Section and Topic	Item No.	Description	Page (Part)
Title			
Title	1	Identify the report as a systematic review (meta-analysis) of DTA studies.	5 (Part C)
Abstract			
Abstract	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2 (Part C)
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 (Part C)
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for a comparative design).	4 (Part C)
Objectives	4	Provide an explicit statement of questions being addressed in terms of participants, index test, and target conditions.	5-7 (Part A)
Methods			
Protocol and registration	5	Indicate where the review protocol can be accessed (eg, web address) and provide trial registration number if available.	4 (Part C)
Eligibility criteria	6	Specify study characteristics (participants, setting, index test, reference standards, target conditions, and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility and providing rationale.	7 (Part A)
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and the date last searched.	8 (Part A)
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used so that they can be repeated.	9 (Part A)
Study selection	9	State the process for selecting studies (e.g., screening, eligibility, whether included in systematic review, and, if applicable, included in the meta-analysis).	10 (Part A)
Data collection process	10	Describe methods of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10-11 (Part A)
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target conditions, index tests, reference standards, and other characteristics (eg, study design, clinical setting).	See background document (Part D)
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	11-12 (Part A)

Diagnostic accuracy measures	13	State the principal diagnostic accuracy measures reported (eg, sensitivity, specificity) and state the unit of assessment (eg, per patient vs per lesion).	7 (Part A)
Synthesis of results	14	Describe the methods of handling the data, combining the results of the studies and describing the variability between studies. This could include, but is not limited to (1) handling of multiple definitions of the target condition, (2) handling of multiple thresholds of test positivity, (3) handling multiple index test readers, (4) handling of indeterminate test results, (5) grouping and comparing tests, and (6) handling of different reference standards.	13-14 (Part A)
Meta-analysis	D2	Report statistical methods used for meta-analyses if performed.	20 (Part C)
Additional analyses	16	Describe the methods of the additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	20-21 (Part C)
Results			
Study selection	17	Provide the numbers of studies screened, assessed for eligibility, included in the review, and included in the meta-analysis if applicable, with reasons for exclusions at each stage, ideally with a flow diagram.	4-5 (Part C)
Study characteristics	18	For each included study, provide citations and present key characteristics including (1) participant characteristics (presentation, prior testing), (2) clinical setting, (3) study design, (4) target condition definition, (5) index test, (6) reference standard, (7) sample size, and (8) funding sources.	6-8 (Part C)
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	9-11 (Part C)
Results of individual studies	20	For each analysis in each study (eg, unique combination of index test, reference standard, and positivity threshold), report 2 × 2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest plot or a receiver operating characteristic curve.	14, 16 & 18 (Part C)
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	13, 15 & 17 (Part C)
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression, analysis of index test, failure rates, proportion of inconclusive results, and adverse events).	19-21 (Part C)
Discussion			
Summary	24	Summarize the main findings including the strength of evidence.	21-25 (Part C)
Limitations	25	Discuss limitations from included studies (eg, risk of bias and concerns regarding applicability) and from the review process (eg, incomplete retrieval of identified research).	25 (Part C)
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (eg, the intended use and clinical role of the index test).	26-28 (Part C)
Funding			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	29 (Part C)

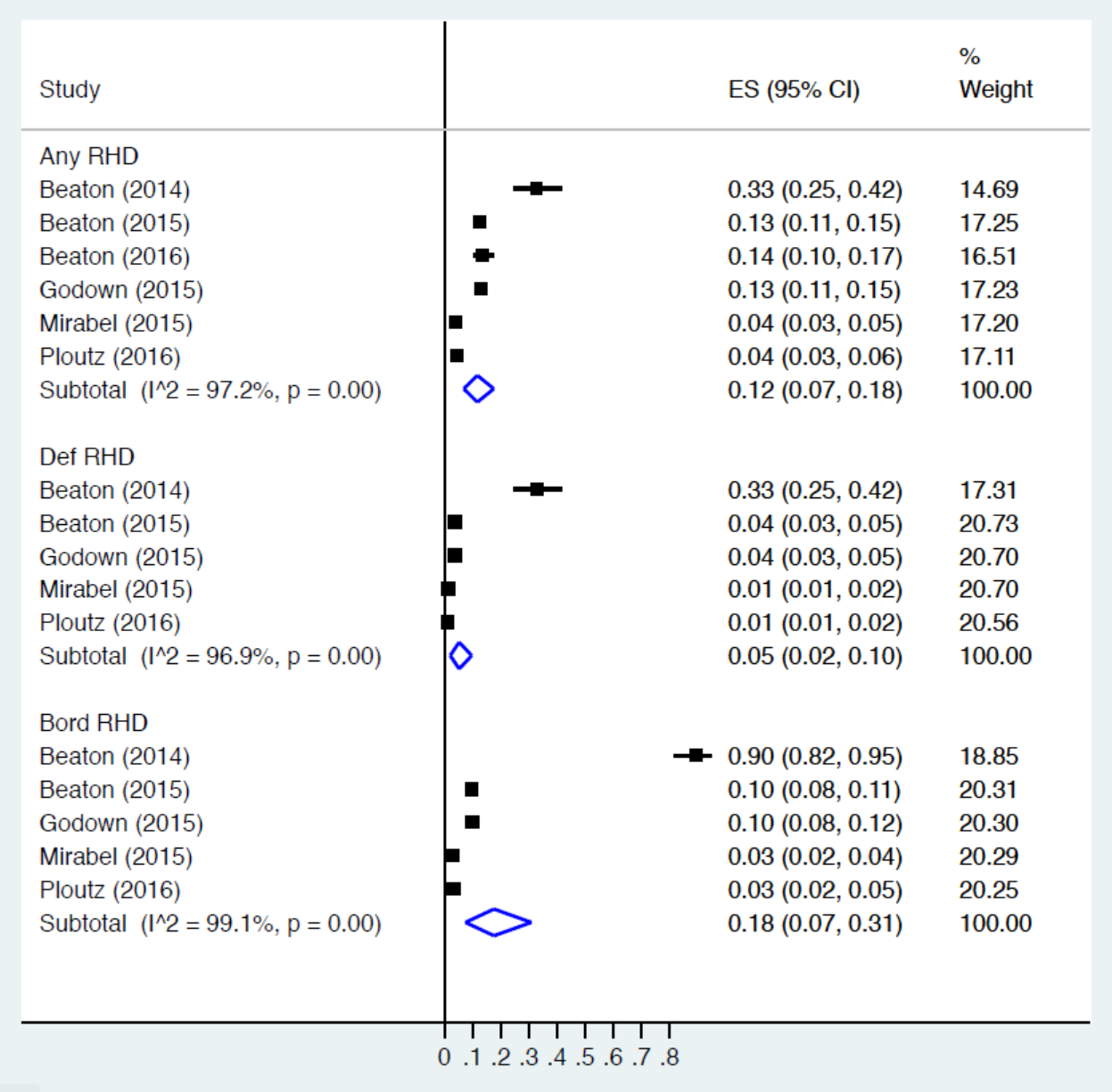
Abbreviations: FN, false negative; FP, false positive; TN, true negative; TP, true positive

From: McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM; and the PRISMA-DTA Group (2018). Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA 319(4): 388 - 396. doi: 10.1001/jama.2017.19163.

APPENDIX 6: SUPPLEMENTARY TABLES AND FIGURES

Appendix 6(a) pooled prevalence estimates

Figure 1. Forest plot of prevalence estimates*



*All pooled prevalence estimates were generated using STATA software.

APPENDIX 7: TECHNICAL APPENDICES

Appendix 7(a) statistical formulae and calculations

Supposing the means are given by M1, M2, M3 and M4 and the SD's are S1, S2, S3 and S4.

Let N1, N2, N3 and N4 represent the respective numbers of observations for each groups.

Formula for and calculation of the pooled mean:

Pooled mean = (N1*M1 + N2*M2 + N3*M3 + N4*M4) / (N1 + N2 + N3 + N4)

= (1217*9.6 + 397*13.9 + 956*11.1 + 1317*10.8 + 1420*10.8) / (1217 + 397 + 956 + 1317 + 1420)

= 10.8 years

Formula for and calculation of the pooled SD:

Pooled SD = {(N1-1)*S1 + (N2-1)*S2 + (N3-1)*S3 + (N4-1)*S4} / (N1 + N2 + N3 + N4)

= {(1217-1)*0.5 + (397-1)*2.6 + (956-1)*2.5 + (1317-1)*2.6 + (1420-1)*2.6} / (1217+397+956+1317+1420)

= 2.1