BMJ Open

Burden of disease and barriers to comprehensive care for rheumatic heart disease in South Africa: an updated systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-073300
Article Type:	Protocol
Date Submitted by the Author:	02-Mar-2023
Complete List of Authors:	Murugasen, Serini; University of Cape Town Faculty of Health Sciences, Division of Paediatric Cardiology, Department of Paediatrics and Child Health Abdullahi, Leyla ; African Institute for Development Policy Moloi, Hlengiwe; South African Medical Research Council Wyber, Rosemary; The George Institute for Global Health; Telethon Kids Institute, abrams, Jessica; University of Cape Town Faculty of Health Sciences, Division of Paediatric Cardiology, Department of Paediatrics and Child Health Watkins, DA; University of Washington School of Medicine, Department of Medicine Engel, Mark; University of Cape Town Faculty of Health Sciences, Department of Medicine, Cape Heart Institute ZUHLKE, LIESL; University of Cape Town Faculty of Health Sciences, Division of Paediatric Cardiology, Department of Paediatrics and Child Health; South African Medical Research Council
Keywords:	Systematic Review, Cardiac Epidemiology < CARDIOLOGY, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Burden of disease and barriers to comprehensive care for rheumatic heart disease in South Africa: an updated systematic review protocol

Serini Murugasen[1], Leila H Abdullahi[2], Hlengiwe Moloi[3], Rosemary Wyber[4,5], Jessica Abrams[1], David Watkins[6,7], Mark Engel[8], Liesl Zühlke[1,3,8,9]

Affiliations:

1. Division of Paediatric Cardiology, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town, South Africa
2. African Institute for Development Policy, Kenya
3. The South African Medical Research Council, South Africa
4. Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Australia
5. National Centre for Aboriginal and Torres Strait Islander Wellbeing Research, Australian National University, Australia
6. Department of Global Health, University of Washington, USA
7. Department of Medicine, School of Medicine, University of Washington, USA
8. Department of Medicine, Cape Heart Institute, Faculty of Health Sciences, University of Cape Town, South Africa
9. Institute of Infectious Diseases and Molecular medicine, Faculty of Health Sciences, University of Cape Town, South Africa

Corresponding author: Dr Serini Murugasen, serini.murugasen@uct.ac.za

Abstract

Introduction: Rheumatic heart disease is responsible for a significant burden of cardiovascular morbidity and mortality, and remains the most common cause of acquired heart disease in children, adolescents and young adults in developing countries. Substantial global heterogeneity in the burden of RHD among regions persists, with sub-Saharan Africa showing minimal improvement over the last decade. Additionally, the global COVID-19 pandemic has forced the emergency restructuring of many health systems including funding mechanisms, which has had a broad impact on health in general, including cardiovascular disease. Despite significant cost to the health system and estimates from 2015 indicating both high incidence and prevalence of RHD in South Africa, no cohesive national strategy exists. An updated review of national burden of disease estimates, as well as literature on barriers to care for patients with RHD, will provide crucial information to assist in the development of a national RHD programme.

Methods and analysis: Using pre-defined search terms that capture relevant disease processes from Group A Streptococcal (GAS) infection through to the sequelae of RHD, a search of archives covering all South African publications, including those not currently indexed, will be performed. All eligible studies on RHD, acute rheumatic fever and GAS infection published from April 2014 to December 2022 will be included. A standardised data extraction form will be used to capture results for both quantitative and qualitative analyses. All studies included in burden of disease estimates will undergo quality assessment using standardised tools. Updated estimates on mortality and morbidity as well as a synthesis of work on primary, secondary and tertiary prevention of RHD will be reported.

Ethics and dissemination: No ethics clearance is required for this study. Findings will be disseminated in a peer-reviewed journal and submitted to national stakeholders in RHD.

PROSPERO Registration number: CRD42023392782

Strengths and limitations of this study

1. This systematic review applies a broad search strategy and uses a mixed-methods approach to maximise capturing all relevant data on RHD in South Africa.

2. By defining this work within two distinct objectives, the search strategies, analysis and reporting methods can be adjusted to the most appropriate tools for the relevant literature.

3. This review only captures information from the last 8 years, but provides current estimates and trends and also allows further detail on the possible impact of the COVID-19 pandemic on the landscape of RHD in South Africa.

4. Studies dealing with challenges to implementing a national RHD programme will involve a wide variety of literature from different disciplines, including non-governmental organisations and ministry of health documents. A broader, more inclusive search strategy is needed, which will likely produce significant heterogeneity and preclude a formal quality assessment, and may limit the ability to draw objective conclusions from the data. However, this objective requires a broad scan of the literature and an analytic approach focused on general concepts and common themes.

1. Introduction

Rheumatic heart disease (RHD) develops as a consequence of acute rheumatic fever (ARF) caused by infection with Group A streptococcus (GAS). RHD is responsible for a significant burden of cardiovascular morbidity and mortality, and remains the most common cause of acquired heart disease in children, adolescents and young adults in developing countries. The global prevalence of RHD has been rising steadily since 1990, reaching 40.5 million (95% uncertainty interval (UI): 32.1 to 50.1 million) affected in 2019 (1). Despite the number of deaths due to RHD appearing to increase in recent years, there has been a reduction in disability-adjusted life years (DALYs) and years of life lost (YLLs) with a corresponding increase in years lived with a disability (YLDs) (1), most likely due to advances in surgery and diagnostics. There remains substantial global heterogeneity in the burden of RHD among regions, with sub-Saharan Africa showing minimal improvement over the 1990-2019 period according to the Global Burden of Disease (GBD) 2019 study's update on cardiovascular diseases (1).

In recognition of RHD as a significant, preventable cause of mortality and morbidity globally, the World Heart Federation (WHF) released a position statement in 2013 on its intention to reduce premature mortality from RHD by 25% in those aged <25 years by 2025 (25x25<25 goal) (2). Five key strategic targets were identified: comprehensive register-based control programmes, global access to benzathine penicillin G, identification and development of public figures as 'RHD champions', expansion of RHD training hubs, and support for vaccine development (2). Subsequently, the World Health Organisation (WHO) released a resolution at the 2018 World Health Assembly (WHA) urging member states to undertake similar key actions, including accelerating multisectoral efforts focused on prevention, improved disease surveillance and good-quality data collection and analysis that facilitate appropriate follow-up and contribute to a broader understanding of the global disease burden (3).

The sub-Saharan African region has seen significant financial and political change in the past decades, with the pace of per capita income growth in developing economies accelerating rapidly, substantially above that of advanced economies (4). Since the transition to democracy in South Africa (SA) in 1994, there have also been significant advances within the health care sector, with various new primary health care initiatives and a renewed focus on improved health care delivery which may impact on the profile of RHD in the country.

RHD was long thought to have its hotspot in Africa in the sub-Saharan region (5), which is borne out by findings in the GBD 2019 study (1), with RHD being endemic across the continent (6). Despite high rates of morbidity and mortality from RHD in East Africa, there is evidence of critical data gaps in the areas of GAS and ARF epidemiology as well as health care utilisation patterns and their determinants (7). Stakeholders across multiple sectors and countries are involved in addressing RHD in this region, highlighting the complexity and need for collaboration in building national RHD programmes in Africa (8). Earlier data from Johannesburg (1976) and Cape Town (1981), SA showed a prevalence of approximately seven per 1000 in school-aged children by cardiac auscultation (9,10). Surgical reports from the pre-1994 era reported significant morbidity and mortality of up to 8% per year, especially in the young (11). A 2015 systematic review on RHD in SA found that the overall crude incidence of symptomatic RHD was 24.7 per 100 000 (95% confidence interval (CI) 22.1 to 27.4) population per annum among adults (aged > 13 years) in Soweto, whilst the prevalence of asymptomatic echocardiographic RHD in schoolchildren was 20.2 cases per 1000 children (95% CI 15.3 to 26.2) in Cape Town (12). The 60-day mortality after admission with acute heart failure due to RHD was 24.8% (95% CI 13.6% to 42.5%) and 180-day mortality was 35.4% (95% CI 21.6% to 54.4%) (12). Postoperative mortality at 30 days was 2% (95% CI 0.0% to 4%), with post-surgical survival was over 75% at 5 years, and over 70% at 10 years (12). Cause-specific mortality rate per 100 000 population decreased from 1.27 (95% CI 1.17 to 1.39) in 1997 to 0.7 (95% CI 0.63 to 0.78) in 2012 (12). As children with RHD live longer and are diagnosed earlier, prevalence has increased in SA with better post-operative survival over the last two decades. However, despite an estimated total cost of RHD care at tertiary centres of USD 2 million in 2017 (13) - of which surgery costs accounted for 65% - no cohesive national RHD strategy has yet emerged in SA.

The global COVID-19 pandemic has forced the emergency restructuring of many health systems including funding mechanisms, which has had a broad impact on health in general, including cardiovascular disease (14). An updated systematic review will reveal the impact of these changes on RHD in SA, as well as clarifying the ongoing trends in incidence, prevalence and outcomes for those affected since the previous review in 2015 (12).

2. Objectives

2.1 Objective one: burden of disease from RHD in South Africa

Our primary objective is to review the most recent estimates of the incidence of newly diagnosed cases and the prevalence of existing RHD in SA, using observational studies published since the 2015 systematic review until December 2022, which is approximately three years after the onset of the global COVID-19 pandemic. Secondary objectives include characterising the fatal and non-fatal outcomes of RHD in SA (including but not limited to heart failure, atrial fibrillation and infective endocarditis), using case-fatality rates and cause-specific mortality rates, and identifying trends in the RHD burden over the same period.

2.2 Objective two: challenges to implementing a comprehensive national RHD programme

In addition, information on the challenges faced by SA in responding to the 2018 WHA RHD resolution (15) will be captured using the 5x5 framework for RHD programmes proposed by Reach (Rheumatic Heart Disease, Evidence, Advocacy, Communication and Hope www.stoprhd.org) (16). Specifically, this framework addresses prevention and control efforts at four levels (baseline, primary, secondary and tertiary) (16), with five main strategic areas identified: system/structure such as governance and finance, social determinants of health, inputs such as health workforce and access to medicines, current clinical services for RHD all levels as well as monitoring and evaluation, and impact or burden of disease from RHD. The last area will already be addressed in objective one, and so this objective focuses on the preceding four strategic areas.

3. Methods

This review protocol was registered with the PROSPERO International Prospective Register of systematic reviews (CRD42023392782 - http://www.crd.york.ac.uk/PROSPERO), prior to data collection and extraction.

3.1 Objective one: burden of disease from RHD, GAS infection and ARF in South Africa

This updated review will be designed to best control for the confounding selection and publication biases (17,18), with the findings reported using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (19). Where available, findings of randomised controlled trials will undergo a separate meta-analysis if there is sufficient data.

3.1.1 Inclusion and exclusion criteria

Similar methods to the previous 2015 systematic review will be employed (20). Any study reporting on the incidence or prevalence of RHD, that had been conducted in South Africa and published in English with patient recruitment already completed between March 2014 and December 2022 will be considered for inclusion. Studies during this same period that investigate burden of disease from GAS infection and ARF will also be considered.

Although RHD does not affect children younger than 3 years of age, there is no age restriction for the patient population. We will include any study that estimates one or more of the following epidemiological measures of disease burden from RHD, GAS infection and ARF: incidence, prevalence, remission rate, relative risk of mortality (i.e., excess mortality), or cause-specific mortality. In addition, we will consider any study of cardiovascular morbidity that quantified the attributable proportion of RHD, ARF or GAS cases, but limited

to disaggregated data pertaining to these conditions. The burden of RHD among pregnant South Africans will be included as estimates were last reported in 2014 (21,22).

The prevalence of RHD has previously been defined by screening programmes of subclinical disease in asymptomatic populations (23–25). Hospital-based studies, however, focus on clinical disease in symptomatic populations. As far as possible, we intend to elucidate diagnostic methods in both echocardiography screening studies and hospital-based studies. In the context of RHD, improvement in severity of valvular disease is due exclusively to medical, percutaneous or surgical intervention, requiring an exploration the surgical literature for rates of disease regression versus long-term progression (i.e., leading to mortality). Based on clinical experience, the most significant morbid outcomes of RHD include heart failure, ischaemic/thromboembolic or haemorrhagic stroke, atrial fibrillation (AF), infective endocarditis (IE), and valve repair or replacement.

Studies will be excluded if they focus on degenerative heart valve disease or rheumatological conditions other than RHD. Autopsy and necropsy studies will be omitted because consent rates are low for these procedures in South Africa, and their conclusions about mortality patterns are highly likely to be biased. Editorials, commentaries, and case reports will be excluded, but their reference lists will be searched for additional references worth consideration for inclusion. While the WHO recommends considering the inclusion of disease register data in burden-of-disease studies, there is evidence that such data collection is unreliable and not representative of the general population (26). From previous experience, rheumatic fever registers tend to exclude information regarding RHD and are thus excluded from our analysis (20). Although the latest South Africa Demographic and Health Survey (2016) does not contain primary data on RHD, we will use the mortality data in this review (27).

3.1.2 Search strategy

Using pre-defined search terms that capture relevant disease processes from GAS infection through to the sequelae of RHD (see Table 1), the three largest databases relevant to the

South African population will be searched: PubMed, ISI Web of Science, and SCOPUS. Additionally, to identify relevant conference proceedings, theses, and abstracts, a search of the following archives at the University of Cape Town's Health Sciences Library will be performed: Current and Completed Research (South Africa), SA Heart, and Sabinet African Journals (which covers all South African publications, including those not currently indexed). The search process will be managed using the online Rayyan platform. Vital registration data from Statistics South Africa will also be collected. Although vital statistics can be flawed, the Global Burden of Disease Study considers these an important source of mortality data, and incorporates specific methods for handling misclassifications and inconsistencies (28). Finally, a manual snowballing search of all reference lists of studies included in the final review will be performed. Given previous experience with the 2015 review (12), a substantial amount of 'grey' literature on RHD is anticipated and so the database search strategy is kept intentionally broad and redundant. Contact will be made with other South African cardiovascular disease researchers and practitioners, as well as with international experts on RHD, in order to identify unpublished works or to obtain additional information. All published and unpublished data will be subject to the same quality assessment and data extraction process.

Following an independent review of the titles and abstracts of the search results of all three databases by two researchers (SM and LA), a secondary review of the full-text manuscripts of potentially eligible reports will be performed. A tertiary review will be conducted, where potential discrepancies over the final inclusion list will be resolved by consensus discussion between the two primary reviewers (SM and LA), with arbitration by a third reviewer (LZ) if required.

3.1.3 Quality assessment and risk of bias

All studies deemed eligible for inclusion will undergo a quality assessment using study design-specific tools from the Joanna-Briggs Institute (29). The purpose of these checklists is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. The quality

assessment can then inform synthesis and interpretation of the results of the study within the systematic review. The number of questions vary among tools, but cover the sampling of study groups, identification and adjustment for confounders, allocation of interventions, validity and reliability of results and methods to address loss to follow up etc. A study must meet at least 80% of applicable criteria in order to be considered of "adequate quality", but studies will not be excluded based on the outcome of the quality assessment.

3.1.4 Data extraction

A standardised data extraction form will be utilised to extract information from included articles that will be independently duplicated (i.e., not split between the two authors) in order to improve reliability. The data extraction form will capture basic study characteristics, including objectives, study population, sample size, years and location of study, as well as study design. Disease-related parameters, including hospitalisation, secondary events, surgical interventions and mortality will be recorded too. Where study data are unclear, the original author of the manuscript will be contacted to clarify the findings. Where not provided, confidence intervals will be incorporated into the formula, SE = (upper limit-lower limit)/3.92 or calculated using the cii command in STATA® ver. 17. Where not stated, RHD mortality per 100,000 will be calculated as follows: RHD deaths/mid-year population. Where population number is not stated, this will be calculated by using age-specific incidence rates and cases stated in the original paper as follows: 100,000 X (number of cases/incidence per 10^5).

3.1.5 Data synthesis and analysis

Prevalence data from individual studies will be combined according to the Mantel-Haenszel method using random-effects meta-analysis, given the anticipated heterogeneity with prevalence studies. Heterogeneity will be evaluated using the χ2-based Q statistic (significant for $P<0.1$) and the I^2 statistic (>50% to be indicative of "notable" heterogeneity)

(30). Meta-analysis will be conducted using the *Metaprop* command(31) using Stata® (version 17). We will perform the Freeman-Tukey double arcsine transformation to ensure stabilisation of the variance of study prevalence ; the transformation is essential in minimising influence from studies with outliers before data are pooled together (31,32). We intend to investigate for potential publication bias, should the number of studies allow.

3.2 Objective two: challenges to implementing a comprehensive national RHD programme.

As conceptualised by Wyber in 2013 (16), this objective will look at 24 of the 25 specific facets of a comprehensive RHD programme, excluding burden of disease (Figure 1). The search strategy will be informed by the systematic review protocol published by Moloi et al, 2016 (33), which identified stakeholders in RHD in Uganda and Tanzania using a mixed-methods approach that included case series, reports, editorials/commentaries and grey literature (8).

3.2.1 Inclusion and exclusion criteria, search strategy and data management

Like objective one, all studies on RHD published between January 2014 and December 2022 (inclusive) are eligible for inclusion, with no age restriction on patient population. Studies during this same period that investigate relevant aspects of GAS infection and ARF, from preventative strategies to diagnosis and management will also be considered. The same limitation to English and human subjects will be applied. However, no restrictions in terms of study or publication type will be made as this objective requires a broad scan of the literature to ascertain information pertinent to the implementation of a national RHD programme. Articles unrelated to the topic of RHD, GAS, ARF, South Africa and health

services will be excluded. Articles already included in burden of disease estimates (i.e., objective one) will also be excluded unless they explicitly deal with the remaining 24 facets of a national RHD programme.

The same search strategy for databases as per objective one will be employed (Table 1). It is anticipated that the same initial results will be returned from each database search as per objective one. The search will be managed using the online Rayyan platform and search results will be exported to EndNote 20® software as reference manager. The title and abstracts will be reviewed by two independent researchers (SM and LA), with HM acting as arbitrator, using the following categories:

- *Category one:* factors influencing diagnosis
- *Category two:* factors influencing treatment or referral
- *Category three:* factors influencing adherence and retention in long-term care

All other articles will be excluded. No quality assessment or risk of bias assessment will be performed as this review is intended to provide broad comment on a national RHD strategy in South Africa, and all available information may be useful at this stage. South Africa also has a robust research community with much of the literature produced by known stakeholders and experts in the field of RHD. As such, it is anticipated that any grey literature, commentaries and editorials published in peer-reviewed journals will have input from one of these expert sources.

3.2.2 Data extraction, synthesis and analysis

Two reviewers will review the full text of each article and enter relevant information into a template for data extraction under the 5x5 framework for objective two. The information collected for each theme will then be combined following discussion by the two reviewers with any disputes mediated by a third reviewer.

The qualitative data will then undergo inductive analysis for overarching themes and inconsistencies, and reported under the five main strategic areas listed in section 2.2. If any numerical estimates are provided, they will be assessed to see if a formal quantitative meta-analysis is feasible, employing similar methods to objective one.

3.3 Presenting and reporting of results.

For both objectives, flow diagrams summarising the study selection process and detailing reasons for exclusion will be used as per 2015 PRISMA guidelines for reporting systematic reviews (34). This protocol as well as the final systematic review will be published in a peer-reviewed journal as was done with the previous 2015 systematic review (12,20). Additionally, this review may help to inform the further development of national RHD programmes, by mapping the current burden of disease from RHD, ARF and GAS infection, associated trends in morbidity and mortality, and challenges faced in South African in for effective prevention and control of RHD.

3.4 Outcomes

3.4.1 Objective one: burden of disease from RHD, GAS infection and ARF in South Africa

Incidence: We will tabulate crude age-specific incidence estimates per 100 000 persons per year in summary tables, along with their 95% confidence intervals (CI). To estimate pooled median incidence rates and assess for heterogeneity, we will fit random effects models to log-transformed observed incidence in STATA® ver. 17 (STATA Corp., TX). We will obtain

estimates of the median incidence and 25th and 75th percentiles of the distribution of true incidence by back-transforming the log estimates to the original incidence scale.

Prevalence: The pooled overall age-specific prevalence of RHD, GAS infection and ARF per 1000 persons will be calculated and expressed with a 95% CI, when appropriate. It is well known that, in screening for and diagnosing RHD, auscultation has limited sensitivity compared with echocardiography, which is the current reference test (23). Therefore, we will report only screening data detected by echocardiography, utilising the 2012 World Heart Federation criteria (35).

Data on both fatal and non-fatal outcomes will be expressed in the pooled analysis. We will tabulate estimates of crude age-specific mortality rates from ARF and RHD per 100,000 persons per year, along with their 95% CIs. Attributable proportions and the relative risks of fatal and non-fatal outcomes will be calculated when data were available, and 95% CIs will be generated using the 'cii' command in STATA® ver. 17. A measure of the consistency of results will be included and, in cases where data are not amenable to meta-analysis, a narrative summary will be presented. Any trends will be reported upon, either using meta-analytic methods such as meta-regression, if possible, or a detailed qualitative assessment.

3.4.2 Objective two: challenges to implementing a comprehensive national RHD programme

Findings will be reported under the five main strategic areas listed in section 2.2. General conclusions will be drawn using inductive analysis to comment on the current state of a national RHD programme in South Africa and the challenges faced in meeting the goals set by the 2018 WHA resolution on RHD. Where robust numerical estimates are found, a quantitative meta-analysis will be performed if feasible. Alternatively, reported estimates with their study context and limitations will be provided.

3.5 Dissemination and anticipated impact

This systematic review will produce current estimates of the burden of disease, including major causes of morbidity and mortality, from RHD, GAS infection and ARF in South Africa. This review will also produce a narrative synthesis on published literature addressing a range of challenges from primary through secondary to tertiary prevention efforts for RHD in the South African context. The conclusions of this review will be critical in providing national stakeholders, public health officials and policymakers with pooled contemporary data on RHD and its antecedent conditions of GAS infection and ARF, as well as possible comment on the impact of the COVID-19 pandemic on both the burden of disease and the restructuring of health services within the country. This information is essential in developing a national RHD programme, particularly in identifying priorities and opportunities within the existing health system. It is vital that any national health programme, particularly one that ambitiously seeks to address both prevention and treatment of RHD, is well-integrated into the existing health system, although this appears to be only partially achieved even in settings that are less resource-constrained than South Africa (36). This work will also help identify key areas for future research across sectors, which may encourage further collaboration among national stakeholders in RHD. The results of the proposed systematic review will be published in a peer-reviewed journal, allowing for wider dissemination beyond South Africa, which will feed into the current information on the profile of RHD in Africa (7,8).

4. Conclusion

Rheumatic heart disease remains an important cause of preventable morbidity and mortality worldwide. Current estimates of the burden of disease and barriers to care for this condition are crucial to facilitate development of a comprehensive national RHD programme in South Africa. The results of this review will inform national policy and provide public health officials with appropriate targets for primary and secondary prevention through diagnosis to chronic and specialised care for patients living with RHD.

Word count: 3674 words

Table 1 Search strategy

Database	*Search terms*	*Limits*
PubMed	((((rheumatic heart disease[Title/Abstract]) OR (rheumatic heart disease[MeSH Terms])) OR ((acute rheumatic fever[Title/Abstract]) OR (acute rheumatic fever[MeSH Terms]))) OR ((Strep sore throat[Title/Abstract]) OR (Strep infect*[Title/Abstract])) OR (streptococc*[Title/Abstract]))) AND ((South Afric*[Title/Abstract]) OR (Eastern Cape[Title/Abstract] OR Free State[Title/Abstract] OR Gauteng[Title/Abstract] OR KwaZulu-Natal[Title/Abstract] OR Limpopo[Title/Abstract] OR Mpumalanga[Title/Abstract] OR Northern Cape[Title/Abstract] OR North West[Title/Abstract] OR Western Cape[Title/Abstract]))	Limited to English and Humans. Restricted to March 2014 to December 2022
ISI Web of Science	((((TS=(rheumatic heart disease)) OR TS=(acute rheumatic fever)) OR TS=(streptococc*)) OR TS=(Strep sore throat OR Strep infect*)) AND (CU=(South Africa))	
SCOPUS	((TITLE-ABS-KEY(rheumatic heart disease) OR TITLE-ABS-KEY(acute rheumatic fever) OR TITLE-ABS-KEY(Streptococc*) OR (Strep sore throat) OR (Strep infect*)))) AND (TITLE-ABS-KEY(South Africa))	
Current and Completed Research	((rheumatic heart disease) OR (rheumatic fever) OR (streptococc*) OR (Strep sore throat) OR (Strep infect*)) AND (South Africa)	
Sabinet African Journals	((rheumatic heart disease) OR (rheumatic fever) OR (streptococc*) OR (Strep sore throat) OR (Strep infect*)) AND (South Africa)	
SA Heart	Manual search of titles over March 2014 – December 2022	
Statistics South Africa	Manual search of all reports on causes of death in South Africa published 2014-2022	

Figure 1. A conceptual framework for comprehensive, register-based RHD control programs (derived from Wyber, 2013).

References

1. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982–3021.
2. Remenyi B, Carapetis J, Wyber R, Taubert K, Mayosi BM. Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. Vol. 10, Nature Reviews Cardiology. 2013. p. 284–92.
3. White A. WHO Resolution on rheumatic heart disease. Eur Heart J [Internet]. 2018 Dec 21;39(48):4233. Available from: https://doi.org/10.1093/eurheartj/ehy764
4. Milanovic B. Global Inequality: From Class to Location, from Proletarians to Migrants. Glob Policy [Internet]. 2012;3(2):125–34. Available from: http://10.0.4.87/j.1758-5899.2012.00170.x
5. Carapetis JR, Steer AC, Mulholland EK, Weber M. The Global Burden of Group A Strep. Lancet Infect Dis. 2005;5(685–94):685–94.
6. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015. N Engl J Med. 2017;377(8):713–22.
7. Moloi AH, Mall S, Engel ME, Stafford R, Zhu ZW, Zühlke LJ, et al. The Health Systems Barriers and Facilitators for RHD Prevalence: An Epidemiological Meta-Analysis From Uganda and Tanzania. Glob Heart [Internet]. 2017;12(1):5-15.e3. Available from: http://dx.doi.org/10.1016/j.gheart.2016.12.002
8. Moloi H, Tulloch NL, Watkins D, Perkins S, Engel M, Abdullahi L, et al. Understanding the local and international stakeholders in rheumatic heart disease field in Tanzania and Uganda: A systematic stakeholder mapping. Int J Cardiol [Internet]. 2022;353:119–26. Available from: https://doi.org/10.1016/j.ijcard.2022.01.030
9. McLaren MJ, Hawkins DM, Koornhof HJ, Bloom KR, Bramwell-Jones DM, Cohen E, et al. Epidemiology of rheumatic heart disease in black shcoolchildren of Soweto, Johannesburg. Br Med J [Internet]. 1975 Aug 23;3(5981):474 LP – 478. Available from: http://www.bmj.com/content/3/5981/474.abstract
10. Bundred PE. The Place of Primary Care in the Prevention and Control of Rheumatic Fever and Rheumatic Heart Disease in Southern Africa: An Epidemiological Approach.

1987.

11. Antunes MJ. Valve repair for the treatment of rheumatic mitral regurgitation. Cardiovasc J South Africa [Internet]. 1997;87(5):C265–72. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-0030705222&partnerID=40&md5=eb4902947d52db87ded39bcf0ebb9a83
12. Zühlke LJ, Engel ME, Watkins D, Mayosi BM. Incidence, prevalence and outcome of rheumatic heart disease in South Africa: A systematic review of contemporary studies. Int J Cardiol [Internet]. 2015;199(April 2014):375–83. Available from: http://dx.doi.org/10.1016/j.ijcard.2015.06.145
13. Hellebo AG, Zuhlke LJ, Watkins DA, Alaba O. Health system costs of rheumatic heart disease care in South Africa. BMC Public Health [Internet]. 2021;21(1):1303. Available from: https://doi.org/10.1186/s12889-021-11314-6
14. Watkins DA. Cardiovascular health and COVID-19: Time to reinvent our systems and rethink our research priorities. Heart. 2020;106(24):1870–2.
15. Muhamed B, Mutithu D, Aremu O, Zühlke L, Sliwa K. Rheumatic fever and rheumatic heart disease: Facts and research progress in Africa. Int J Cardiol. 2019;295:48–55.
16. Wyber R. A conceptual framework for comprehensive rheumatic heart disease control programs. Glob Heart [Internet]. 2013;8(3):241–6. Available from: http://dx.doi.org/10.1016/j.gheart.2013.07.003
17. Mueller M, D'Addario M, Egger M, Cevallos M, Dekkers O, Mugglin C, et al. Methods to systematically review and meta-analyse observational studies: A systematic scoping review of recommendations. BMC Med Res Methodol. 2018;18(1):1–18.
18. Dekkers OM, Vandenbroucke JP, Cevallos M, Renehan AG, Altman DG, Egger M. COSMOS-E: Guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. PLOS Med [Internet]. 2019 Feb 21;16(2):e1002742. Available from: https://doi.org/10.1371/journal.pmed.1002742
19. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Jama. 2000;283(15):2008–12.
20. Zühlke L, Watkins D, Engel ME. Incidence, prevalence and outcomes of rheumatic heart disease in South Africa: A systematic review protocol. BMJ Open. 2014;4(6):1–6.
21. Watkins DA, Sebitloane M, Engel ME, Mayosi BM. The burden of antenatal heart

disease in South Africa: a systematic review. BMC Cardiovasc Disord [Internet]. 2012;12(1):23. Available from: https://doi.org/10.1186/1471-2261-12-23

22. Sliwa K, Libhaber E, Elliott C, Momberg Z, Osman A, Zühlke L, et al. Spectrum of cardiac disease in maternity in a low-resource cohort in South Africa. Heart [Internet]. 2014 Dec 15;100(24):1967 LP – 1974. Available from: http://heart.bmj.com/content/100/24/1967.abstract

23. Saxena A, Zühlke L, Wilson N. Echocardiographic Screening for Rheumatic Heart Disease: Issues for the Cardiology Community. Glob Heart [Internet]. 2013;8(3):197–202. Available from: https://www.sciencedirect.com/science/article/pii/S2211816013001105

24. Zühlke L, Mirabel M, Marijon E. Congenital heart disease and rheumatic heart disease in Africa: Recent advances and current priorities. Heart. 2013;99(21):1554–61.

25. Zühlke L, Mayosi BM. Echocardiographic Screening for Subclinical Rheumatic Heart Disease Remains a Research Tool Pending Studies of Impact on Prognosis. Curr Cardiol Rep [Internet]. 2013;15(3):343. Available from: https://doi.org/10.1007/s11886-012-0343-1

26. Nkgudi B, Mayosi BM, Robertson KA, Volmink J. Notification of rheumatic fever in South Africa - Evidence for underreporting by health care professionals and administrators. South African Med J. 2006;96(3):206–8.

27. National Department of Health (NDoH), Statistictics South Africa (Stats SA), South African Medical Research Council (SAMRC) I. South Africa Demographic and Health Survey 2016: Key findings. NDoH, Stats SA, SAMRC, ICF [Internet]. 2018;(January):1–20. Available from: http://documents1.worldbank.org/curated/en/688761571934946384/pdf/Doing-Business-2020-Comparing-Business-Regulation-in-190-Economies.pdf

28. Murray CJL, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. GBD 2010: design, definitions, and metrics. Lancet [Internet]. 2012;380(9859):2063–6. Available from: https://www.sciencedirect.com/science/article/pii/S0140673612618996

29. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K MP-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E MZ, editor. JBI Manual for Evidence Synthesis [Internet]. Joanna Briggs Institute; 2020. Available from: https://synthesismanual.jbi.global/

30. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med [Internet]. 2002;21(11):1539–58. Available from: http://europepmc.org/abstract/MED/12111919

31. Nyaga VN, Arbyn M, Aerts M. Metaprop: A Stata command to perform meta-analysis of binomial data. Arch Public Heal. 2014;72(1):1–10.

32. Lin L, Xu C. Arcsine-based transformations for meta-analysis of proportions: Pros, cons, and alternatives. Heal Sci Reports. 2020;3(3):1–6.

33. Moloi AH, Watkins D, Engel ME, Mall S, Zühlke L. Epidemiology, health systems and stakeholders in rheumatic heart disease in Africa: A systematic review protocol. BMJ Open. 2016;6(5).

34. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev [Internet]. 2015;4(1):1. Available from: https://doi.org/10.1186/2046-4053-4-1

35. Reméanyi B, Wilson N, Steer A, Ferreira B, Kado J, Kumar K, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease-an evidence-based guideline. Nat Rev Cardiol [Internet]. 2012;9(5):297–309. Available from: http://dx.doi.org/10.1038/nrcardio.2012.7

36. Abrams J, Watkins DA, Abdullahi LH, Zühlke LJ, Engel ME. Integrating the prevention and control of rheumatic heart disease into country health systems: A systematic review and meta-analysis. Glob Heart. 2020;15(1):1–14.

Author contributions

LZ and ME conceived of the review. SM wrote the first draft and took primary responsibility for all subsequent revisions, but all authors contributed input to the various versions. LZ and ME provided key scientific and statistical oversight of the protocol. All authors approved the final version of the protocol and given permission for publication.

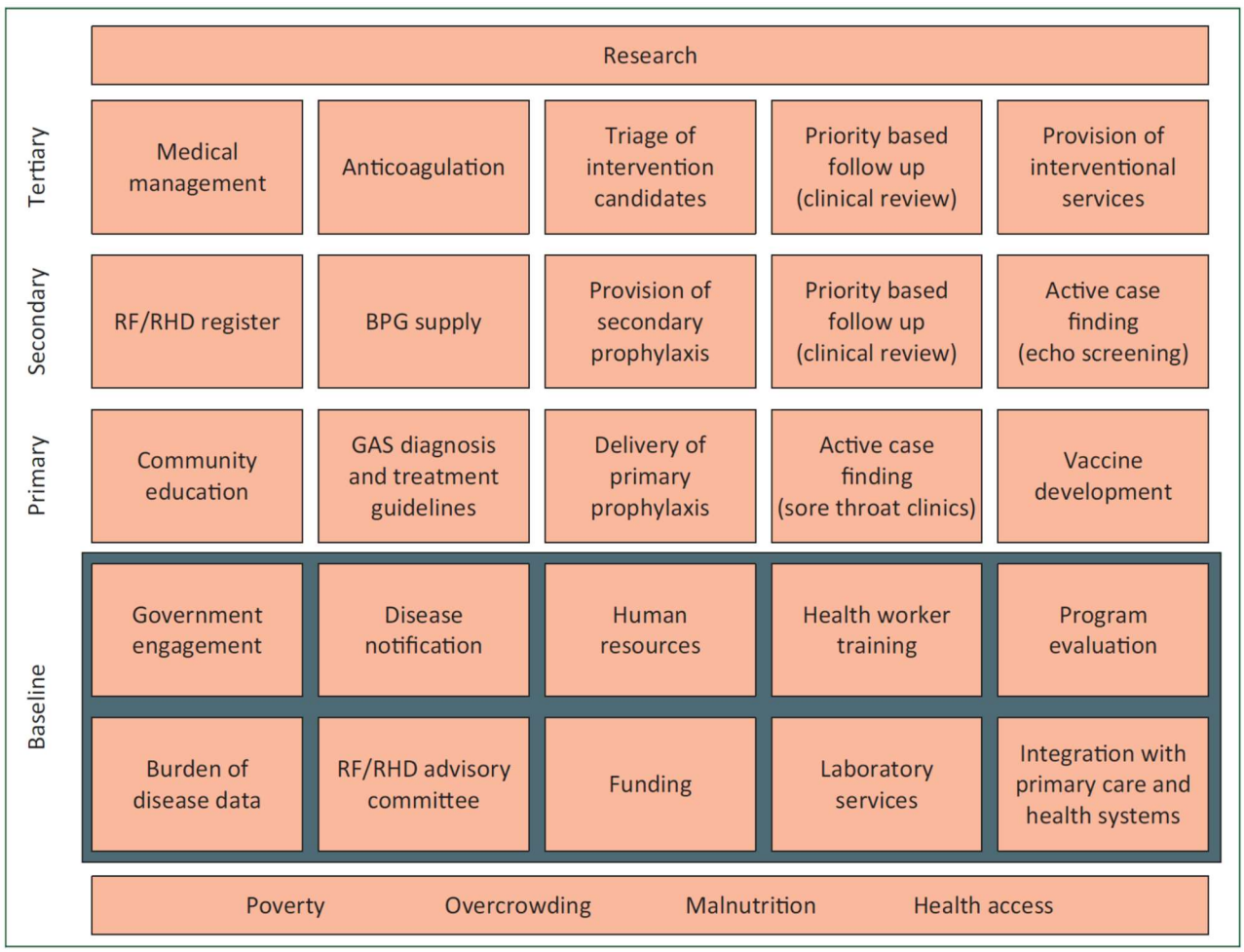
Funding

The work reported herein was made possible through funding by the South African Medical Research Council (SAMRC) through its Division of Research Capacity Development under the Mid-Career Scientist Programme from funding received from the South African National Treasury. The content hereof is the sole responsibility of the authors and do not necessarily represent the official views of the SAMRC. LZ also receives support from the National Research Foundation of South Africa (NRFSA), as well as the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement, via the African Research Leader Award (MR/S005242/1).

Competing interests

None declared.

Figure 1. A conceptual framework for comprehensive, register-based RHD control programs (derived from Wyber, 2013).



BPG: benzathine penicillin G; *GAS:* group A streptococcus; *RF:* rheumatic fever

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1,2,6
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2,8
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	24
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support			
Sources	#5a	Indicate sources of financial or other support for the review	24
Sponsor	#5b	Provide name for the review funder and / or sponsor	Not applicable
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Not applicable
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8,9,12
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9,10,12
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	18

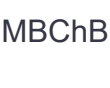
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10,12
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10,13
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11,13
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11,12,13
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	14,15
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10,11,13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11,12,13
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	11,12,13
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	11,12,13
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	11,12,13
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	15

Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

Title: Burden of disease and barriers to comprehensive care for rheumatic heart disease in South Africa: an updated systematic review protocol

Completed 23 February 2023.

Yours faithfully,



Dr Serini Murugasen

MBChB (UCT), MPH (Oxon), MSc (Oxon), FCPaed(SA), MMed(Paed) cum laude

Clinical Research Officer, Children's Heart Disease Research Unit

Department of Paediatrics and Child Health, University of Cape Town

BMJ Open

Burden of disease and barriers to comprehensive care for rheumatic heart disease in South Africa: an updated systematic review protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-073300.R1
Article Type:	Protocol
Date Submitted by the Author:	02-May-2023
Complete List of Authors:	Murugasen, Serini; University of Cape Town Faculty of Health Sciences, Division of Paediatric Cardiology, Department of Paediatrics and Child Health Abdullahi, Leyla ; African Institute for Development Policy Moloi, Hlengiwe; South African Medical Research Council Wyber, Rosemary; The George Institute for Global Health; Telethon Kids Institute, Abrams, Jessica; University of Cape Town Faculty of Health Sciences, Division of Paediatric Cardiology, Department of Paediatrics and Child Health Watkins, DA; University of Washington School of Medicine, Department of Medicine Engel, Mark E; University of Cape Town Faculty of Health Sciences, Department of Medicine, Cape Heart Institute ZUHLKE, LIESL; University of Cape Town Faculty of Health Sciences, Division of Paediatric Cardiology, Department of Paediatrics and Child Health; South African Medical Research Council
Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Epidemiology, Health services research, Public health
Keywords:	Systematic Review, Cardiac Epidemiology < CARDIOLOGY, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Burden of disease and barriers to comprehensive care for rheumatic heart disease in South Africa: an updated systematic review protocol

Serini Murugasen[1], Leyla H Abdullahi[2], Hlengiwe Moloi[3], Rosemary Wyber[4,5], Jessica Abrams[1], David Watkins[6,7], Mark Engel[8], Liesl Zühlke[1,3,8,9]

Affiliations:

1. Division of Paediatric Cardiology, Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Cape Town, South Africa
2. African Institute for Development Policy, Kenya
3. The South African Medical Research Council, Francie van Zijl Drive, Parow, South Africa
4. Wesfarmers Centre of Vaccines and Infectious Diseases, Telethon Kids Institute, Australia
5. National Centre for Aboriginal and Torres Strait Islander Wellbeing Research, Australian National University, Australia
6. Department of Global Health, University of Washington, USA
7. Department of Medicine, School of Medicine, University of Washington, USA
8. Department of Medicine, Cape Heart Institute, Faculty of Health Sciences, University of Cape Town, South Africa
9. Institute of Infectious Diseases and Molecular medicine, Faculty of Health Sciences, University of Cape Town, South Africa

Corresponding author: Dr Serini Murugasen, serini.murugasen@uct.ac.za

Abstract

Introduction: Rheumatic heart disease (RHD) is responsible for a significant burden of cardiovascular morbidity and mortality, and remains the most common cause of acquired heart disease among children and young adults in low- and middle-income countries. Additionally, the global COVID-19 pandemic has forced the emergency restructuring of many health systems, which has had a broad impact on health in general, including cardiovascular disease. Despite significant cost to the health system and estimates from 2015 indicating both high incidence and prevalence of RHD in South Africa, no cohesive national strategy exists. An updated review of national burden of disease estimates, as well as literature on barriers to care for patients with RHD, will provide crucial information to assist in the development of a national RHD programme.

Methods and analysis: Using pre-defined search terms that capture relevant disease processes from Group A Streptococcal (GAS) infection through to the sequelae of RHD, a search of PubMed, SCOPUS, ISI Web of Science, Sabinet African Journals, SA Heart and Current and Completed Research databases will be performed. All eligible studies on RHD, acute rheumatic fever and GAS infection published from April 2014 to December 2022 will be included. Vital registration data for the same period from Statistics South Africa will also be collected. A standardised data extraction form will be used to capture results for both quantitative and qualitative analyses. All studies included in burden of disease estimates will undergo quality assessment using standardised tools. Updated estimates on mortality and morbidity as well as a synthesis of work on primary, secondary and tertiary prevention of RHD will be reported.

Ethics and dissemination: No ethics clearance is required for this study. Findings will be disseminated in a peer-reviewed journal and submitted to national stakeholders in RHD.

PROSPERO Registration number: CRD42023392782

Strengths and limitations of this study

1. This systematic review applies a broad search strategy and uses a mixed-methods approach to maximise capturing all relevant data on RHD in South Africa.

2. By defining this work within two distinct objectives, the search strategies, analysis and reporting methods can be adjusted to the most appropriate tools for the relevant literature.

3. This review will provide current estimates and trends on the burden of disease from RHD in South Africa (Objective One) and also allow further detail on the possible impact of the COVID-19 pandemic on the landscape of RHD in this country.

4. Studies dealing with challenges to implementing a national RHD programme (Objective Two) will involve a wide variety of literature from different disciplines, including non-governmental organisations and ministry of health documents. A broader, more inclusive search strategy is needed, which will likely produce significant heterogeneity and preclude a formal quality assessment, and may limit the ability to draw objective conclusions from the data. However, this objective requires a broad scan of the literature and an analytic approach focused on general concepts and common themes.

1. Introduction

Rheumatic heart disease (RHD) develops as a consequence of acute rheumatic fever (ARF) caused by infection with Group A streptococcus (GAS). RHD is responsible for a significant burden of cardiovascular morbidity and mortality, and remains the most common cause of acquired heart disease in children, adolescents and young adults in low- and middle-income countries (LMICs). The global prevalence of RHD has been rising steadily since 1990, reaching 40.5 million (95% uncertainty interval (UI): 32.1 to 50.1 million) affected in 2019 [1]. Despite the number of deaths due to RHD appearing to increase in recent years, there has been a reduction in disability-adjusted life years (DALYs) and years of life lost (YLLs) with a corresponding increase in years lived with a disability (YLDs) [1], most likely due to advances in surgery and diagnostics. There remains substantial global heterogeneity in the burden of RHD among regions, with sub-Saharan Africa showing minimal improvement over the 1990-2019 period according to the Global Burden of Disease (GBD) 2019 study's update on cardiovascular diseases [1].

In recognition of RHD as a significant, preventable cause of mortality and morbidity globally, the World Heart Federation (WHF) released a position statement in 2013 on its intention to reduce premature mortality from RHD by 25% in those aged <25 years by 2025 (25x25<25 goal) [2]. Five key strategic targets were identified: comprehensive register-based control programmes, global access to benzathine penicillin G, identification and development of public figures as 'RHD champions', expansion of RHD training hubs, and support for GAS vaccine development [2]. Subsequently, the World Health Organization (WHO) released a resolution at the 2018 World Health Assembly (WHA) urging member states to undertake similar key actions, including accelerating multisectoral efforts focused on prevention, improved disease surveillance and good-quality data collection and analysis that facilitate appropriate follow-up and contribute to a broader understanding of the global disease burden [3].

The sub-Saharan African region has seen significant financial and political change in recent decades, with the pace of per capita income growth in LMICs economies accelerating rapidly, substantially above that of advanced economies [4]. Since the transition to democracy in South Africa (SA) in 1994, there have also been significant advances within the health care sector, with various new primary health care initiatives and a renewed focus on improved health care delivery which may impact on the profile of RHD in the country.

Although RHD was long thought to have its hotspot in Africa in the sub-Saharan region [5], as supported by findings in the GBD 2019 study [1], RHD appears to be endemic across the continent [6]. Despite high rates of morbidity and mortality from RHD in East Africa, there is evidence of critical data gaps in the areas of GAS and ARF epidemiology as well as health care utilisation patterns and their determinants [7]. Stakeholders across multiple sectors and countries are involved in addressing RHD in this region, highlighting the complexity and need for collaboration in building national RHD programmes in Africa [8]. Earlier data from Johannesburg (1976) and Cape Town (1981), SA showed a prevalence of approximately seven per 1000 in school-aged children by cardiac auscultation [9,10]. Surgical reports from the pre-1994 era reported significant morbidity and mortality of up to 8% per year, especially in the young [11]. A 2015 systematic review on RHD in SA found that the overall crude incidence of symptomatic RHD was 24.7 per 100 000 (95% confidence interval (CI) 22.1 to 27.4) population per annum among adults (aged > 13 years) in Soweto, whilst the prevalence of asymptomatic echocardiographic RHD in schoolchildren was 20.2 cases per 1000 children (95% CI 15.3 to 26.2) in Cape Town [12]. The 60-day mortality after admission with acute heart failure due to RHD was 24.8% (95% CI 13.6% to 42.5%) and 180-day mortality was 35.4% (95% CI 21.6% to 54.4%) [12]. Postoperative all-cause mortality at 30 days was 2% (95% CI 0.0% to 4%), with post-surgical survival was over 75% at 5 years, and over 70% at 10 years [12]. Cause-specific mortality rate per 100 000 population decreased from 1.27 (95% CI 1.17 to 1.39) in 1997 to 0.7 (95% CI 0.63 to 0.78) in 2012 [12]. As children with RHD live longer and are diagnosed earlier, prevalence of RHD has increased in SA with better post-operative survival over the last two decades. However, despite an estimated total cost of RHD care at tertiary centres of USD 2 million in 2017 [13] - of which surgery costs accounted for 65% - no cohesive national RHD strategy has yet emerged in SA.

The global COVID-19 pandemic has forced the emergency restructuring of many health systems including funding mechanisms, which has had a broad impact on health in general, including cardiovascular disease [14]. An updated systematic review will reveal any impact of these changes on RHD in SA, as well as clarifying the ongoing trends in incidence, prevalence and outcomes and identifying barriers to care for those affected since the previous review in 2015 [12].

2. Objectives

2.1 Objective one: burden of disease from RHD in South Africa

Our primary objective is to review the most recent estimates of the incidence of newly diagnosed cases and the prevalence of existing RHD in SA, using studies published since the 2015 systematic review until December 2022, which is approximately three years after the onset of the global COVID-19 pandemic. Secondary objectives include characterising the fatal and non-fatal outcomes of RHD in SA (including but not limited to heart failure, atrial fibrillation and infective endocarditis), using case-fatality rates and cause-specific mortality rates, and identifying trends in the RHD burden over the same period.

2.2 Objective two: challenges to implementing a comprehensive national RHD programme

In addition, information on the challenges faced by SA in responding to the 2018 WHA RHD resolution [15] will be captured using the 5x5 framework for RHD programmes proposed by Reach (Rheumatic Heart Disease, Evidence, Advocacy, Communication and Hope www.stoprhd.org) [16]. Specifically, this framework addresses prevention and control efforts at four levels (baseline, primary, secondary and tertiary) [16], with five main strategic areas identified: system/structure such as governance and finance, social determinants of health, inputs such as health workforce and access to medicines, current clinical services for RHD all levels as well as monitoring and evaluation, and impact or burden of disease from RHD. The last area will already be addressed in objective one, and so this objective focuses on the preceding four strategic areas.

3. Methods

This review protocol was registered with the PROSPERO International Prospective Register of systematic reviews (CRD42023392782 - http://www.crd.york.ac.uk/PROSPERO), prior to the start of data collection and extraction.

3.1 Objective one: burden of disease from RHD, GAS infection and ARF in South Africa

This updated review will be designed to best control for the confounding selection and publication biases [17,18], with the findings reported using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines [19]. Where available, findings of randomised controlled trials will undergo a separate meta-analysis if there is sufficient data.

3.1.1 Inclusion and exclusion criteria

Similar methods to the previous 2015 systematic review will be employed [20]. Any study reporting on the incidence or prevalence of RHD, that had been conducted in South Africa and published in English with patient recruitment already completed between March 2014 and December 2022 will be considered for inclusion. Studies during this same period that investigate burden of disease from GAS infection and ARF will also be considered.

Although RHD does not affect children younger than 3 years of age, there is no age restriction for the patient population. We will include any study that estimates one or more of the following epidemiological measures of disease burden from RHD, GAS infection and ARF: incidence, prevalence, remission rate, relative risk of mortality (i.e., excess mortality), or cause-specific mortality. In addition, we will consider any study of cardiovascular morbidity that quantified the attributable proportion of RHD, ARF or GAS cases, but limited

to disaggregated data pertaining to these conditions. The burden of RHD among pregnant South Africans will be included as estimates were last reported in 2014 [21,22].

The prevalence of RHD has previously been defined by screening programmes of subclinical disease in asymptomatic populations [23–25]. Hospital-based studies, however, focus on clinical disease in symptomatic populations. As far as possible, we intend to elucidate diagnostic methods in both echocardiography screening studies and hospital-based studies. In the context of RHD, improvement in severity of valvular disease is due exclusively to medical, percutaneous or surgical intervention, requiring an exploration the surgical literature for rates of disease regression versus long-term progression (i.e., leading to mortality). Based on clinical experience, the most significant morbid outcomes of RHD include heart failure, ischaemic/thromboembolic or haemorrhagic stroke, atrial fibrillation (AF), infective endocarditis (IE), and valve repair or replacement.

Studies will be excluded if they focus on degenerative heart valve disease or rheumatological conditions other than RHD. Autopsy and necropsy studies will be omitted because consent rates are low for these procedures in South Africa, and their conclusions about mortality patterns are highly likely to be biased. Editorials, commentaries, and case reports will be excluded, but their reference lists will be searched for additional references worth consideration for inclusion. While the WHO recommends considering the inclusion of disease register data in burden-of-disease studies, there is evidence that such data collection is unreliable and not representative of the general population [26]. From previous experience, rheumatic fever registers tend to exclude information regarding RHD and are thus excluded from our analysis [20]. Although the latest South Africa Demographic and Health Survey (2016) does not contain primary data on RHD, we will use the mortality data in this review [27].

3.1.2 Search strategy

Using pre-defined search terms that capture relevant disease processes from GAS infection through to the sequelae of RHD (see Table 1), the three largest databases relevant to the

South African population will be searched: PubMed, ISI Web of Science, and SCOPUS. The search strategy for this review is consistent with the original search strategy employed by Zuhlke et al [20], but has been updated to include terms relevant to ARF and GAS and is informed by the strategy employed by Moloi et al for their 2016 systematic review of RHD in Africa [28]. Additionally, to identify relevant conference proceedings, theses, and abstracts, a search of the following archives at the University of Cape Town's Health Sciences Library will be performed: Current and Completed Research (South Africa), SA Heart, and Sabinet African Journals (which covers all South African publications, including those not currently indexed). The search process will be managed using the online Rayyan platform and search results will be exported to EndNote 20® software as reference manager. Vital registration data from Statistics South Africa will also be collected. Although vital statistics can be flawed, the Global Burden of Disease Study considers these an important source of mortality data, and incorporates specific methods for handling misclassifications and inconsistencies [29]. Finally, a manual snowballing search of all reference lists of studies included in the final review will be performed. Given previous experience with the 2015 review [12], a substantial amount of 'grey' literature on RHD is anticipated and so the database search strategy is kept intentionally broad. Contact will be made with other South African cardiovascular disease researchers and practitioners, as well as with international experts on RHD, in order to identify unpublished works or to obtain additional information. All published and unpublished data will be subject to the same quality assessment and data extraction process.

Following an independent review of the titles and abstracts of the search results of all three databases by two researchers (SM and LA), a secondary review of the full-text manuscripts of potentially eligible reports will be performed. A tertiary review will be conducted, where potential discrepancies over the final inclusion list will be resolved by consensus discussion between the two primary reviewers (SM and LA), with arbitration by a third reviewer (LZ) if required.

3.1.3 Quality assessment and risk of bias

All studies deemed eligible for inclusion will undergo a quality assessment using study design-specific tools from the Joanna-Briggs Institute [30]. The purpose of these checklists is to assess the methodological quality of a study and to determine the extent to which a study has addressed the possibility of bias in its design, conduct and analysis. The quality assessment can then inform synthesis and interpretation of the results of the study within the systematic review. The number of questions vary among tools, but cover the sampling of study groups, identification and adjustment for confounders, allocation of interventions, validity and reliability of results and methods to address loss to follow up etc. A study must meet at least 80% of applicable criteria in order to be considered of "adequate quality", but studies will not be excluded based on the outcome of the quality assessment.

3.1.4 Data extraction

A standardised data extraction form - developed for this review and based on the template used for the original review by Zuhlke et al in 2015[12] - will be utilised to extract information from included articles that will be independently duplicated (i.e., not split between the two authors) in order to improve reliability. The data extraction form will capture basic study characteristics, including objectives, study population, sample size, years and location of study, as well as study design. Disease-related parameters, including hospitalisation, secondary events, surgical interventions and mortality will be recorded too. Where study data are unclear, the original author of the manuscript will be contacted to clarify the findings. Where not provided, confidence intervals will be incorporated into the formula, SE = (upper limit-lower limit)/3.92 or calculated using the cii command in STATA® ver. 17. Where not stated, RHD mortality per 100,000 will be calculated as follows: RHD deaths/mid-year population. Where population number is not stated, this will be calculated by using age-specific incidence rates and cases stated in the original paper as follows: 100,000 X (number of cases/incidence per 10^5).

3.1.5 Data synthesis and analysis

Prevalence data from individual studies will be combined according to the Mantel-Haenszel method using random-effects meta-analysis, given the anticipated heterogeneity with prevalence studies. Heterogeneity will be evaluated using the χ2-based Q statistic (significant for $P<0.1$) and the I^2 statistic (>50% to be indicative of "notable" heterogeneity) [31]. Meta-analysis will be conducted using the *Metaprop* command[32] using Stata® (version 17). We will perform the Freeman-Tukey double arcsine transformation to ensure stabilisation of the variance of study prevalence ; the transformation is essential in minimising influence from studies with outliers before data are pooled together [32,33]. To minimize publication bias, we will conduct an extensive literature search to identify completed studies or ongoing studies with preliminary results. If we include more than 10 studies, we will investigate publication bias by generating a funnel plot and using Egger's test to assess funnel plot asymmetry [34].

3.2 Objective two: challenges to implementing a comprehensive national RHD programme.

As conceptualised by Wyber in 2013 [16], this objective will look at 24 of the 25 specific facets of a comprehensive RHD programme, excluding burden of disease (Figure 1). The search strategy will be informed by the systematic review protocol published by Moloi et al, 2016 [28], which identified stakeholders in RHD in Uganda and Tanzania using a mixed-methods approach that included case series, reports, editorials/commentaries and grey literature [8].

3.2.1 Inclusion and exclusion criteria, search strategy and data management

Like objective one, all studies on RHD published between January 2014 and December 2022 (inclusive) are eligible for inclusion, with no age restriction on patient population. Studies during this same period that investigate relevant aspects of GAS infection and ARF, from preventative strategies to diagnosis and management will also be considered. The same limitation to English and human subjects will be applied. However, no restrictions in terms of study or publication type will be made as this objective requires a broad scan of the literature to ascertain information pertinent to the implementation of a national RHD programme. Articles unrelated to the topic of RHD, GAS, ARF, South Africa and health services will be excluded. Articles already included in burden of disease estimates (i.e., objective one) will also be excluded unless they explicitly deal with the remaining 24 facets of a national RHD programme.

The same search strategy for databases as per objective one will be employed (Table 1) and results will be managed via the online Rayyan platform and EndNote 20® software as above. It is anticipated that the same initial results will be returned from each database search as per objective one. The search will be managed using the online Rayyan platform and search results will be exported to EndNote 20® software as reference manager. The title and abstracts will be reviewed by two independent researchers (SM and LA), with HM acting as arbitrator, using the following categories:

- *Category one:* factors influencing diagnosis
- *Category two:* factors influencing treatment or referral
- *Category three:* factors influencing adherence and retention in long-term care

These three categories reflect the pathway of care that patients undergo from GAS infection through to the sequelae of RHD. Barriers at each point of care highlight issues that can then be captured under the five main strategic areas listed in section 2.2. For example, factors

influencing diagnosis (category one) could fall under system, inputs or current clinical services which overlap, but require involvement from multiple stakeholders to effect change. All other articles will be excluded. No quality assessment or risk of bias assessment will be performed as this review is intended to provide broad comment on a national RHD strategy in South Africa, and all available information may be useful at this stage. South Africa also has a robust research community with much of the literature produced by known stakeholders and experts in the field of RHD. As such, it is anticipated that any grey literature, commentaries and editorials published in peer-reviewed journals will have input from one of these expert sources.

3.2.2 Data extraction, synthesis and analysis

Two reviewers will review the full text of each article and enter relevant information into a template for data extraction under the 5x5 framework for objective two. The information collected for each theme will then be combined following discussion by the two reviewers with any disputes mediated by a third reviewer.

The qualitative data will then undergo inductive analysis for overarching themes and inconsistencies, and reported under the five main strategic areas listed in section 2.2. If any numerical estimates are provided, they will be assessed to see if a formal quantitative meta-analysis is feasible, employing similar methods to objective one.

3.3 Presenting and reporting of results.

For both objectives, flow diagrams summarising the study selection process and detailing reasons for exclusion will be used as per 2020 PRISMA guidelines for reporting systematic reviews [35]. This protocol as well as the final systematic review will be published in a peer-reviewed journal as was done with the previous 2015 systematic review [12,20].

Additionally, this review may help to inform the further development of national RHD programmes, by mapping the current burden of disease from RHD, ARF and GAS infection, associated trends in morbidity and mortality, and challenges faced in South African in for effective prevention and control of RHD.

3.4 Outcomes

3.4.1 Objective one: burden of disease from RHD, GAS infection and ARF in South Africa

Incidence: We will tabulate crude age-specific incidence estimates per 100 000 persons per year in summary tables, along with their 95% confidence intervals (CI). To estimate pooled median incidence rates and assess for heterogeneity, we will fit random effects models to log-transformed observed incidence in STATA® ver. 17 (STATA Corp., TX). We will obtain estimates of the median incidence and 25th and 75th percentiles of the distribution of true incidence by back-transforming the log estimates to the original incidence scale.

Prevalence: The pooled overall age-specific prevalence of RHD, GAS infection and ARF per 1000 persons will be calculated and expressed with a 95% CI, when appropriate. It is well known that, in screening for and diagnosing RHD, auscultation has limited sensitivity compared with echocardiography, which is the current reference test [23]. Therefore, we will report only screening data detected by echocardiography, utilising the 2012 World Heart Federation criteria [36].

Data on both fatal and non-fatal outcomes will be expressed in the pooled analysis. We will tabulate estimates of crude age-specific mortality rates from ARF and RHD per 100,000 persons per year, along with their 95% CIs. Attributable proportions and the relative risks of fatal and non-fatal outcomes will be calculated when data were available, and 95% CIs will be generated using the 'cii' command in STATA® ver. 17. A measure of the consistency of

results will be included and, in cases where data are not amenable to meta-analysis, a narrative summary will be presented. Any trends will be reported upon, either using meta-analytic methods such as meta-regression, if possible, or a detailed quantitative assessment.

3.4.2 Objective two: challenges to implementing a comprehensive national RHD programme

Findings will be reported under the five main strategic areas listed in section 2.2. General conclusions will be drawn using inductive analysis to comment on the current state of a national RHD programme in South Africa and the challenges faced in meeting the goals set by the 2018 WHA resolution on RHD. Where robust numerical estimates are found, a quantitative meta-analysis will be performed if feasible. Alternatively, reported estimates with their study context and limitations will be provided.

3.5 Patient and public involvement

There was no direct patient or public involvement in the design of this protocol and none is anticipated in the course of the review.

4. Discussion

4.1 Strengths and limitations of proposed review

There are several strengths to this systematic review. This protocol applies a broad search strategy and uses a mixed-methods approach to maximise capturing all relevant data on RHD in South Africa. By defining this work within two distinct objectives, the search strategies, analysis and reporting methods can be adjusted to the most appropriate tools for the relevant literature. This review will provide current estimates and trends on the burden of disease from RHD in South Africa (Objective One) and also allow further detail on the possible impact of the COVID-19 pandemic on the landscape of RHD in this country.

As with any study, several limitations are anticipated. Studies dealing with challenges to implementing a national RHD programme (Objective Two) will involve a wide variety of literature from different disciplines, including non-governmental organisations and ministry of health documents. In addition, we intend to use key networks to identify relevant unpublished literature which may limit the reproducibility of this review. However, a broader, more inclusive search strategy is needed, which will likely produce significant heterogeneity and preclude a formal quality assessment, and may limit the ability to draw objective conclusions from the data. However, this objective requires a broad scan of the literature and an analytic approach focused on general concepts and common themes.

4.2 Dissemination and anticipated impact

This systematic review will produce current estimates of the burden of disease, including major causes of morbidity and mortality, from RHD, GAS infection and ARF in South Africa. This review will also produce a narrative synthesis on published literature addressing a range of challenges from primary through secondary to tertiary prevention efforts for RHD in the South African context. The conclusions of this review will be critical in providing national stakeholders, public health officials and policymakers with pooled contemporary

data on RHD and its antecedent conditions of GAS infection and ARF, as well as possible comment on the impact of the COVID-19 pandemic on both the burden of disease and the restructuring of health services within the country. This information is essential in developing a national RHD programme, particularly in identifying priorities and opportunities within the existing health system. The results of this review will inform national policy and provide public health officials with appropriate targets for primary and secondary prevention through diagnosis to chronic and specialised care for patients living with RHD. It is vital that any national health programme, particularly one that ambitiously seeks to address both prevention and treatment of RHD, is well-integrated into the existing health system, although this appears to be only partially achieved even in settings that are less resource-constrained than South Africa [37]. This work will also help identify key areas for future research across sectors, which may encourage further collaboration among national stakeholders in RHD. The results of the proposed systematic review will be published in a peer-reviewed journal, allowing for wider dissemination beyond South Africa, which will feed into the current information on the profile of RHD in Africa [7,8].

Word count: 4099 words

Table 1 Search strategy

Database	*Search terms*	*Limits*
PubMed	((((rheumatic heart disease[Title/Abstract]) OR (rheumatic heart disease[MeSH Terms])) OR ((acute rheumatic fever[Title/Abstract]) OR (acute rheumatic fever[MeSH Terms]))) OR ((Strep sore throat[Title/Abstract]) OR (Strep infect*[Title/Abstract]) OR (streptococc*[Title/Abstract]))) AND ((South Afric*[Title/Abstract]) OR (Eastern Cape[Title/Abstract] OR Free State[Title/Abstract] OR Gauteng[Title/Abstract] OR KwaZulu-Natal[Title/Abstract] OR Limpopo[Title/Abstract] OR Mpumalanga[Title/Abstract] OR Northern Cape[Title/Abstract] OR North West[Title/Abstract] OR Western Cape[Title/Abstract]))	
ISI Web of Science	((((TS=(rheumatic heart disease)) OR TS=(acute rheumatic fever)) OR TS=(streptococc*)) OR TS=(Strep sore throat OR Strep infect*)) AND (CU=(South Africa))	Limited to English and Humans. Restricted to March 2014 to December 2022
SCOPUS	((TITLE-ABS-KEY(rheumatic heart disease) OR TITLE-ABS-KEY(acute rheumatic fever) OR TITLE-ABS-KEY(Streptococc*) OR (Strep sore throat) OR (Strep infect*)))) AND (TITLE-ABS-KEY(South Africa))	
Current and Completed Research	((rheumatic heart disease) OR (rheumatic fever) OR (streptococc*) OR (Strep sore throat) OR (Strep infect*)) AND (South Africa)	
Sabinet African Journals	((rheumatic heart disease) OR (rheumatic fever) OR (streptococc*) OR (Strep sore throat) OR (Strep infect*)) AND (South Africa)	
SA Heart	Manual search of titles over March 2014 – December 2022	

Statistics South Africa	Manual search of all reports on causes of death in South Africa published 2014-2022	

Figure 1. A conceptual framework for comprehensive, register-based RHD control programs (derived from Wyber, 2013).

Author contributions

LZ and ME conceived of the review. SM wrote the first draft and took primary responsibility for all subsequent revisions. LA, HM, RW, JA, DAW, ME and LZ contributed input to the various versions on search strategy, risk of bias assessments and planned analytic strategy. LZ and ME provided key scientific and statistical oversight of the protocol. All authors approved the final version of the protocol and gave permission for publication.

Funding

The work reported herein was made possible through funding by the South African Medical Research Council (SAMRC) through its Division of Research Capacity Development under the Mid-Career Scientist Programme from funding received from the South African National Treasury. The content hereof is the sole responsibility of the authors and do not necessarily represent the official views of the SAMRC. LZ also receives support from the National Research Foundation of South Africa (NRFSA), as well as the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement, via the African Research Leader Award (MR/S005242/1).

Competing interests

None declared.

References

1 Roth GA, Mensah GA, Johnson CO, *et al.* Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020;**76**:2982–3021. doi:10.1016/j.jacc.2020.11.010

2 Remenyi B, Carapetis J, Wyber R, *et al.* Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. Nat. Rev. Cardiol. 2013;**10**:284–92. doi:10.1038/nrcardio.2013.34

3 White A. WHO Resolution on rheumatic heart disease. *Eur Heart J* 2018;**39**:4233. doi:10.1093/eurheartj/ehy764

4 Milanovic B. Global Inequality: From Class to Location, from Proletarians to Migrants. *Glob Policy* 2012;**3**:125–34. doi:10.1111/j.1758-5899.2012.00170.x

5 Carapetis JR, Steer AC, Mulholland EK, *et al.* The Global Burden of Group A Strep. *Lancet Infect Dis* 2005;**5**:685–94.

6 Watkins DA, Johnson CO, Colquhoun SM, *et al.* Global, Regional, and National Burden of Rheumatic Heart Disease, 1990–2015. *N Engl J Med* 2017;**377**:713–22. doi:10.1056/nejmoa1603693

7 Moloi AH, Mall S, Engel ME, *et al.* The Health Systems Barriers and Facilitators for RHD Prevalence: An Epidemiological Meta-Analysis From Uganda and Tanzania. *Glob Heart* 2017;**12**:5-15.e3. doi:10.1016/j.gheart.2016.12.002

8 Moloi H, Tulloch NL, Watkins D, *et al.* Understanding the local and international stakeholders in rheumatic heart disease field in Tanzania and Uganda: A systematic stakeholder mapping. *Int J Cardiol* 2022;**353**:119–26. doi:10.1016/j.ijcard.2022.01.030

9 McLaren MJ, Hawkins DM, Koornhof HJ, *et al.* Epidemiology of rheumatic heart disease in black shcoolchildren of Soweto, Johannesburg. *Br Med J* 1975;**3**:474 LP – 478. doi:10.1136/bmj.3.5981.474

10 Bundred PE. *The Place of Primary Care in the Prevention and Control of Rheumatic Fever and Rheumatic Heart Disease in Southern Africa: An Epidemiological Approach*. (Doctoral dissertation) 1987.

11 Antunes MJ. Valve repair for the treatment of rheumatic mitral regurgitation. *Cardiovasc J South Africa* 1997;**87**:C265–72.

12 Zühlke LJ, Engel ME, Watkins D, *et al.* Incidence, prevalence and outcome of

rheumatic heart disease in South Africa: A systematic review of contemporary studies. *Int J Cardiol* 2015;**199**:375–83. doi:10.1016/j.ijcard.2015.06.145

13 Hellebo AG, Zuhlke LJ, Watkins DA, *et al.* Health system costs of rheumatic heart disease care in South Africa. *BMC Public Health* 2021;**21**:1303. doi:10.1186/s12889-021-11314-6

14 Watkins DA. Cardiovascular health and COVID-19: Time to reinvent our systems and rethink our research priorities. *Heart* 2020;**106**:1870–2. doi:10.1136/heartjnl-2020-318323

15 Muhamed B, Mutithu D, Aremu O, *et al.* Rheumatic fever and rheumatic heart disease: Facts and research progress in Africa. *Int J Cardiol* 2019;**295**:48–55. doi:10.1016/j.ijcard.2019.07.079

16 Wyber R. A conceptual framework for comprehensive rheumatic heart disease control programs. *Glob Heart* 2013;**8**:241–6. doi:10.1016/j.gheart.2013.07.003

17 Mueller M, D'Addario M, Egger M, *et al.* Methods to systematically review and meta-analyse observational studies: A systematic scoping review of recommendations. *BMC Med Res Methodol* 2018;**18**:1–18. doi:10.1186/s12874-018-0495-9

18 Dekkers OM, Vandenbroucke JP, Cevallos M, *et al.* COSMOS-E: Guidance on conducting systematic reviews and meta-analyses of observational studies of etiology. *PLOS Med* 2019;**16**:e1002742. doi:10.1371/journal.pmed.1002742

19 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. *Jama* 2000;**283**:2008–12.

20 Zühlke L, Watkins D, Engel ME. Incidence, prevalence and outcomes of rheumatic heart disease in South Africa: A systematic review protocol. *BMJ Open* 2014;**4**:1–6. doi:10.1136/bmjopen-2014-004844

21 Watkins DA, Sebitloane M, Engel ME, *et al.* The burden of antenatal heart disease in South Africa: a systematic review. *BMC Cardiovasc Disord* 2012;**12**:23. doi:10.1186/1471-2261-12-23

22 Sliwa K, Libhaber E, Elliott C, *et al.* Spectrum of cardiac disease in maternity in a low-resource cohort in South Africa. *Heart* 2014;**100**:1967 LP – 1974. doi:10.1136/heartjnl-2014-306199

23 Saxena A, Zühlke L, Wilson N. Echocardiographic Screening for Rheumatic Heart Disease: Issues for the Cardiology Community. *Glob Heart* 2013;**8**:197–202.

doi:10.1016/j.gheart.2013.08.004

24 Zühlke L, Mirabel M, Marijon E. Congenital heart disease and rheumatic heart disease in Africa: Recent advances and current priorities. *Heart* 2013;**99**:1554–61. doi:10.1136/heartjnl-2013-303896

25 Zühlke L, Mayosi BM. Echocardiographic Screening for Subclinical Rheumatic Heart Disease Remains a Research Tool Pending Studies of Impact on Prognosis. *Curr Cardiol Rep* 2013;**15**:343. doi:10.1007/s11886-012-0343-1

26 Nkgudi B, Mayosi BM, Robertson KA, *et al.* Notification of rheumatic fever in South Africa - Evidence for underreporting by health care professionals and administrators. *South African Med J* 2006;**96**:206–8.

27 National Department of Health (NDoH), Statistictics South Africa (Stats SA), South African Medical Research Council (SAMRC) I. South Africa Demographic and Health Survey 2016: Key findings. *NDoH, Stats SA, SAMRC, ICF* 2018;:1–20.

28 Moloi AH, Watkins D, Engel ME, *et al.* Epidemiology, health systems and stakeholders in rheumatic heart disease in Africa: A systematic review protocol. *BMJ Open* 2016;**6**. doi:10.1136/bmjopen-2016-011266

29 Murray CJL, Ezzati M, Flaxman AD, *et al.* GBD 2010: design, definitions, and metrics. *Lancet* 2012;**380**:2063–6. doi:10.1016/S0140-6736(12)61899-6

30 Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K MP-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E MZ, ed. *JBI Manual for Evidence Synthesis*. Joanna Briggs Institute 2020. doi:https://doi.org/10.46658/JBIMES-20-08

31 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. In: *Statistics in medicine*. MRC Biostatistics Unit, Institute of Public Health, Robinson Way, Cambridge CB2 2SR, UK.: 2002. 1539–58. doi:10.1002/sim.1186

32 Nyaga VN, Arbyn M, Aerts M. Metaprop: A Stata command to perform meta-analysis of binomial data. *Arch Public Heal* 2014;**72**:1–10. doi:10.1186/2049-3258-72-39

33 Lin L, Xu C. Arcsine-based transformations for meta-analysis of proportions: Pros, cons, and alternatives. *Heal Sci Reports* 2020;**3**:1–6. doi:10.1002/hsr2.178

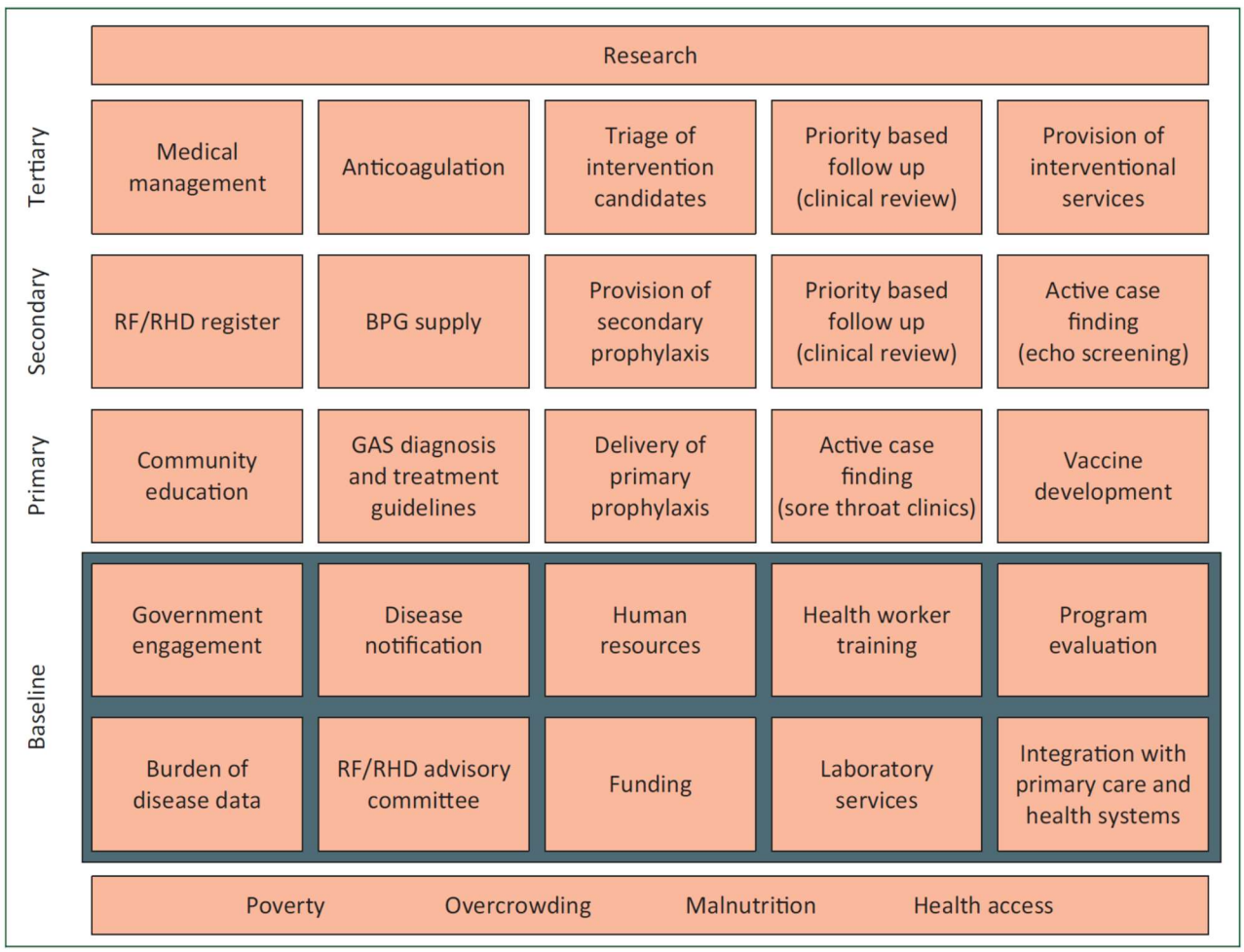
34 Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M et al. Chapter 23: Including variants on randomized trials. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Cochrane Training 2020. 6:1–48.

35 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. doi:10.1136/bmj.n71

36 Reméanyi B, Wilson N, Steer A, *et al.* World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease-an evidence-based guideline. *Nat Rev Cardiol* 2012;**9**:297–309. doi:10.1038/nrcardio.2012.7

37 Abrams J, Watkins DA, Abdullahi LH, *et al.* Integrating the prevention and control of rheumatic heart disease into country health systems: A systematic review and meta-analysis. *Glob Heart* 2020;**15**:1–14. doi:10.5334/GH.874

Figure 1. A conceptual framework for comprehensive, register-based RHD control programs (derived from Wyber, 2013).



BPG: benzathine penicillin G; *GAS:* group A streptococcus; *RF:* rheumatic fever

Reporting checklist for protocol of a systematic review and meta analysis.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	1
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2, 8
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the	24

		guarantor of the review	
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support			
Sources	#5a	Indicate sources of financial or other support for the review	24
Sponsor	#5b	Provide name for the review funder and / or sponsor	n/a
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	24
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9, 12-13
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	9-10, 13
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9-10, 12-13
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10, 13
Study records -	#11b	State the process that will be used for selecting studies (such	10, 13

selection process		as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	11, 14
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	11, 13-14
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	14-15
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11, 13
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	11-12, 14
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	14-15
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14-15
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14,15
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11-12
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11-12, 15

Notes:

- 10: 9-10, 12-13 The PRISMA-P elaboration and explanation paper is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 27. April 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Title: Burden of disease and barriers to comprehensive care for rheumatic heart disease in South Africa: an updated systematic review protocol

Completed 27 April 2023.

Yours faithfully,

Dr Serini Murugasen

MBChB (UCT), MPH (Oxon), MSc (Oxon), FCPaed(SA), MMed(Paed) cum laude

Clinical Research Officer, Children's Heart Disease Research Unit

Department of Paediatrics and Child Health, University of Cape Town