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Incidence, prevalence and outcomes of rheumatic heart disease in South Africa: a systematic review protocol

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ABSTRACT

Background: Rheumatic heart disease (RHD) is the principal cause of acquired heart disease affecting people living largely in poverty and deprived conditions. Sub-Saharan Africa was long thought to be the hotspot of the disease but recent reports suggest that this is no longer the case. South Africa is the leading economic force within this region yet contends with continued extreme income disparities. It is of interest to ascertain whether the strides that have been made in healthcare since the democratic transition in South Africa have translated into decreased RHD burden. We therefore propose to review the current best estimates of incidence of newly diagnosed RHD and prevalence of existing RHD within the past two decades. We also propose to characterise the fatal and non-fatal outcomes of RHD and identify any trends in this period.

Methods and design: We plan to search electronic databases and reference lists of relevant articles published from April 1994 to April 2014. Studies will be included if they estimated one of the following epidemiological measures: incidence, prevalence, remission rate, relative risk of mortality or cause-specific mortality. For studies deemed eligible for inclusion, we will assess overall study quality, reliability and risk of bias using design-specific criteria. We will extract data using a standardised form and perform descriptive and quantitative analysis to assess RHD prevalence, mortality and morbidity. This review protocol is registered in the PROSPERO International Prospective Register of systematic reviews, registration number CRD42014007072.

Dissemination: Our planned review will provide healthcare providers, public health officials and policymakers with pooled contemporary data regarding RHD, in particular regarding the effect the new political dispensation has had on the burden of this preventable disease within South Africa. In addition, these important country-specific data could influence policy decisions regarding prevention, management and control of RHD.

Strengths and limitations of the study

- Protocols provide researchers the opportunity to be informed of current research—this is of importance in rheumatic heart disease, which is traditionally a neglected disease.
- This protocol informs researchers of a planned review, which could potentially provide important information regarding the burden of rheumatic heart disease in the current era in the most important economic force in Sub-Saharan Africa.
- This is only the protocol which will be followed by the review in due course; hence, inferences regarding outcomes cannot be reliably made.
- The time period chosen is short; however, it speaks of an important era in South Africa in which significant public health changes have been made which theoretically could have impacted on the burden of rheumatic heart disease in the country. Currently, little information exists regarding the trends in the burden of rheumatic heart disease in South Africa.

BACKGROUND

Rheumatic heart disease (RHD) is the principal cause of acquired heart disease in the world, particularly targeting children, adolescents and young adults.[1] It is the only long-term sequel of acute rheumatic fever and is conservatively estimated to affect 36 million people worldwide, the majority of whom are living in impoverished and marginalised settings.[2]

Sub-Saharan Africa was long thought to be the region of the world with the greatest burden of RHD; a school screening study using auscultation conducted in Soweto in 1974 reported a prevalence of 5.9/1000 in asymptomatic schoolchildren[3] while several surgical reviews published in the following decade reported significant morbidity and mortality associated with chronic RHD.[4 5] Recent evidence, however, suggests that this distinction may now apply to the Central Asian republics.[6] South Africa has emerged as a leading economic force within the Sub-Saharan region, with major sociopolitical changes since the transition to democratic leadership and the first free elections in

1994. Yet extreme income disparities still remain. South Africa has the dubious distinction of having the highest income inequality in the world, which is comparable only with Brazil and Chile.[7] These disparities translate to continued high levels of diseases of poverty in the population, such as RHD and tuberculosis, resulting in significant morbidity and mortality.[8]

In the period since 1994, there have been significant advances within the healthcare sector with primary healthcare initiatives, renewed focus on improved healthcare delivery and a national healthcare insurance pilot.[9] It is of interest to ascertain whether these efforts have translated into decreased RHD burden within the country. We thus propose to critically appraise the contemporary estimates of burden of RHD disease in the period 1994–2014 and report on the fatal and non-fatal outcomes of RHD. Our primary objective is to review the current best estimates of incidence of newly diagnosed RHD and prevalence of existing RHD using observational studies published within the past two decades. We also propose to characterise the fatal and non-fatal outcomes of RHD using case death rates and cause-specific mortality rates and identify any trends in the past 20 years in terms of RHD burden.

METHODS AND DESIGN

This review protocol has been published in the PROSPERO International Prospective Register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42014007072.

Inclusion and exclusion criteria

Any study reporting the incidence or prevalence of RHD that were conducted in South Africa and published in English or Afrikaans between the periods 27 April 1994 and 26 April 2014 will be considered.

No age restrictions will be used during the article retrieval process. We will include any study that estimated one or more of the following epidemiological measures of RHD burden: incidence, prevalence, remission rate and relative risk of mortality (ie, excess mortality) or cause-specific mortality. Prevalence of RHD has in the recent past been defined by screening programmes of subclinical disease in asymptomatic populations.[10–12] Hospital-based studies, however, focus on clinical disease in symptomatic populations. As far as possible, we will elucidate the diagnostic methods in either echocardiography screening studies or hospital-based studies. In the context of RHD, 'remission' is due exclusively to surgical intervention; thus, we will explore the surgical literature for rates of disease regression versus long-term progression (ie, mortality). In our clinical experience, the following morbid outcomes are considered the most significant and we will thus include: heart failure, ischaemic/thromboembolic or haemorrhagic stroke, atrial fibrillation, infective endocarditis and valve repair or replacement. In addition, we will consider any study of cardiovascular morbidity that quantified the attributable proportion of RHD cases.

The burden of structural heart disease (including RHD) in South Africans seeking antenatal care was recently reviewed,[13] so for the purpose of this review we will exclude studies of RHD in pregnancy. Studies will be excluded if they focused on degenerative heart valve disease, rheumatological conditions other than RHD or solely on acute rheumatic fever. As a rule, we will also exclude autopsy and necropsy studies because the consent rates for these procedures in South Africa are low, and their conclusions about mortality patterns are highly likely to be biased. We will immediately exclude editorials, commentaries and case reports. Although excluded from the final analysis, reviews pertaining to RHD in South Africa will be retained temporarily in order to manually search reference lists. While the WHO recommends considering the inclusion of disease register data in the burden of disease studies, previous experience with RHD registers in South Africa has demonstrated that such data collection is unreliable and not representative of the general population.[14] In addition, rheumatic fever registers excluded information regarding RHD, one of our outcomes, during the period of interest. They are thus excluded from our analysis. Similarly, the latest South Africa Demographic and Health Survey (2003) does not contain primary data on RHD and thus could not be reviewed.[15]

Search strategy

Two clinician researchers (LZ paediatric cardiology; DW internal medicine) will compile lists of articles obtained from three large databases relevant to the South African population: PubMed, ISI Web of Science and EMBASE. Additionally, to identify South African conference proceedings, theses and abstracts, we will manually search the following archives at the University of Cape Town Health Sciences Library: Current and Completed Research (South Africa), and two journals not indexed on MEDLINE: SA Heart and the Cardiovascular Journal of South Africa. References will be managed using EndNote X7 software. We will collect vital registration data from Statistics South Africa. Although the flaws in vital statistics are well known, the Global Burden of Disease study considers them an important source of mortality data and incorporates specific methods for handling misclassifications and inconsistencies.[16] Owing to the fact that no RHD registers are used within the country, these cannot be included. Finally, we will hand search the reference lists of all studies included in the final review. Prior consultation with other RHD experts led us to suspect a substantial 'grey' literature around RHD. Thus, we will intentionally keep the database search strategy broad and redundant. We will also communicate with other South African cardiovascular disease researchers and practitioners, as well as international experts on RHD when possible, to identify unpublished works. Published and unpublished data

will be subject to the same quality assessment. The prespecified search strategy for each database mentioned previously is listed in table 1.

The two researchers (LZ and DW) will independently, in the first instance, select articles on the basis of relevant title and abstract, after which full-text manuscripts will be obtained from potentially eligible reports. When discrepancies arise over the inclusion of titles/abstracts or full-text articles, we plan to resolve them by consensus discussion between the two primary reviewers (LZ and DW), with arbitration by a third reviewer (MEE) as necessary.

Data extraction

The primary reviewers will use a standardised data extraction form to independently extract information from included articles. This extraction will be duplicated (ie, 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, and study design. Disease-related parameters including hospitalisation, secondary events, surgical interventions and mortality will also be recorded. Where study data are unclear, the original author of the manuscript will be contacted to clarify his or her findings.

Quality assessment

For all studies deemed eligible for inclusion, we will assess overall study quality according to four basic criteria: (1) representativeness of cases to the general population with RHD, (2) completeness of dataset (including follow-up), (3) validity of case definitions and methods of ascertainment and (4) appropriateness of the study design to the research question. These criteria were adapted from general criteria used in the Global Burden of Disease study[17] and will each be assigned one point on a four-point scale. For specific estimates reported in a study, we assigned each estimate a grade A, B or C based on the quality of the data and study methods. For instance, a population-based study of incidence would receive an 'A', a hospital-based study of incidence accounting for the catchment area would receive a 'B', and a study reporting rates of hospitalisation as incidence would receive a 'C'. The quality assessment will evaluate the reliability of the estimates of the outcome measures. Again, we will resolve discrepancies in data extraction or quality assessment of study quality by consensus discussion between the two primary reviewers (LZ and DW), with arbitration by a third reviewer (MEE) as necessary.

Risk of bias assessment

In addition to the quality assessment, we will also include an assessment of risk of bias. The Cochrane collaboration suggests that the phrase 'risk of bias' is the preferred terminology in reflecting the risk of underlying bias in study design or execution, in addition to the effect of the exposure of intervention under study. The risk of bias will be assessed using the design-specific criteria outlined in the publication by the Agency of Health-related Research and Quality and listed in table 2. These permit the assessment of selection, performance, attrition, detection and reporting biases.[18]

Data synthesis

Prevalence data from individual studies will be combined by random-effects meta-analysis according to the

Table 1 Search strategy

Database	Search terms	Limits
PubMed	("Rheumatic Heart Disease"[Mesh] OR "Rheumatic Heart Disease"[TIAB]) AND ("South Africa"[Mesh] OR "South Africa *"[TIAB]) MeSH terms were exploded during the search	Limited to English/humans 1994–2014
ISI Web of Science	TS=Rheumatic heart disease AND CU=South Africa	Limited to English/ Afrikaans 1994–2014
EMBASE	"Rheumatic heart" and ("South Africa" or "South African" or "South Africans") Advanced search: checked options for free-text search and explosion of terms	Limited to English/humans 1994–2014
Current and Completed Research	TS: 'rheumatic heart disease'	Limited to English/Humans 1994–2014
CVJSA, SA Heart	Manually-searched titles over 1994–2014	
Statistics South Africa (http://www.statssa.gov.za/publications/findpublication.asp)	Searched all reports on causes of death in South Africa that were published over 1994–2014	

CVJSA, Cardiovascular Journal of Africa; SA, South Africa.

Table 2 Design-specific criteria to assess for risk of bias*

Risk of bias	Criterion	Cohort	Case–control	Case series	Cross-sectional
Selection bias	Were participants analysed within the groups they were originally assigned to?	x			
	Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?	x			x
	Were cases and controls selected appropriately (eg, appropriate diagnostic criteria or definitions, equal application of exclusion criteria to case and controls, sampling not influenced by exposure status)?		x		
	Did the strategy for recruiting participants into the study differ across study groups?	x			
	Does the design or analysis control account for important confounding and modifying variables through matching, stratification, multivariable analysis or other approaches?	x	x	x	x
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	x	x	x	x
	Did the study maintain fidelity to the intervention protocol?	x	x	x	
Attrition bias	If attrition (overall or differential non-response, dropout, loss to follow-up or exclusion of participants) was a concern, were missing data handled appropriately (eg, intention-to-treat analysis and imputation)?	x	x	x	x
Detection bias	In prospective studies, was the length of follow-up different between the groups, or in case-control studies, was the time period between the intervention/exposure and outcome the same for cases and controls?	x	x		
	Were the outcome assessors blinded to the intervention or exposure status of participants?	x	x	x	x
	Were interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants?	x	x	x	x
	Were outcomes assessed/defined using valid and reliable measures implemented consistently across all study participants?	x	x	x	x
	Were confounding variables assessed using valid and reliable measures implemented consistently across all study participants?	x	x	x	x
Reporting bias	Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?	x	x	x	x

*Adapted from Viswanathan *et al.*[18]

Mantel-Haenszel method. Heterogeneity will be evaluated using the χ^2-based Q statistic (significant for p<0.1) and the I2 statistic (>50% to be indicative of 'notable' heterogeneity.[19] STATA software V.11.2 (STATA Corporation, College Station, Texas, USA) will be used to perform calculations and the meta-analysis and to produce the forest plots using the *metan* routine. Should standard error (SE) not be provided, CIs will be incorporated into the formula, SE=(upper limit—lower limit)/3.92.

Presenting and reporting of results

We plan to make use of flow diagrams to summarise the study selection process and detail reasons for exclusion. This will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting of systematic reviews.[20] We will publish our search strategy and quality-scoring tool as supplementary documents.

Primary outcomes

Incidence

We will tabulate crude age-specific incidence estimates per 100 000 persons per year in summary tables along with their 95% CIs. To estimate the pooled median incidence rates and assess for heterogeneity, we will fit random effects models to log-transformed observed incidence in STATA V.11.2 (Stata Corp, Texas, USA). We will obtain estimates of the median incidence and the 25th and 75th centile 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 per 1000 persons will be calculated and expressed with 95% CIs, if appropriate. It is well known that, in screening for and diagnosing RHD, auscultation has limited sensitivity compared with echocardiography, which is the current gold standard test.[12] Data permitting, we will attempt to adjust the prevalence estimates from auscultation-based studies using a cross-walking procedure and report these effects on the pooled prevalence estimates separately.[21]

Secondary outcomes

Fatal and non-fatal outcomes data will be expressed in the pooled analysis where possible. We will tabulate estimates of crude age-specific mortality rates from RHD per 100 000 persons per year along with their 95% CIs. Attributable proportions and relative risks of fatal and non-fatal outcomes will be calculated if data are available and 95% CIs generated. A measure of the consistency of results will be included and in cases where a meta-analysis cannot be performed, a narrative summary will be presented. Any trends will be reported on, either using meta-analytic methods such as meta-regression if possible or a detailed qualitative assessment.

Dissemination

This protocol will result in a systematic review of the contemporary incidence, prevalence and fatal and non-fatal outcomes of RHD in South Africa. The burden of RHD in developed nations has changed dramatically over the past century while far fewer reductions have occurred in developing countries.[10] Emerging economies such as South Africa, although demonstrating some important medical and healthcare advances, struggle with the continued health burden of diseases of poverty and marginalised communities, such as those living with RHD. The conclusions of this review will be critical to provide high-level healthcare providers, public health officials and policymakers with pooled contemporary data regarding RHD, in particular regarding the effect the new political dispensation has had on the burden of a preventable disease within the country.

A recent publication outlining the most important research priorities for RHD has stressed that high-quality country-specific data are crucially important to determine the research priorities for a particular region.[22] We propose that this review will provide these data to affect policy decisions regarding prevention, management and control of RHD. Contemporary measures of fatal and non-fatal outcomes of RHD are also crucially needed to change or amend current practice and plan outcome-based research in RHD.

Finally, we anticipate that this review will identify trends in the burden of disease over the past two decades within South Africa. These trends may, in turn, identify key areas of intervention for future research and practice, such as specific evidence-based interventions or innovative secondary prophylaxis measures.

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Contributors LZ conceived of the review. LZ and DW wrote the first draft and all authors edited the subsequent versions of the draft. LZ and DW developed the protocol, will conduct the searches and extract the data. MEE will oversee the final analysis of the data. All authors have reviewed and accepted the final version of the protocol and given their permission for publication.

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