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.

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 schoolchildren3 while several surgical reviews published in the following decade reported significant morbidity and mortality associated with chronic RHD.1 4 Recent evidence, however, suggests that this distinction may now apply to the Central Asian republics.5 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

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.
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. 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.

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. 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. 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, 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. 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.

Search strategy
Two clinician researchers (LZ paediatric cardiologist; 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. 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 pre-
specified 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 rele-
vant 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
(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, and
study design. Disease-related parameters including hos-
pitalisation, 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 cri-
teria: (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 study17 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 inci-
dence 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 hospitalisa-
tion as incidence would receive a ‘C’. The quality assess-
ment 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 col-
aboration suggests that the phrase ‘risk of bias’ is the
preferred terminology in reflecting the risk of under-
laying 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, per-
formance, attrition, detection and reporting biases.18

Data synthesis
Prevalence data from individual studies will be com-
bined by random-effects meta-analysis according to the

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

1. Zühlke L, Watkins D, Engel ME. BMJ Open 2014;4:e004844. doi:10.1136/bmjopen-2014-004844
| 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      |              |             |                 |
|               | 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      |              |             |                 |
|               | Did 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      |              |             |                 |
| **Attrition bias** | Did the study maintain fidelity to the intervention protocol? | x      |              |             |                 |
|               | 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      |              |             |                 |
|               | 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      |              |             |                 |

*Adapted from Viswanathan et al.*

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18 Zühlke L, Watkins D, Engel ME. BMJ Open 2014;4:e004844. doi:10.1136/bmjopen-2014-004844

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Mantel-Haenszel method. Heterogeneity will be evaluated using the \( \chi^2 \)-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, \( SE = (\text{upper limit} - \text{lower limit}) \)/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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### Provenance and peer review

Not commissioned; externally peer reviewed.

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