

# BMJ Open Prevalence of group A streptococcal disease in North and Sub-Saharan Africa: a systematic review protocol

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## ABSTRACT

**Introduction:** The true burden of group A streptococcal (GAS) disease in Africa is not known. GAS is a significant cause of mortality and morbidity on the global scale and in developing countries. According to Carapetis *et al*, the prevalence of severe GAS disease is at least 18.1 million cases with an incidence of at least 1.78 million cases per year.

**Methods and analyses:** We aim to provide a systematic review of studies measuring the prevalence of GAS infection among people in North and Sub-Saharan African countries. A comprehensive literature search of a number of databases will be undertaken, using an African search filter, to identify GAS prevalence studies that have been published. Full copies of articles will be identified by a defined search strategy and will be considered for inclusion against predefined criteria. Statistical analysis will include two steps: (1) identification of data sources and documenting of estimates, and (2) the application of the random-effects and fixed-effects meta-analysis model to aggregate prevalence estimates, and to account for between study variability in calculating the overall pooled estimates and 95% CI for GAS prevalence. Heterogeneity will be evaluated using the I<sup>2</sup> statistic to determine the extent of variation in effect estimates that is due to heterogeneity rather than chance. This systematic review protocol was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement. This review will provide updated evidence of a review published in 2009. Our data will have implications for the development of a GAS vaccine.

**Ethics and dissemination:** Ethics approval is not required for this study given that this is a protocol for a systematic review of published studies. The results of this study will be disseminated through a peer-reviewed publication and conference presentation.

**Systematic review registration number:** PROSPERO CRD4201401290 0. ([http://www.crd.york.ac.uk/PROSPERO/display\\_record.asp?ID=CRD42014012900](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014012900)).

## INTRODUCTION

*Streptococcus pyogenes*, also known as group A streptococcus (GAS), is responsible for a wide range of diseases prevalent worldwide.<sup>1 2</sup>

## Strengths and limitations of this study

- To our knowledge, this is the first attempt at a systematic review to summarise the burden of laboratory-confirmed group A streptococcal (GAS) infection in Africa.
- This study could potentially inform the provision of treatment strategies including the development of putative GAS vaccines in the future.
- Conclusions cannot be drawn from the implications of the present systematic review protocol but they will be reported following the systematic review and meta-analysis as described in Methods section.

These diseases range from mild infections such as impetigo and pharyngitis to more serious diseases including streptococcal toxic shock syndrome (STSS), endocarditis and necrotising fasciitis. Moreover, repeated episodes of GAS infection may trigger autoimmune diseases such as acute post-streptococcal glomerulonephritis and acute rheumatic fever (ARF).<sup>3</sup> Approximately 40–60% of episodes of ARF result in rheumatic heart disease (RHD).<sup>4</sup>

According to global disease burden figures, the WHO ranked GAS as the ninth leading cause of human mortality, with the majority of deaths attributable to invasive GAS infections and RHD.<sup>5</sup> In the developed world, a decline in the prevalence and incidence of ARF/RHD has been observed over the past 150 years as a result of improved living conditions and the extensive use of penicillin, including for the treatment of GAS pharyngitis.<sup>6</sup> Conversely, however, developing countries, which account for 80% of the world's population, continue to experience high cases of ARF/RHD affecting some 2.4 million children aged 5–14 years old residing in developing countries.<sup>6</sup> Together, ARF and RHD affect around 15.6 million people worldwide,<sup>6</sup> and lead to the death of at least 350 000 people per annum worldwide.<sup>3</sup>

ARF and RHD remain endemic in developing countries of the world due to the failure of the application of comprehensive prevention programmes.<sup>7</sup> Thus, the introduction of safe, effective and affordable vaccines to prevent GAS infections may be the most cost-effective method of primary prevention of ARF/RHD. Potential vaccine coverage in different geographic regions, especially those with high rates of ARF/RHD, requires a detailed understanding of the molecular epidemiology of GAS infections and the prevalent *emm* types circulating in the community.<sup>8</sup> Currently, in the preclinical stage, there is a 30-valent vaccine (reformulated from a 26-valent vaccine) based on the variable N-terminal regions of the surface M protein of GAS.<sup>9</sup> Furthermore, another vaccine (J8 vaccine), based on antigens from the conserved C-repeat portion of the M-protein, has recently entered a phase 1 trial.<sup>10</sup>

*Emm* sequence typing has been widely used in many regions of the world as the preferred method to study and define the molecular epidemiology of GAS strains.<sup>11</sup> An earlier systematic review by Steer *et al*<sup>8</sup> documented the global distribution of *emm* types of GAS to define prevalent strains, and to assess the coverage and implications for the experimental multivalent vaccine. The *emm* types included in the vaccine covered less than 65% of all isolates in four of six regions (the Middle East, Asia, Africa and the Pacific region) with particularly poor coverage in Africa. One of the main limitations of the Steer review was the extent of heterogeneity within study regions and possible selection bias, given that the majority of data were based on studies from high-income countries. Furthermore, the report also noted that the small number of studies in regions such as Africa could be a potential bias and the results may not be generalisable to all countries in this region.

As part of the AFRO *Strep* Registry initiative within the ASAP Programme for rheumatic fever and RHD,<sup>12</sup> we propose to conduct a systematic review and meta-analysis to investigate the burden of GAS disease among children and adults in North and Sub-Saharan Africa. In addition, we will document the frequency and distribution of *emm* types among isolates, thereby informing the development of putative vaccines in the future.

## Objectives

The objective of this review is to provide a systematic review of studies reporting the prevalence of laboratory-confirmed GAS among people in North and Sub-Saharan African countries. This review will complement the findings of an existing review published in 2009.<sup>8</sup>

## Review question

This systematic review will be guided by the following research question: What is the burden of laboratory-confirmed invasive GAS (STSS and post-streptococcal glomerulonephritis) and non-invasive GAS (pharyngitis) in North and Sub-Saharan African countries? We will

also conduct a subanalysis of the distribution of GAS *emm* subtypes in GAS-related disease in North and Sub-Saharan African countries.

The primary outcome of this systematic review is to determine the burden of laboratory-confirmed GAS infection in North and Sub-Saharan Africa. Secondary outcomes include scrutinising the quality of the studies included in this review, analysing demographic data of cases with laboratory-confirmed GAS and other characteristics including the distribution of GAS *emm* subtypes in North and Sub-Saharan African countries.

## METHODS

This review protocol has been published in the PROSPERO International Prospective Register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO/>), registration number CRD42014012900, and is prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P) 2015 Statement.<sup>13</sup> The methods for this review will follow those published previously.<sup>14</sup>

### Criteria for considering studies for the review

#### Inclusion criteria

1. Studies describing the prevalence of GAS across all age groups, resident in countries belonging to the African continent, in the geographic regions of North and Sub-Saharan Africa, diagnosed with a laboratory-confirmed GAS isolate from all ethnicities, socioeconomic and educational backgrounds.
2. All study designs will be included. For the purpose of this review, the diagnosis of GAS should be determined by throat culture, rapid antigen detection and PCR tests. When pooling data for analysis, prevalence estimates will be adjusted for based on errors of known magnitude pertaining to the test used to measure the presence of GAS infection (eg, sensitivity and specificity) as used in a previous systematic review elsewhere.<sup>15</sup> We will also consider published articles and unpublished studies from conference proceedings. Articles published in any language, with full English abstracts, will be eligible for inclusion.

#### Exclusion criteria

1. Duplicate publications of the same material. When the study has been published in more than one journal/conference, the most complete recent version will be used.
2. Narrative reviews, opinion pieces, letters or any other publications lacking primary data and/or explicit method descriptions.

### Search strategy to identify relevant studies

A broad search strategy will be designed to maximise sensitivity (table 1). The main search comprises individual searches using detailed medical subject heading (MeSH) terms for GAS infection combined with terms

**Table 1** Search strategy

SEARCH	MeSH term (modified as needed for use in other databases)
#1	Prevalen*
#2	frequency
#3	rate*
#4	proportion
#5	epidemiolog*
#6	statistic*
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	GAS
#9	Group A Streptococc*
#10	streptococc* pharyngitis
#11	streptococc* pyogenes
#12	streptococc* pyogenes pharyngitis
#13	#8 OR #9 OR #10 OR #11 OR #12
#14	<i>African Search Filter</i> (see online supplementary appendix s1)
#15	#7 AND #13 AND #14

relevant to Africa. We plan to search Medline (accessed via PubMed), Web of Science (accessed via IST Web of Knowledge), Africa-Wide: NiPAD, Scopus, WHOLIS and Africa Wide databases from the earliest inception to the latest published data. In an attempt to identify all relevant articles, no filters will be placed on the initial search to restrict age or language of publication or publication type. In addition, results will be complemented with searches in Google Scholar, conference proceedings and theses databases (using variations in the search strategy), as well as by scanning reference lists of included articles. We will have no time period cut-off and the included studies will not be restricted by language.

We will conduct a comprehensive search of the existing literature using an African search filter developed by Siegfried and colleagues, in order to identify prevalence studies of GAS conducted in Africa.<sup>16 17</sup> The African filter encompasses all African country names as well as

truncated terms, for example, 'west\* Africa', to ensure that records using regional index terms as opposed to country index terms will all be included (see online supplementary appendix S1). The African search filter also includes the English name as well as the name of the country in the language relevant to that region. Where the name of a country has changed over time, the current and former names are included.

### Selecting studies for inclusion

Full text articles identified by the search that will potentially meet inclusion criteria based on the title and abstract will be obtained for data synthesis. Studies will be screened and scrutinised against predefined inclusion and exclusion criteria. Two authors will be assigned to evaluate and appraise the results of the searches, based on the title and abstract. The reviewers will then either mark the studies as included or excluded. If a reviewer is uncertain, the study will be marked as pending. Once all the studies have been reviewed independently, the reviewers will together compare their scripts; discrepancies will be discussed and, if necessary, a third reviewer will be called on to resolve any disagreements. A flow chart will facilitate transparency of the selection process. African studies with well-defined study populations, laboratory-based reporting on GAS isolates and recorded prevalence will be included. We will not limit eligibility on the basis of study design, and will include retrospective and prospective clinical studies. There will be no restriction on the clinical setting, allowing studies analysing both in-patients and out-patients at any level within the healthcare system to be included.

### Quality appraisal of included studies

A quality assessment tool developed by Hoy *et al*<sup>18</sup> and adapted by Werfalli *et al*<sup>14</sup> (table 2), will be applied and adapted, if necessary, to all screened full-text articles, in order to assess study quality. Using this assessment tool, studies will be graded as low risk, moderate risk and high risk for scores  $\leq 5$ , 6–8 and  $>8$ , respectively. An

**Table 2** The quality assessment criteria for prevalence studies<sup>18</sup>

External validity	Score
1. Was the study's target population a close representation of the national population in relation to relevant variables?	(1 point)
2. Was the sampling frame a true or close representation of the target population?	(1 point)
3. Was some form of random selection used to select the sample, OR was a census undertaken?	(1 point)
4. Was the likelihood of nonresponse bias minimal?	(1 point)
Total	(4 points)
Internal validity	Score
1. Were data collected directly from the subjects (as opposed to a proxy)?	(1 point)
2. Was an acceptable case definition used in the study?	(1 point)
3. Was the study instrument that measured the parameter of interest shown to have validity and reliability?	(1 point)
4. Was the same mode of data collection used for all subjects?	(1 point)
5. Was the length of the shortest prevalence period for the parameter of interest appropriate?	(1 point)
6. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	(1 point)
Total	(6 points)

independent investigator will be consulted through discussion to reach consensus where there is uncertainty or disagreement between reviewers. An evaluation of the risk of bias will allow for sensitivity analysis.

### Data extraction and management

Following the assessment of the quality of studies, data will be collected independently from each eligible publication and captured onto a standardised form. We plan to extract data from text, tables and figures. Study authors will be contacted in cases of missing data or unclear eligibility criteria. Study characteristics such as the study population, country in which the study was conducted, year of publication, language of publication, journal, age range, study design, criteria for sample selection and sample size, diagnostic criteria and outcomes measured, will be recorded. Corresponding authors will be contacted if there is unclear or missing information. Eligible studies will be categorised according to the outcome data they provide (ie, prevalence, mortality, case fatality) and the clinical setting in which the participants are assessed. Any disagreements regarding inclusion of studies will be resolved by discussion or by consulting a third author. A table of all included studies will be included and the reasons for exclusion of studies documented.

### Data synthesis and assessment of heterogeneity

Our data analysis will be based on two steps, the first being the identification of data sources together with the extraction of the prevalence estimates and the second being the application of statistical models to estimate trends by country and age, and using a random-effects and fixed-effects meta-analysis model to aggregate prevalence estimates, and to account for variability between studies, by calculating the overall pooled estimate and the 95% CI. If the data allow, a trend analysis will also be conducted to investigate trends in GAS infection in North and Sub-Saharan Africa. In addition, we will also stratify the results by decade: (1) 2015–2006; (2) 2005–1996; (3) 1995–1986; (4) 1985 and before. We will derive SEs where studies have provided the corresponding numerator and denominator for GAS prevalence estimates. We will consider non-overlapping CIs as an indication of statistically significant differences. The prevalence of GAS infection from different studies will be pooled by way of a meta-analysis using STATA V.12.

The heterogeneity between the included studies will be assessed using the  $I^2$  heterogeneity statistic, reported as a percentage (%), to determine the extent of variation between the studies.<sup>19</sup> Higgins defines categories of heterogeneity with a value  $\leq 25\%$  as low, 26–50% moderate, 51–75% substantial and 76–100% as considerable heterogeneity. Forest plots will also be used to further identify heterogeneity by means of the  $\chi^2$  test (with significance defined at the  $\alpha$ -level of 10%) and the  $I^2$  statistic (where  $\geq 50\%$  indicates substantial heterogeneity). Where heterogeneity is statistically significant, subgroup

and sensitivity analysis will be conducted to establish if the meta-analysis results are influenced by the effect of study design as well as the geographical settings (low-income vs middle-income countries). Sensitivity analysis will also be performed to determine potential sources and explanations for the heterogeneity. These analyses include plotting studies of a high quality, and compare the results to see how they differ from the overall result. Studies that are considerably heterogeneous and where pooling of data is not possible, the findings will be narratively explained together with tables and figures, where applicable. Any discrepancies or disagreements will be discussed by the reviewers and, if necessary, they will call on an independent reviewer to provide clarification.

### Assessment of reporting biases

Symmetry of funnel plots will be used to assess for publication or selective reporting bias if we identify 10 or more eligible studies.

### Reporting of this review

We will make use of flow diagrams to summarise the inclusion criteria and selection process of studies, and also detail the reasons for exclusion. This systematic review will be reported according to the PRISMA 2009 guidelines.<sup>20</sup> The search strategy and quality appraisal tool will also be published as supplementary documents.

### Ethics and dissemination

Systematic reviews draw on publicly available data and therefore do not require formal ethical review. The findings of this systematic review will be disseminated through peer-reviewed journal publications and conference proceedings.

To our knowledge, there are no systematic reviews that have specifically looked at the burden of laboratory-confirmed GAS infection in Africa. We expect this review to complement that of Steer *et al*<sup>8</sup> from 2009, which reported on the global *emm* type distribution of GAS. Finally, we believe that the results of this systematic review will have implications for policy, practice and vaccine development, informed by data solely from North and Sub-Saharan Africa, where the burden of GAS disease is among the greatest.

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**Contributors** All the authors conceived of this review. DDB wrote the first draft, and the other authors edited subsequent versions of the draft. MEE and BMM are the senior researchers. MEE provided methodological guidance on the overall development of the protocol and BMM reviewed the draft for clinical content.

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