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Rationale and design of the African group A streptococcal infection registry: the AFRO*Strep* study

Dylan D Barth,[1] Mark E Engel,[1] Andrew Whitelaw,[2] Abdissa Alemseged,[3] Wilson E Sadoh,[4] Sulafa K M Ali,[5] Samba O Sow,[6] James Dale,[7] Bongani M Mayosi[1]

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DDB and MEE contributed equally to this work.

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For numbered affiliations see end of article.

Correspondence to
Associate Professor Mark E Engel;
mark.engel@uct.ac.za

ABSTRACT

Introduction: Group A β-haemolytic *Streptococcus* (GAS), a Gram-positive bacterium, also known as *Streptococcus pyogenes*, causes pyoderma, pharyngitis and invasive disease. Repeated GAS infections may lead to autoimmune diseases such as acute post-streptococcal glomerulonephritis, acute rheumatic fever (ARF) and rheumatic heart disease (RHD). Invasive GAS (iGAS) disease is an important cause of mortality and morbidity worldwide. The burden of GAS infections is, however, unknown in Africa because of lack of surveillance systems.

Methods and analysis: The African group A streptococcal infection registry (the AFRO*Strep* study) is a collaborative multicentre study of clinical, microbiological, epidemiological and molecular characteristics for GAS infection in Africa. The AFRO*Strep* registry comprises two components: (1) active surveillance of GAS pharyngitis cases from sentinel primary care centres (non-iGAS) and (2) passive surveillance of iGAS disease from microbiology laboratories. Isolates will also be subjected to DNA isolation to allow for characterisation by molecular methods and cryopreservation for long-term storage. The AFRO*Strep* study seeks to collect comprehensive data on GAS isolates in Africa. The biorepository will serve as a platform for vaccine development in Africa.

Ethics and dissemination: Ethics approval for the AFRO*Strep* registry has been obtained from the Human Research Ethics Committee at the University of Cape Town (HREC/REF: R006/2015). Each recruiting site will seek ethics approval from their local ethics' committee. All participants will be required to provide consent for inclusion into the registry as well as for the storage of isolates and molecular investigations to be conducted thereon. Strict confidentiality will be applied throughout. Findings and updates will be disseminated to collaborators, researchers, health planners and colleagues through peer-reviewed journal articles, conference publications and proceedings.

Strengths and limitations of this study

- AFRO*Strep* will provide the first insights into the epidemiology of Group A β-haemolytic *Streptococcus* (GAS) disease in Africa.
- Health facilities collaborating in this study have huge catchment areas; thus, we anticipate large numbers of enrolment into the registry.
- The AFRO*Strep* study is a clinic-based and laboratory-based registry and will not address the true burden of disease in the community.
- Given the financial constraints facing many centres in Africa, it is conceivable that specimens submitted for laboratory evaluation will represent the more severe cases.
- The registry may be rendered incomplete by not including skin cultures.

INTRODUCTION

Group A β-haemolytic *Streptococcus* (GAS), a Gram-positive bacterium, also known as *Streptococcus pyogenes*, causes skin, mucosal, systemic and autoimmune diseases.[1] Repeated pharyngeal and skin infections with GAS may lead to serious autoimmune diseases such as acute post-streptococcal glomerulonephritis, acute rheumatic fever (ARF) and rheumatic heart disease (RHD).[2 3] Invasive GAS (iGAS) disease is associated with significant morbidity and mortality in children and young adults worldwide.[4] Increases in the number of cases of both invasive and non-invasive GAS diseases have been observed globally since the 1980s[5 6] possibly due, inter alia, to the acquisition of multiple virulence determinants giving rise to a single clone,[7] subsequently prompting many countries to start active surveillance systems for iGAS to closely document the epidemiology of the disease.

A patient disease registry is a powerful surveillance tool in epidemiology.[8] Guided by research questions, registries are developed to serve multiple purposes and provide a platform to study the natural history of disease, clinical features, cost-effectiveness of treatment strategies and care, to assess safety

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and harm, and to provide measures of improved quality of care.[9] Registries for streptococcal surveillance have been established in some developed countries—for example, Canada, England and the USA, where iGAS is a notifiable disease.[10–13]

In 2004, the Eurosurveillance programme began to capture comprehensive information on all cases of iGAS infection in Europe.[14 15] This surveillance programme was successful in tracking trends in iGAS infection, monitoring clusters and outbreaks, and conducting molecular epidemiological *emm* sequence typing on all isolates. In the UK, routine surveillance data indicate a significant increase of iGAS isolates from December 2008 (n=143) compared to the same period in 2007 (n=86).[16] In Alberta, Canada, surveillance of iGAS infection collects information that informs vaccine development and contributes to the implementation and evaluation of new intervention strategies for controlling GAS disease.[13]

Currently, there exists no registry for documenting GAS-related disease in Africa, despite the importance of GAS infections in this region. Thus, there is limited information regarding the emm types of GAS in the African population. In a study conducted in Cape Town to identify the emm types of GAS causing symptomatic pharyngeal infections, 26 different emm types were recovered.[17] Of the 26 emm types in the Cape Town collection, 17 (65%) were represented within the 30-valent M protein-based vaccine under development.[18] In Mali, a collection of 372 pharyngeal GAS isolates from symptomatic children contained 67 different emm types of which 18 (27%) were represented in the 30-valent vaccine.[19] Given that systematically collected data are essential for an effective disease-control programme,[20] we have established the AFRO*Strep* registry as an essential first step towards understanding the prevalence of laboratory-confirmed GAS disease in African countries.

Rationale

In a WHO report, GAS was put in the top 10 leading causes of mortality worldwide, with the majority of deaths attributed to RHD, a chronic sequel of GAS pharyngitis.[21] Prevalence and incidence data on laboratory-confirmed GAS infection from African countries are lacking when compared with industrialised nations,[22] although a number of studies in Africa have previously published data on GAS in a number of countries including Ethiopia, Mali, Nigeria, Sudan and Tunisia.[22–25]

The AFRO*Strep* study is a collaborative study that aims to establish the first registry and biorepository of laboratory-confirmed GAS isolates in Africa, with one of its main objectives being to collect comprehensive epidemiological, clinical, microbiological and molecular data for GAS infections on the continent. AFRO*Strep* will serve as a platform for further investigations including molecular characterisation of isolates in order to contribute to the growing body of knowledge informing vaccine development.

METHODS AND ANALYSIS

A flow chart of the procedures for the AFRO*Strep* study is depicted in online supplementary material S1.

Study design

This is a prospective, regional, multicentre, clinic-based and laboratory-based registry involving centres in Africa, many of which are part of the Stop Rheumatic Heart Disease A.S.A.P. Programme[26] and related studies such as the Global Rheumatic Heart Disease Registry (the REMEDY study).[27] AFRO*Strep* seeks to document the prevalence, incidence, clinical and molecular characteristics of laboratory-confirmed GAS infection in Africa. The pilot phase will focus on South African centres in Cape Town, Pretoria, Polokwane and Durban. iGAS is defined as GAS isolated in culture from a sterile site such as blood and cerebrospinal fluid.[28] GAS isolated from a non-sterile site such as the skin and throat is considered to be non-iGAS.

The registry will comprise two components:

1. Active surveillance of GAS pharyngitis cases from which GAS has been isolated at clinics and community health centres (non-iGAS).
2. Passive surveillance of laboratory data on GAS isolated from patients with invasive streptococcal disease (iGAS).

Surveillance objectives of the AFROStrep registry

1. To collect demographic and clinical information from patients with non-invasive and invasive laboratory-confirmed GAS infection.
2. To determine the molecular epidemiology of non-invasive and invasive GAS infection.
3. To assess strategies for treatment, control and prevention of GAS infection.
4. To conduct studies that contribute to the development of appropriate intervention such as a vaccine.

Study eligibility

All patients presenting with a sore throat (including tonsillitis) at participating clinics and community health centres regardless of age, and who have not had antibiotics in the prior 30 days, will be eligible to participate in the active surveillance arm of AFRO*Strep*.

For the passive surveillance component, all patients, irrespective of age, confirmed as having invasive GAS disease are eligible for inclusion.

Inclusion criteria

Inclusion into AFRO*Strep* is subject to anyone presenting with a sore throat, microbiological laboratory confirmation of GAS, informed consent and the availability of clinical data.

Exclusion criteria

Patients will be excluded if no informed consent was obtained.

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Data collection

Active surveillance

Using existing prevalence estimates of around 21% GAS among patients with sore throat[17] with a 95% CI and a precision level of 5%, a minimum sample size of 246 participants with pharyngitis needs to be enrolled at each participating site.[29] The study nurse in each site will seek participation in the study among eligible patients attending healthcare facilities for treatment of sore throat. Consenting patients will be examined clinically on a number of symptoms after which a throat swab will be taken for microbiological culture. A case report form (see online supplementary material S2) will be used for recording data. Patient care will remain within the domain of the attending clinician or nurse. Antibiotics prescribed will also be documented. Data entry will take place at each of the participating sites by a designated data capturer.

Passive surveillance

Eligible patients will be identified from positive iGAS cultures isolated from laboratories serving participating sites. Clinical data will be obtained from hospital folders. All participating laboratories will use standardised protocols for identifying GAS from clinical specimens. Data entry will take place at the AFRO*Strep* Cape Town office.

Clinical data and accompanying laboratory data will be entered into the AFRO*Strep* database designed on the OpenClinica platform V.3.0 (https://www.openclinica.com). In addition, isolates will be subjected to cryopreservation for long-term storage in the AFRO*Strep* biorepository, housed at the University of Cape Town, before being subjected to *emm* typing according to standardised protocols.[30] Material transfer agreements will be formulated according to the policies of the respective countries of participating centres.

The institutions inputting data to the registry own their data. Requests for data sharing will be decided on by a registry committee, consisting of the principal investigators from all participating sites, and will be subjected to satisfactory evidence regarding the intended use of the data, maintenance of confidentiality and benefit to the entire community of patients, including the individual.

Data analysis plan

The information to be collected will include (but not limited to) date of birth, gender, date and duration of illness, presenting clinical features and microbiological findings. To protect the privacy of patients, a file will be created that will have no specific identifiers. Analysis will be conducted using Stata V.11.2 (StataCorp, College Station, Texas, USA). Descriptive statistics will be used to describe the clinical syndromes associated with invasive and non-iGAS disease by age. The number of positive samples obtained each month will be analysed to determine prevalence of GAS among pharyngitis cases treated at the health facilities. Geographical information systems technology (flowing out of recent work by our group)[31] will be used to plot the residences of participants. *Emm* typing will be reported as previously described.[30]

Ethics and dissemination

Each recruiting site will seek ethics approval from their local ethics committee. Using standardised case report forms tailored to local requirements, eligible patients will be informed about the AFRO*Strep* registry, and their consent to participate will be recorded prior to enrolment. Children aged 8 years and older will also be requested to provide assent. Reports and publications emanating from the AFRO*Strep* registry will not include any information that identifies either the patient themselves, their parents or guardians. Participants will be identified throughout the study duration by the study number allocated to them at the time of enrolment. All data will be stored on a password-protected computer and handled in the strictest confidence. The establishment of the biorepository will follow prescribed guidelines and documentation will be drawn up to afford maximum protection for the participants, who will be requested to provide specific consent for the long-term storage of their isolates. Findings and updates will be disseminated to collaborators, researchers, health planners and colleagues through peer-reviewed journal articles, conference publications and proceedings.

Status of the study and sites participation

The active and passive surveillance arms of AFRO*Strep* will commence in February 2016; initially, pilot sites in South Africa will participate in the AFRO*Strep* registry, after which, enrolment will involve centres from the rest of Africa. All participating sites will enrol patients for a minimum of 2 years. The participating regions in Africa are shown in figure 1. A similar study has already been conducted in Cape Town.[17]

DISCUSSION

To the best of our knowledge, the AFRO*Strep* study is the first prospective study of clinical, epidemiological and microbiological characteristics of group A streptococcal disease in Africa. Our registry, which includes the documenting of non-invasive GAS such as pharyngitis, represents an improvement on current registries limited to iGAS information. We will collect detailed data on clinical features at the time of presentation which will be stored together with corresponding detailed laboratory information including *emm* typing profiles of GAS strains. This will contribute to an understanding of potential vaccine coverage in different geographic regions, especially those with high rates of ARF/RHD, which require a detailed understanding of the molecular epidemiology of GAS infections and the prevalent emm types circulating in the community.[32] Also, the AFRO*Strep* study will document current practices in

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Figure 1 Map showing the current collaborating sites in the AFRO*Strep* registry. Coordinating centres: Ethiopia, Jimma University; Mali, Centre pour le Développement des Vaccins; Nigeria, University of Benin; South Africa, University of Cape Town; Sudan, University of Khartoum.

treating group A streptococcal infection, with particular reference to prescription of penicillin antibiotics. Finally, AFRO*Strep*, because of its multicentre nature, presents the scope for examining regional similarities and differences in clinical and molecular features and outcomes of GAS infection.

Strengths and limitations

Health facilities collaborating in this study have huge catchment areas; thus, we anticipate large numbers of enrolment which will provide an acceptable population from which to draw conclusions on the general and molecular epidemiology of GAS in patients. However, the AFRO*Strep* study is a clinic-based and laboratory-based registry and will not address the true burden of disease in the community. Furthermore, concerning the passive surveillance component, given the financial constraints facing many centres in Africa, it is conceivable that specimens submitted for laboratory evaluation will represent the more severe cases. Finally, in the light of the hypothesis that GAS impetigo plays a role in the pathogenesis of post-streptococcal diseases,[33] we acknowledge that the registry may be rendered incomplete by not including skin cultures, for reasons of the risk of mixed infections. But, given that many cases of iGAS begin on the skin, the molecular epidemiology of the most pathogenic GAS should be captured. In addition, the physical examination will include notation of coexistent pyoderma. Nevertheless, despite the limitations, AFRO*Strep* will provide the first insights into the epidemiology of laboratory-confirmed GAS disease in African countries.

Summary

Group A streptococcal infection and its complications continue to be widely prevalent in the world. The overwhelming burden of GAS-related diseases confirms the need for improved and effective monitoring and control strategies. The AFRO*Strep* study represents the first attempt to collect contemporary and comprehensive data on laboratory-confirmed GAS disease in Africa. The AFRO*Strep* study will help quantify the burden of GAS infection, document the prevalent strains presenting in the respective communities and provide information that could inform the development of locally sensitive guidelines, future research programmes and policy development, all of which have the potential to improve the management of individuals with GAS infection and GAS-related diseases.

Author affiliations
[1]Department of Medicine, Faculty of Health Sciences, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa
[2]Department of Microbiology, National Health Laboratory Service, Tygerberg Hospital and Stellenbosch University, Tygerberg, South Africa
[3]Department of Laboratory Sciences and Pathology, College of Health Sciences, Jimma University, Jimma, Ethiopia
[4]Department of Child Health, School of Medicine, University of Benin and University of Benin Teaching Hospital, Benin City, Nigeria
[5]Department of Pediatrics and Child Health, Faculty of Medicine, University of Khartoum and Sudan Heart Institute, Khartoum, Sudan
[6]Centre pour le Développement des Vaccins—Mali, Bamako, Mali
[7]Department of Medicine, Division of Infectious Diseases, University of Tennessee Health Science Center, Memphis, Tennessee, USA

Contributors MEE and BMM conceived of the study. DBB and MEE wrote the first draft of this paper. All authors contributed to the final design of this study, the drafting and editing of the paper, and its final contents.

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Competing interests None declared.

Ethics approval Human Research Ethics Committee of the University of Cape Town (HREC/REF: R006/2015).

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Correction

Barth DD, Engel ME, Whitelaw A, *et al*. Rationale and design of the African group A streptococcal infection registry: the AFROStrep study. *BMJ Open* 2016;6:e010248. The first and last names of the fourth author were inadvertently transposed. 'Alemseged' is the author's first name and 'Abdissa' is the last name.

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