PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Rationale and design of the African group A streptococcal infection registry: the AFRO*Strep* Study
AUTHORS	Barth, Dylan; Engel, Mark; Whitelaw, AC; Alemseged, Abdissa; Sadoh, Wilson; Ali, Sulafa; Sow, Samba; Dale, J; Mayosi, Bongani

VERSION 1 - REVIEW

REVIEWER	Greg Tyrrell University of Alberta, Canada
REVIEW RETURNED	09-Nov-2015

GENERAL COMMENTS	This is a manuscript describing how an initiative termed the AFROStrep will be set up and conducted. This is a collaborative study that will collect data from cases of GAS pharyngitis through active surveillance and cases of invasive group A streptococcal (iGAS) infection through a passive surveillance system. Authors state that “AFROStrep seeks to document the prevalence, incidence, clinical and molecular characteristics of laboratory-confirmed GAS infection in Africa” (page 6, line 50). The authors indicate that a pilot will be done that will focus on four South African Centres. This will be important work as authors state on page 5 line 54 that there currently exists no registry for documenting GAS-related disease in Africa. Points for authors to consider: 1. Page 5, line 18. Authors indicate that the reasons for increases in invasive and non-invasive GAS infections are not well understood. That is not completely correct. The Musser group in 2014, provided a nice description of how the M1 GAS has acquired multiple virulence determinants and arose as a single clone leading to increases in iGAS disease. (Nasser et al PNAS 2014, 111(17):E1768-E1776). This reference should be included. 2. A flow chart describing how the surveillance will be set up would be helpful for the reader to better understand the organization of the AFROStrep surveillance system proposed. 3. It would also be helpful to have a clear description of what the knowledge gaps are in relation to GAS is Africa. What emm types are currently known to predominant? Are they different between pharyngitis and iGAS? Are there any known geographical differences? 4. Authors should provide a clear definition for invasive group A streptococcal disease. This is important as a consistent definition needs to be used by all sites otherwise there will be different types of specimens collected that are considered iGAS at one site and not iGAS at another site. 5. Authors should provide a copy of the case report form with their manuscript or as complete a list of the clinical data they wish to collect. This can be provided as supplemental data. This data collection form should be as complete as possible at the start of this study otherwise the investigators may be going back multiple times to add new parameters they would like to collect as the study

	progresses. 6. Page 8, line 39. It is unclear who are the members of “The Registry Committee”. What will its structure be? 7. Who is responsible for entering the clinical data into the AFROStrep database? Does each site enter their own data or is the completed data collection tool sent to one site for consistent entry? 8. Page 8, line 35. Where is the location of the AFROStrep biorespository for the long term storage of the isolates? Can this be stated in the manuscript? 9. Do all microbiology laboratories have their own protocols for identifying GAS from clinical specimens? Or is a standardized SOP developed by the investigators being used. 10. Page 8, line 37. What is the “wider vaccine initiative spanning a number of sites worldwide.”? This is not discussed in the manuscript nor is a reference provided on line 37. Please give a brief description of what this initiative is. 11. There is very limited description of molecular characterization of GAS isolates other than emm-typing on page 9, line 8-9. Will other molecular characterization be done? If none, then authors should use the words “emm-typing” in place of “molecular characterization” in the manuscript.

REVIEWER	Lesley McGee Centers for Disease Control and Prevention 1600 Clifton Rd Atlanta GA 30329-4027 USA
REVIEW RETURNED	01-Dec-2015

GENERAL COMMENTS	The authors provide in this paper an overview of the rationale for a GAS registry focused in Africa and some high-level information on the design of this registry. This would be a useful registry as there is limited data from Africa on GAS. Some general comments and questions The AFROStrep Registry will include 5 coordinating centers in 5 countries. It was not clear but I assume that GAS isolates would be collected only in these 5 countries? Page 8, lines 5-19. Active collection. You indicate a minimum of 246 participants per site? Is this per country or will there be multiple sites (clinics, hospitals) contributing within each country? You indicate that health facilities collaborating in this study have huge catchment areas (page 10, line 28), so is there a maximum number of participants that would get enrolled or are all cases in a year to be included regardless of number? Page 8, lines 23-45. Passive surveillance. I assume that there would also be a standard case report form for the iGAS cases identified in participating laboratories? Are participating laboratories already identified and is here a single laboratory per country where lab testing will be performed? Where will the AFROStrep biorepository be housed? Will each country have their own repository or will there be a single one for the continent? Page 9, lines 8-20. So emm-typing will be performed on all isolates? Will this be done in a single lab or in multiple labs? Please correct spelling errors: Page 9, line 4. “heatlh” and page 10, line 34 “adress”

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

This will be important work as authors state on page 5 line 54 that there currently exists no registry for documenting GAS---related disease in Africa.
Thank you.
1. Page 5, line 18. Authors indicate that the reasons for increases in invasive and non---invasive GAS infections are not well understood. That is not completely correct. The Musser group in 2014, provided a nice description of how the M1 GAS has acquired multiple virulence determinants and arose as a single clone leading to increases in iGAS disease. (Nasser et al PNAS 2014, 111(17):E1768---E1776). This reference should be included.
The following sentence was inserted at the end of the first paragraph of the introduction: *" 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 (Nasser et al PNAS 2014, 111(17):E1768---E1776), subsequently prompting many countries to commence active surveillance systems for iGAS to closely document the epidemiology of the disease."*
2. A flow chart describing how the surveillance will be set up would be helpful for the reader to better understand the organization of the AFROStrep surveillance system proposed.
Agreed. A flow chart describing the organization of The AFRO*Strep* Registry has been included as supplement S1.
3. It would also be helpful to have a clear description of what the knowledge gaps are in relation to GAS is Africa. What emm types are currently known to predominant? Are they different between pharyngitis and iGAS? Are there any known geographical differences?
The concluding paragraph of the introduction was modified with the insertion of the following sentences on Page 7: *"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, twenty---six different emm types were recovered [18]. Of the 26 emm types in the Cape Town collection, 17 (65%) were represented within the 30---valent M protein---based vaccine under development [16]. 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].*

And to the Discussion on page 13, the following was added: *"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"*
4. Authors should provide a clear definition for invasive group A streptococcal disease. This is important as a consistent definition needs to be used by all sites otherwise there will be different types of specimens collected that are considered iGAS at one site and not iGAS at another site.
The following definition was added on Page 8 : *"iGAS is defined as GAS isolated in culture from a sterile site such as blood and cerebrospinal fluid. GAS isolated from a non---sterile site such as the skin and throat is considered to be non---iGAS."*
5. Authors should provide a copy of the case report form with their manuscript or as complete a list of the clinical data they wish to collect. This can be provided as supplemental data. This data collection form should be as complete as possible at the start of this study otherwise the investigators may be going back multiple times to add new parameters they would like to collect as the study progresses.
A copy of the case report form will be submitted with the manuscript as a supplement.
6. Page 8, line 39. It is unclear who are the members of "The Registry Committee". What will its structure be?
The following sentence was added to clarify this query: *"Requests for data sharing will be decided upon 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."*
7. Who is responsible for entering the clinical data into the AFROStrep database? Does each site enter their own data or is the completed data collection tool sent to one site for consistent entry?

The following was added under on page 9, Active surveillance:
"… Data entry will take place at each of the participating sites by a designated data capturer."
Passive surveillance:
"…Data entry will take place at the AFROStrep Cape Town office."

8. Page 8, line 35. Where is the location of the AFROStrep biorespository for the long term storage of the isolates? Can this be stated in the manuscript?

Page 9: paragraph modified to read as follows:

isolates will be subjected to cryo---preservation for long---term storage in the AFROStrep biorepository, housed at the University of Cape Town. Material transfer agreements will be formulated according to the policies of the respective countries of participating centres.

9. Do all microbiology laboratories have their own protocols for identifying GAS from clinical specimens? Or is a standardized SOP developed by the investigators being used.

Following sentence was added under Data Collection (pg 9):

"All participating laboratories will use standardized protocols for identifying GAS from clinical specimens."

10. Page 8, line 37. What is the "wider vaccine initiative spanning a number of sites worldwide."? This is not discussed in the manuscript nor is a reference provided on line 37. Please give a brief description of what this initiative is.

Sentence has been removed given that the vaccine discussion is entertained elsewhere in the manuscript with more detail and citation.
"Multivalent M protein---based vaccines have been developed that contain up to 30 different M protein peptides expressed as components of recombinant hybrid vaccine proteins"

11. There is very limited description of molecular characterization of GAS isolates other than emm---typing on page 9, line 8---9. Will other molecular characterization be done? If none, then authors should use the words "emm---typing" in place of "molecular characterization" in the manuscript

Agreed. Text amended accordingly. (Also under the discussion, Pg 12).

"Emm---Typing will be reported as previously described [32]."

Reviewer 2

The authors provide in this paper an overview of the rationale for a GAS registry focused in Africa and some high---level information on the design of this registry. This would be a useful registry as there is limited data from Africa on GAS.
Thank you.
The AFROStrep Registry will include 5 coordinating centers in 5 countries. It was not clear but I assume that GAS isolates would be collected only in these 5 countries?
The authors of the manuscript are from the five coordinating centers which have already agreed to participate in the registry. We envisage that more countries will participate in future.
Page 8, lines 5---19. Active collection. You indicate a minimum of 246 participants per site? Is this per country or will there be multiple sites (clinics, hospitals) contributing within each country? You indicate that health facilities collaborating in this study have huge catchment areas (page 10, line 28), so is there a maximum number of participants that would get enrolled or are all cases in a year to be included regardless of number? Page 8, lines 23---45.
Text modified to provide more clarity as follows: *a minimum sample size of 246 participants with pharyngitis needs to be enrolled at each participating site*
Passive surveillance. I assume that there would also be a standard case report form for the iGAS cases identified in participating laboratories? Are participating laboratories already identified and is here a single laboratory per country where lab testing will be performed?
This is covered in a response to Query 5 of Reviewer 1 above.

Where will the AFROStrep biorepository be housed? Will each country have their own repository or will there be a single one for the continent?
Page 9: paragraph modified to read as follows: *isolates will be subjected to cryo---preservation for long---term storage in the AFROStrep biorepository, housed at the University of Cape Town. Material transfer agreements will be formulated according to the policies of the respective countries of participating centres.*
Page 9, lines 8---20. So emm---typing will be performed on all isolates? Will this be done in a single lab or in multiple labs?
The following sentece was modifed to provide clarity on this query (Page 9). *In addition, isolates will be subjected to cryo---preservation for long---term storage in the AFROStrep biorepository, housed at the University of Cape Town, before being subjected to emm---typing according to standardized protocols*
Please correct spelling errors: Page 9, line 4. “heatlh” and page 10, line 34 “adress”
Thank you. Spelling errors have been corrected.

VERSION 2 – REVIEW

REVIEWER	Gregory J Tyrrell University of Alberta, Canada
REVIEW RETURNED	27-Jan-2016

GENERAL COMMENTS	Authors have addressed my earlier concerns.

REVIEWER	Lesley McGee Centers or Disease Control and Prevention
REVIEW RETURNED	01-Feb-2016

GENERAL COMMENTS	The authors have adequately addressed all the reviewers previous comments.

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.

BMJ Open 2016;**6**:e010248corr1. doi:10.1136/bmjopen-2015-010248corr1