Studies of Rheumatic Heart Disease in South Africa and beyond

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RHDGen Network

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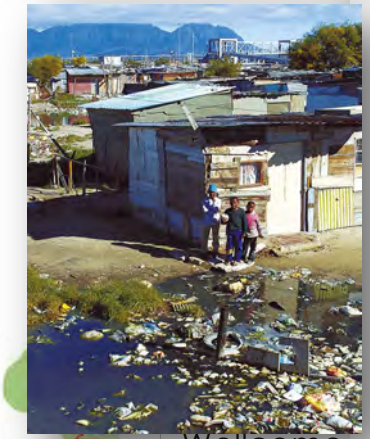
Rheumatic Fever &
Rheumatic Heart Disease

Global Burden of RHD



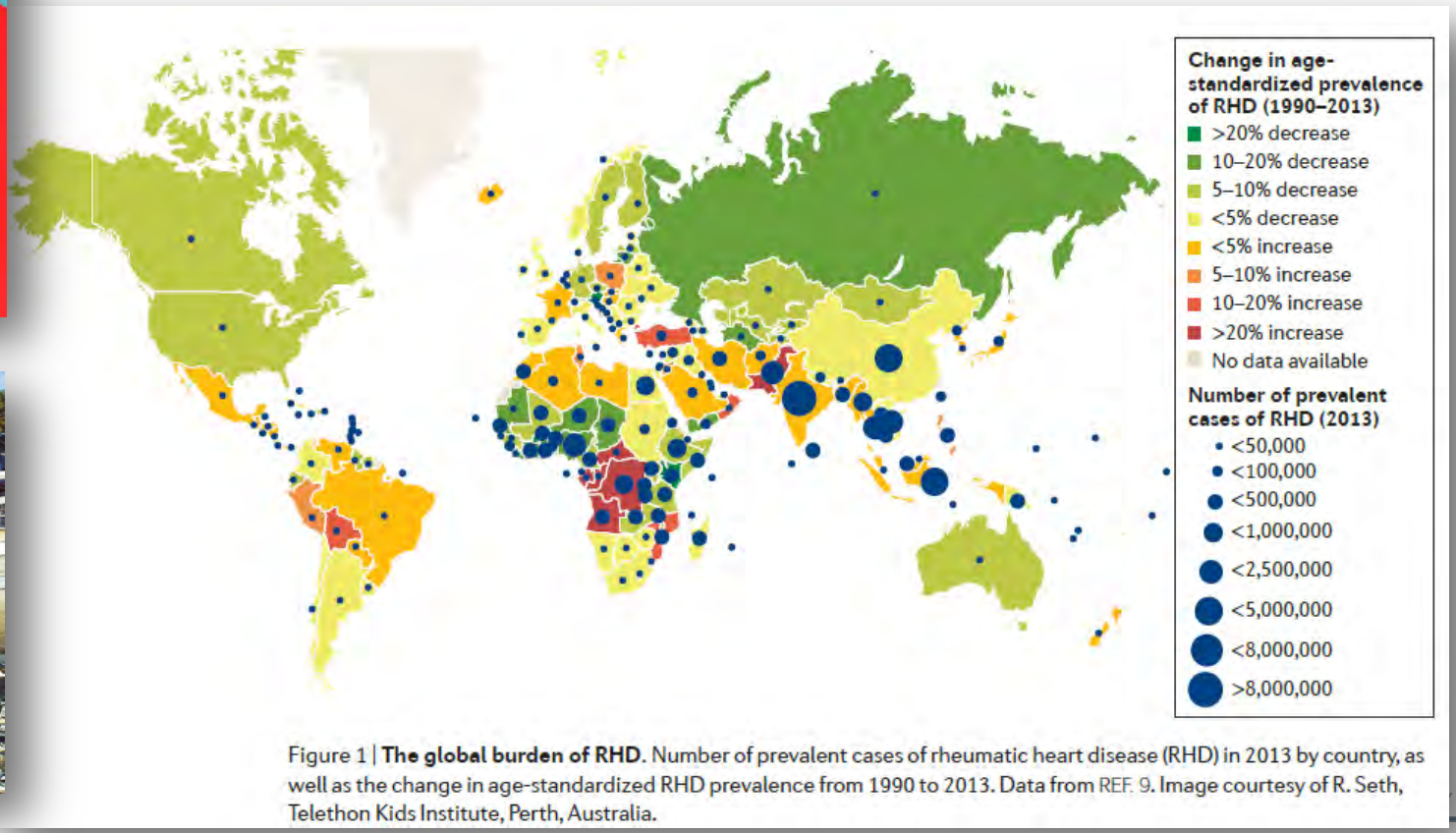


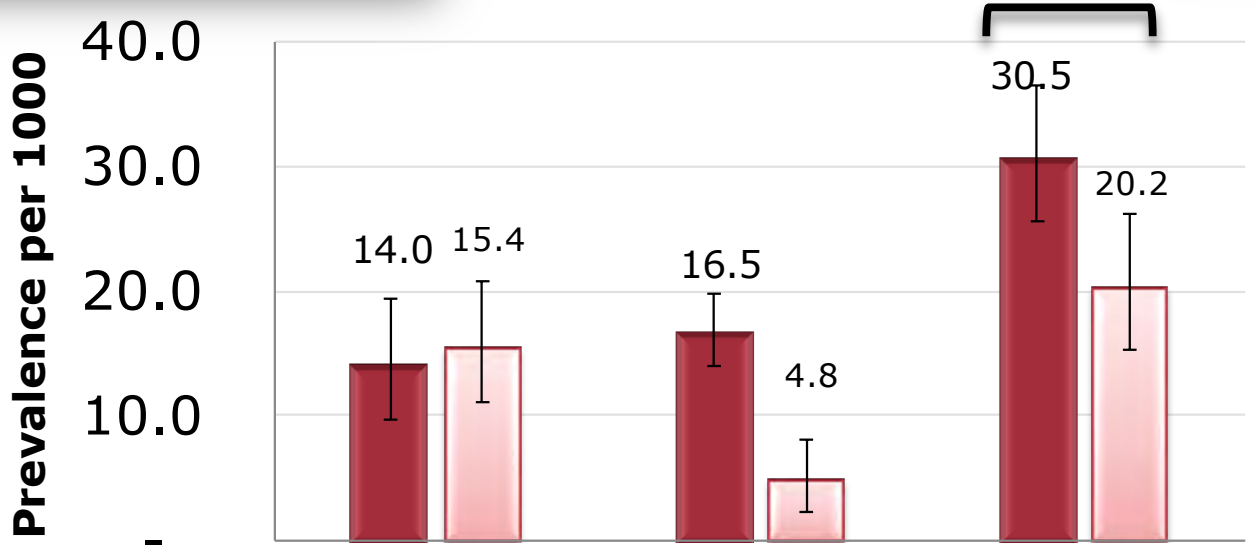
Figure 1 | **The global burden of RHD.** Number of prevalent cases of rheumatic heart disease (RHD) in 2013 by country, as well as the change in age-standardized RHD prevalence from 1990 to 2013. Data from REF. 9. Image courtesy of R. Seth, Telethon Kids Institute, Perth, Australia.

Valvular heart disease

ORIGINAL ARTICLE

Prevalence of rheumatic heart disease in 4720 asymptomatic scholars from South Africa and Ethiopia

Mark E Engel,[1] Abraham Haileamlak,[2] Liesl Zühlke,[1,3] Carolina E Lemmer,[1] Simpiwe Nkepu,[1] Marnie van de Wall,[1] Wandimu Daniel,[2] Maylene Shung King,[4] Bongani M Mayosi[1]



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Rheumatic Fever &
Rheumatic Heart Disease

Cardiology in the Young 2015; Page 1 of 10
doi:10.1017/S1047951115001857

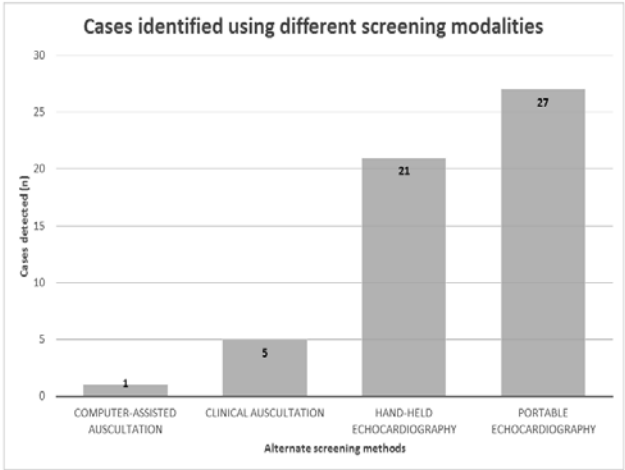
Original Article

Evaluation of a focussed protocol for hand-held echocardiography and computer-assisted auscultation in detecting latent rheumatic heart disease in scholars

Liesl J. Zühlke,[1,2] Mark E. Engel,[1] Simpiwe Nkepu,[1] Bongani M. Mayosi[1]

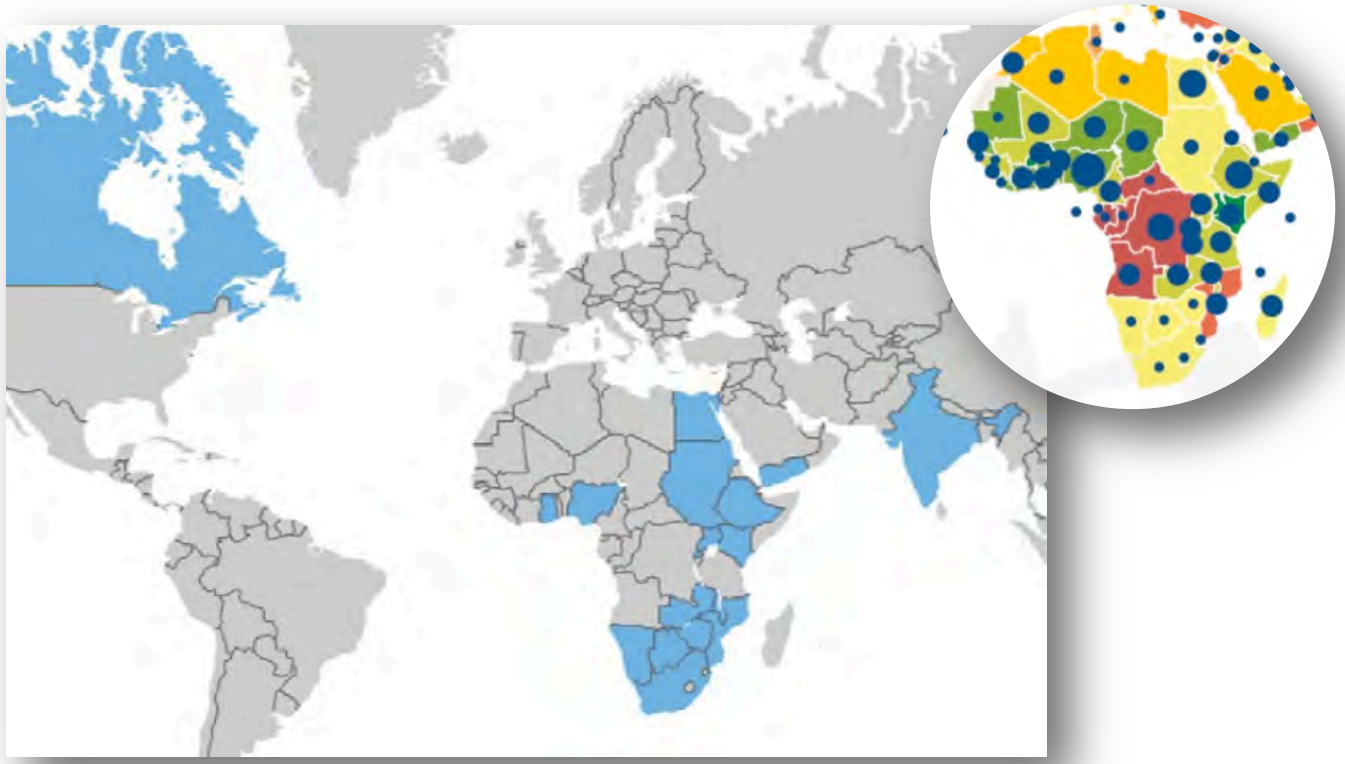
Table 4. Classification of definite and borderline cases.

Definite RHD	Cases	CAA	FOCUS pr
Morphological features of MV plus MR	12	1	12
Mitral stenosis	0	0	0
Morphological features of AV plus AR	1	0	0
Borderline disease of MV and AV	0	0	0
Total	13	1	12
Borderline RHD	**Cases**		**FOCUS pr**
At least two morphological features of MV	3		0
Pathological mitral regurgitation	11		9
Pathological aortic regurgitation	0		0
At least two morphological features of AV	0		0
Total	14		9



Global Rheumatic Heart Disease Registry: The REMEDY study

Country	# of Sites
Egypt	2
Ethiopia	2
India	2
Kenya	1
Malawi	1
Mozambique	2
Namibia	1
Nigeria	5
South Africa	3
Sudan	2
Rwanda	1
Uganda	1
Yemen	1
Zambia	1



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A.S.A.P. Rheumatic Fever & Rheumatic Heart Disease

Trial Design

Rationale and design of a Global *Rheumatic* Heart *Disease* Registry: The REMEDY study

Ganesan Karthikeyan, DM,[a,e] Liesl Zühlke, MBChB,[b,e] Mark Engel, MPH,[c,e] Sumathy Rangarajan, MSc,
Salim Yusuf, DPhil,[d,e] Koon Teo, PhD,[d,e] and Bongani M. Mayosi, DPhil[c,e] *New Delhi, India; Cape Town,*
South Africa; and Ontario, Canada

Background Rheumatic heart disease (RHD) is the principal cause of valvular heart disease–related mo
morbidity in low- and middle-income countries. The disease predominantly affects children and young adults. It is esti
RHD may potentially be responsible for 1.4 million deaths annually worldwide and 7.5% of all strokes occurring in c
countries. Despite the staggering global burden, there are no contemporary data documenting the presentatio
course, complications, and treatment practices among patients with RHD.

Methods The REMEDY study is a prospective, international, multicenter, hospital-based registry planned in 2 p
vanguard phase involving centers in Africa and India will enrol 3,000 participants with RHD over a 1-year perio
document clinical and echocardiographic characteristics of patients at presentation. Over a 2-year follow-up, we will
disease progression and treatment practices with particular reference to adherence to secondary prophylaxis
anticoagulation regimens. With 3,000 patients, we will be able to reliably determine the incidence of all-cause
worsening heart failure requiring hospitalization, systemic embolism (including stroke), and major bleeding individua
all participants. We will identify barriers to care in a subgroup of 500 patients.

Conclusion The REMEDY study will provide comprehensive, contemporary data on patients with RHD and will
development of strategies to prevent and manage RHD and its complications. (Am Heart J 2012;163:535-540.e

European Heart Journal (2015) **36**, 1115–1122
doi:10.1093/eurheartj/ehu449

CLINICAL RESEARCH
Valvular heart disease

Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study)

Liesl Zühlke[1,2], Mark E. Engel[1], Ganesan Karthikeyan[3], Sumathy Rangarajan[4], Pam Mackie[4], Blanche Cupido[1], Katya Mauff[5], Shofiqul Islam[4], Alexia Joachim[1], Rezeen Daniels[1], Veronica Francis[1], Stephen Ogendo[6], Bernard Gitura[7], Charles Mondo[8], Emmy Okello[9], Peter Lwabi[9], Mohammed M. Al-Kebsi[10], Christopher Hugo-Hamman[2,11], Sahar S. Sheta[12], Abraham Haileamlak[13], Wandimu Daniel[13], Dejuma Y. Goshu[14], Senbeta G. Abdissa[14], Araya G. Desta[14], Bekele A. Shasho[14], Dufera M. Begna[14], Ahmed ElSayed[15], Ahmed S. Ibrahim[15], John Musuku[16], Fidelia Bode-Thomas[17], Basil N. Okeahialam[17], Olukemi Ige[17], Christopher Sutton[18], Rajeev Misra[19], Azza Abul Fadl[20], Neil Kennedy[21], Albertino Damasceno[22], Mahmoud Sani[23], Okechukwu S. Ogah[24,25,26], Taiwo Olunuga[26], Huda H.M. Elhassan[27], Ana Olga Mocumbi[28], Abiodun M. Adeoye[24], Phindile Mntla[29], Dike Ojii[30], Joseph Mucumbitsi[31], Koon Teo[4], Salim Yusuf[4], and Bongani M. Mayosi[1*]

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ORIGINAL RESEARCH ARTICLE

Clinical Outcomes in 3343 Children and Adults With Rheumatic Heart Disease From 14 Low- and Middle-Income Countries

Two-Year Follow-Up of the Global Rheumatic Heart Disease Registry (the REMEDY Study)

BACKGROUND: There are few contemporary data on the mortality and morbidity associated with rheumatic heart disease or information on their predictors. We report the 2-year follow-up of individuals with rheumatic heart disease from 14 low- and middle-income countries in Africa and Asia.

METHODS: Between January 2010 and November 2012, we enrolled 3343 patients from 25 centers in 14 countries and followed them for 2 years to assess mortality, congestive heart failure, stroke or transient ischemic attack, recurrent acute rheumatic fever, and infective endocarditis.

RESULTS: Vital status at 24 months was known for 2960 (88.5%) patients. Two-thirds were female. Although patients were young (median age, 28 years; interquartile range, 18–40), the 2-year case fatality rate was high (500 deaths, 16.9%). Mortality rate was 116.3/1000 patient-years in the first year and 65.4/1000 patient-years in the second year. Median age at death was 28.7 years. Independent predictors of death were severe valve disease (hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.80–3.11), congestive heart failure (HR, 2.16; 95% CI, 1.70–2.72), New York Heart Association functional class III/IV (HR, 1.67; 95% CI, 1.32–2.10), atrial fibrillation (HR, 1.40; 95% CI, 1.10–1.78), and older age (HR, 1.02; 95% CI, 1.01–1.02 per year increase) at enrollment. Postprimary education (HR, 0.67; 95% CI, 0.54–0.85) and female sex (HR, 0.65; 95% CI, 0.52–0.80) were associated

Liesl Zühlke, PhD*; Ganesan Karthikeyan, DM*; Mark E. Engel, PhD; Sumathy Rangarajan, MSc; Pam Mackie, CCRA; Blanche Cupido-Katya Mauff, MSc; Shofiqul Islam, MSc; Rezeen Daniels, CPM; Veronica Francis, RN; Stephen Ogendo, MMed; Bernard Gitura, MMed; Charles Mondo, PhD; Emmy Okello, PhD; Peter Lwabi, MMed; Mohammed M. Al-Kebsi, MBBS; Christopher Hugo-Hamman; Sahar S. Sheta, PhD; Abraham Haileamlak, MD; Wandimu Daniel, BSc; Dejuma Yadeta Goshu, MD; Senbeta G. Abdissa, MD; Araya G. Desta, MD; Bekele A. Shasho, MD; Dufera M. Begna, MD; Ahmed ElSayed; Ahmed S. Ibrahim, MD; John Musuku, MMed; Fidelia Bode-Thomas; Christopher C. Yilgwan, MBBS; Ganiyu A. Amusa; Olukemi Ige, MBBS; Basil Okeahialam; Christopher Sutton; Rajeev Misra, MBBS; Azza Abul Fadl, MBChB; Neil Kennedy, MBChB; Albertino Damasceno, PhD; Mahmoud U. Sani; Okechukwu S. Ogah; Taiwo OlunugaHuda H. M. Elhassan, CFC (Turkey); Ana Olga Mocumbi, PhD; Abiodun M. Adeoye; Phindile Mntla; Dike Ojji, PhD;

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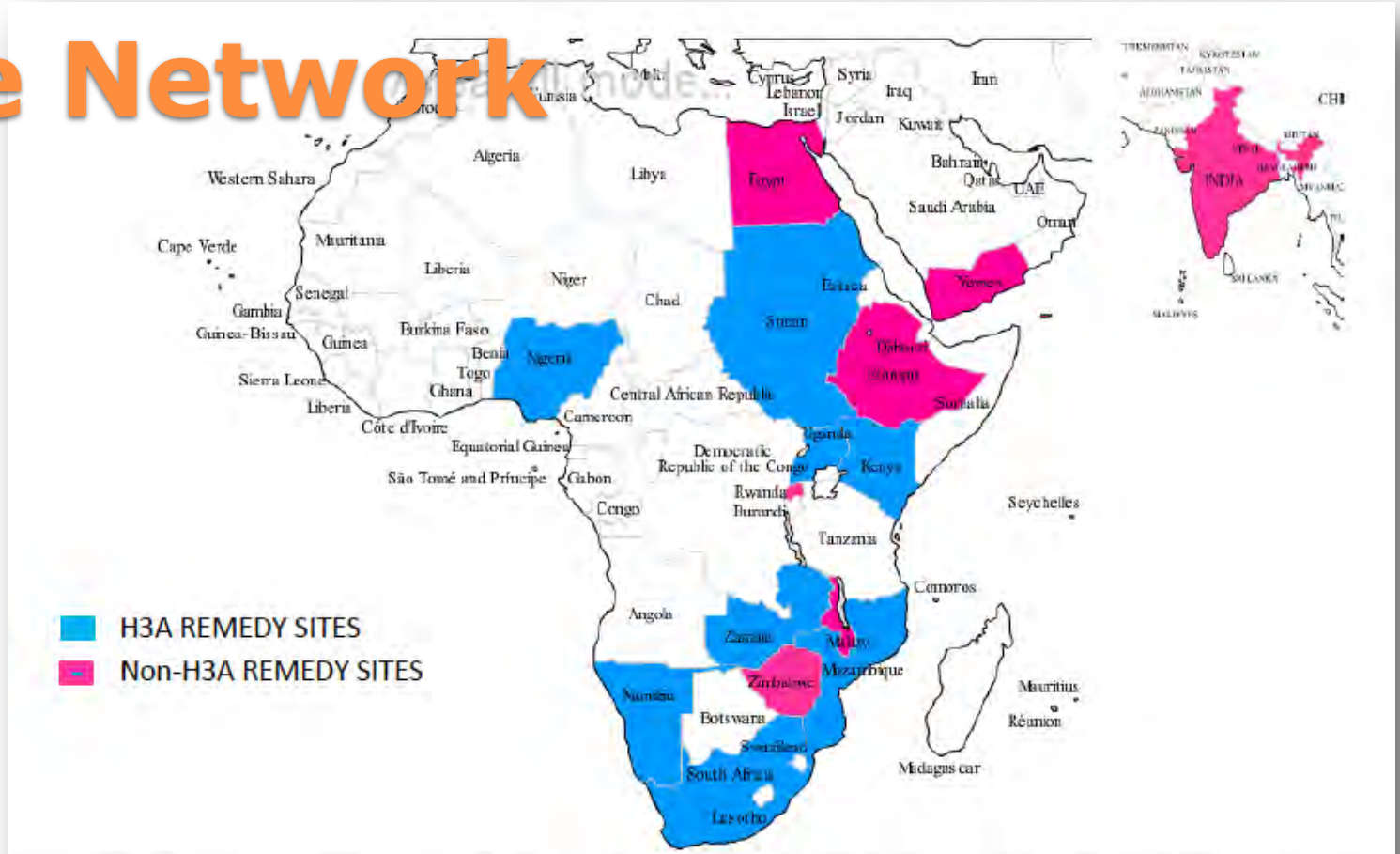
The Network



Appendix: The map shows in colour the 15 African and non-African countries with collaborative centres in the REMEDY study. The blue countries are participating in the RHDGen Network, and the pink countries are not participants in the RHDGen Network.

We
RI

The RHDGen Study

- To build a network for phenotyping of RHD
- To identify genetic variants affecting susceptibility and resistance to RHD
- To train a group of scientists and clinicians in genomic studies of multifactorial disease
- To address ELSI relevant to Africa

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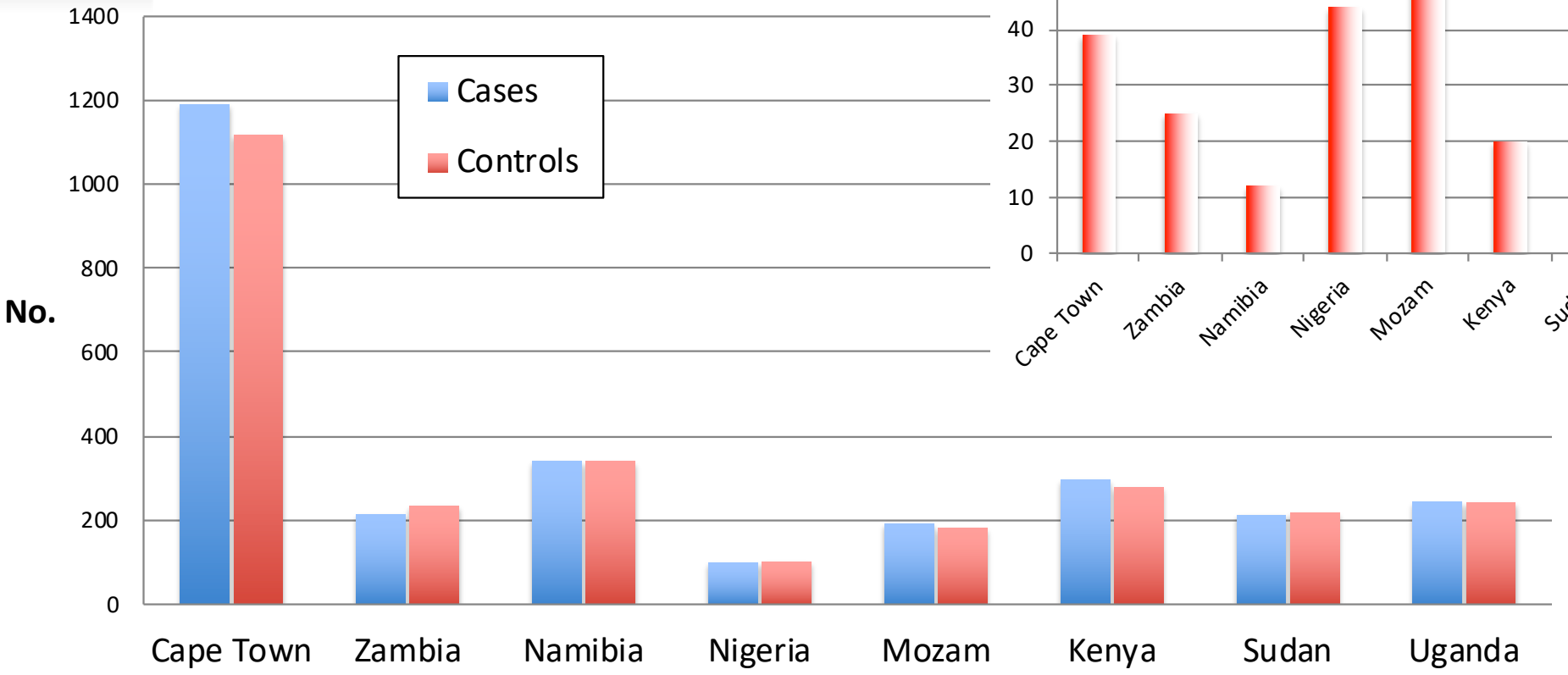
RHDGen: Cases (2798) and Controls (2720)



Trios Recruited n=225

RHDGen Health Scholars Programme

- Postdoctoral Fellow:
  Dr Chishala, Zambia
  (graduated with MMed)
- MSc studentships in bioethics:
  Francis Masiye, Malawi
  Syntia Munung, Cameroon
  Olivia
  Marlyn Faure, South Africa
- Msc studentships in molecular genetics:
  Stephen Kamuli, Kenya
  Tafadzwa Machipisa, Zimbabwe
- PhD studentships in molecular genetics:
  Babu Muhamed, Burundi;
  Stephen Kamuli, Kenya and Tafadzwa Machipisa, Zimbabwe
- 8X MMED Fellows from participating sites have undergone training

"Professor Mayosi never forgot the challenges he had to overcome, and he therefore dedicated himself to mentoring and supporting students faced with similar challenges…"

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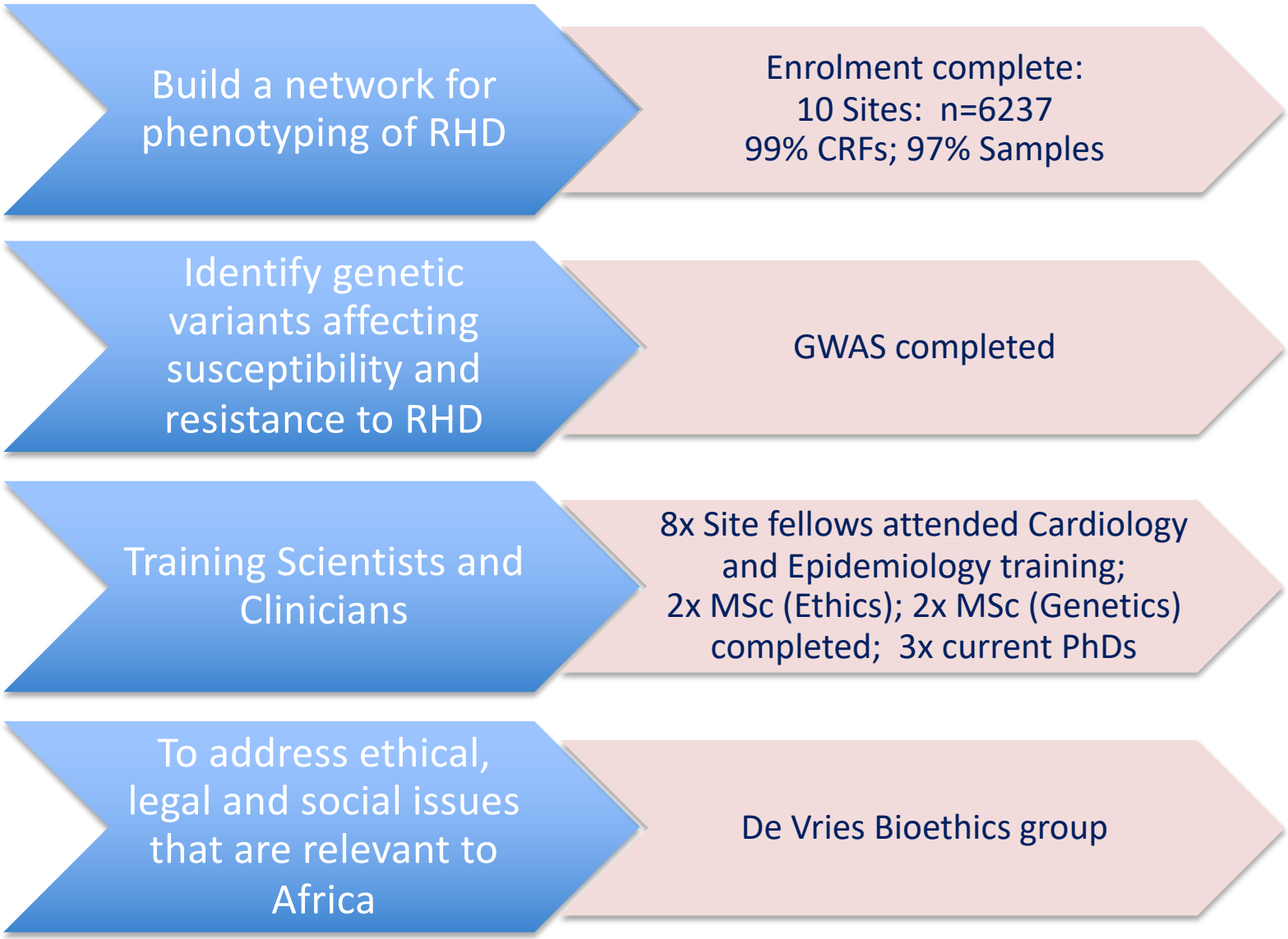
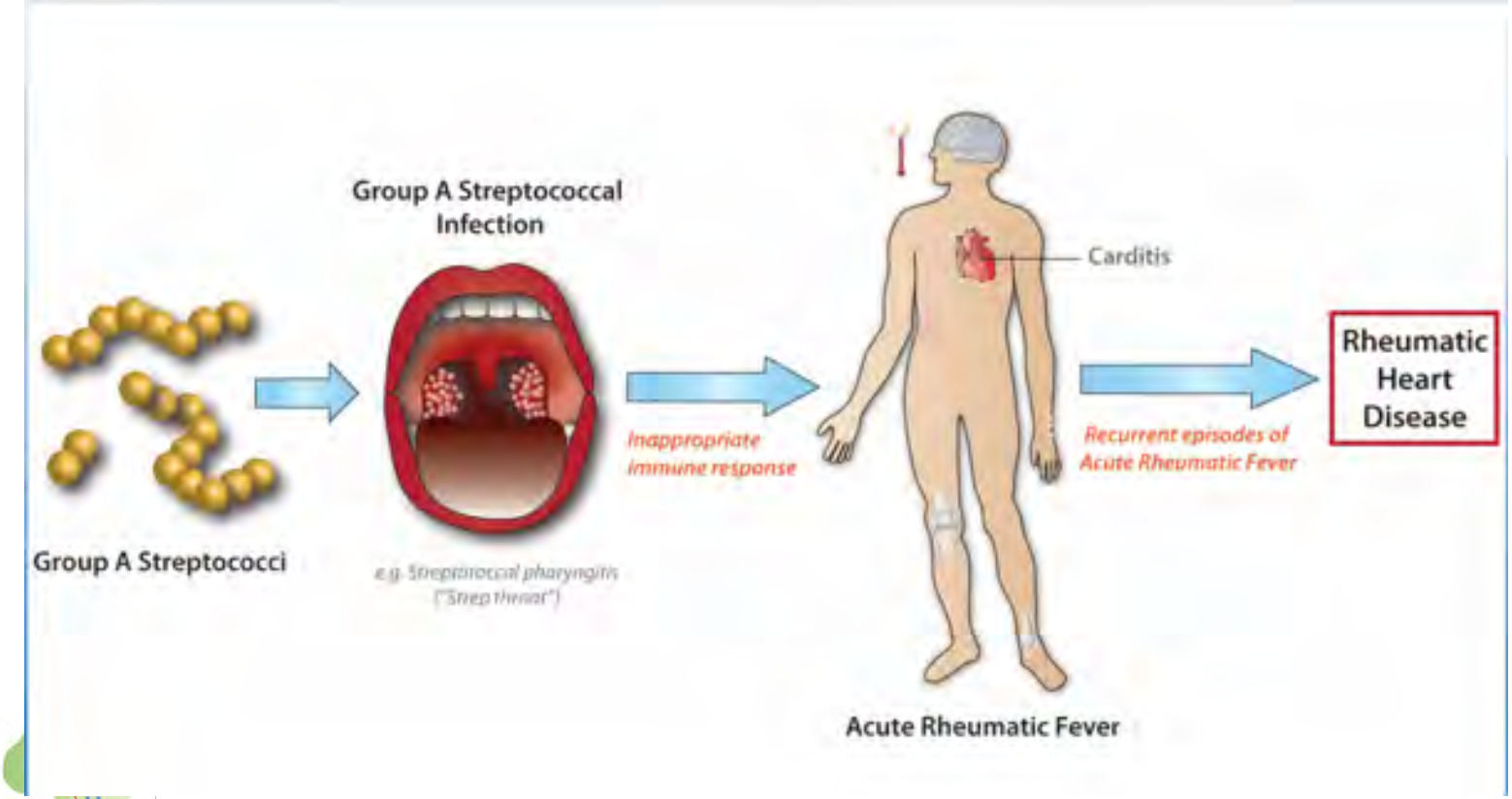

Build a network for phenotyping of RHD
Enrolment complete:
10 Sites: n=6237
99% CRFs; 97% Samples
Identify genetic variants affecting susceptibility and resistance to RHD
GWAS completed
Training Scientists and Clinicians
8x Site fellows attended Cardiology and Epidemiology training;
2x MSc (Ethics); 2x MSc (Genetics) completed; 3x current PhDs
To address ethical, legal and social issues that are relevant to Africa
De Vries Bioethics group

Beyond RHDGen

- De Vries Bioethics Group (coordinated from UCT)
  - Established platform for postgraduate research
  - *Collaboration* with other African genomics projects
  - *Supporting reflection* on ethics of genomics research
  - Substantial number of publications
  - Patient-centred community engagement workshops undertaken
- International Rheumatic Heart Disease Genetics Consortium: n=12,000 cases and controls
- Dr Muehlschlegel (Harvard): exome sequencing n=300
- Dr Whetton (University of Manchester): proteomics

Focusing on Group A Strep



What about a vaccine...?

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A surveillance system for group A streptococcal infection in Africa

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www.rhdafrica.org

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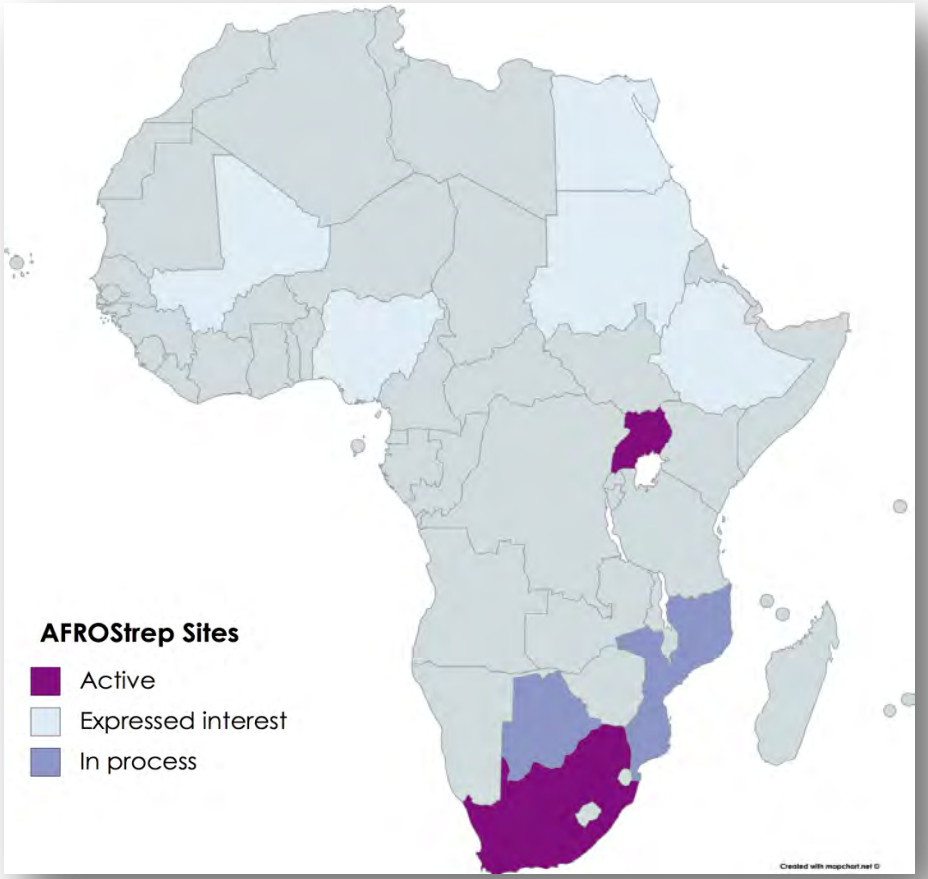
Open Access Protocol

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



AFROStrep is the first registry and biorepository of GAS in Africa, collecting comprehensive clinical and microbiological data for GAS infections in Africa

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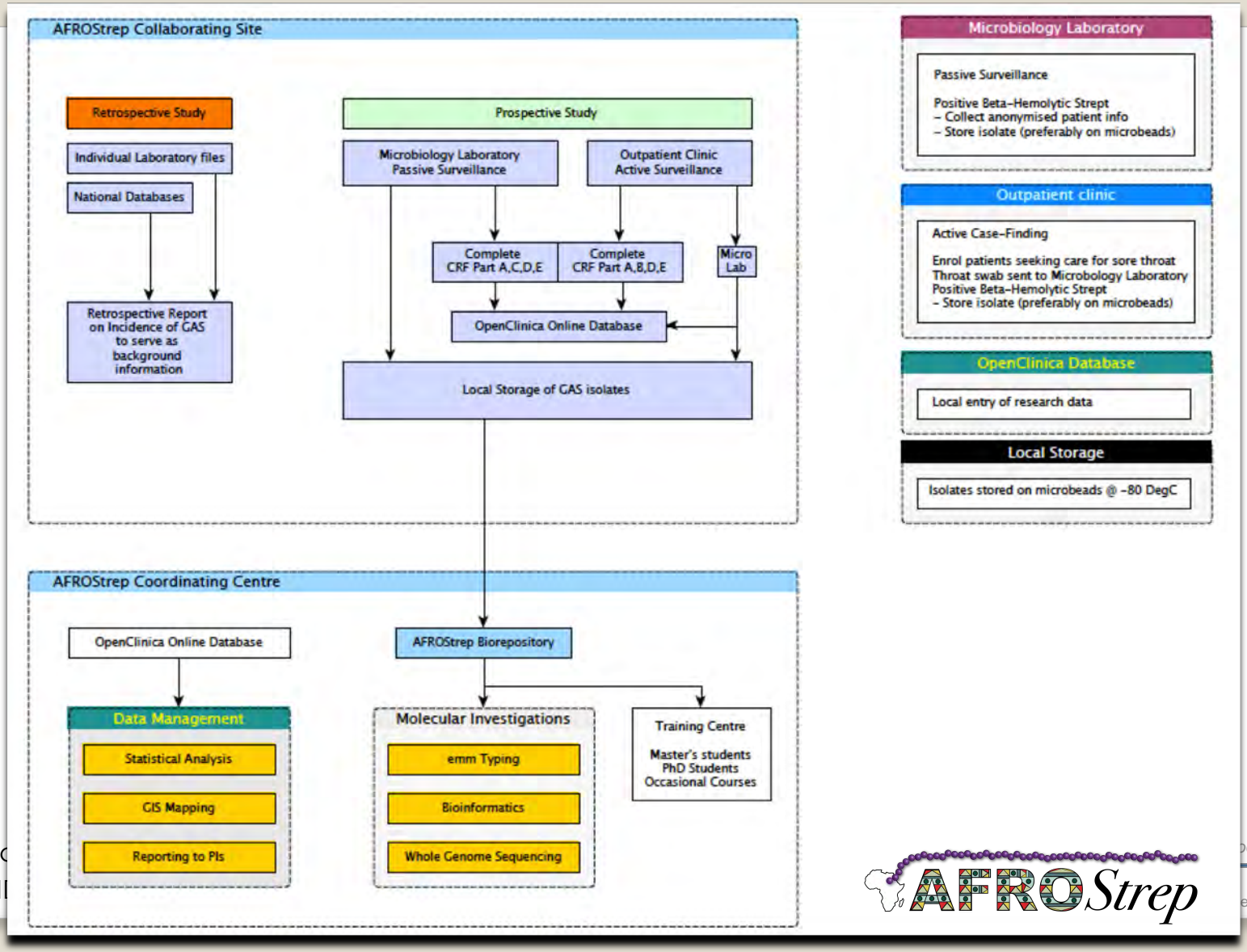
AFROStrep Collaborating Site
Retrospective Study
Individual Laboratory files
National Databases
Retrospective Report on Incidence of GAS to serve as background information
Prospective Study
Microbiology Laboratory Passive Surveillance
Outpatient Clinic Active Surveillance
Complete CRF Part A,C,D,E
Complete CRF Part A,B,D,E
Micro Lab
OpenClinica Online Database
Local Storage of GAS isolates
Microbiology Laboratory
Passive Surveillance
Positive Beta-Hemolytic Strept
– Collect anonymised patient info
– Store isolate (preferably on microbeads)
Outpatient clinic
Active Case-Finding
Enrol patients seeking care for sore throat
Throat swab sent to Microbiology Laboratory
Positive Beta-Hemolytic Strept
– Store isolate (preferably on microbeads)
OpenClinica Database
Local entry of research data
Local Storage
Isolates stored on microbeads @ -80 DegC
AFROStrep Coordinating Centre
OpenClinica Online Database
AFROStrep Biorepository
Data Management
Statistical Analysis
GIS Mapping
Reporting to PIs
Molecular Investigations
emm Typing
Bioinformatics
Whole Genome Sequencing
Training Centre
Master's students
PhD Students
Occasional Courses

Active and Passive collection protocols

- Diagnostic microbiology laboratories:
- GAS isolates stored in biorepository

NATIONAL HEALTH LABORATORY SERVICE

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AFROStrep

AFROStrep Site No ____ Participant No ____

Patient Data

1 Enrolment Date		5 Age	
2 Clinic name		6 Gender	
3 Clinic folder #		7 Race	
4 Date of birth		8 Place of residence	

Antibiotics administered in the last 30 days? N Y — Informed consent obtained? N Y

Pharyngitis

1 Cough	N	Y	8 Exudate on the tonsils	N	Y		
2 Rhinorrhoea	N	Y	9 Oropharyngeal candidiasis	N	Y		
3 Hoarseness	N	Y	10 Tender anterior cervical node	N	Y		
4 Temperature > 38C	N	Y	11 Ant. cervical node >1.5cm in diam	N	Y		
5 Tonsillar erythema	N	Y	12 Rash	N	Y		
6 Tonsilla swelling	N	Y	13 Conjunctivitis	N	Y		
7 Exudate on the pharynx	N	Y	14 Rapistrep	Neg	Pos	ND	

Time of swab collection ____ (Name) (Signature)

Invasive GAS

Specimen details — *Invasive* N Y

Isolated from:

Blood	N	Y	Bacteraemia	N	Y
Aspirate	N	Y	Septic arthritis	N	Y
Deep tissue	N	Y	Toxic shock -like syndrome	N	Y
CSF	N	Y	Necrotising fasciitis	N	Y
Abscess	N	Y	Pneumonia	N	Y
Pus swab	N	Y	Erysipelas/Cellulitis	N	Y
Other	N	Y	Other	N	Y
Please specify:			*Please specify:*		

Clinical details — Date of onset: ____ — *Clinical presentation:*

Clinical management

Admitted to ICU? N Y Unclear (if YES, number of days spent in ICU following GAS isolation?)
Surgical intervention N Y Unclear (if YES, number of days spent in ICU following GAS isolation?)
Outcome (one week after GAS isolation) : alive/RIP/unsure
If RIP: date of death (dd/mm/yyyy)

Notes: ____ Person completing form: ____ Initials: ____ Date: ____

Microbiology

Lab number ____ Isolate stored N Y
Date of specimen ____ Storage details ___/___
Organism isolated GAS / GCS / GFS / GGS / NEG
Emm Type ____ Comment ____

AFSP_CRF001 Version 2.0 / January 2017

♦ Prevention

eumatic Fever &
c Heart Disease

AFROStrep Registry | RE

redcap.uct.ac.za/redcap_v8.4.3/DataEntry/index.php?pid=279&id=10200001&event_id=1410&page=patient_data

Project Setup

Project status: **Production**

Data Collection

- Record Status Dashboard
- Add / Edit Records

Participant ID **10200001**

Select other record

Event: **Visit 1 (Enrolment)**

Data Collection Instruments:

- Patient Data
- Pharyngitis
- Invasive Gas
- Clinical Management
- Microbiology
- ELISA

Applications

- Calendar
- Data Exports, Reports, and Stats
- Field Comment Log
- File Repository
- Data Quality
- External Modules

Help & Information

- Help & FAQ
- Video Tutorials
- Suggest a New Feature

Contact REDCap administrator

Data Access Group: **102 CP**

Save & Exit Form | Save & Go To Next Form | -- Cancel --

Editing existing Participant ID **10200001**

Event Name: **Visit 1 (Enrolment)**

Participant ID	10200001 — To rename the record, see the record action drop-down at top of the Record Home Page
Site ID * must provide value	102
Collection Kit No	00001
Date of enrolment	2018-04-10 Today
Clinic name	VAN
Clinic folder number	45236056
Date of birth	2010-09-05 Today
Age	7 View equation
Gender	○ Female ○ Male reset
Race	○ White ○ Black ◉ Mixed ethinicity ○ Indian ○ NA reset
Place of residence	BONTEHEUWEL
Used antibiotics within last 30 days?	◉ No ○ Yes reset

REDCap
Research Electronic Data Capture

REDGen Network

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Southern African Journal of Infectious Diseases 2017; 1(1):1–6
https://doi.org/10.1080/23120053.2017.1376546

South Afr J Infect Dis
ISSN 2312-0053 EISSN 2313-1810

RESEARCH

Invasive and non-invasive group A β-haemolytic streptococcal infections in patients attending public sector facilities in South Africa: 2003–2015

Dylan Barth[a], Bongani M Mayosi[a], Motasim Badri[b], Andrew Whitelaw[c] and Mark E Engel[a]*

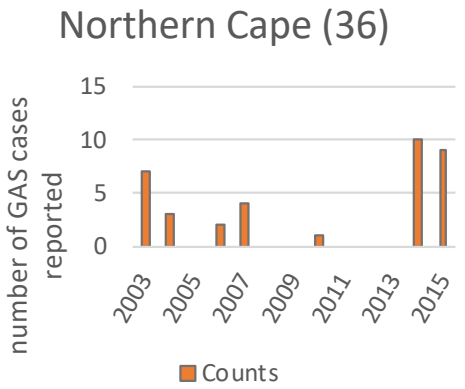
[a]*Department of Medicine, University of Cape Town and Groote Schuur Hospital, Cape Town, South Africa*
[b]*College of Medicine, King Saudi Bin Abdulaziz University for Medical Sciences, Riyadh, Kingdom of Saudi Arabia*
[c]*Department of Microbiology, National Health Laboratory Service, Tygerberg Hospital and Stellenbosch University, Tygerberg, South Africa*
**Corresponding author, email: mark.engel@uct.ac.za*

Background: The burden of disease caused by group A streptococcus (GAS) in Africa is largely unknown. The aim of this study

mean annual IR for non-*i*GAS infection ($n = 4828$) was 5.48 (Range: 0.19–11.55) cases/10^5py; IR showed a decrease (RD, 11.36/10^5 py; 95% CI: 10.53–12.19/10^5 py). The Mann-Kendall test and the Theil-Sen estimator showed a decreasing trend in the incidence of non-*i*GAS infection ($p = 0.002$) over the study period.

Conclusions: The incidence of non-*i*GAS infection in the Eastern Cape province of South Africa declined from 2003 to 2015. The trends from the Eastern Cape and incomplete data from other provinces indicate the need for a detailed prospective evaluation of GAS infection in South Africa to verify this trend and provide information for planning appropriate interventions.

Keywords: epidemiology, group A streptococcus, incidence, infectious disease, public sector, South Africa



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Contents lists available at SciVerse ScienceDirect

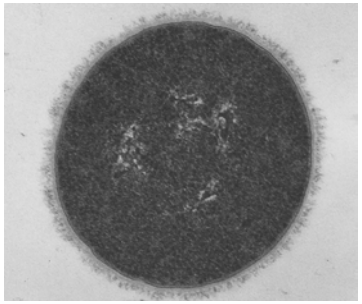
Vaccine

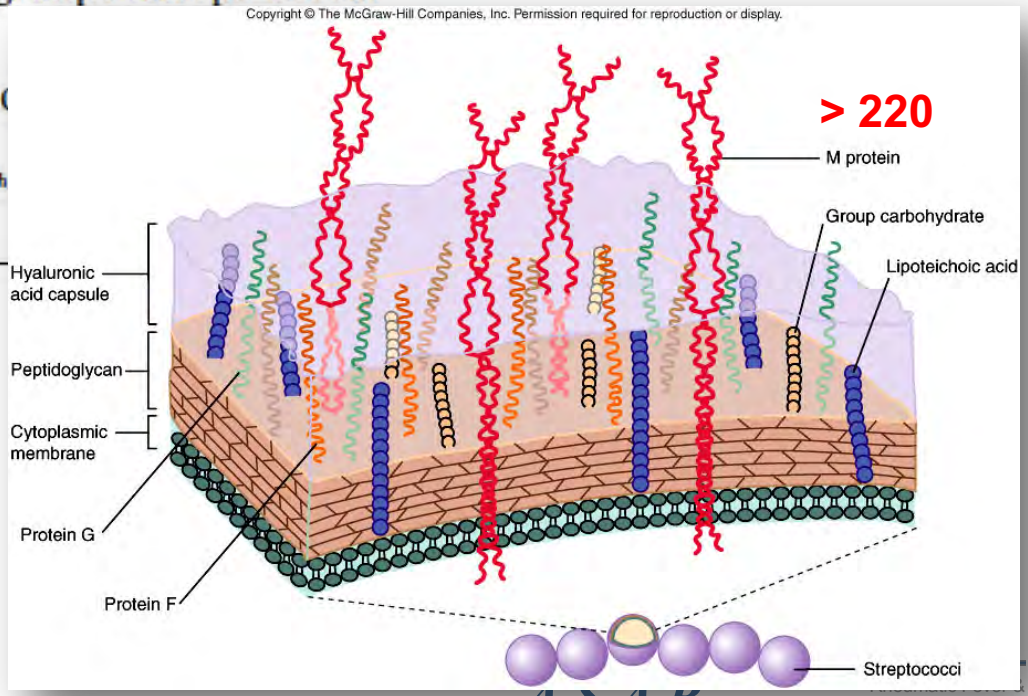
journal homepage: www.elsevier.com/locate/vaccine

Potential coverage of a multivalent M protein-based group A streptococcal vaccine

James B. Dale[a,*], Thomas A. Penfound[a], Boubou Tamboura[b], Samba
Milagritos Tapia[c], Karen L. Kotloff[c]

[a] University of Tennessee Health Science Center, Department of Medicine and Veterans Affairs Medical Center Research
[b] Centre pour le Developpment des Vaccins (CVD-Mali), Bamako, Mali
[c] Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, MD, USA





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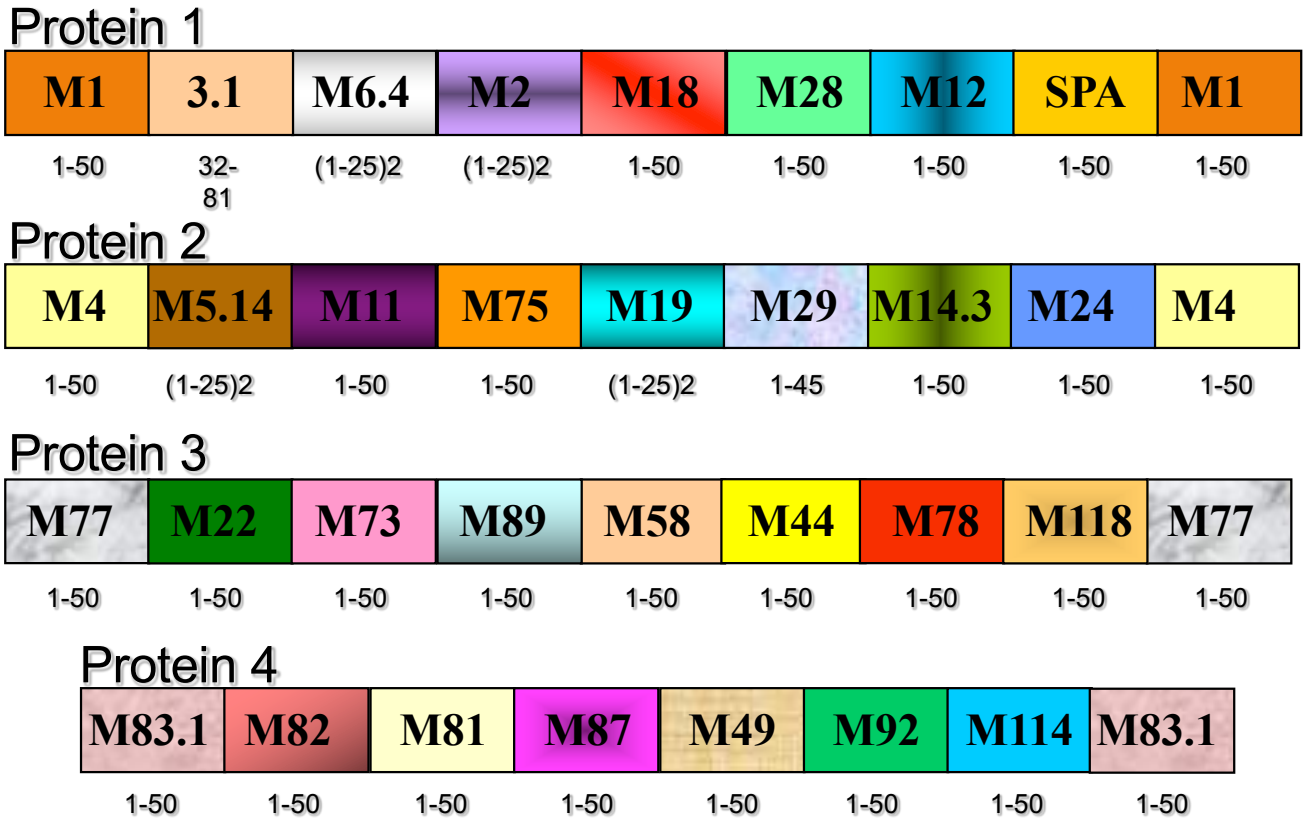

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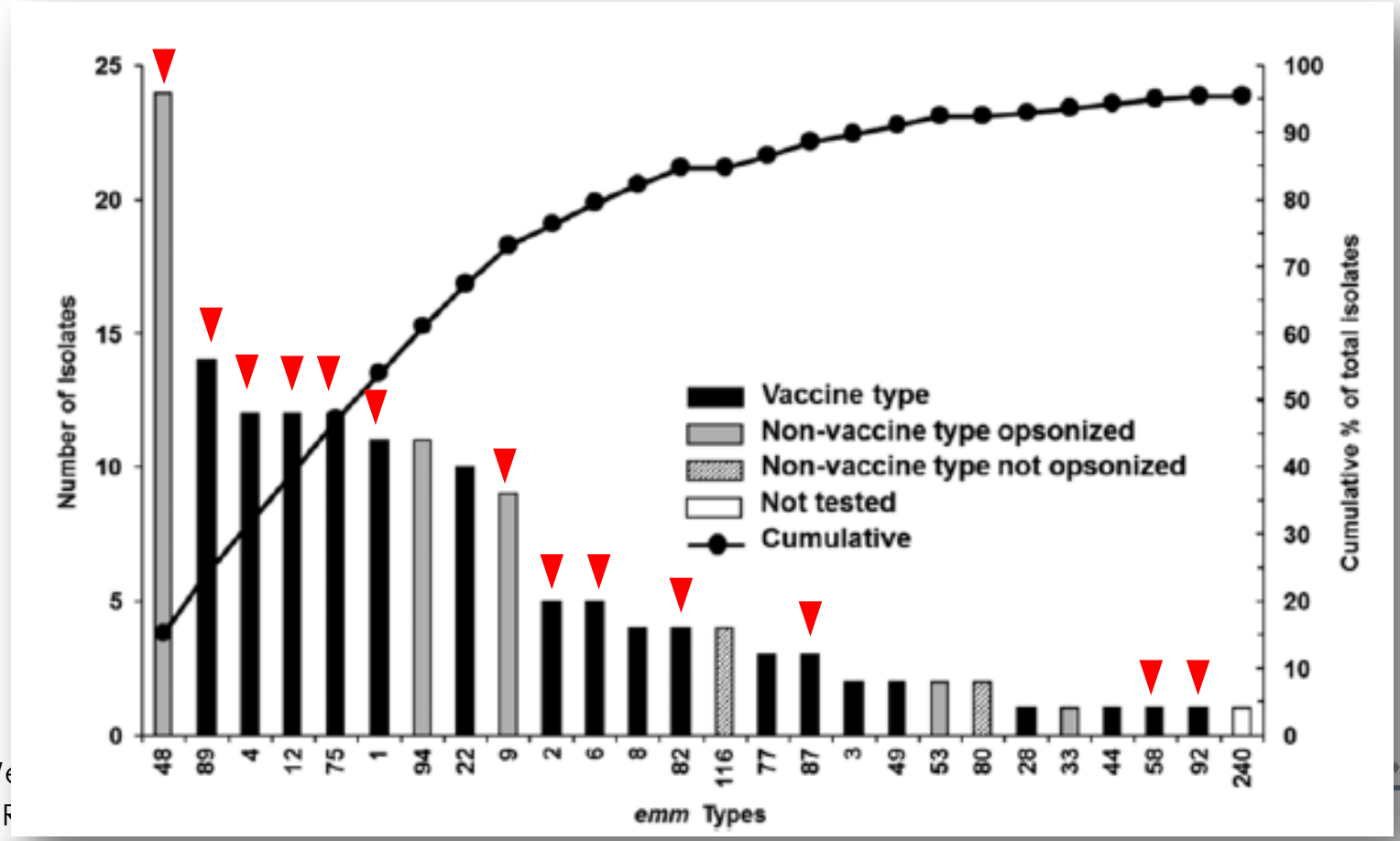
Bactericidal Activity of 30-Valent Vaccine Antisera against Cape Town Pharyngitis *emm* Types, N=157 (Vaccine and Non-vaccine Serotypes)



♦ Advocacy ♦ Prevention

Rheumatic Fever &
Rheumatic Heart Disease

Diagnosing ARF … ent GAS infection?

Human Im… e Antigens

300
Participants

2
years

1) Swabs + s…
2) Assess th… nce of new pharynge…
3) Assess se…

ELISA Antigens for this Study (> 30)		
Antigen	Bacterial Location	Function
Type-Specific M peptides (estimated 35 synthetic peptides)	Cell surface	Opsonic epitopes
M-related peptides (Mrp) Groups I, II, III	Cell surface	Opsonic epitopes
C-repeat M peptide (J14)	Cell surface	Opsonic epitopes
Streptolysin O (SLO)	Secreted	Hemolysin
DNaseB	Secreted	Degrades neutrophil nets
C5a peptidase (SCPA)	Cell surface and Secreted	Cleaves C5a
Serine protease (SpyCEP)	Cell surface and Secreted	Cleaves IL8
Serine esterase (SSE)	Secreted	Tissue invasion
Serum opacity factor (SOF)	Cell surface and secreted	Opsonic epitopes/Fibronectin binding
Fibronectin binding protein (FBP54)	Cell surface	Adhesin/Fibronectin binding
SpyAD	Cell surface	Cell division and adhesion
GAC	Cell Surface	Opsonic Epitopes

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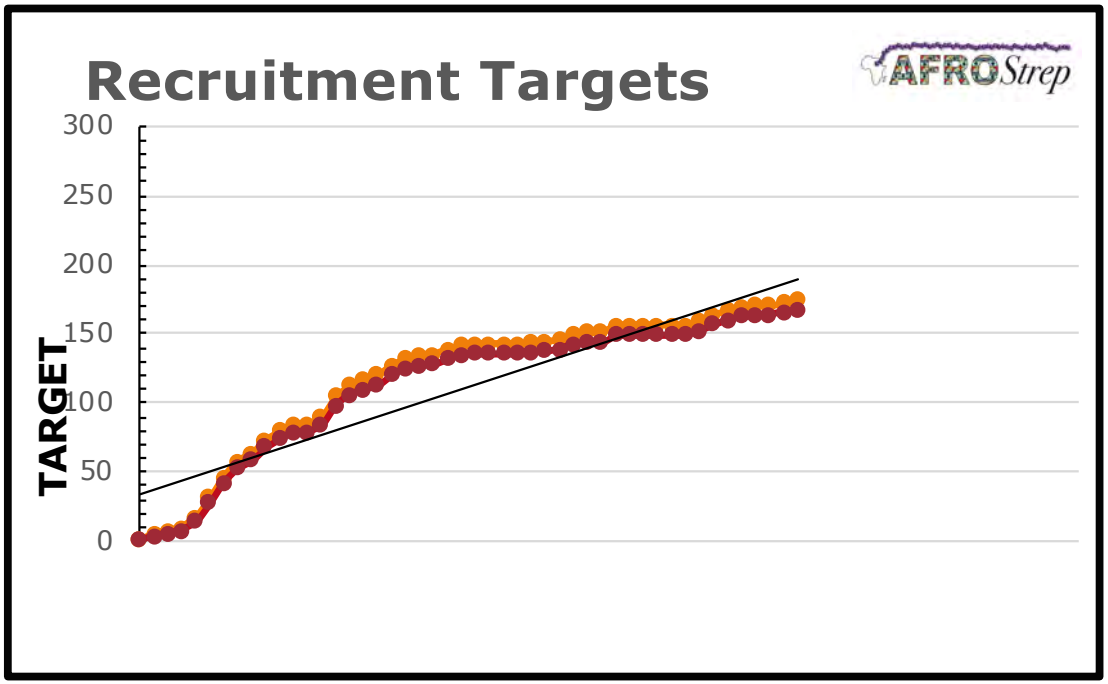
…eness ♦ Sur… Prevention
A.S.A.P. AFRO Strep
Rheumatic Heart Disease

Results: Recruitment/Follow-up



Follow-up visits: n= 175
2nd visit- 92 (62%- 92/149)
3rd visit- 53 (62%- 53/86)
4th visit- 25 (64%- 25/39)
5th visit- 5 (63%- 5/8)

The loss to follow-up: n = 28
The number of withdrawals: n= 22

Impact of concerted mapping of GAS in Africa:

- Document the epidemiological burden on the continent
  - Resource allocation including awareness efforts
  - Basis for monitoring progress
  - Identify risk factors
- Uniform approach ensures comparability of data
- Contribute to understanding the biology of GAS: implications for diagnostic test and vaccine development
- Registry and Biorepositories: reservoir for future opportunities

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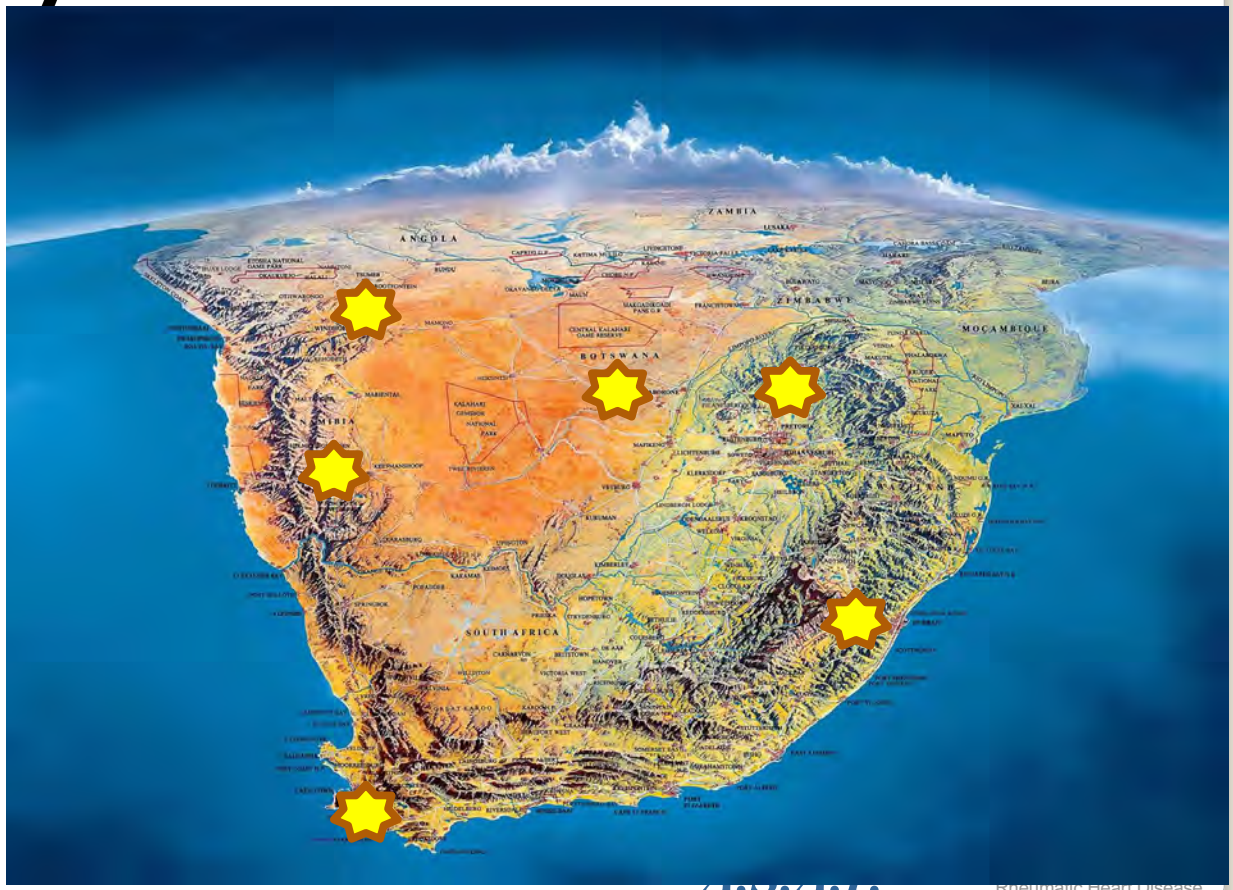

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Inge

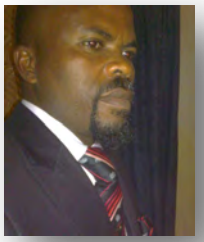
Dylan

AIs / CoIs / Co-PIs

Recruitment

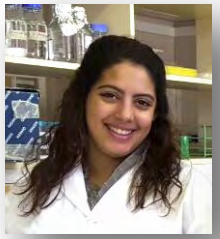
Laboratory

Data M

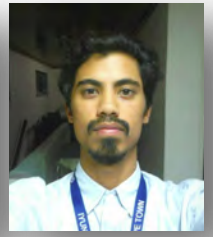


Simpiwe

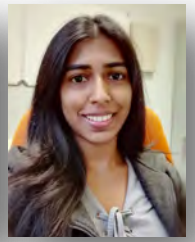
Mpho



Kelin



Taariq



Kimona

Lwazi

RHDGen Network

A.S.A.P.

Rheumatic Fever & Rheumatic Heart Disease

Make your research beyond yourself. Be humble, pray for wisdom each day and, don't worry about who gets the credit...!

Professor Bongani Mayosi
Healer of Hearts, Pioneering Researcher, Beloved Mentor
Hamba Kahle, Rest in Peace.

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