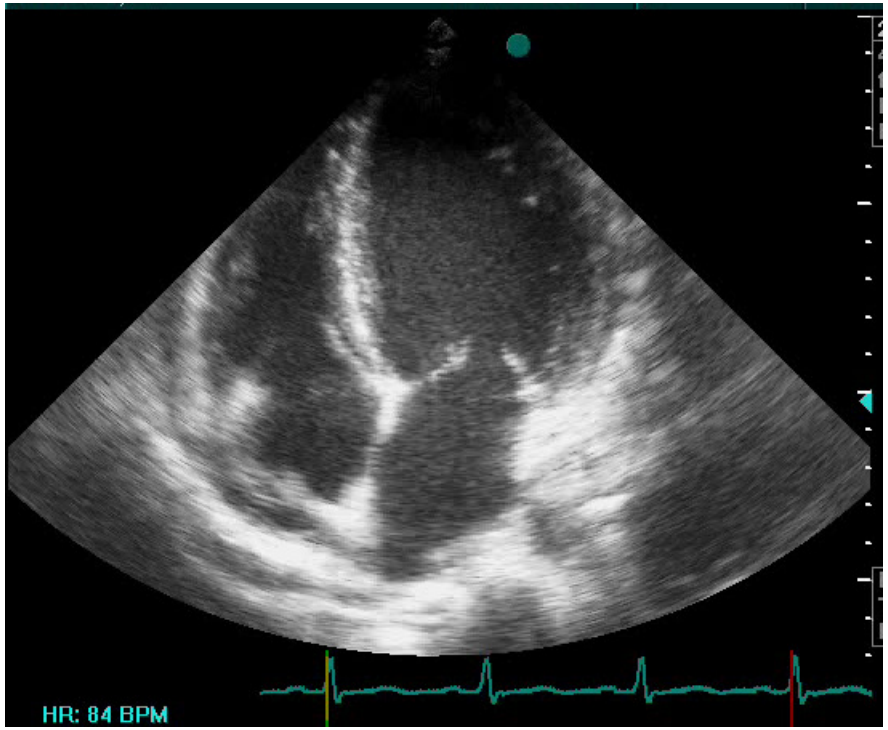
The RHDGen Network

Genetics of ***R***heumatic ***H***eart ***D***isease

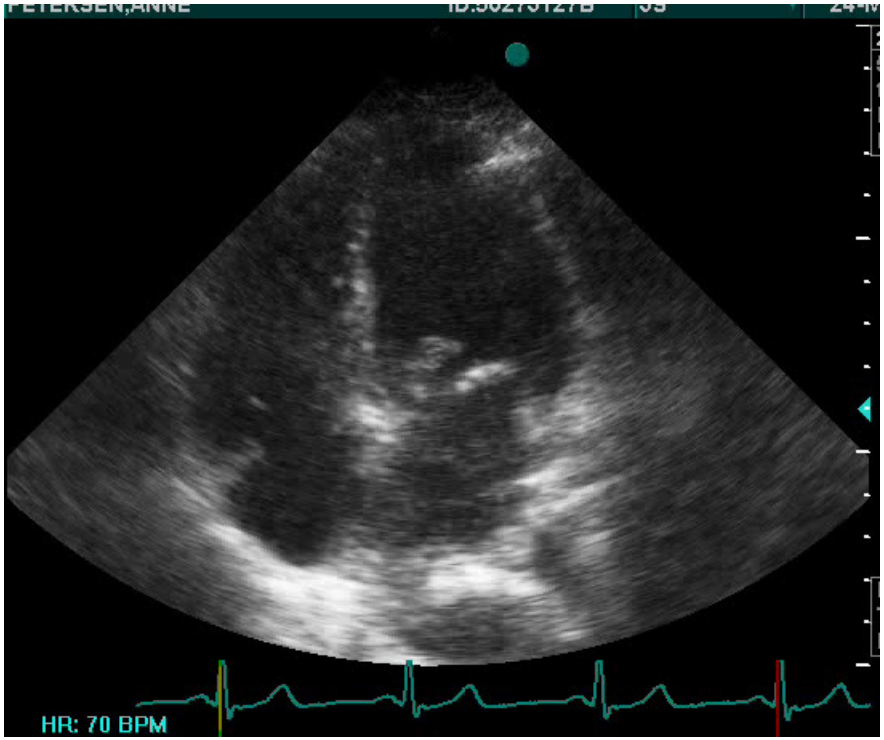
The RHDGen Network

- Rationalé for RHDGen Network
- Proposed activities
- Key goals
- Organisation
- Progress

Mitral Stenosis: The Cardinal Sign of RHD



Normal mitral valve



Mitral valve stenosis

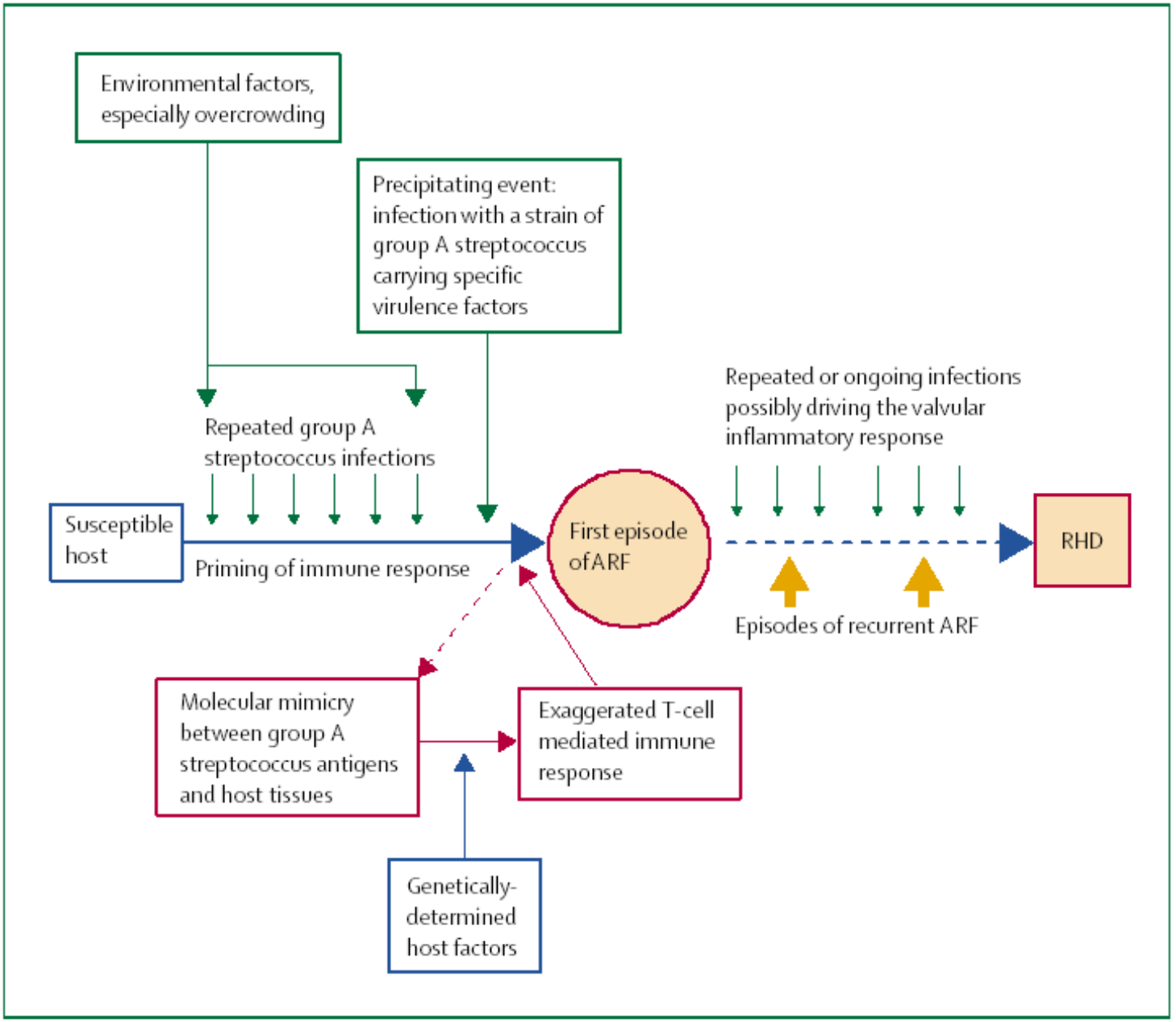
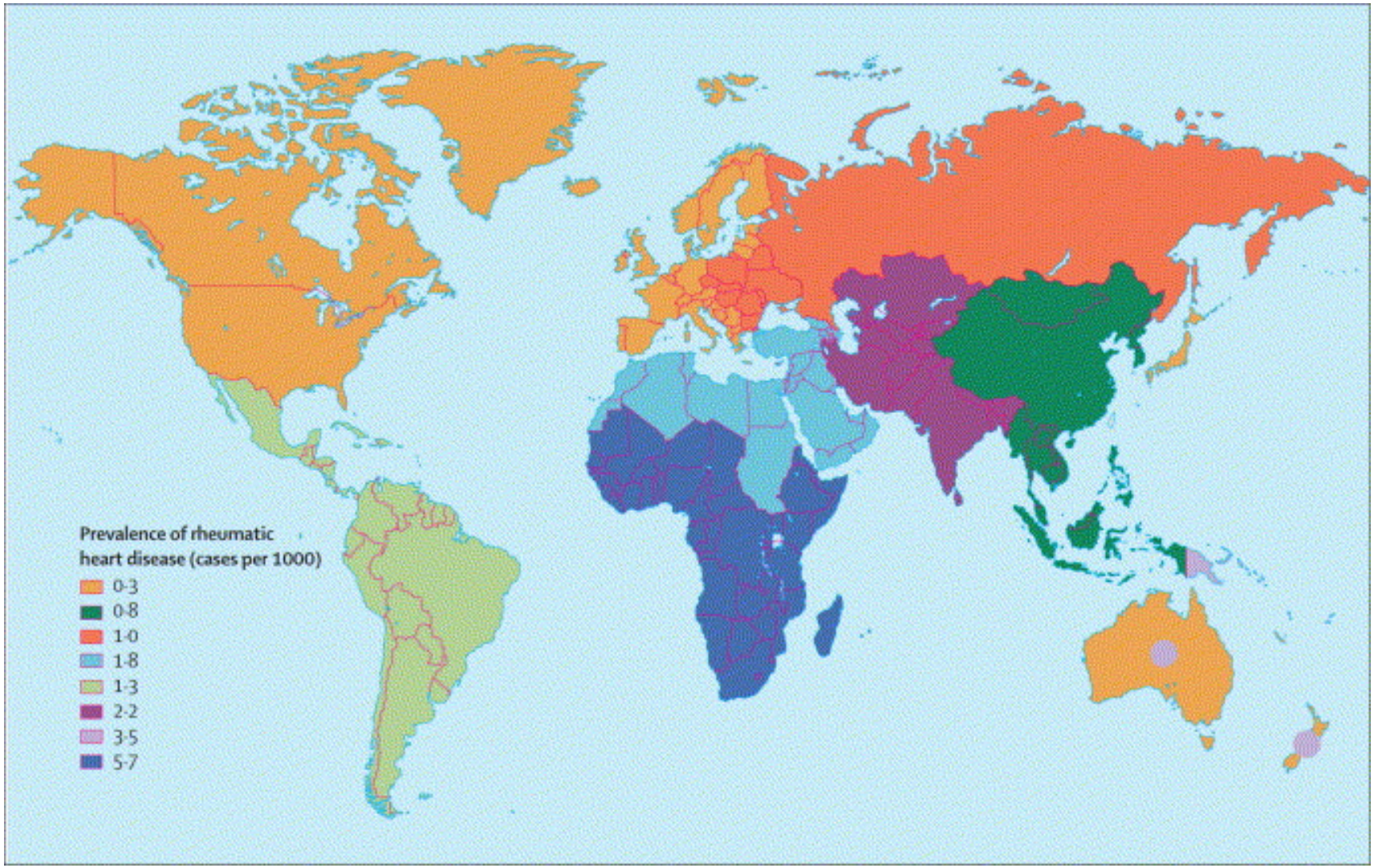


Figure 2: Pathogenetic pathway for ARF and RHD

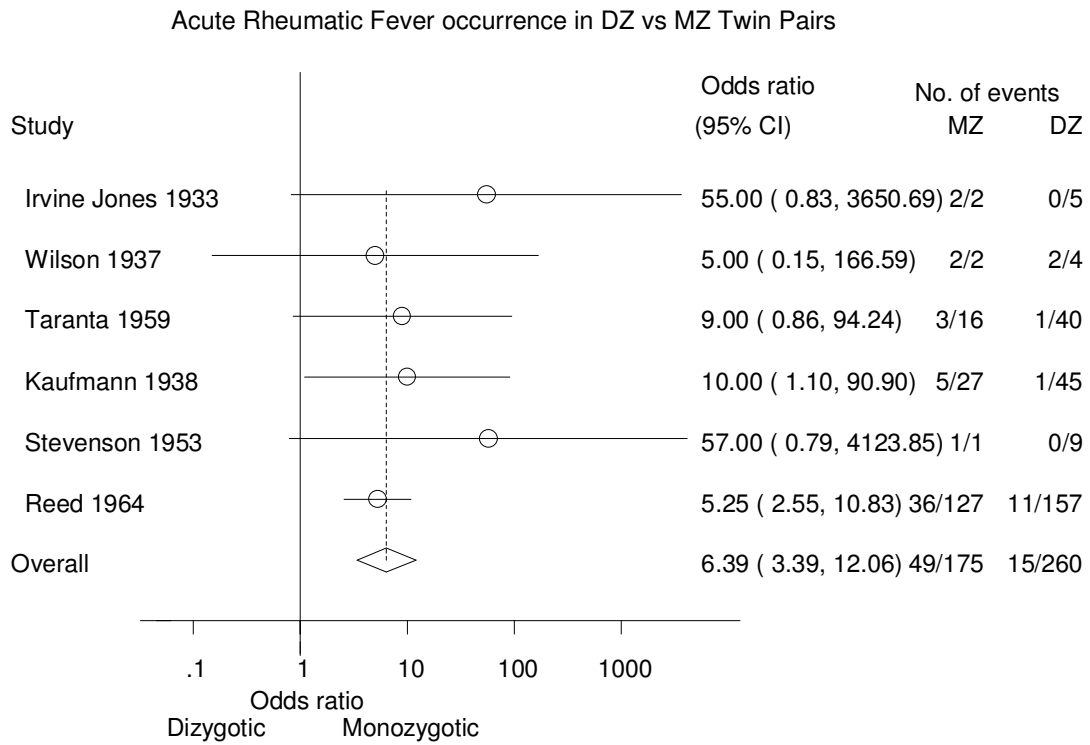
Carapetis. Lancet 2005;366:155

Africa is the RHD Capital of the World



Carapetis 2005

Genetically determined host factors



Odds ratio of concordance for acute rheumatic fever according to type of zygosity in a random-effects synthesis of data from studies included in the meta-analysis.

Engel M et al. PLoS ONE 20116(9):e25326

Platform for RHDGen: Global Registry of RHD

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

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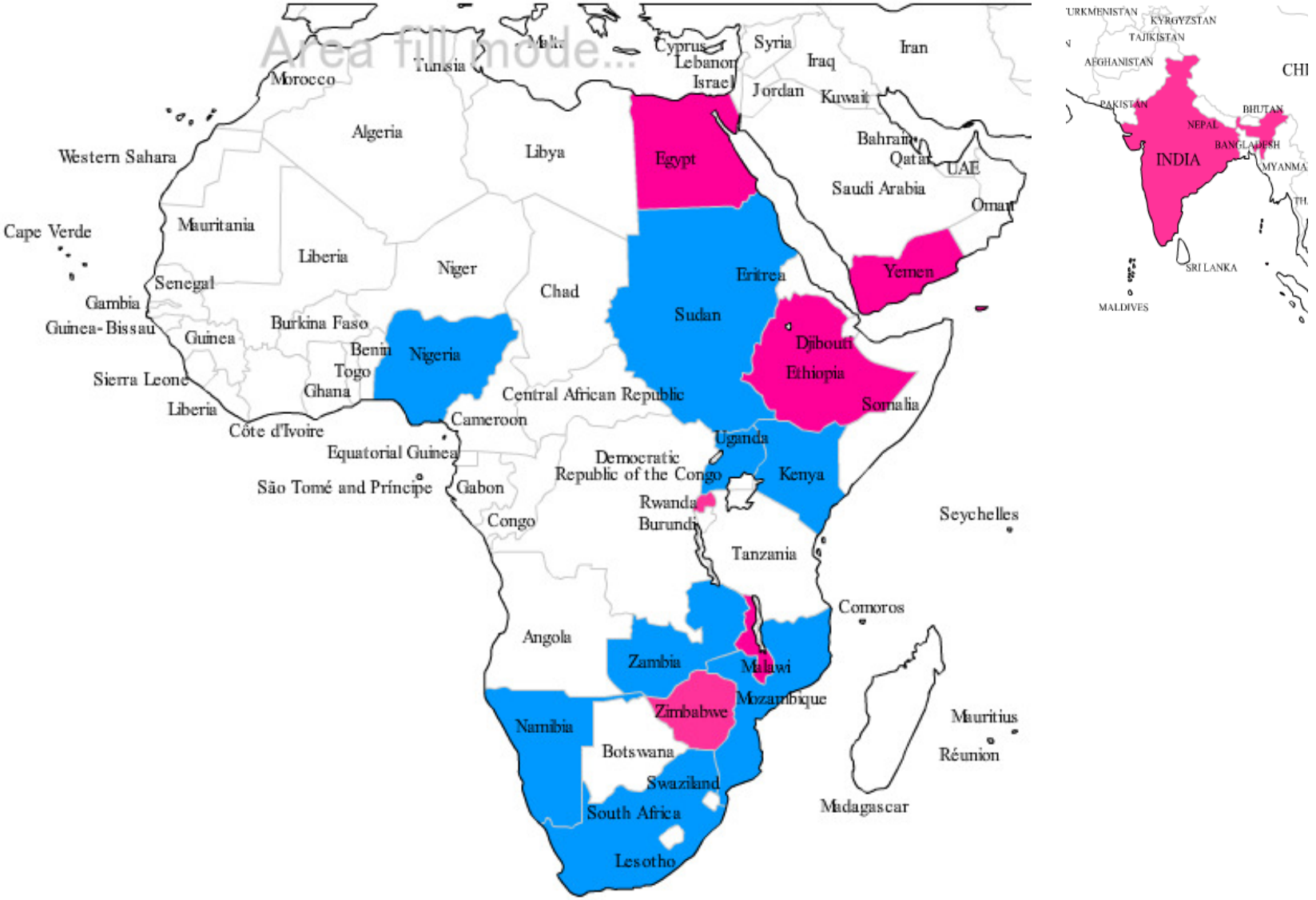
Background Rheumatic heart disease (RHD) is the principal cause of valvular heart disease–related mortality and morbidity in low- and middle-income countries. The disease predominantly affects children and young adults. It is estimated that RHD may potentially be responsible for 1.4 million deaths annually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

Methods The REMEDY study is a prospective, international, multicenter, hospital-based registry planned in 2 phases: the vanguard phase involving centers in Africa and India will enrol 3,000 participants with RHD over a 1-year period. We will document clinical and echocardiographic characteristics of patients at presentation. Over a 2-year follow-up, we will document disease progression and treatment practices with particular reference to adherence to secondary prophylaxis and oral anticoagulation regimens. With 3,000 patients, we will be able to reliably determine the incidence of all-cause mortality, worsening heart failure requiring hospitalization, systemic embolism (including stroke), and major bleeding individually among 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 help in the development of strategies to prevent and manage RHD and its complications. (Am Heart J 2012;163:535-540.e1.)

African Countries Participating in REMEDY I (RHDGen Network Countries in blue)



Key Goals

- Phenotyping: To recruit 1,500 cases and 1,500 controls AND 1,000 cases with two parents (Trios)
- Genotyping: To identify genetic variants affecting susceptibility and resistance to RHD by GWAS in two phases: Discovery (Case-control) and Replication (Trios)
- Training: To train a group of scientists and clinicians in genomic studies of multifactorial disease in the *RHDGen Health Scholars Program*
- ELSI: To address ethical, legal and social issues that are relevant to Africa

Proposed Activities

- 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 ethical, legal and social issues that are relevant to Africa

Progress I: Building the Network

- Investigators' Meeting: 16 November 2012, and two subsequent tele-conference calls
- Staff recruited at the Project Coordinating Centre
- Identification of the first 1,500 index cases is complete
- Ethics submissions in progress (Cape Town approved)
- Contracts and MTAs with 7 sites in progress

Progress II: GWAS

- Visit to GWAS laboratory at the Population Health Research Institute in April 2014
- About 100 standard operating procedures have been finalised
- Laboratory equipment and procedures finalised
- Dedicated clinic facility at PCO refurbished
- First participant recruited on 01 October 2013

Progress III: RHDGen Scholars Programme

- 16 studentships advertised through consortium and Nature Jobs in September 2013, with excellent response (
- Postdoctoral Fellow / Study Medical Officer appointed on 01 October 2013
- PhD and MMed studentships to be appointed before the end of the year, in addition to Babu Mohamed who is funded by MRC
- PhDs to spend first year in the laboratories of collaborators working on existing GWAS data (Universities of Newcastle, Birmingham and McMaster)

Progress IV: Bioethics

- Bioethics is an integral part of RHDGen
- Informed consent is the main question that is being addressed
    - What constitutes minimal information and how much is too much?
    - Is the use of pictures helpful?
- 2 x MSc studentships in empirical ethics awarded
  - 35 applications received from 12 African countries
  - 2 students with track record in bioethics appointed
  - projects on informed consent and data sharing

Plans for the next 12 months

- Initiation and training at 7 sites over the next 6 months
- Identify cases with parents for the trio study (10% yield at present)
- Push for the collection of DNA from the existing 2,500 cases
- Commence collection of phenotypes and genotypes from unrelated controls