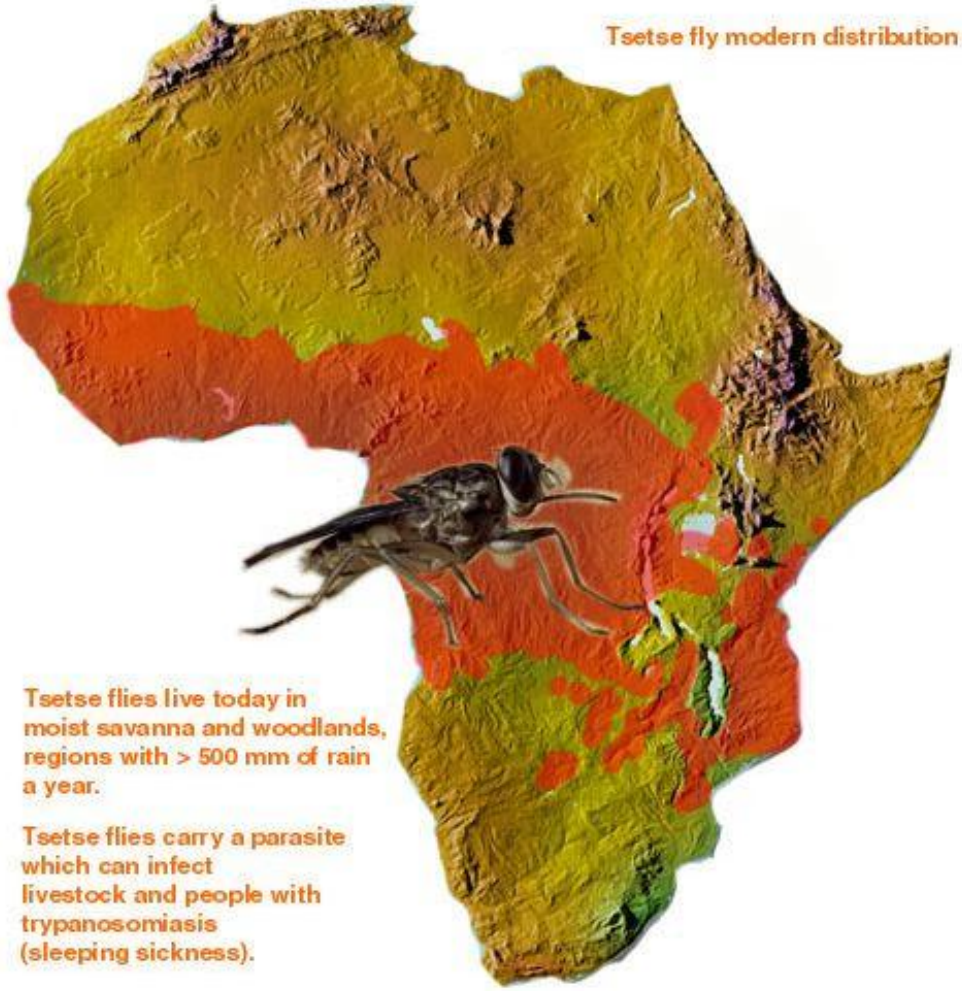
TrypanoGEN: An integrated approach to the identification of genetic determinants of susceptibility to trypanosomiasis

African Trypanosomiasis Associates with Tsetsefly Distribution

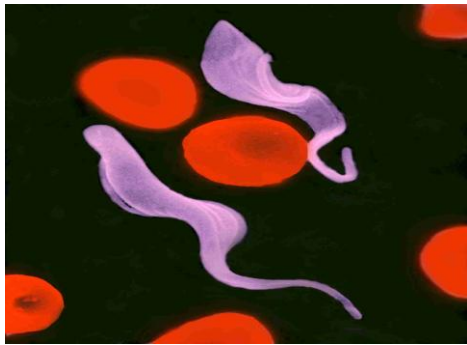


Animal African Trypanosomiasis (AAT)

- *T. Vivax*
- *T. Congolense*
- *T. brucei brucei*

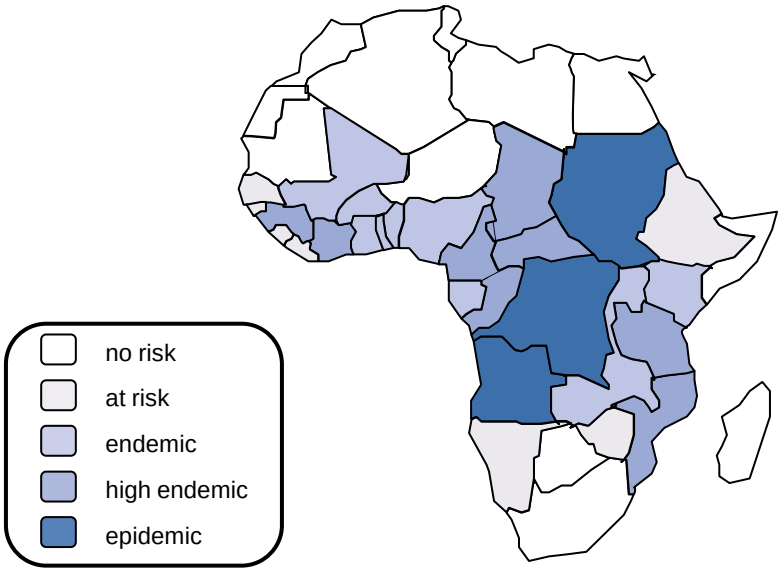
Human African Trypanosomiasis (HAT)

- *T. brucei rhodesiense*
- *T. b. gambiense*

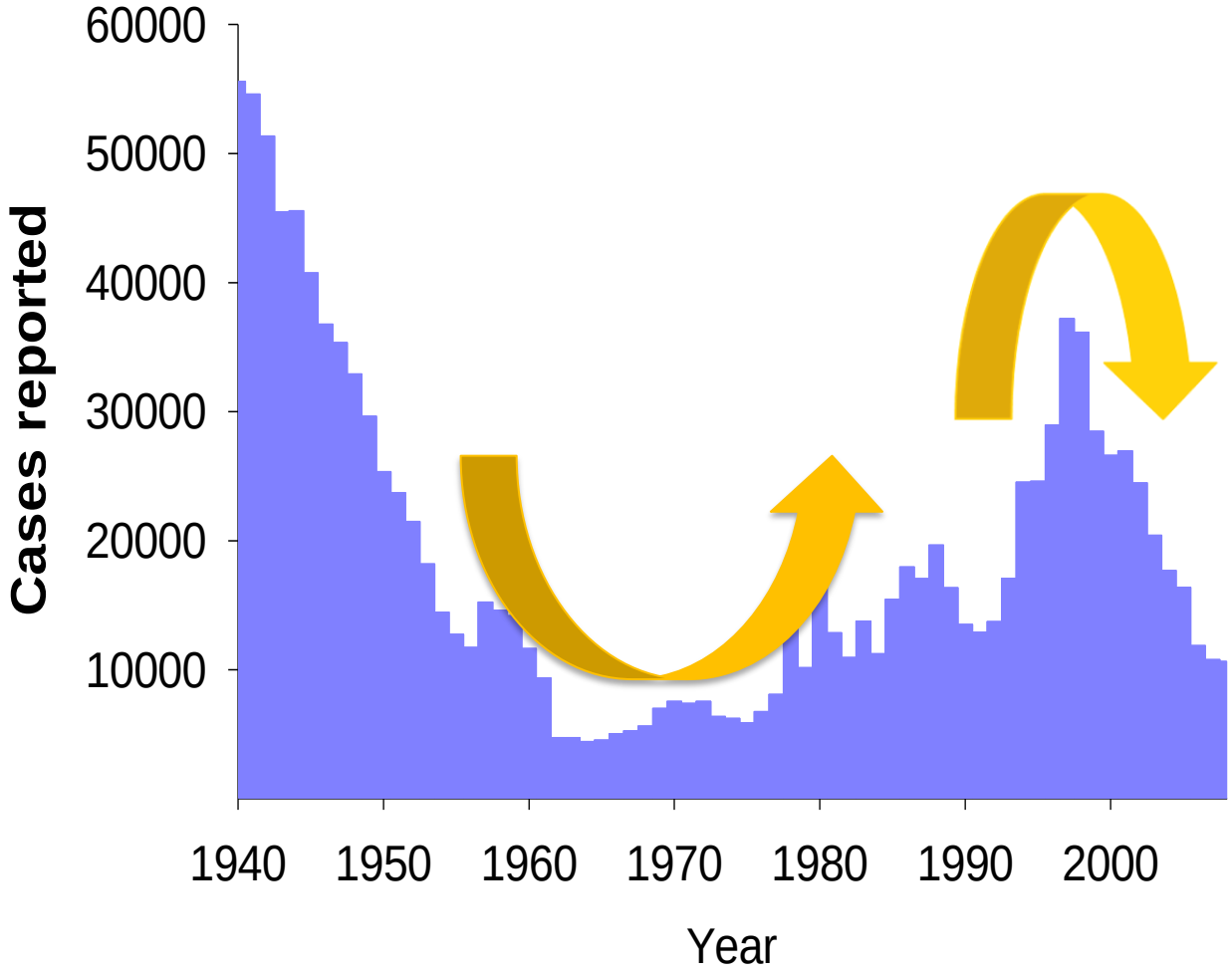


The problem

- HAT is a fatal neglected disease
- Estimated 70,000 human cases/year
- No vaccine
- Drugs are toxic
- Zoonotic - livestock cases estimated cost $1.3bn/year
- Major impact on human and animal health



Reported incidence of disease



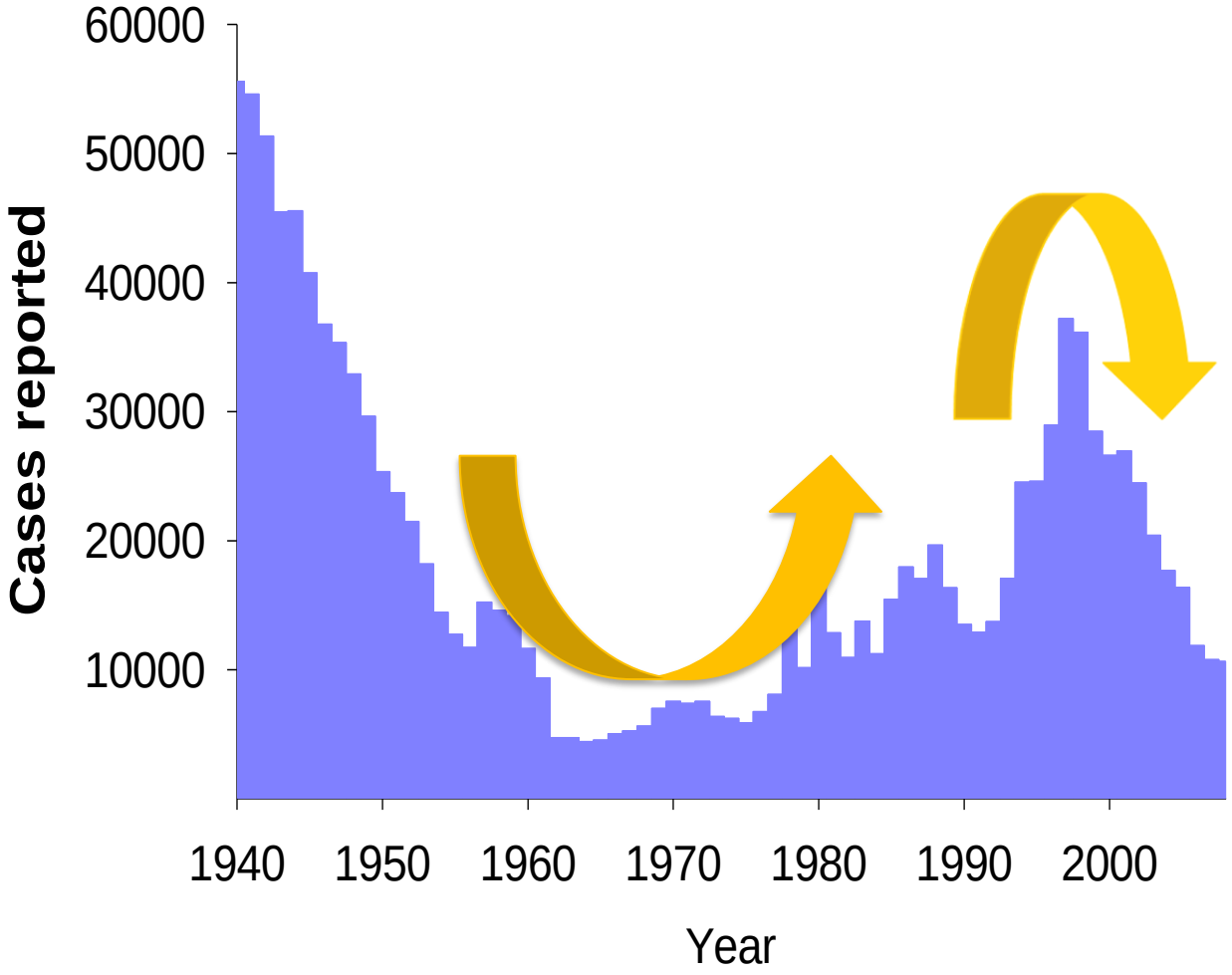
Estimated that 7-10 x more people are affected than reported

New tools are needed

- Wide-spread consensus of the need for novel approaches to achieve elimination or sustainable control

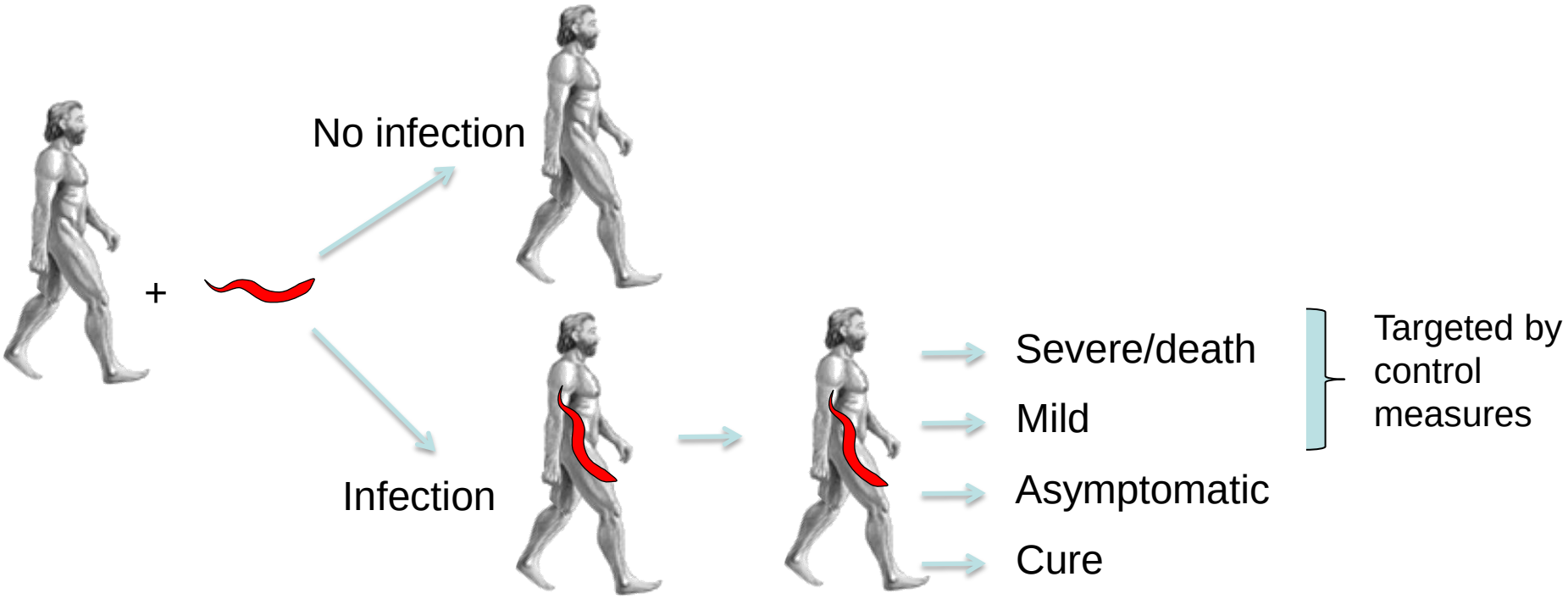
  - New control strategies
  - New therapies

The threat of re-emergence



What are the factors that are responsible for re-emergence/ maintenance of disease foci?

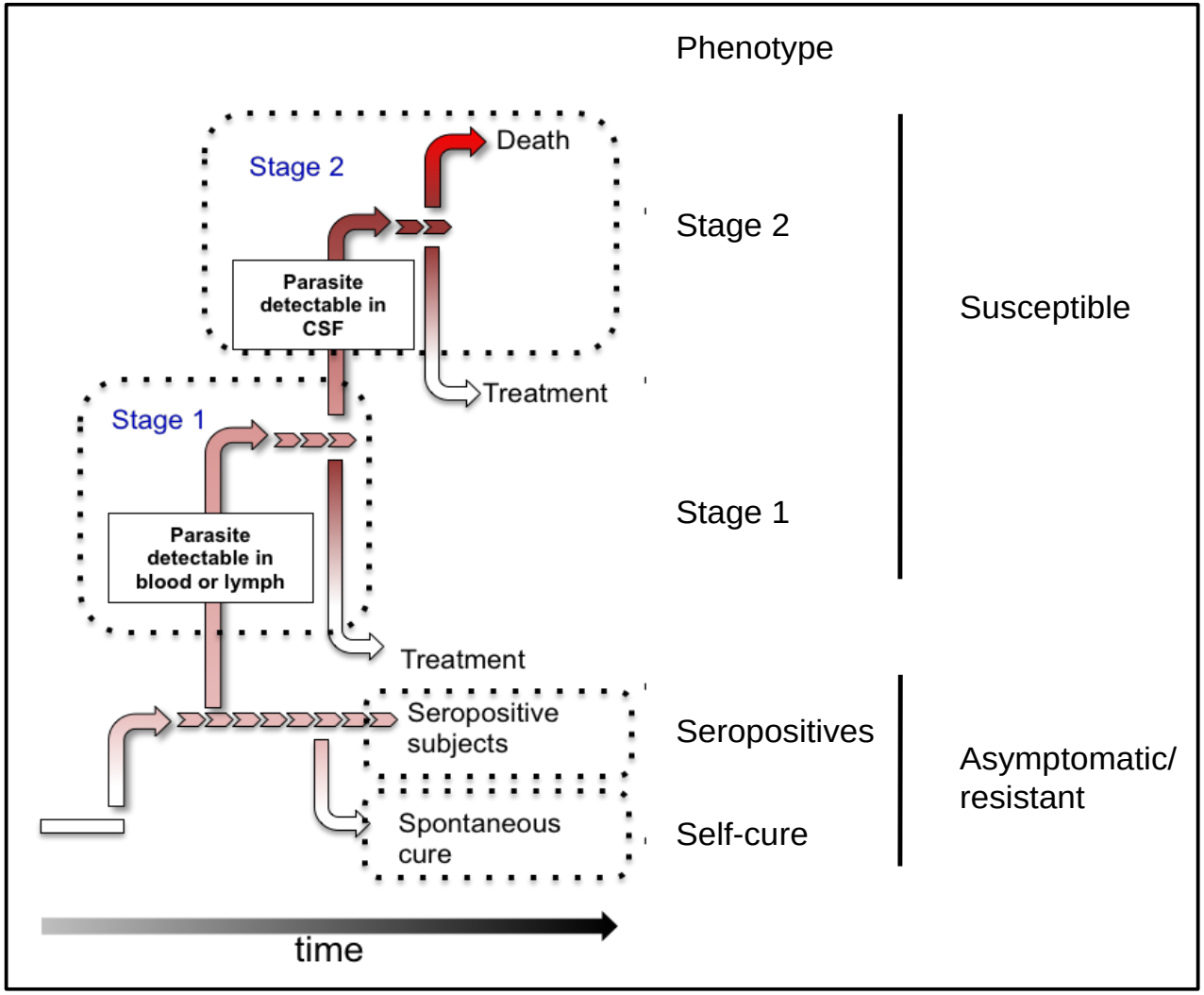
The diversity of infection outcomes



Parasite genetic diversity – virulence / pathogenicity

Human genetic diversity – resistance / susceptibility

The diversity of infection outcomes



The aim

Exploit human genetic diversity to find the key to combating the disease:

In developing new control strategies

In developing new therapies

Research Question and Objectives

What are the host genetic determinants of disease susceptibility/resistance?

Objectives

- To create an extensive biobank of both retrospective and prospective samples with standardised parasitological and clinical metadata

- To generate a database of human genetic variation from different African countries
  - ➢ In order to identify loci associated with HAT susceptibility

Hypotheses

HYPOTHESIS 1:

HAT per se is controlled by susceptibility/resistance loci and the GWAS that will be carried out in this project will reveal candidate loci for this phenotype.

HYPOTHESIS 2:

ASYMPTOMATIC PATIENTS CAN BE INCLUDED AS ENDEMIC CONTROLS TO INCREASE THE PROBABLITY OF IDENTIFYING RESISTANT/SUSCEPTIBILTY LOCI

The current situation for genetic association studies

- Current research is small-scale
- Asymptomatics are not taken into account
- Two published studies that lack power

Consequence

- Waste of resources
- Samples not logged properly and not available to others, often different sampling strategies
- Lack of provision of infrastructure, training and long-term legacy

Our proposal

- To create for the first time a network that systematically investigates genetic diversity in relation to HAT in endemic areas across the whole of Africa

- Enhance capacity for African-led research into an African disease

Project overview

The TrypanoGEN Biobank

Existing samples

Controls	SERO	HAT
390	165	1060

Minimum required for GWAS

Controls	SERO	HAT
600	400	1200

Year 1 **Year 2** **Year 3** **Year 4** **Year 5**

Activities

Biobanking existing samples
Ethical agreement

WGS of 130 controls → Candidate gene testing

Design custom Omni2.5 Illumina

Genotyping 2800 individuals → Candidate gene testing

GWAS

Training

Ethics

Sampling/biobanking
Sequence bioinfo

Ethics

NGS bioinfo
SNPs arrays

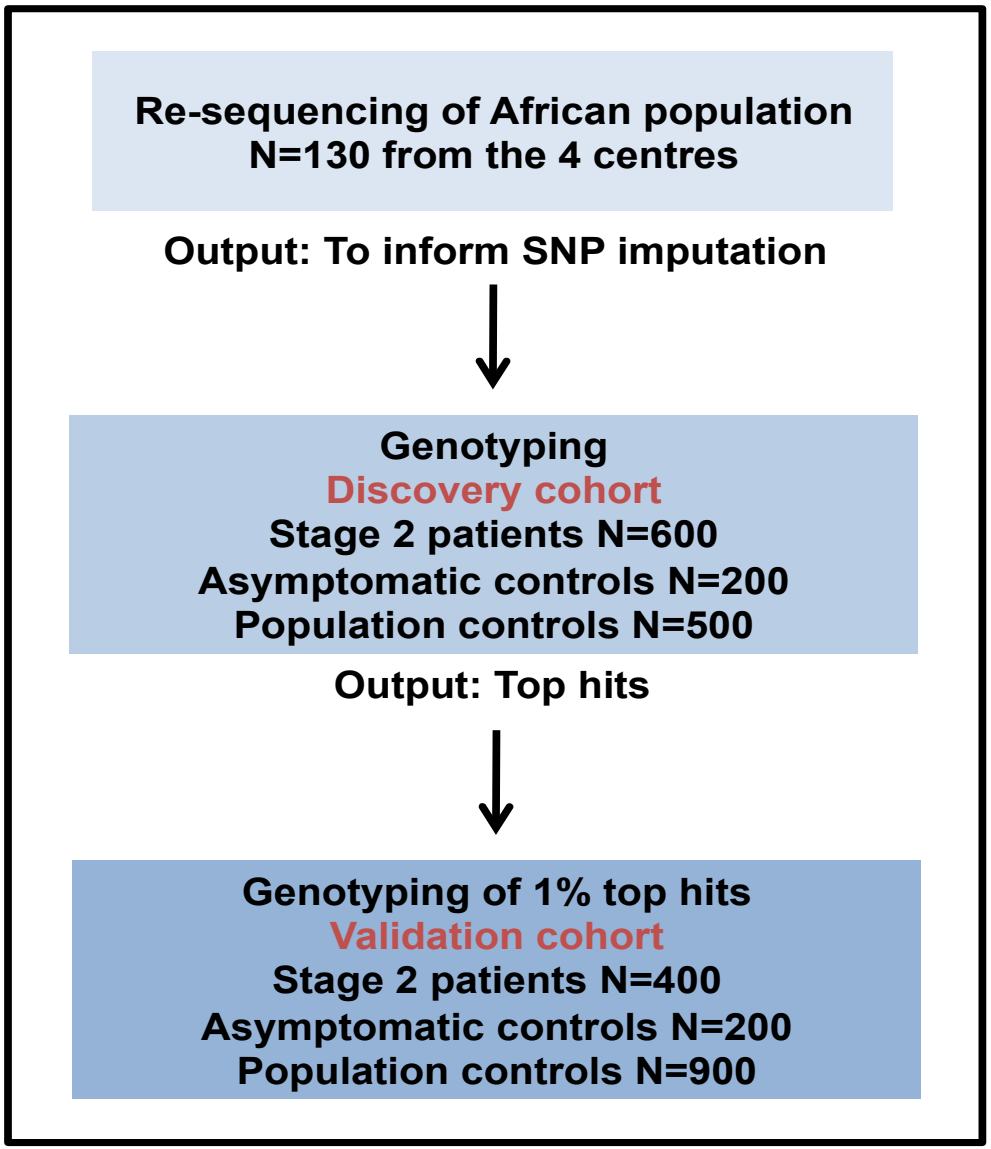
Imputation meth.
GWAS statistics

3rd Generation Seq
Grantmanship

Our GWAS plan

- To collect biological samples and clinical data from patients and controls.
    - At least 1000 cases
    - At least 1400 controls
- To conduct a GWAS
    - Sequence 130 individuals to obtain local SNPs
        - Focus on four regions:
          Uganda, DRC, Cote d'Ivoire, Guinea
    - Genotype ~half the samples- discovery cohort
    - Genotype the rest for top 1% hits- validation cohort

Details of GWAS



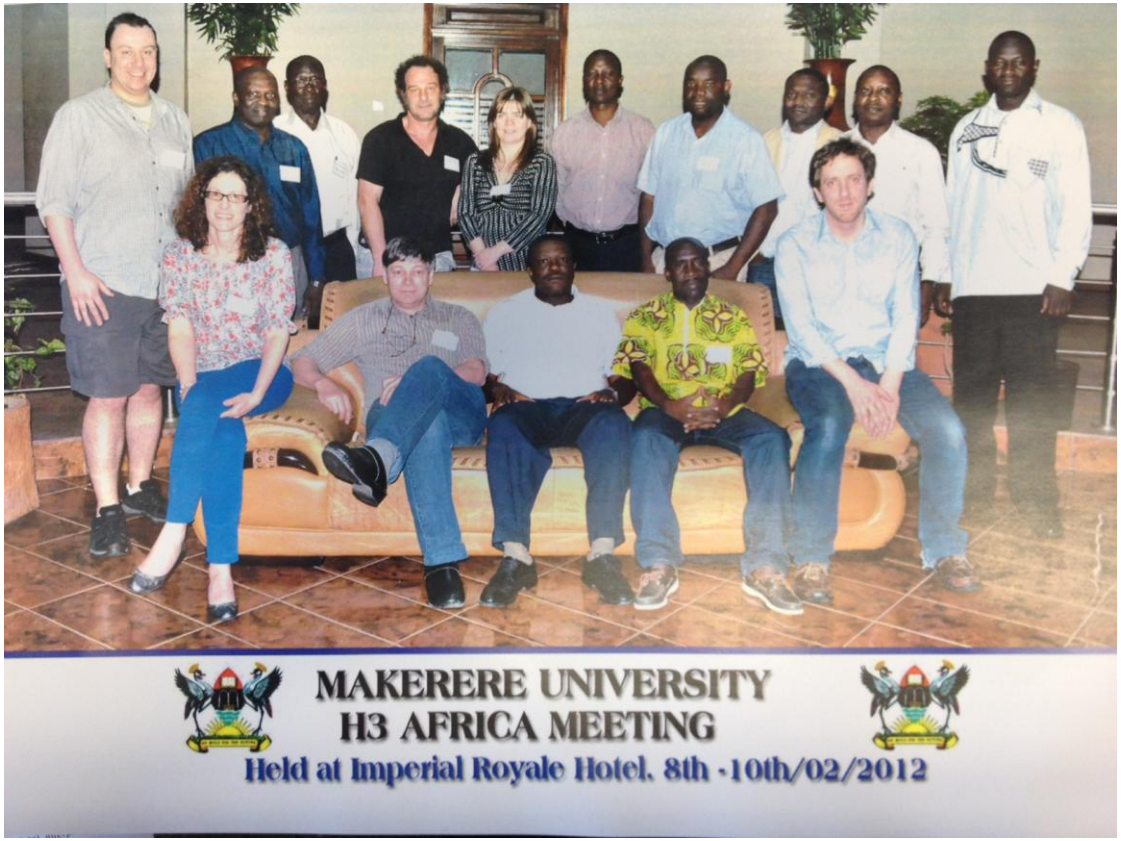
What we will deliver - science

Short-term	- New African genomes - Biobank - Epidemiological data
Medium-term	- HAT susceptibility loci/pathways - Intervention strategies - policy change? - Biomarkers for disease severity - Relevance of asymptomatics in GWAS
Long-term	- New therapies - New diagnostic tools

What we will deliver –capacity development

Short-term	- Biobanking facilities - Computer infrastructure for storage and analysis of genomic data
Medium-term	- Panel of skilled African scientists in genomic analysis - Bioinformaticians - PhDs - Masters - Technicians
Long-term	- Self-sustaining research projects

Team - Who we are



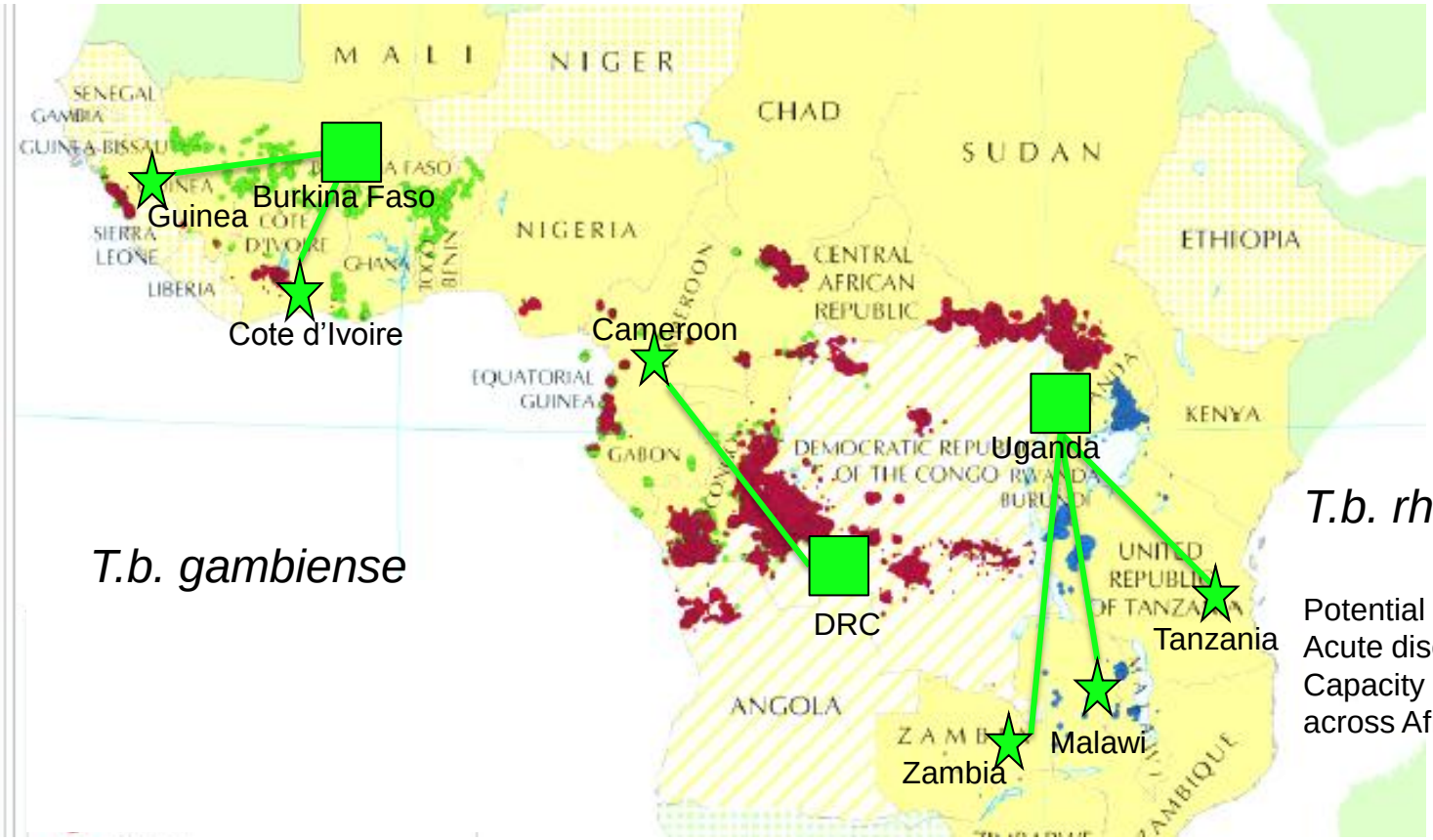
Leading experts in different aspects of HAT

Who we are

- 9 African + 3 European countries
- Experienced
- Existing infrastructure in hubs
- 4 institutes linked with AfriqueOne, SACIDS, SACORE, CARTA, THRiVE
- Already several successful collaborations between individual network members on various projects
- eg WT, Gates, EU, AU and PATTEC.

Where we are

UK France Belgium



T.b. gambiense

T.b. rhodesiense

Potential for epidemics
Acute disease
Capacity building
across Africa

Training/capacity building

Training provision:

- Workshops in sample collection and biobanking
- Workshops in genome analysis WT course in genome association studies
- Workshop on bioethics
- On the job training by hub-embedded bioinformatician
- Training on demand by external collaborators
- Scientific conferences/meetings

Capacity building:

- SOPs for diagnosis and sampling
- Biobanking
- Expand on existing computational infrastructure

Ethics

Informed consent

- Secured and anonymised data and samples
- Sample and data access committee

Benefit to patients

- Short-term - Good diagnosis and follow-up

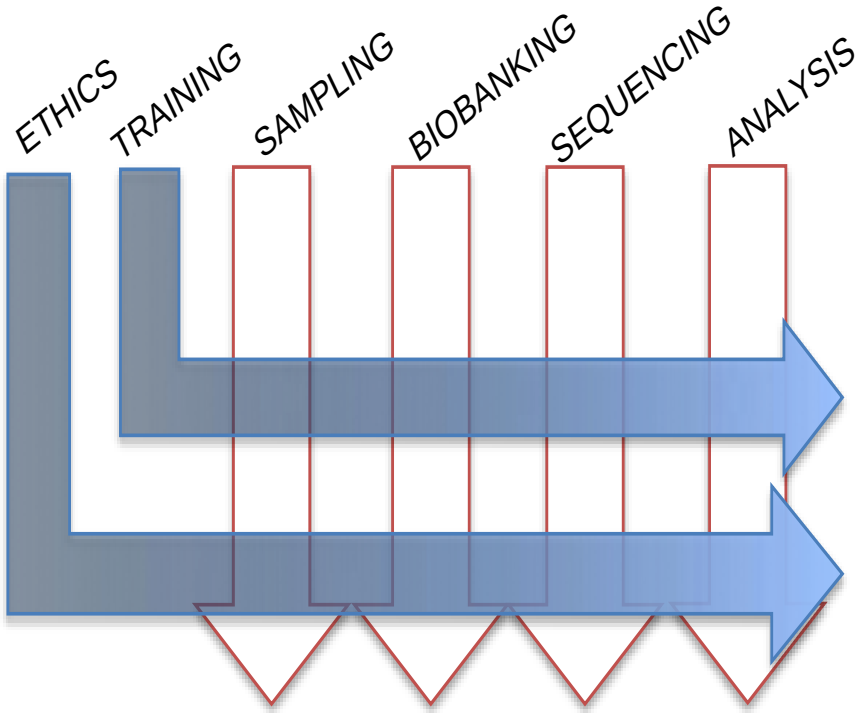
Benefit to community

- Short-term - Reduced transmission
  - Awareness of disease through public engagement activities
- Long-term - New diagnostic tools / therapies
  - New policies / control strategies

Ethics- obtaining approval

- Research into ethical sensitivities in different countries (PhD)
- Ethics manager and expert ethicists in field of human genetics
- Ethical approval already obtained for Cote d'Ivoire cohorts

Ensuring delivery



ETHICS
Lead: S. MacLean
Deputy: P. Alibu, M. Parker

TRAINING
Lead: I. Sidibe
Deputy: D. Mumba

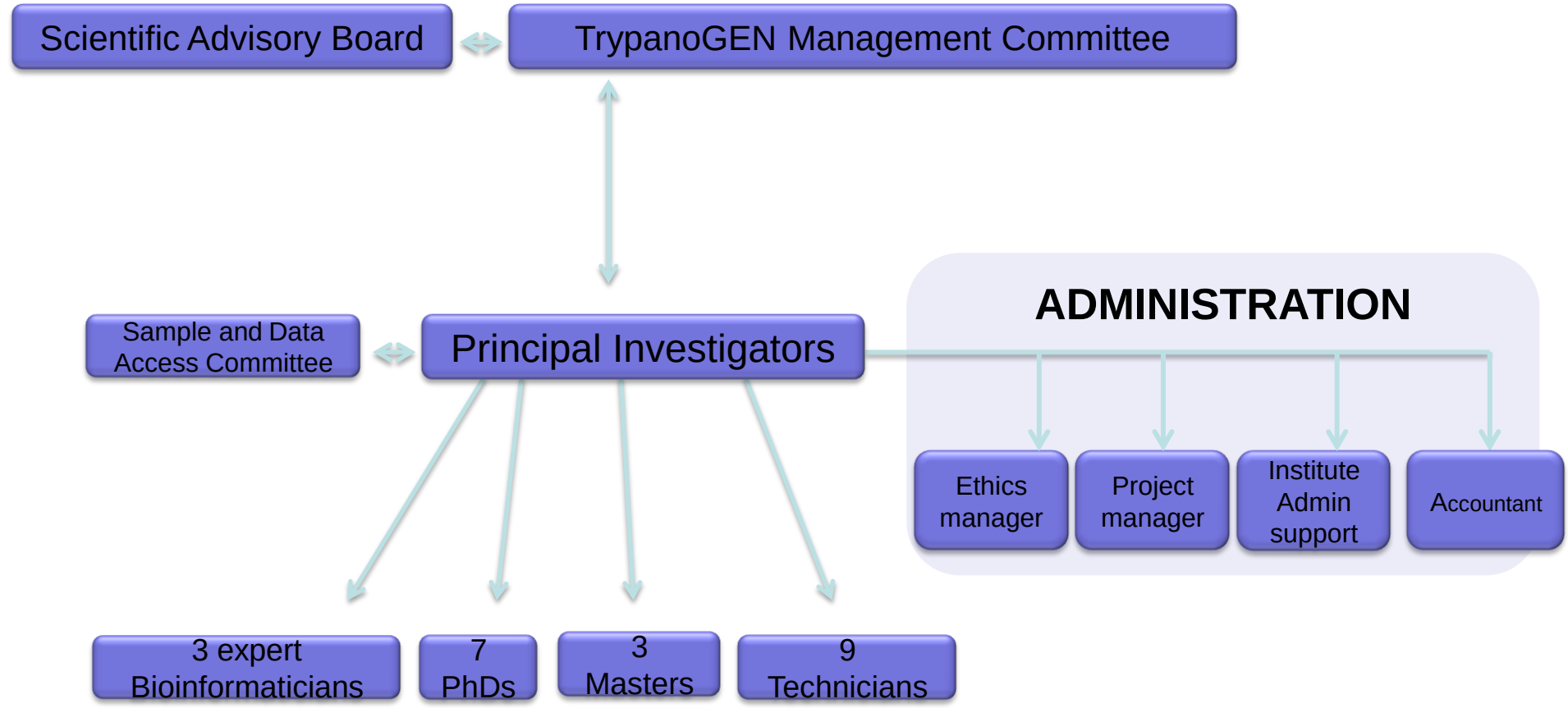
SAMPLING
Lead: M. Simuunza
Deputy: D. Mumba

BIOBANK
Lead: D. Mumba
Deputy: E. Matovu, I. Sidibe

SEQUENCING
Lead: G. Simo
Deputy: C. Hertz-Fowler

ANALYSIS
Lead: K. Mathurin
Deputy: E. Matovu

Ensuring delivery



Ensuring delivery

Evaluation procedures

- Kick-off meeting milestones and detailed plan agreed
- Monitoring progress regularly
  - -quarterly conference calls
  - -6 monthly reports
- Annual review process – ISAB
- Project manager to facilitate smooth running of project
- Ethics manager to ensure ethical agreement is obtained
- Funds for field work released based on performance

Ensuring good communication

- Regular scientific and managerial meetings
- Forum for discussion and feedback of stakeholders

Sustainability

- Network PI members have permanent positions
- PhD students have skills in genome analysis to ensure employability and be in a position to lead or collaborate on future African genomic projects
- Ensure future funding through:
  - Funding opportunities workshop
  - Workshops and training in grant writing
  - Grant polishing team
- Links with other consortia through invitation to annual scientific meetings, joint training sessions

Areas of potential synergy with other H3 Africa networks

- Ethics
- Training -grantsmanship
  -bioinformatics and GWAS
  -ethics workshops
- Sharing data policies
- Shared controls
  SNP database
  potential problems – rural Africa
- Logistics
- Infrastructure building
- Communication across Africa