Malaria Clinical Research In Africa: Recent Developments

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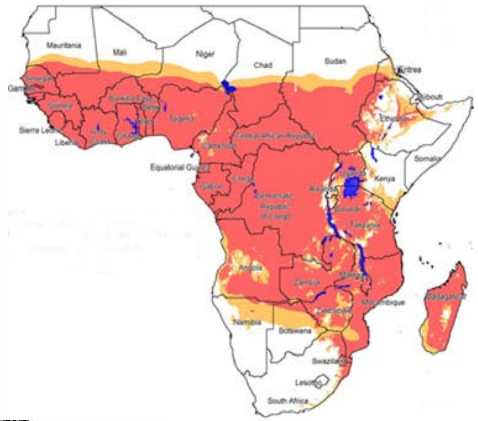
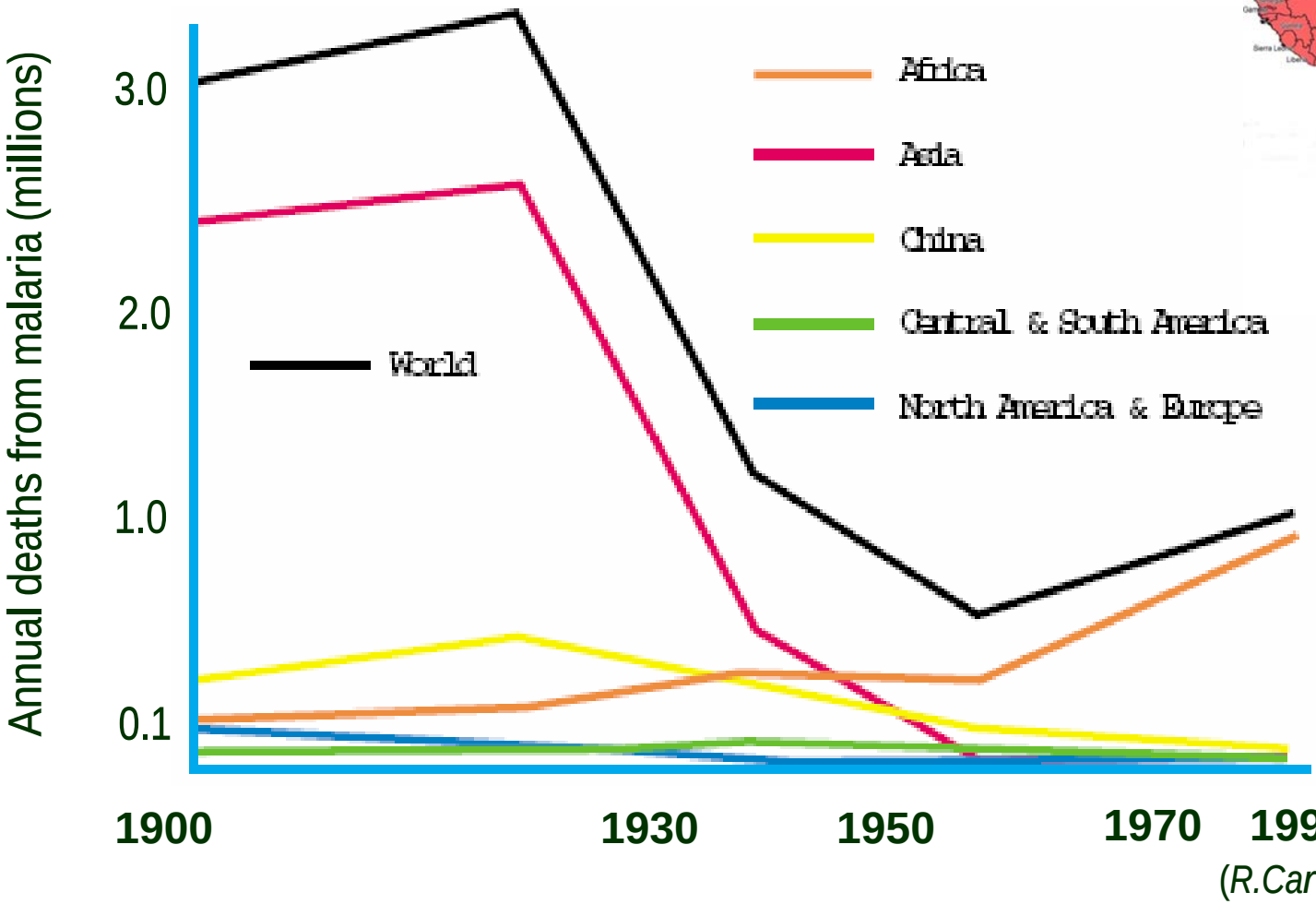
Overview

- Historical burden and African gaps
- Malaria research financial trends
- Antimalarial drug pipeline
- Global malaria vaccine portfolio thoughts
- Traditional medicines
- Basic science research
- Immunological assay efforts
- Diagnostics
- PDP issues and the AMANET example
- Concluding thoughts

The malaria challenge





Africa contributes the bulk of the global burden

(*R.Carter,1999*)

99/1 Gap Illustrated

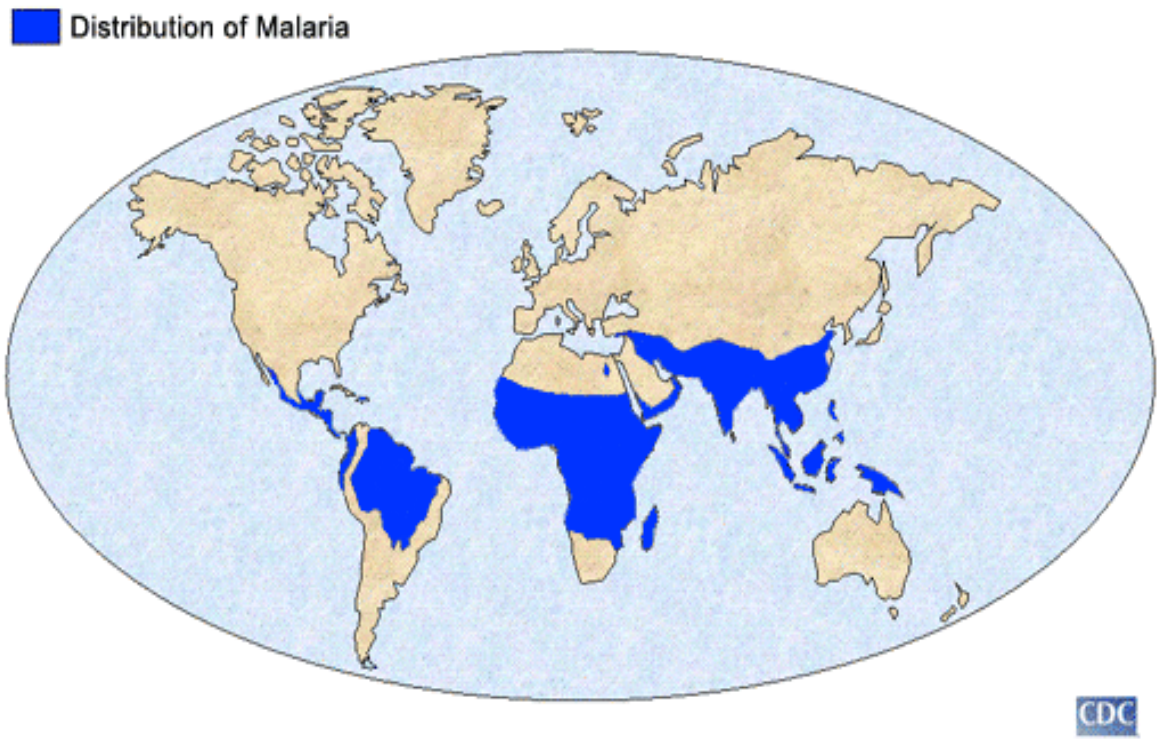
1.2% Biomedical papers overall come from Africa with northern collaborations

79% of malaria papers on Africa have authors from Europe and US

88% grants listed as for African laboratories are managed outside Africa

Only 17% **malaria** papers on science citation index and medline databases have an African address

Distribution of Malaria



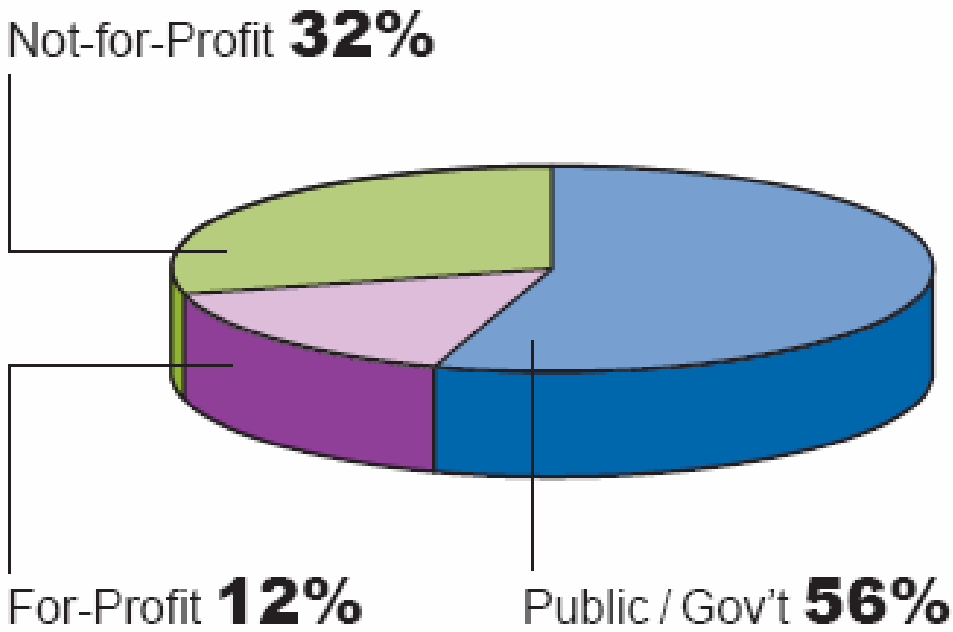
Phyllida Brown http://www.wellcome.ac.uk/publications

Who invests how much in malaria R&D?

2004 investment: US$ 323 Million

Growth of US$166 million in spending on malaria R&D investment between 1993 & 2004

By DALYs would be US$ 3Billion



2004 Investment by Sector

Chart source: Malaria Research & Development: An Assessment of Global Investment
Malaria R&D Alliance: www.MalariaAlliance.org

Malaria R&D Expenditure (2002-2006)

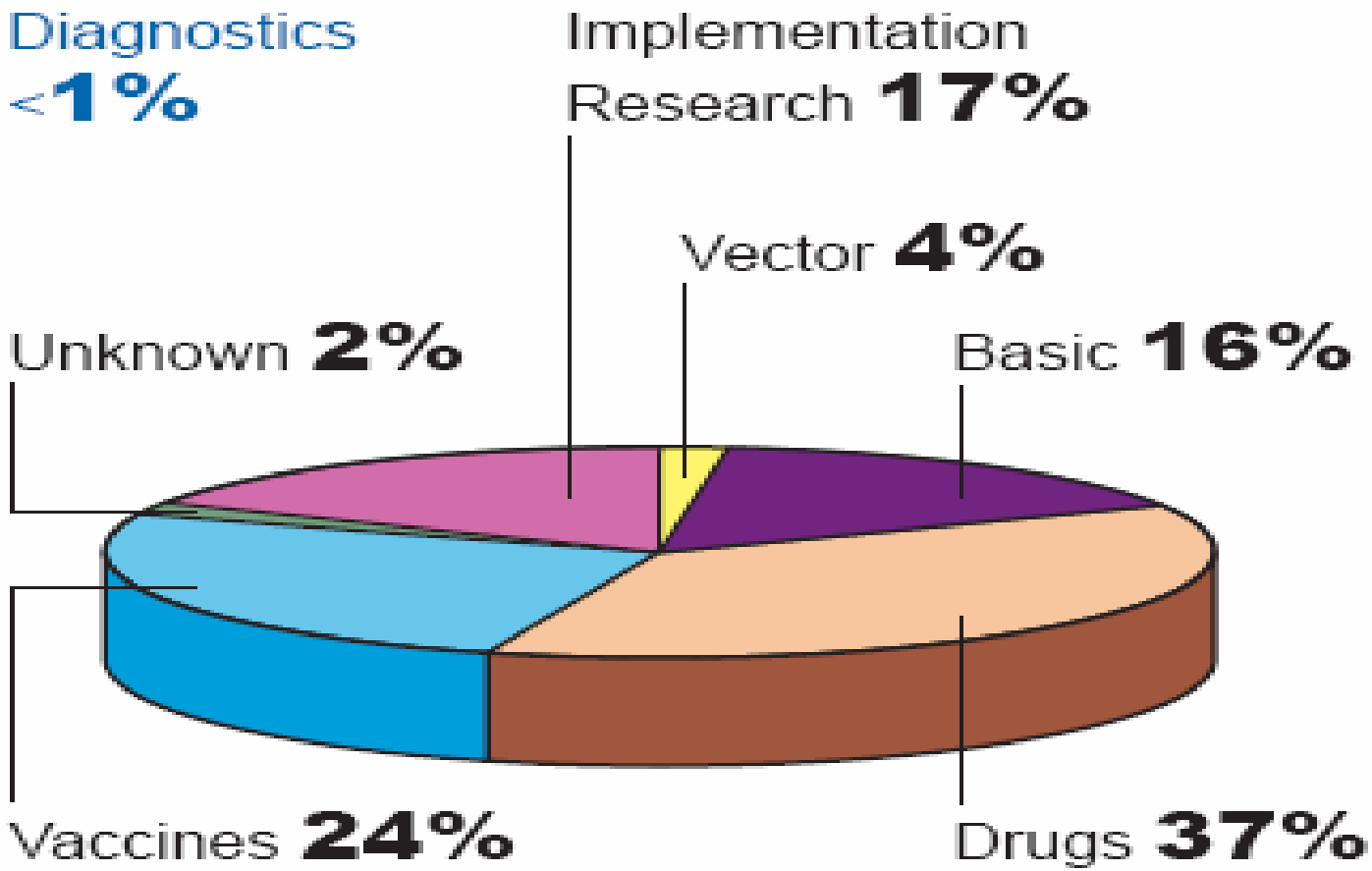


Chart source: Malaria Research & Development: An Assessment of Global Investment
Malaria R&D Alliance: www.MalariaAlliance.org

WHY MORE FUNDING FOR MALARIA RESEARCH

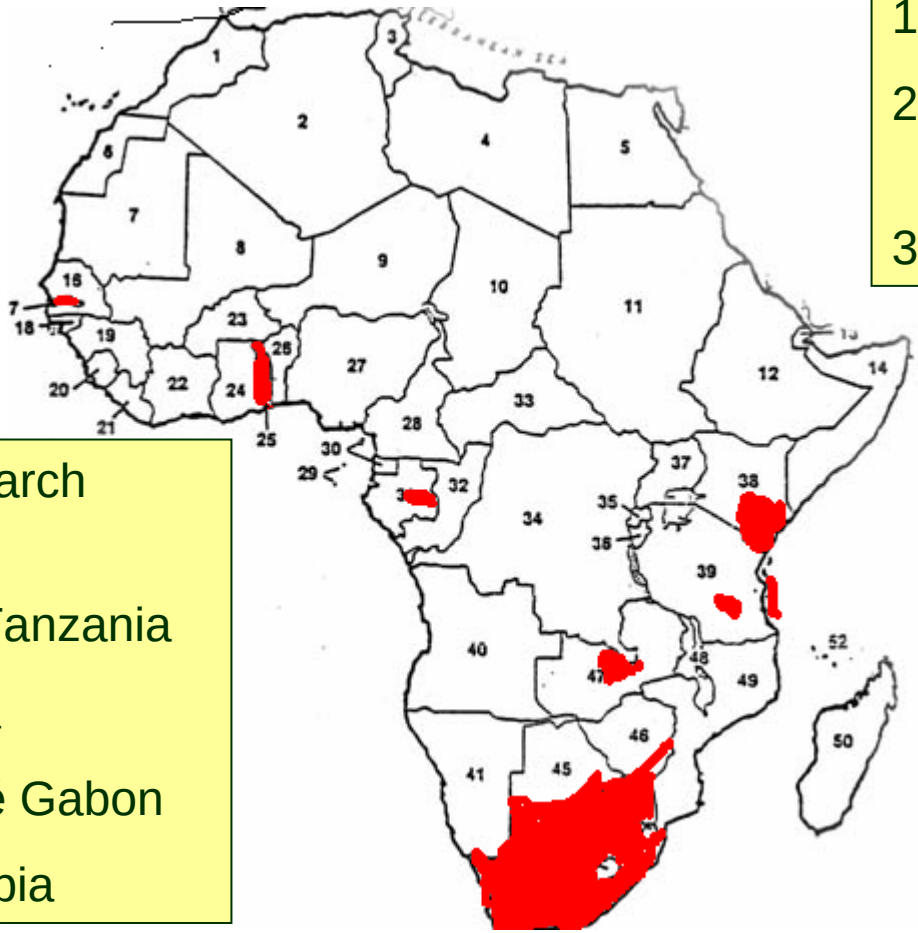
- Failure of safest and most affordable anti-malarials.
- No preventive vaccine currently
- Vector research and control was previously successful and should be taken on.
- Bridge the 10/90 gap
- Research must answer our real health needs.

"Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality". *(Declaration of Helsinki, Intro, Paragraph 6)*

Some success stories

Sustained environmental management and RIS:

1. RSA,
2. Zambian copper mines district
3. Ashanti Gold Ghana



Massive Research Activities:

1. Ifakara in Tanzania
2. Kilifi Kenya
3. Lambaréné Gabon
4. MRC Gambia

ITN use with intensive control programme:

1. Zanzibar

What is happening in the malaria drug research world?

Malaria Drugs in Development

- Pipeline mixed with drugs at various stages: Ready to register, new combinations of already marketed products
- Breakthrough innovations targeting malaria in completely new way
- Known class (with non-novel mechanisms), but with novel candidate molecules.

Global Drug portfolio in December 2006

6 ACTs- Lapdap/Artesunate, DHA/Piperaquine, Pyramax, AS/AQ, AS/MQ, Ferroquine/AS

2 Preclinical candidates targeted also at P. vivax- tinidazole-primaquine and tefenoquine)

1 Paediatric ACT formulation- Coartem Dispersible

6 Preclinical falciparum candidates – Isoquine, PS-26, tetracycline, trioxanes, 4(1H)-pyridone GSK 932121 & SAR9726A/T3

2 Non ACT's – Fosmidomycin/clindamycine, AQ13

Note: Recent policy change requiring ACT also implies that new drugs must now be developed as combination drugs and not stand alone ones.

If all ingredients are new, then they must be individually proven first before combining them.

3 Monotherapies for severe malaria- Rectal AS, rectal quinine, IV artesunate

1 Non ACT for MIP, IPTi or IPTp – Azithromycin-chloroquine

Source: Malaria product pipeline: Planning the future, Moran *et al*

What is happening in malaria vaccine research world?

General Malaria vaccine background

- Difficult and changing target in the parasite
- Antigens & technologies still being discovered
- No clear regulatory pathway
- Likely larger trials and much more expensive
- Lack of reliable animal models require direct human trials; no validated model for phase IIa

Current vaccine targets

Category	Life cycle stage	Surface antigens	Secreted antigens
Pre-rythrocytic	Sporozoite	Circumsporozoite protein (CSP)	Thrombospondin-related adhesive protein (TRAP)
	Liver stages	Liver stage antigen 1 (LSA-1) Liver stage antigen 3 (LSA-3)	Exported protein-1
Erythrocytic or Blood stage	Merozoites	Merozoite suface protein1 (MSP-1) Merozoite suface protein 2 (MSP-2) Merozoite suface protein3 (MSP-3) Merozoite suface protein4 (MSP-4) Merozoite surface protein5 (MSP5)	Rhoptry-associated protein-1 (RAP-1) Apical Membrane Antigene 1 (AMA-1) Glutamate-Rich Protein (GLURP) Erythrocyte-Binding Antigen (EBA-175) Serine-Rich Antigen (SERA)
	Infected red cell	Erythrocyte membrane protein 1(PfEMP1)	
Sexual stage	Gametocytes	Pfs 230	
		Pfs 48/45	
	Gametes	Pfg 25/27	

Global vaccine Portfolio

- 47 candidates in global portfolio
- 31 in preclinical development
- 16 in clinical trials
- Recent increased antigen diversity
- Trend has shifted to increase in blood stage candidates and decrease pre-ethrythrocytic stage proportions
- Possibilities now ranging from whole sporozoite, recombinant proteins, LSP, DNA epitope string, Viral vectored, and virosomally expressed vaccines
- Chimeric candidates are also on increase

Some problems in vaccine R&D

- Non coordination and lack of tools to evaluate best candidates
- Iterative developmental process; with more blood stage candidate where there is no model for screening- Cost and trial site pressure
- Possibly 90% work by PDP's with much innovation but need pharmaceutical technical skills
- As per Roadmap recommendation, there is urgent need to standardize and validate both Elisa and T-cell assays

Efforts in immunological assays

GIA assay protocol developed by MVDB of NIAID for some blood stage candidates supported by MVI

ADCI assay developed by Institute Pasteur being standardised and optimised to explore evaluation of immunogenicity

AIA Network of 6 African labs coordinated from Noguchi and supported by AMANET. Have standardised ELISA assay for MSP1, MSP3, AMA1 and GLURP, and now going into phase II activities which would include expansion of the network, assay validation and introduction of GIA activities

MSL at the WRAIR has developed several ELISA assays which are optimised for sensitivity and proceeding to full validation

The Traditional/Herbal remedies

Health practices, approaches, knowledge and beliefs incorporating plant, animal and mineral based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being.

- In Africa, up to 80% of the population uses traditional medicine for primary health care.
- In Ghana, Mali, Nigeria and Zambia, the first line of treatment for ~ 60% of children with high fever resulting from malaria
- In the US, 158 million use complementary medicines and according to the USA Commission for Alternative and Complementary medicines, US $17 billion was spent on traditional remedies in 2000.
- In the United Kingdom, annual expenditure on alternative medicine is US$ 230 million.
- The global market for herbal medicines currently stands at over US $ 60 billion annually and is growing steadily

Traditional medicines continued

- At present, WHO is supporting clinical studies on antimalarials in three African countries; the studies are reportedly revealing good potential for herbal antimalarials.

- Other collaboration is taking place with Burkina Faso, the Democratic Republic of the Congo, Ghana, Mali, Nigeria, Kenya, Uganda, and Zimbabwe in the research and evaluation of herbal treatments for HIV/ AIDS, malaria, sickle cell anaemia and Diabetes Mellitus.

- In Tanzania, WHO, in collaboration with China, is providing technical support to the government for the production of antimalarials derived from Artemisia annua. Local production is expected to bring the price of one dose down from US $6-7 to a more affordable $2

Source: http://www.who.int/mediacentre/factsheets/fs134/en/

Note on Basic science research

- There is much preclinical activity in malaria in northern countries
- Not much is heard of within the continent
- With breakthroughs on the human genome, parasite genome, high throughput technologies the risk of the 99/1 gap widening is even higher.

Note on diagnostics

- Mainly operational research on RDT's
- Novel approaches presently evaluating:
  - Use of saliva and other secretions in Gambia
  - Use of HRP2 Elisa Kenya
- Improvements of microscopy methods

Most challenging issue facing clinical trials today is the case definition of malaria

  - What symptoms and signs
  - What parasite density threshold is specific enough

Note on vector & other studies

There are other studies on going on the continent including, but not limited to:

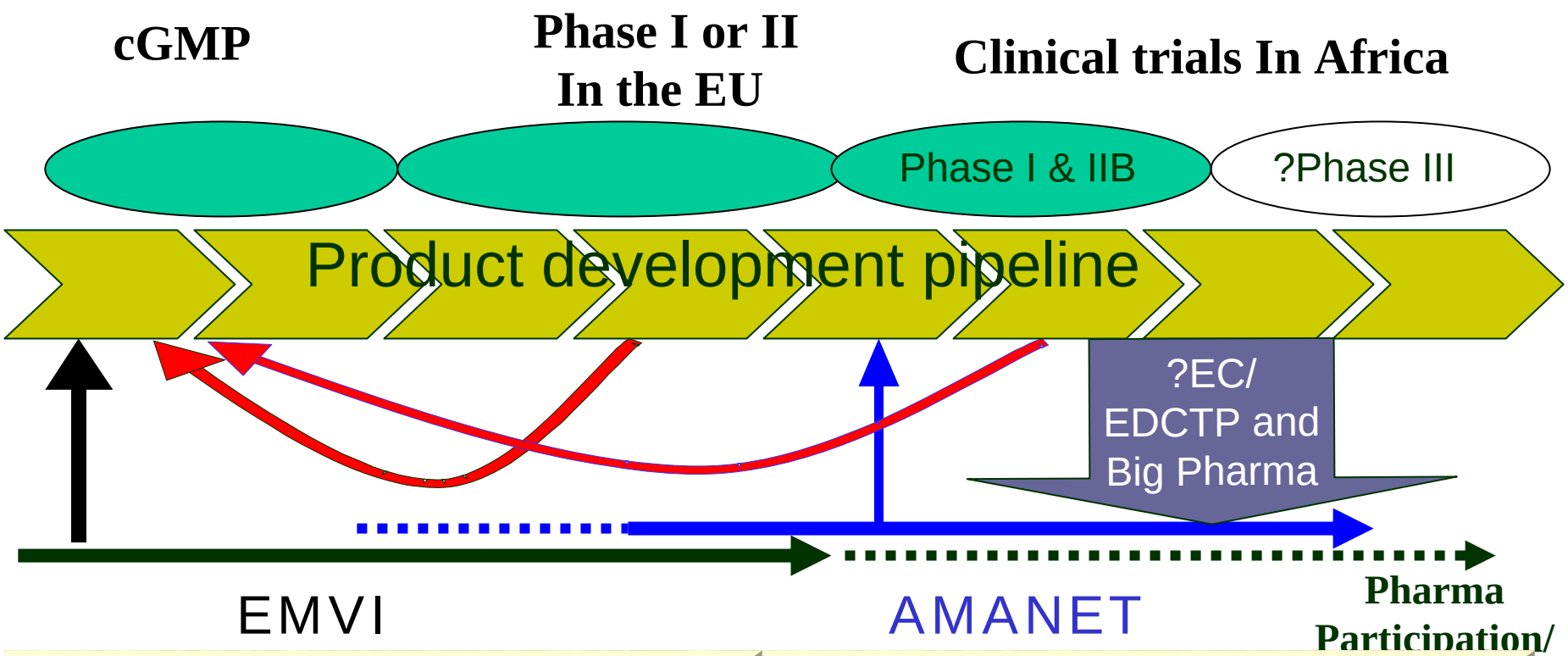
- Treatment access;
- Impact/longevity of ITN,
- SP on gametocytes,
- Genetic host factors,
- Biomarkers in SM,
- Placenta malaria,
- Cost evaluation of diagnostic strategies,
- Bio-ecology & population genetics for vector,
- Effectiveness of ACT's and other drugs

The trial site situation

- Few trial sites with licensure study capabilities:
  - Capable PI's
  - Strong collaborations with the north
  - Ongoing training programmes and career plans
- With decreasing malaria rates at field sites:
  - Mature sites will have to open other virgin sites
  - Larger/complicated efficacy study designs
  - Funding for younger potential sites to meet up coming challenge of malaria interventions in early in clinical development

Is PDP the answer for malaria R&D?

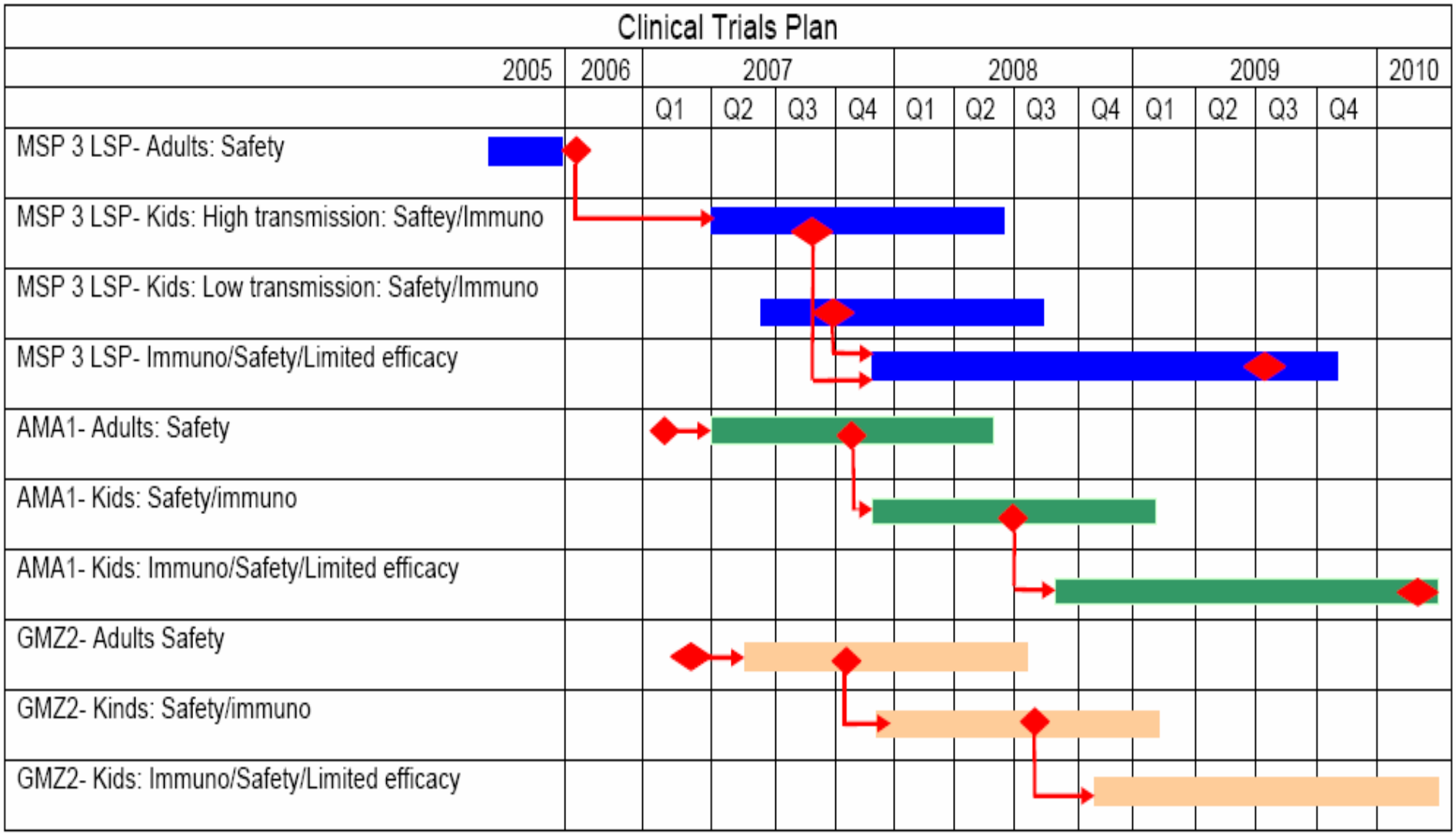
AMANET-EMVI Seamless Malaria vaccine Strategy



Pre-clinical development
GMP production of clinical batches
Early clinical development
Sponsor phase I-IIa studies

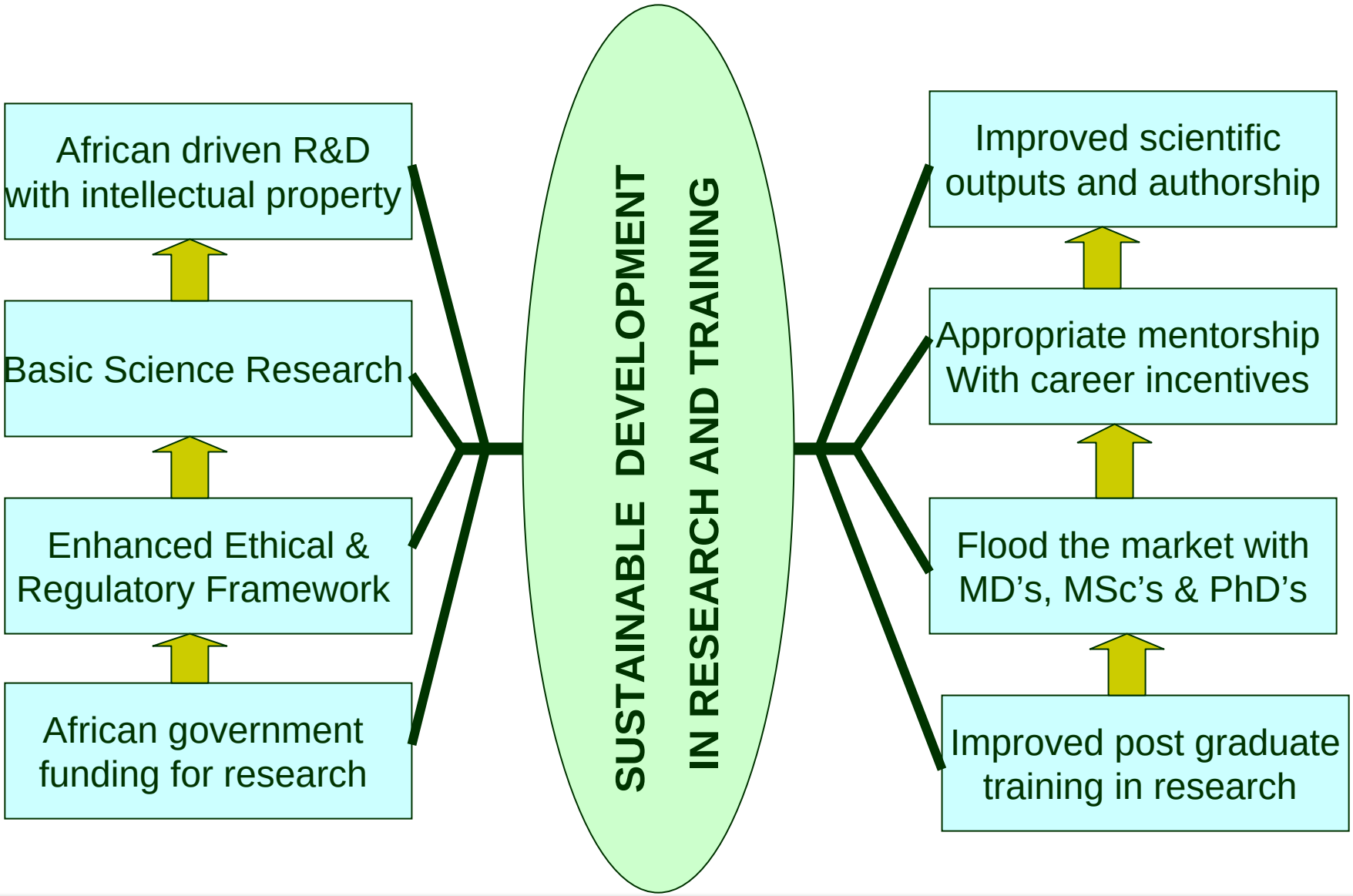
Trial sites in Africa
Human resource/equipment
Strengthen capacity for trials
Sponsor phase I-IIb studies
Proof of concept

Outlook of AMANET Sponsored Vaccine Trials



A wish list for malaria research in Africa

Conditions for jumbo jet to take off



Acknowledgements

- AMANET is grateful to:
  - DANIDA, Dutch Ministry of Foreign Affairs, EC's Directorate General Research, EC's AIDCO, The Gates Foundation
- AMANET has also received assistance from:
  - EDCTP, WHO-AFRO, WHO/TDR, AU, SIDA/Sarec, GSK, Wellcome Trust, US-NIH, US-NIMR,US-OHRP