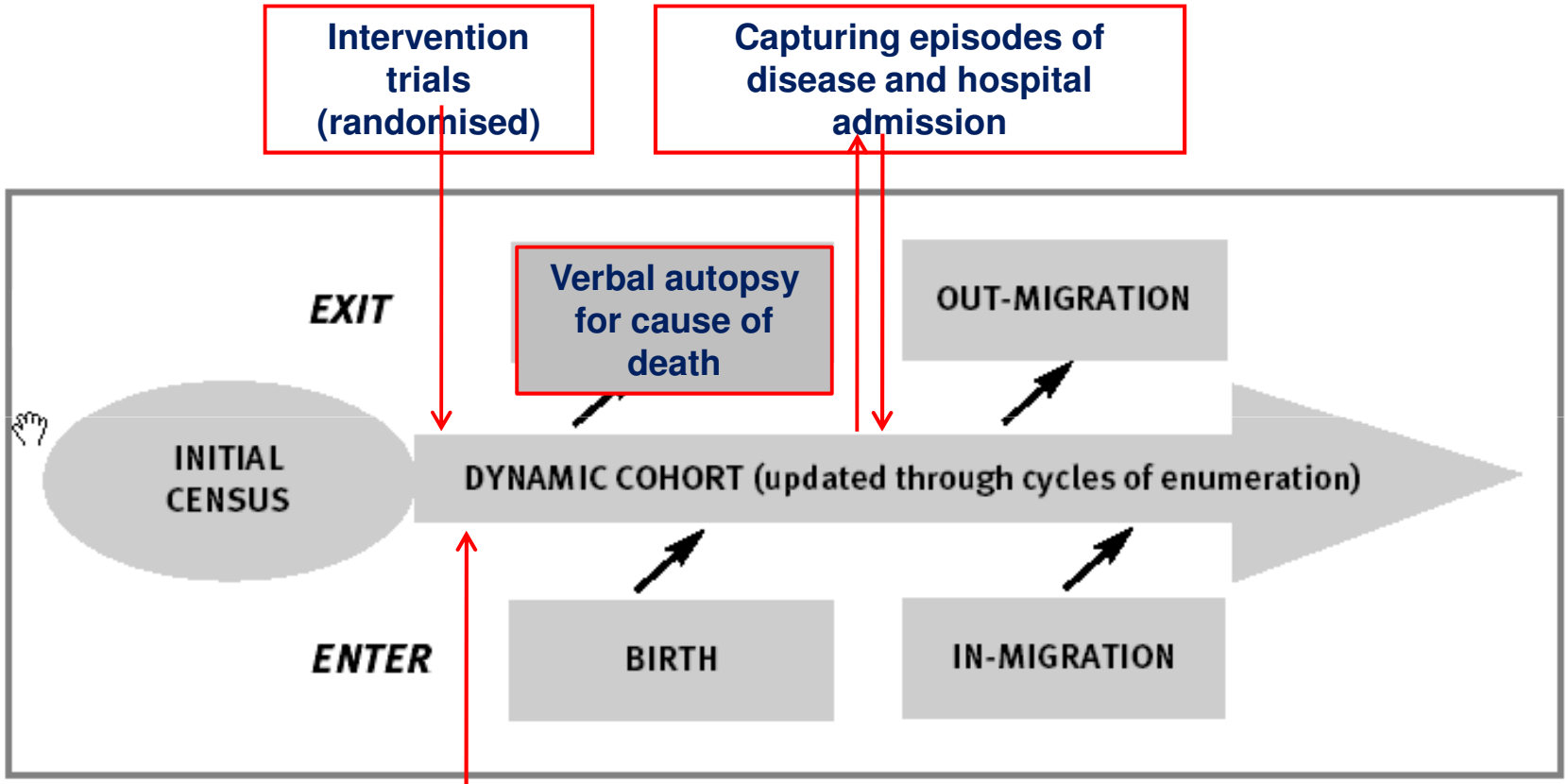
INDEPTH Network for Effectiveness and Safety Studies (INESS) of Antimalarials in Africa

Prof. Fred Binka

Prospective monitoring of Demographic and Health EVENTS



INDEPTH Network

WHO DG and Minister for Health (Tanzania) Launch INESS

Current Consortium membership

- HDSS sites in; Ghana, Tanzania, Burkina Faso and Mozambique (Rufiji, Ifakara, Manhica, Nouna, Nanoro, Kintampo, Navrongo and Dodowa)
- Ghana School of Public Health, Ghana
- London School of Hygiene and Tropical Medicine, UK
- Swiss TPH, Switzerland
- CDC Atlanta, USA.

INESS

Assessing effectiveness and safety of new antimalarials in real life health systems

What is the health system ?

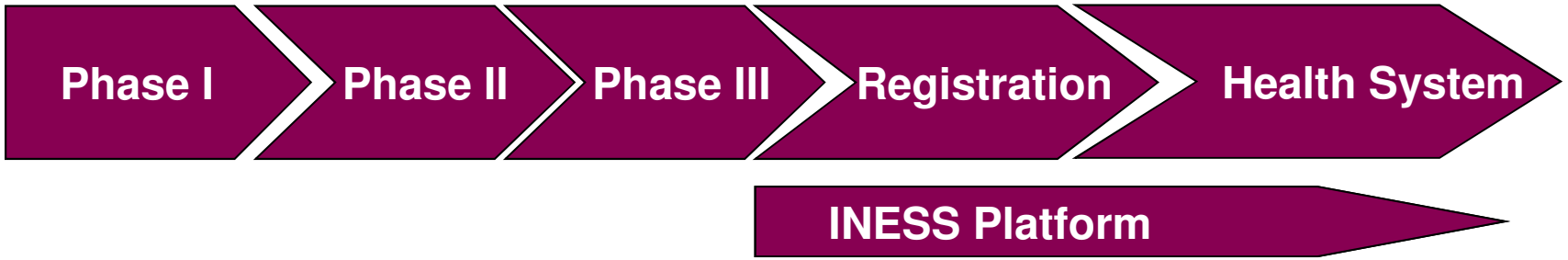
- *organisations, people and actions whose primary intent is to promote, restore or maintain health*

- *With the goal to improve health and health equity in ways that are responsive, financially fair and make the best or most efficient use of available resources (WHO 2000)*

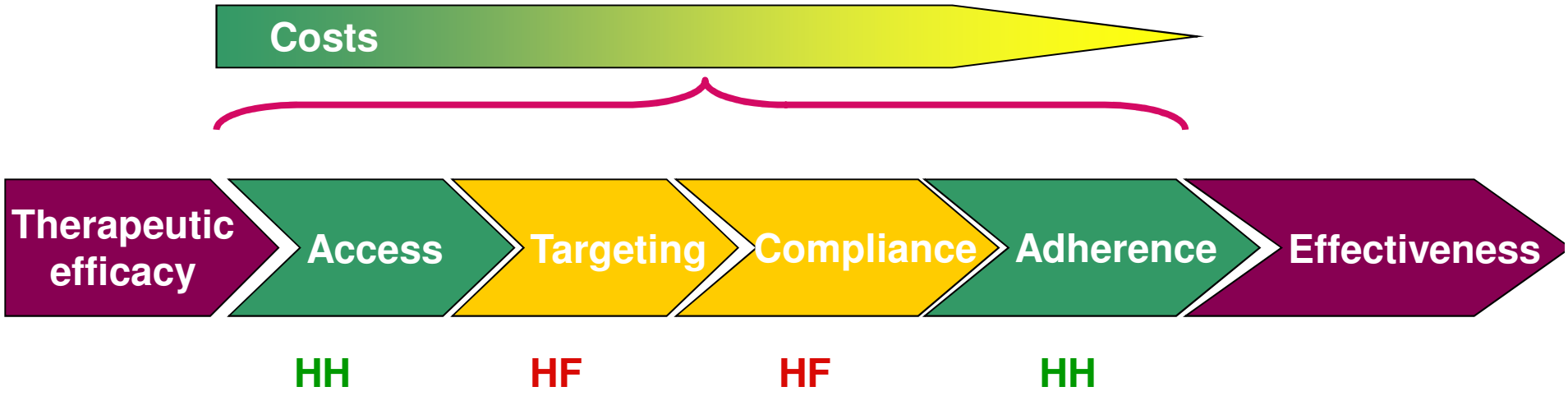
Why INESS?

- Careful, highly controlled, highly-regulated trials assess safety and efficacy
- Total number of people dosed with a new drug by the time of registration almost always less than 10,000
- Very little information available on rare but severe side effects
- Determinants of effectiveness in real life condition
- Framework for development malaria treatment policy

INESS: Fill the gap in the drug development pipeline

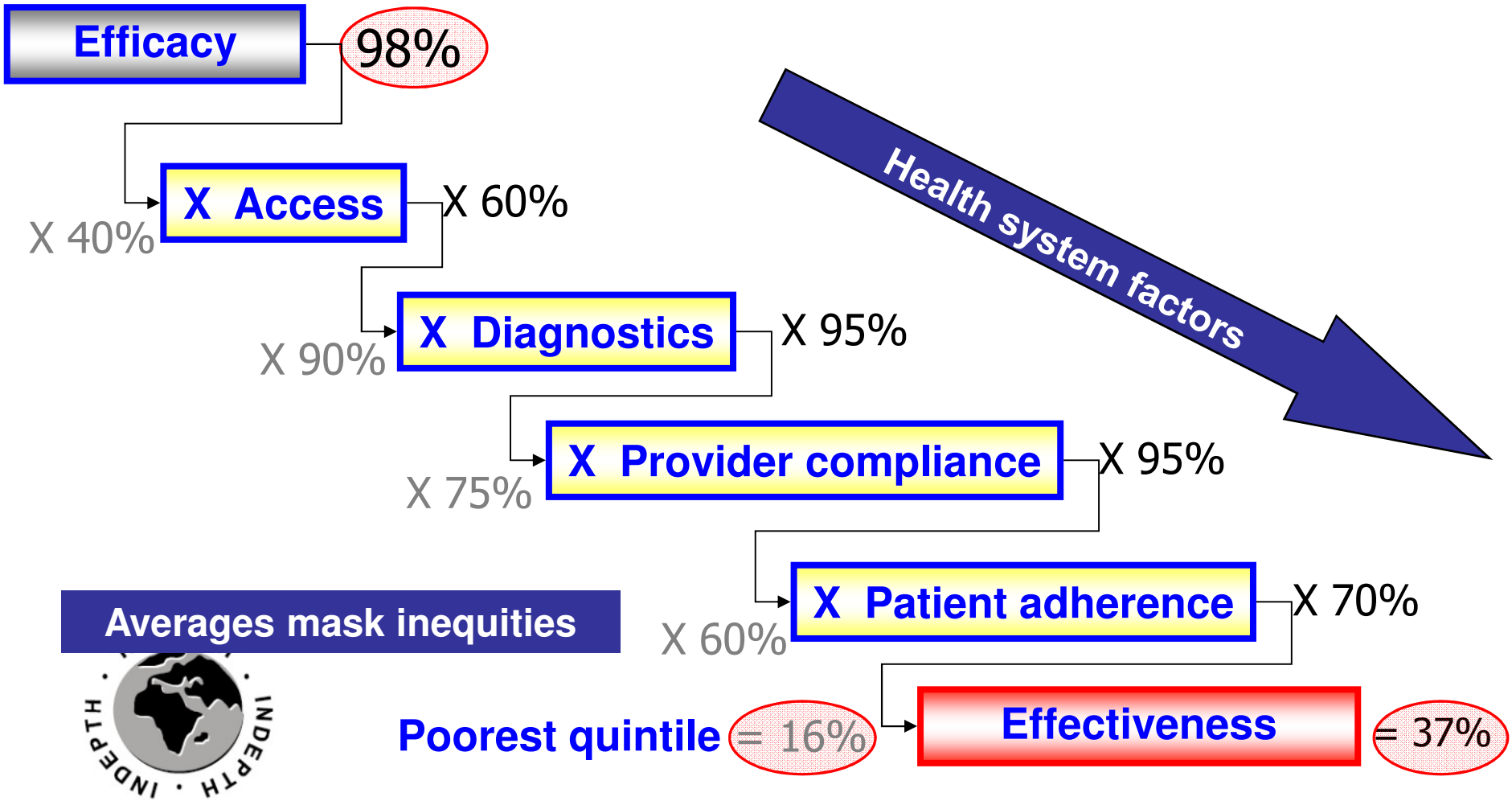


INESS: Understanding & Mitigating determinants of effectiveness



Driving with the brakes on: How interventions lose traction in health systems

Example of ACT anti-malarial treatment in Rufiji HDSS in 2006



Data source: IMPACT Tanzania. Effectiveness data are actual. Poorest quintile estimates are hypothetical

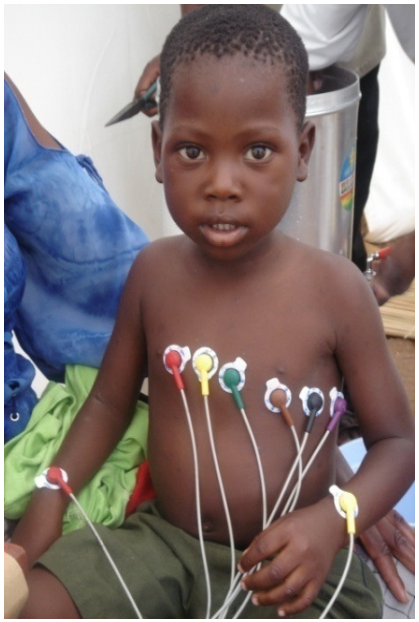
Clinical Development Plan Eurartesim

THREE ADDITIONAL TRIALS REQUESTED BY EMA

- Food Interaction
- PK in Caucasian vs Asian healthy subjects
- Thorough QTc trial

Safety recording

ECG



- In the DHA-PQP group, the proportion of patients with borderline and prolonged QTc interval at day 2 corrected by the Fridericia's correction were 1.0% and 0.2% in the DHA-PQP group and 1.2% and 0.2% in the AL group

- A ≥60 ms increase of the QTc interval between day 0 and day 2 (Bazett's correction) was observed in just 2.7% (DHA-PQP) and 2.0% (AL) patients

- Only two patients per group showed a QTc at day 2 higher than 500 ms

Safety Monitoring

- Yellow card system
- Linked database approach
- Cohort follow up

Goal

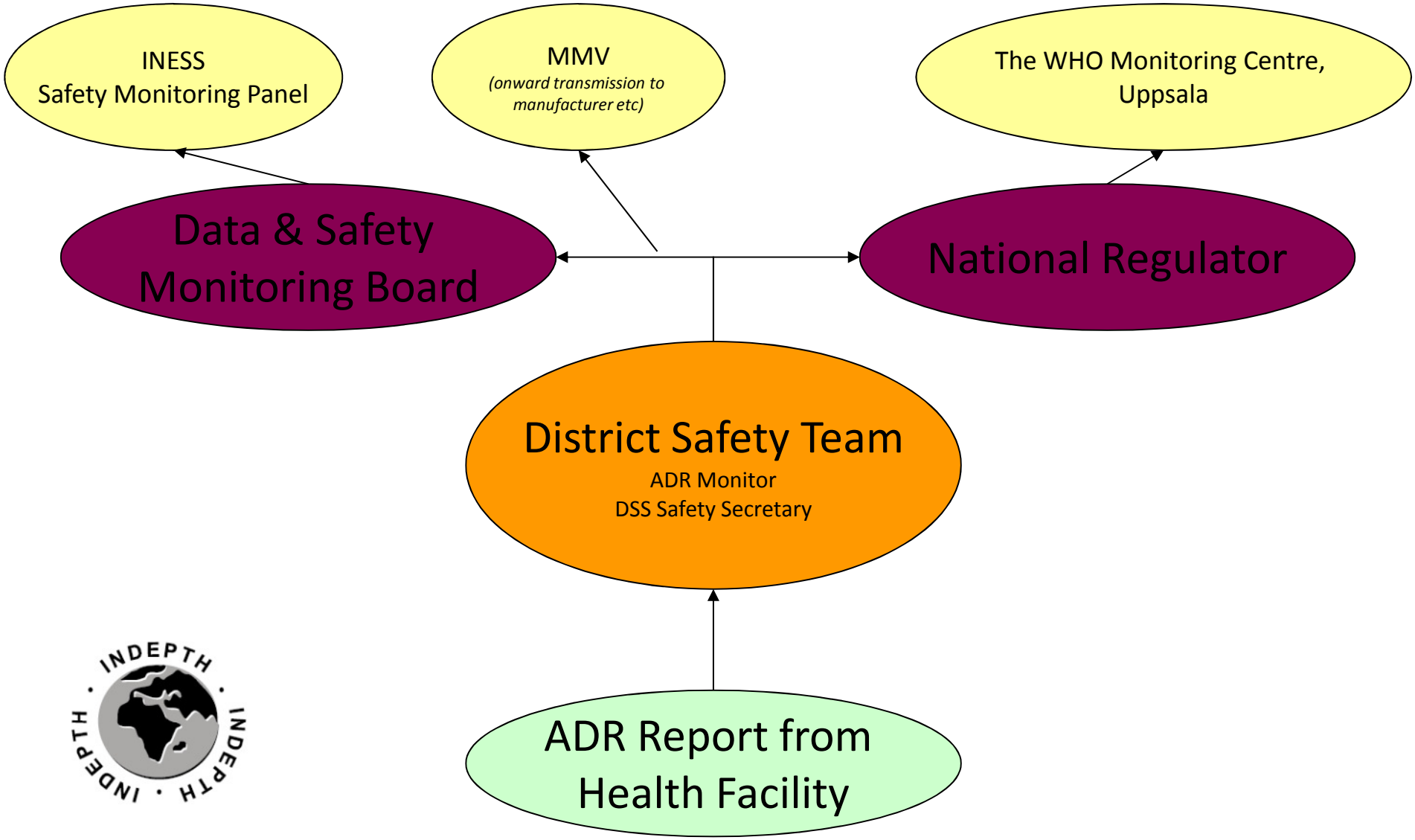
- **Overall Goal**

  → **To provide national, regional and international health decision makers with independent and objective evidence on the safety and effectiveness of new anti-malarial drugs as a basis for malaria treatment policy.**

Outcome

- **Minimise time between licensure and adoption of antimalarial drugs**
- **Missing link in drug development pipeline**
- **Longitudinal evidence of safety and effectiveness of new antimalarial drugs**
- **Determinants of health systems effectiveness**
- **Framework for malaria treatment policy**

INESS Safety Reporting Channels



Key features of INESS

- Strengthening of safety monitoring system in districts
- Innovating means for data linkage (between DSS and health facilities and use of information)
- Continuous and collaborative data analysis, sharing and dissemination with all key stakeholders (ownership)
- Proactive measures to influence policy decisions
- Use of the platform to inform other health commodities (vaccines, antibiotics, health tools etc)

Safety & Effectiveness of ACTs in INESS

- The INESS safety event database on ACTs in the biggest ever in WHO database…Generally Safe ACTs
- Pregnancy register one of the largest for ACTs as well (Strength of DSS)
- Surprising low Health system effectiveness of efficacious ACTs in Ghana and Tanzania

Spontaneous Adverse Event Reporting

Site	Number of Reports
Dodowa	100
Kintampo	77
Navrongo	48
Ifakara	56
Rufiji	51

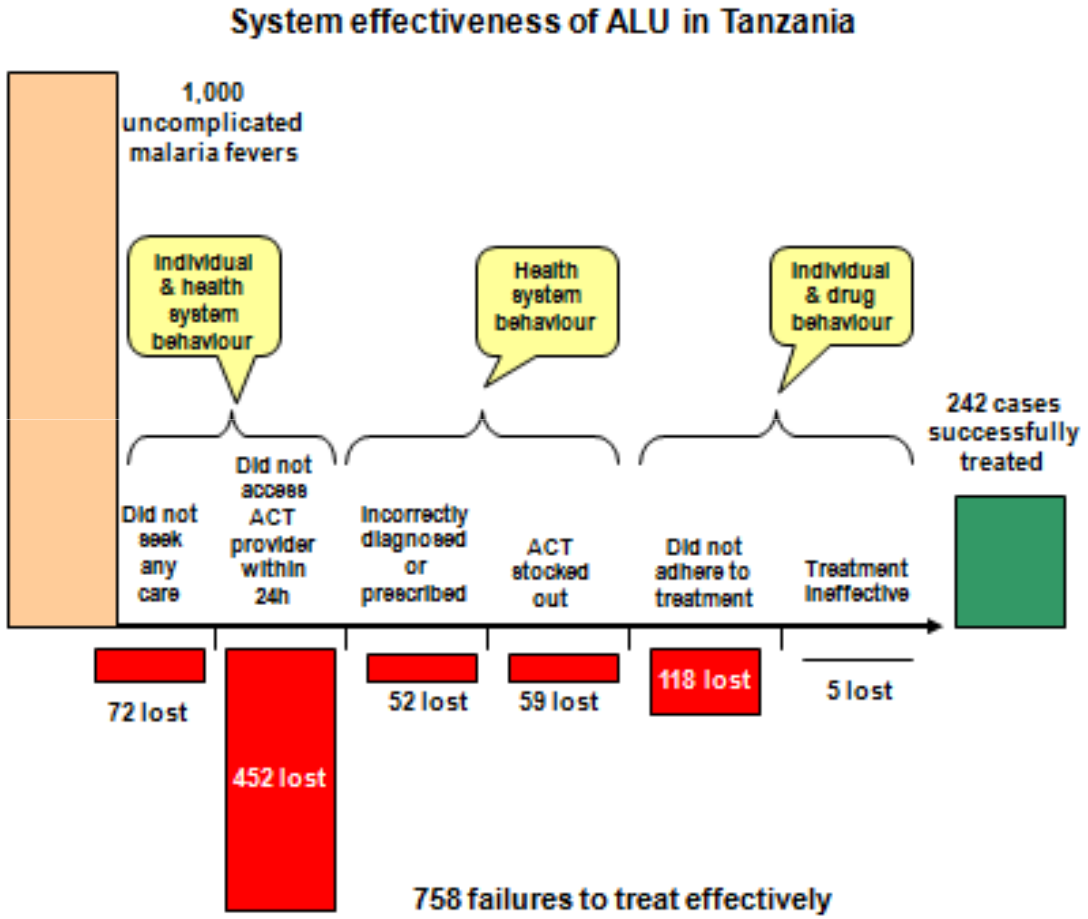
Table 1.6 Cohort event monitoring for Ghana (ASAQ) and Tanzania (AL)

Country	Site	No. of Patients Treated Jul 2011 - Jun 2012	No. of Events reported Jul 2011 - Jun 2012
Ghana	Dodowa	5,518	2,304
	Kintampo	6,017	723
	Navrongo	3,427	3,720
	Total	**14,962**	**6,747**
Tanzania	Ifakara	3,226	1,649
	Rufiji	3720	1554
	Total	**6,946**	**3203**

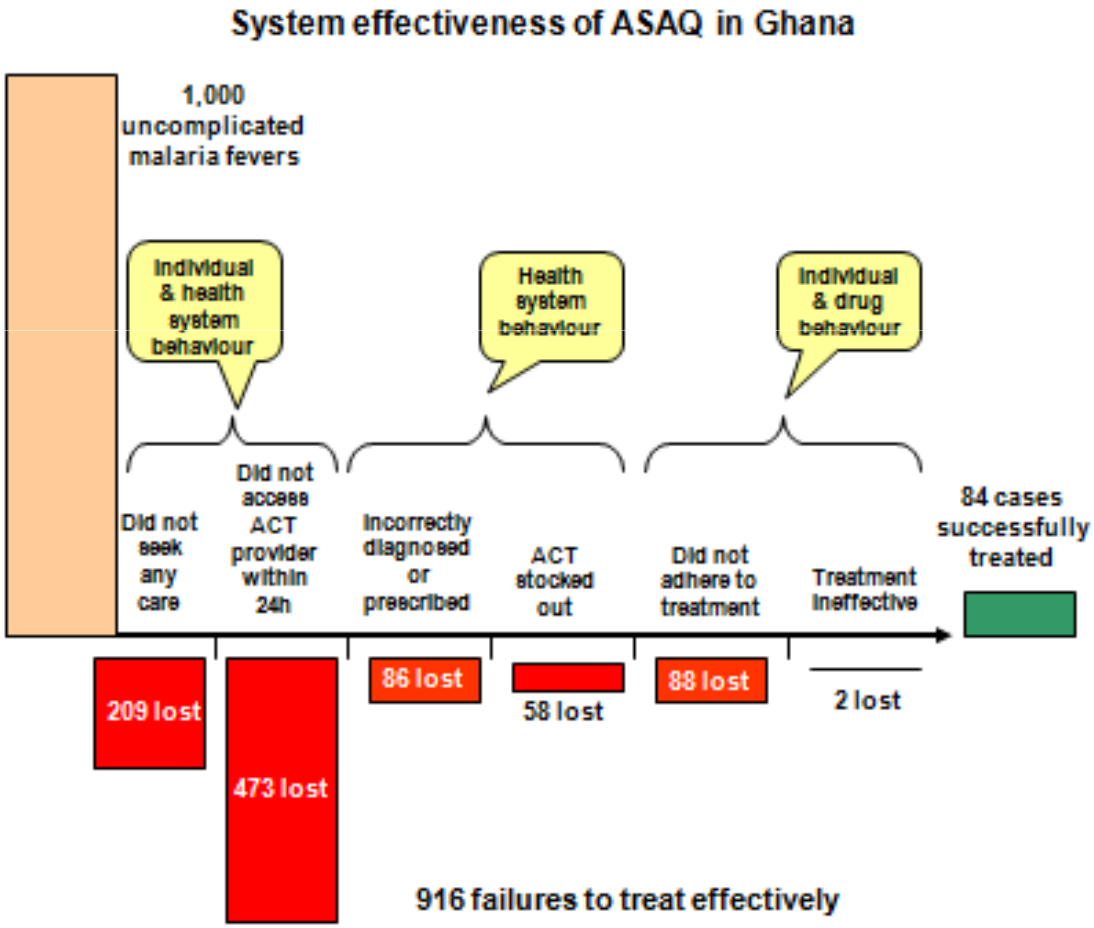
Outcome: Scientific Publications

- 26 scientific papers submitted for all the modules as follows:
  - →Costing (4)
  - →Data linkage (4)
  - →Effectiveness (8)
  - →Qualitative (4)
  - →Safety (6)

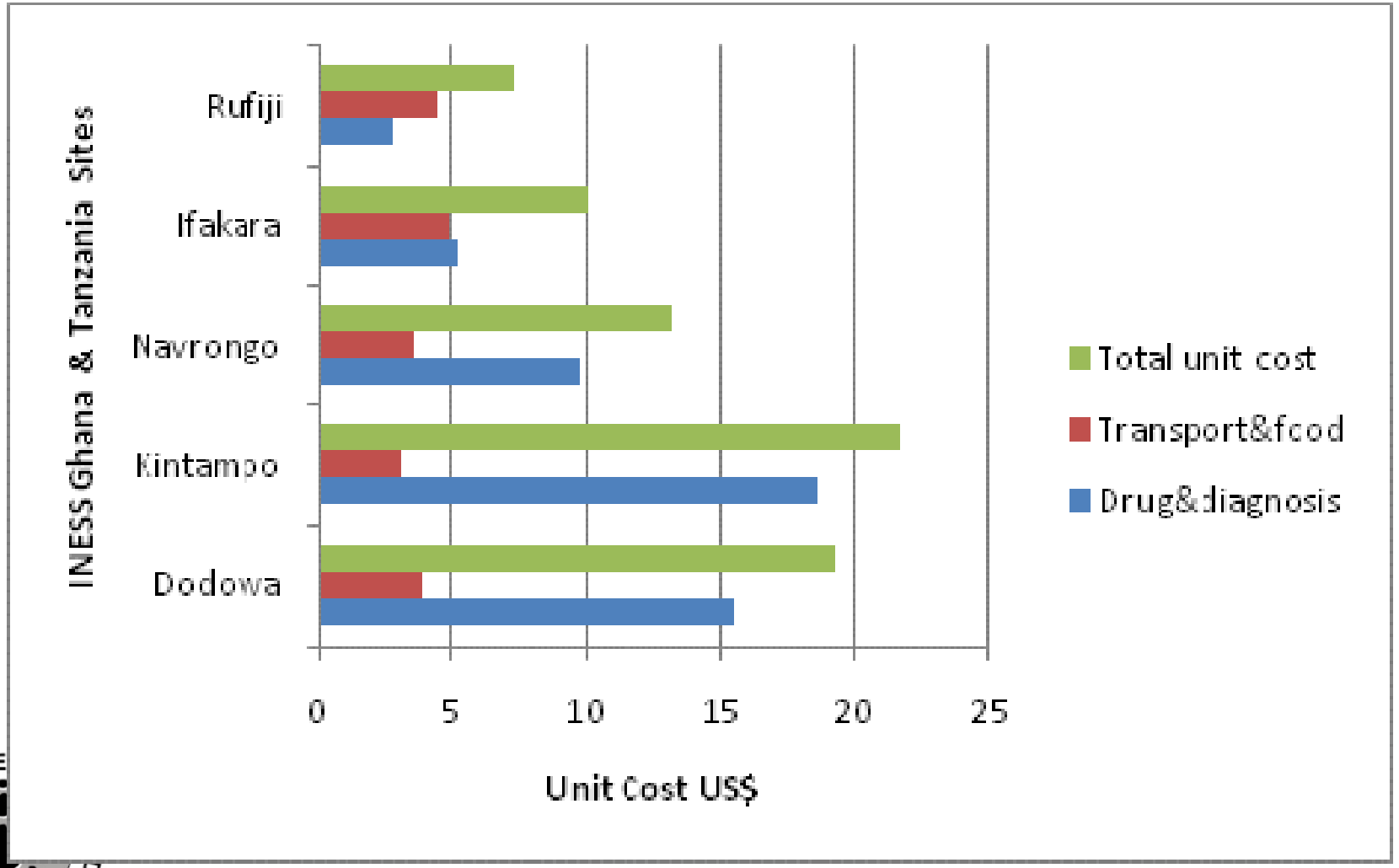
AL Effectiveness in Tanzania



ASQA Effectiveness in Ghana



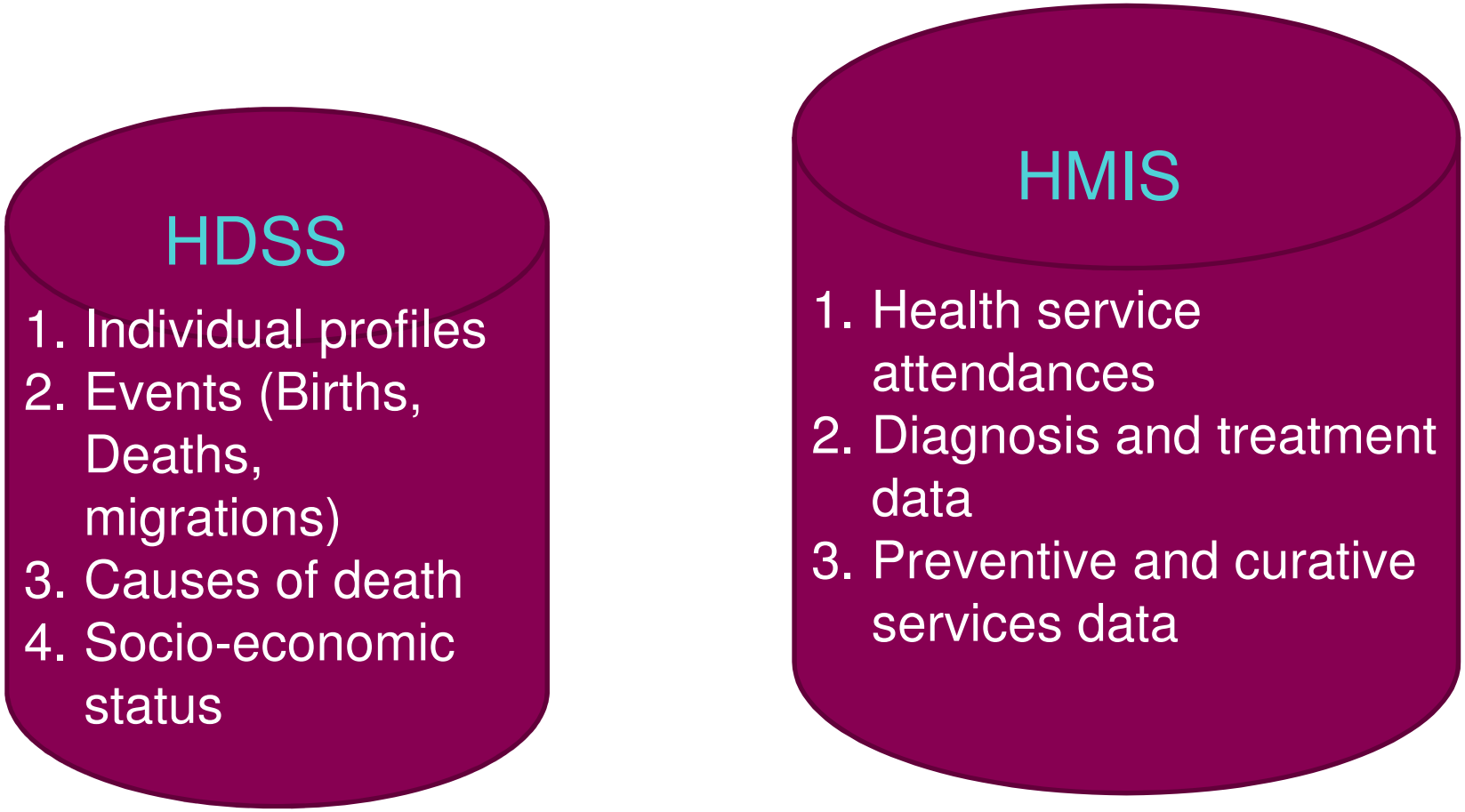
Average Costs of treating Fever episode in Tanzania & Ghana



Outcome: Scientific Publications II

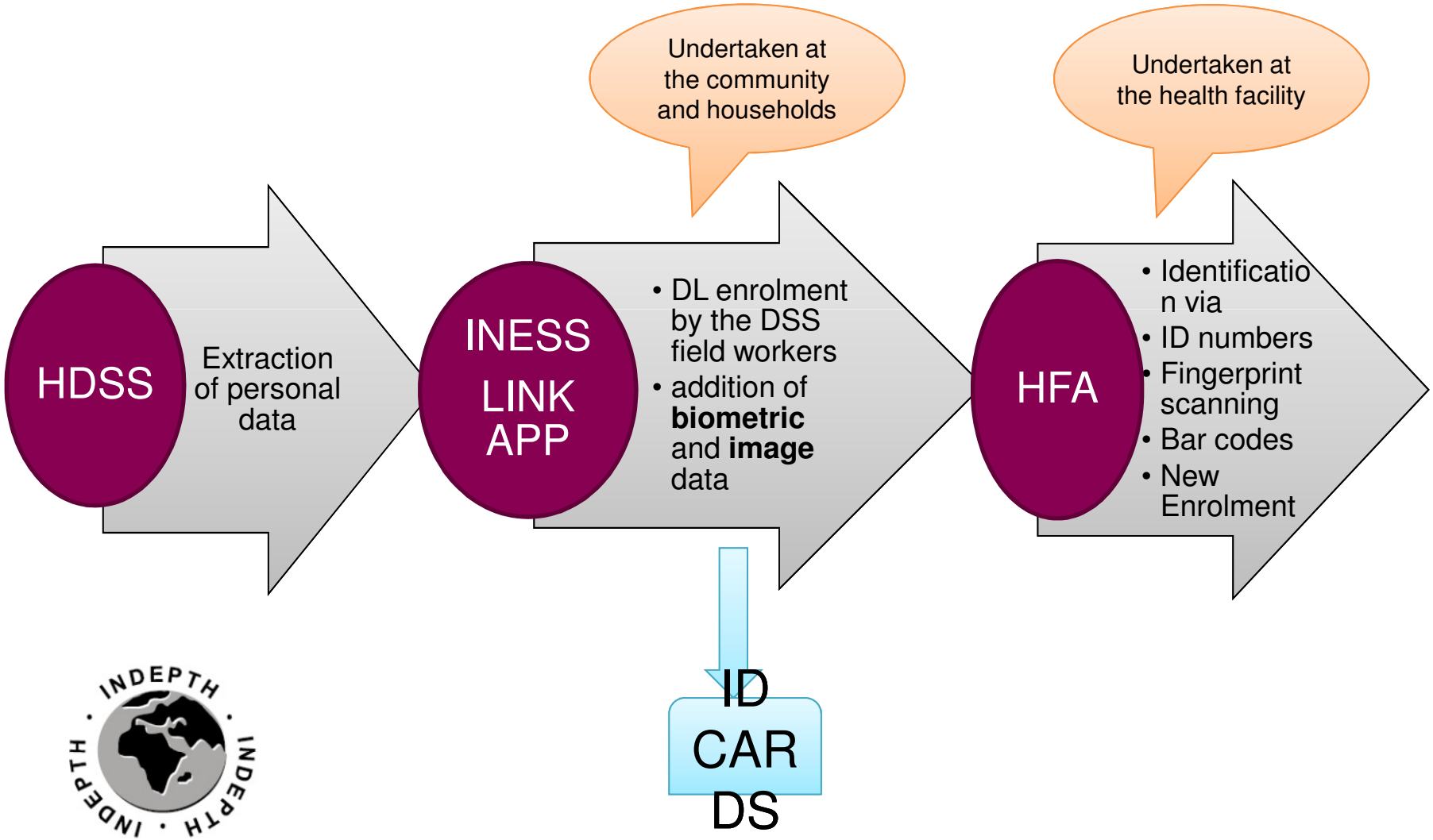
- 15 papers presented at INDEPTH SC, Maputo
- 10 papers presented at ASTMH 2011
- 5 papers presented at ASTMH 2012
- Over 12 manuscripts in preparation
- ONLY 6 Manuscripts published

Data Linkage Module

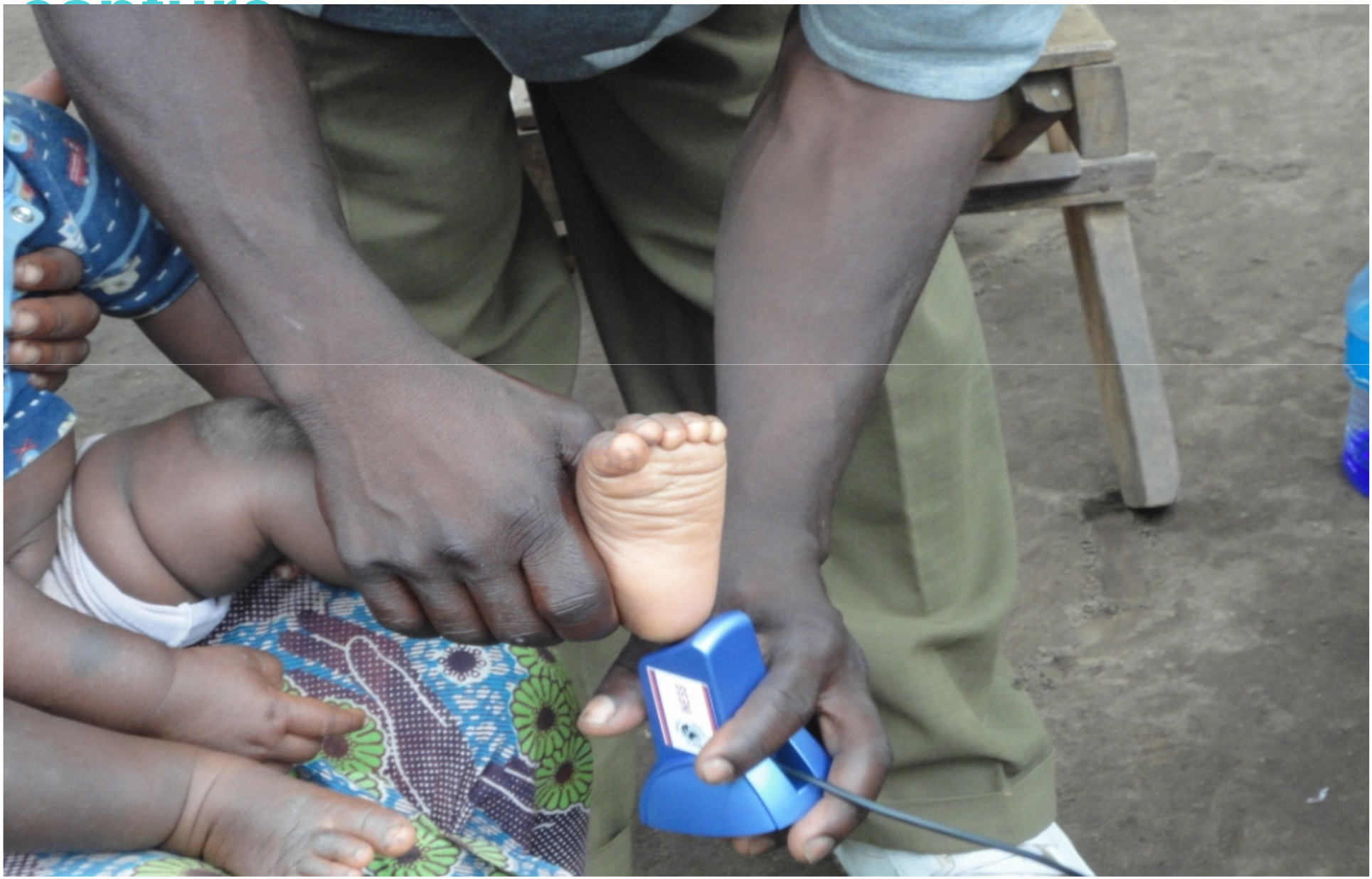


HDSS: Health Demographic Surveillance System
HMIS: Health Management Information System

Data Collection Process



INESS methods: Fingerprints



HDSS Platform

- Funding for 4 years for each DSS
- Support for data linkage to enhance population data with health services data
- Support the DSS data especially with issues related to migration
- Create broad platform for Health Systems Research

Spin Offs

- SMS for Life in Tanzania and Ghana, Kenya

Current activity

- **POST REGISTRATION evaluation**

“OBSERVATIONAL STUDY TO EVALUATE THE CLINICAL SAFETY AFTER INTRODUCTION OF THE FIXED DOSE ARTEMISININ-BASED COMBINATION THERAPY EURARTESIM® (DIHYDROARTEMISININ/PIPERAQUINE [DHA/PQP]) IN PUBLIC HEALTH DISTRICTS IN BURKINA FASO, MOZAMBIQUE, GHANA AND TANZANIA”

Primary Objective

- Evaluate the safety of Eurartesim® when used under usual conditions in 10,000 patients with signs and symptoms of uncomplicated malaria confirmed by a parasitological diagnosis (Microscopy/Rapid Diagnostic Test) or, when this test is not available, by WHO diagnostic criteria

Secondary Objectives

- Although it is expected that the vast majority of patients will be infected with *P. falciparum,* comparisons of the clinical tolerability of *Plasmodium falciparum* infected patients versus patients infected with other *Plasmodia*, as confirmed by the thick blood smear results, will be carried-out in the nested subset of 1,000 patients.
- Assessment of the relationship between the occurrence of Adverse Events and the administration of concomitant medications will also be evaluated in the subset of 1,000 patients.

Design

- The subset of 1,000 patients will be intensively followed-up. These patients will have haematology (Hb and full blood counts (RBC, WBC and differential count)) and standard biochemistry (BUN, Creat, ALT/AST, Bilirubine, electrolytes (K^+ and Cl^-)) undertaken at Day 1 (before drug administration), Day 3 (3-4 hours after the last dose of treatment), and Day 7.
- If the results are abnormal and clinically relevant, the blood examination will be repeated until normalization. In selected centers (about 200 patients), a plasma sample will be collected on Day 1 (before drug administration), twice on Day 3 (i.e. before and 3-4 hours after the last drug administration) as well as on Day 7 to assess plasma PQ concentration.

Design

- ECGs being undertaken on Day 1 (before drug administration), twice on Day 3 (i.e. before and 3-4 hours after the last drug administration) as well as on Day 7 (ECG on Day 1 and Day 3 after last drug administration will be collected in triplicate); safety information will be collected at all these visits.

Achieved

- Training of study teams
- Protocol approval in all the countries
- Study Drug registration in all the countries
- Drug shipped to all countries except Mozambique
- Study initiated in **Nouna, Navrongo, Kintampo, Dodowa, Ruifiji**

Investigators Meeting in Ho

Recruited

- About 1000 enrolled
- Web based data entry using open Clinica
- About 400 entered into the database
- **Competitive enrolment and payment**

Challenges

- The pipeline of ACTs
  →Other antimalarials (IV Artesunte)
- The pipeline of Vaccines
- Response of the National programs to findings
- Keeping the Safety Platform Viable
- The provision of reports by the Centres

INESS Team

- Tanzania
  - → Salim Abdulla, Rashid Khatib, Irene Masanja, Baraka Amuri, Majige Selemani, Msomhe Sadick, Mahmoud Kamusi
- Ghana
  - → Margaret Gyapong, , Elizabeth Awuni,
  - → Seth Owusu-Agyei, Livesy Abokyi, KP Asante, Dennis Boateng,Eliezer Odei-Lartey, Anthony Kwarteng
  - → ABRAHAM ODURO Frank Atuguba, Victor Asola, Isaiah Agorinya
- Mozambique
  - → Eusebio Macete, Dr Esparance, & team
- Burkina Faso
  - → Ali sie, Cheik Bagagnan &team
  - → Tinto Hallido, Innocent & team

- **Task teams**
  - → Don de Savigny, Irene Kuepfer,
  - → Patrick Kurchar, Dennis Allen
  - → Patricia Akweongo, Moses Aikins
  - → Alex Dodoo, David Schellenberg
- **Secretariat**:
  - → Accra
    - Fred Binka, Rita Baiden, Ogutu Bernhard, Martin Adjuik,Raymond Akparibo, Titus Tei, Sixtus Apaliyah

Acknowledgements

- Governance Council (Chair Dr. Gabriel Upunda)
- Scientific Advisory Panel (chair Prof. Peter Smith)
- International Safety Panel
- Hospital Superintendents, NMCP, in Ghana, Tanzania, Burkina Faso, Mozambique, Sierra Leone, Nigeria
- FDB (Ghana) TFDA (Tanzania), DF (Mozambique), Burkina Faso
- WHO AFRO Brazzaville & sub-regional teams
- MMV

Risky Businesss – Goals & Targets