INDEPTH effectiveness and Safety studies for antimalarials (INESS)

Fred Binka
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Objectives

- Objective 1: to develop and maintain phase IV effectiveness studies of antimalarials in Africa.
- Objective 2: to assess effectiveness of new malaria treatments and its determinants in real life.
- Objective 3: to evaluate the safety of new treatments through a comprehensive pharmacovigilance in a health system context.

Objective 2

To assess effectiveness of new malaria treatments and its determinants in real life

- ACT Drugs
  - Artesunate + Amodiaquine (ASAQ) in Ghana
  - Artesunate + Lumenfantrine (ALU) in Tanzania

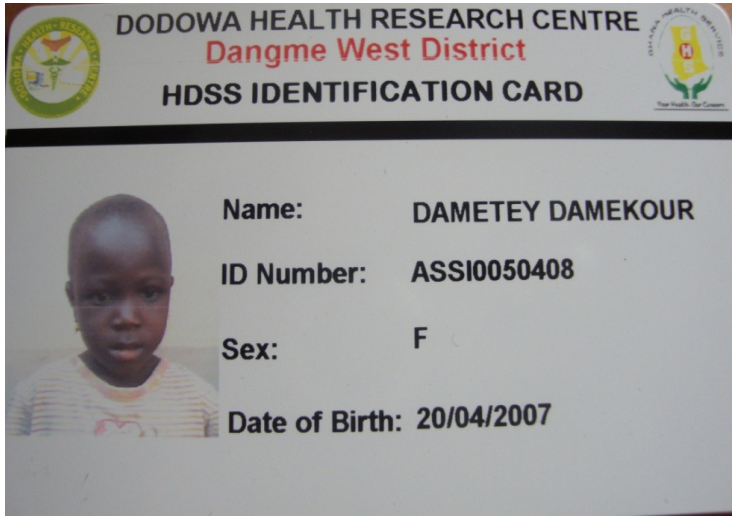
Operational sites

- 5 Sites in Ghana & Tanzania
  - Navrongo, Kintampo, Dodowa
  - Rufiji & Ifakara

  - Sites in Burkina Faso and Mozambique (Newly approved ACTs)

Modules

- System Effectiveness
  - Access
  - Population parasite prevalence
  - Patient adherence
- Community compliance
- Cost and cost effectiveness
- Drug efficacy
- Safety
  - Spontaneous adverse event reporting
  - Cohort event reporting
  - Patient Adherence
- Data linkage
- Data synthesis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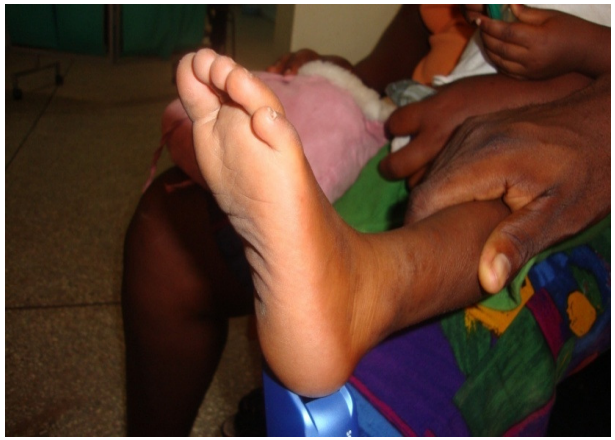

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Data

- ✓ Data Collection (Oct, 2009 – June 2011) except efficacy
- ✓ Efficacy and Safety modules on-going
- ✓ Data linkage (Nouna & Manhica)
- ✓ Data cleaning and analysis on-going

Access

Indicators

- Proportion of people with fever who have sought contact with provider who should have the drug
- Proportion of people with fever who seek care from other providers

Access to ACT providers within 24 and 48 hours in Ghana and Tanzania, October 2009 – June 2011

	Ghana				Tanzania		
	Dodowa [N=620]	**Kintampo [N=971]**	**Navrongo [N=1,315]**	**Overall [N=2,906]**	**Ifakara [N=1,040]**	**Rufiji [N=882]**	**Overall [N=1922]**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Fever cases that sought treatment outside home	519 (**83.7**)	877 (**90.3**)	902 (**68.6**)	**2298 (79.1)**	991 (**95.3**)	793 (**89.9**)	**1784 (92.8)**
Access to a provider within 24 hr	**245 (39.5)**	**358 (36.9)**	**321 (24.4)**	**924 (31.8)**	**485 (46.6)**	**429 (48.6)**	**914 (47.6)**
Access to a provider within 48 hr†	**330 (53.2)**	**557 (57.4)**	**536 (40.8)**	**1423 (49.0)**	**787 (75.7)**	**612 (69.4)**	**1399 (73)**

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Access cont.....

- ***Access to ACT provider***

  proportion of people with fever episode in previous two weeks and sought care outside home was **79% in Ghana** and **93% in Tanzania.**

Access cont.....

- **Overall, access to an ACT provider**
  - within 24 hours was **32% in Ghana and 48% in Tanzania.**
  - Within 48 hours was **41% in Ghana** and **73% in Tanzania**

Results from surveys on (i) Population Parasite Prevalence, (ii) Targeting Accuracy and Provider Compliance and (iii) Patient Adherence, Ghana and Tanzania, October 2009 to June 2011

	Ghana (Artesunate Amodiaquine)				Tanzania (Artemether-lumefantrine)		
	Dodowa	**Kintampo**	**Navrongo†**	**Overall**	**Ifakara**	**Rufiji**	**Overall**
	n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Population Parasitaemic by RDT	167/1306 **(12.8)**	233/919* **(25.4)**	72/307 **(23.5)**	472/2532 **(18.6)**	49/1460 (**3.4**)	251/1116 (**22.5**)	300/2576 **(12.0)**
Targeting Accuracy‡	242/502 (**48.2**)	136/243 (**56.0**)	87/497 **(16.1)**	378/745 (**50.7**)	276/637 (**44.1**)	212/620 (**34.2**)	488/1247 (**39.1**)
Provider compliance	131/175 **(75.7)**	58/93 **(62.4)**	37/208 **(17.8)**	189/268 (**70.5**)	37/54 (**68.5**)	76/96 **(79.2)**	113/150 (**75.3**)
ACT Availability (In Stock)	718/719 (**99.9**)	325/328 (**99.1**)	147/542 **(27.1)**	1190/1589 (**74.9**)	602/ 761 (**79.1**)	666/710 **(93.8)**	1268/1471 (**86.2**)
Patient Adherence	156/379 **(41.2)**	88/225 **(39.1)**	215/331 **(65.0)**	459/935 (**49.1**)	223/307 **(72.8)**	247/388 **(63.7)**	470/695 (**67.6**)

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Population parasite prevalence (PPP)

The annual average of PPP

- 19% in Ghana
- 12% in Tanzania

Targeting accuracy

Indicator

- Proportion of malaria positive patients correctly diagnosed/ classified by health providers

- The overall proportion for **Ghana was 51%** and **Tanzania was 39%**

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Compliance (health system and worker)

Indicator

- Proportion of prescriptions which are correct (in accordance with manufacturer's or MOH guidelines)

- Overall rate for **Ghana was 71%** and **Tanzania was 75%**

Patient adherence

- *Indicator*
  - Proportion of people who receive product and take as prescribed

Patient adherence

- 49% completely adhered to prescribed treatment (ASAQ) in Ghana
- 68% of the patients completely adhered to the prescribed treatment (ALU) in Tanzania
- Due to better tolerability of ALU, patient adherence was expected to be higher in Tanzania

Results from surveys on (i) Population Parasite Prevalence, (ii) Targeting Accuracy and Provider Compliance and (iii) Patient Adherence, Ghana and Tanzania, October 2009 to June 2011

	Ghana (Artesunate Amodiaquine)				Tanzania (Artemether-lumefantrine)		
	Dodowa	**Kintampo**	**Navrongo†**	**Overall**	**Ifakara**	**Rufiji**	**Overall**
	n/N (%)	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
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Availability

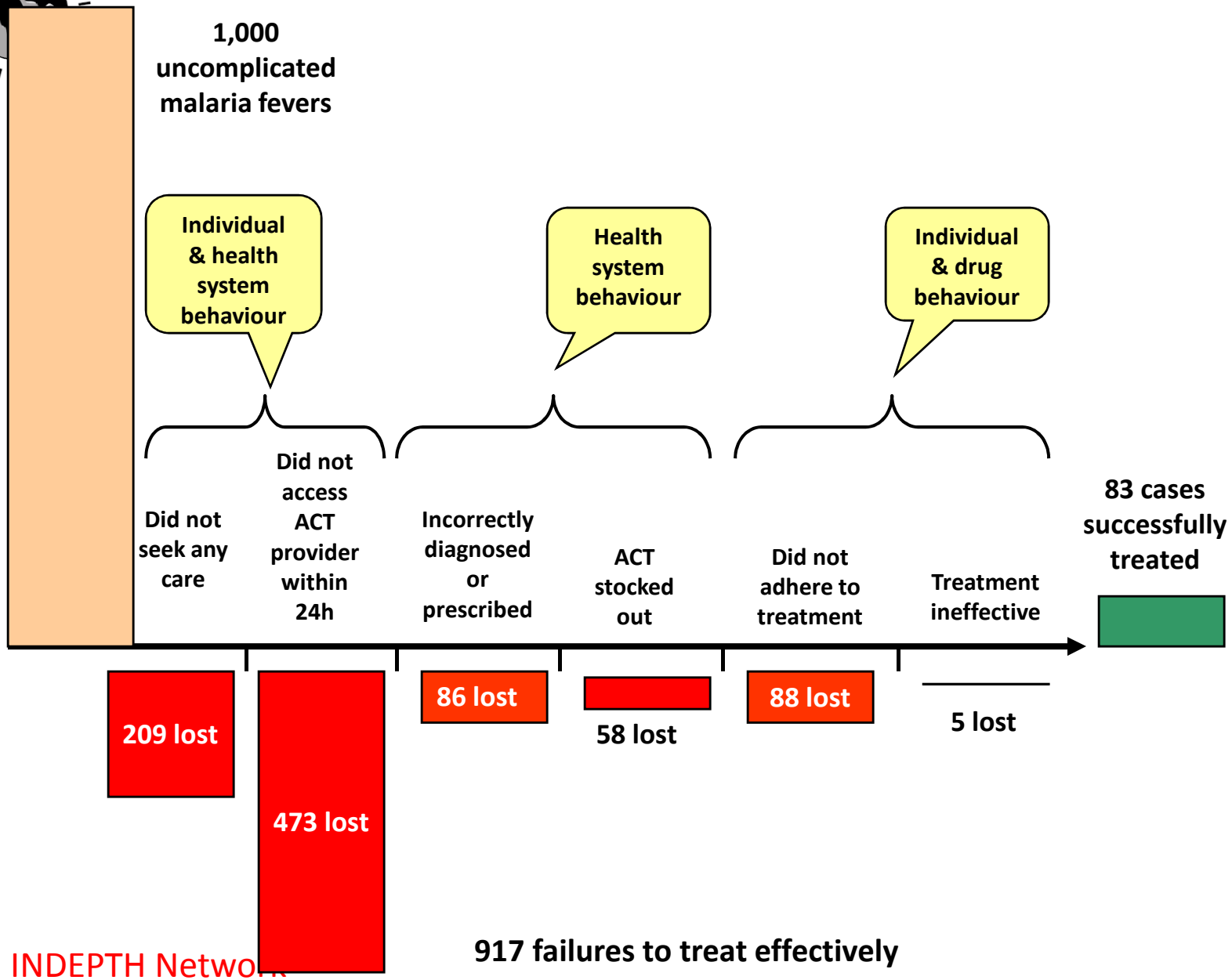
Indicator

- Proportion of providers with the product in stock
- Proportion of time product in stock

- 100% in Dodowa and Kintampo
- 27% in Navrongo
- 75% as overall rate for Ghana

- 79% in Ifakara
- 94% in Rufiji
- 86% overall rate for Tanzania

System effectiveness of ASAQ in Ghana



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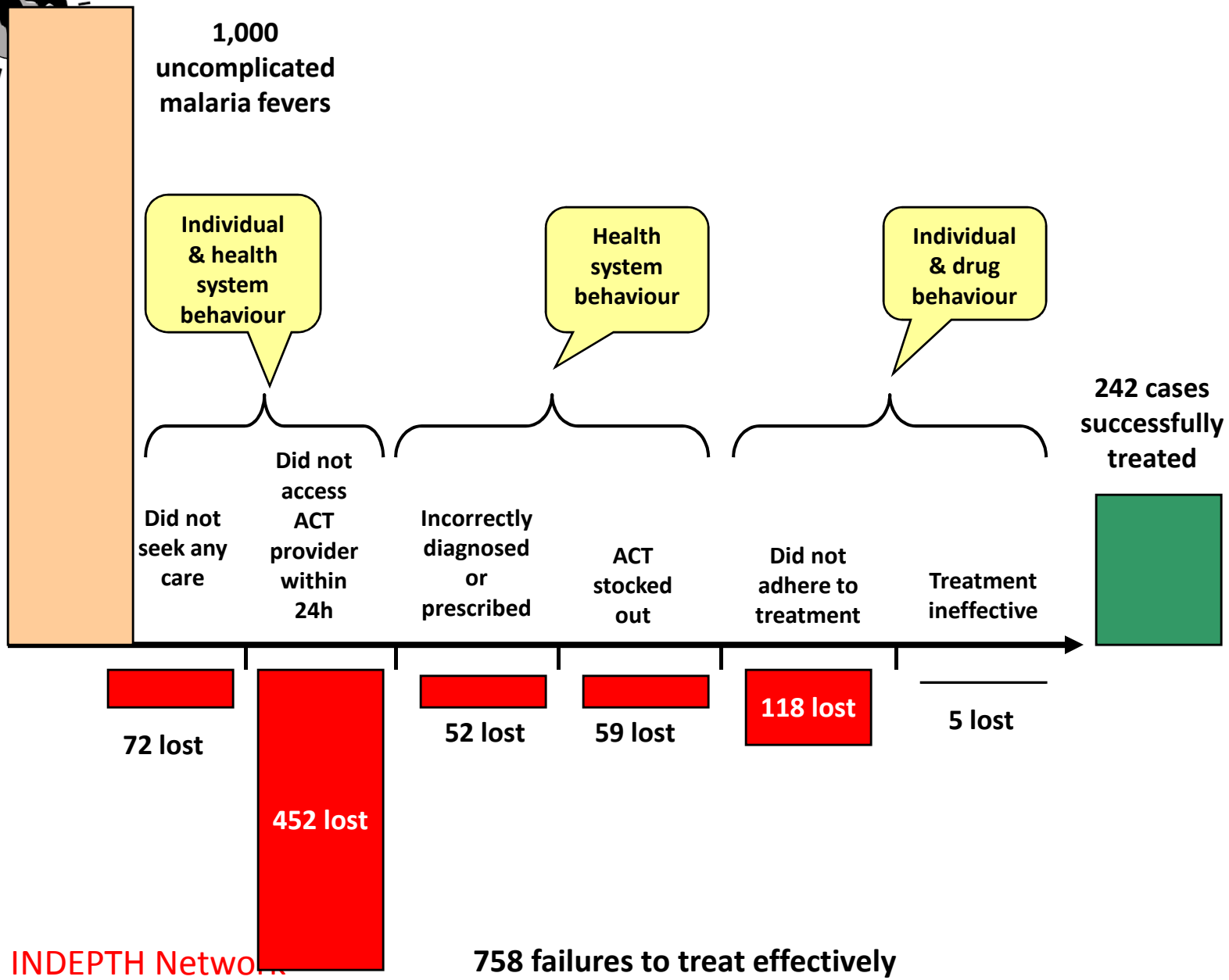
System effectiveness of ALU in Tanzania



758 failures to treat effectively

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Summary on system effectiveness and Policy implications

- platform successfully set up to collect data on ACT systems effectiveness

- Activities successfully integrated into routine HDSS activities & District Health Management

- many health system issues need to be addressed to improve effectiveness

Community and provider acceptability module

- Social, Cultural & behavioural factors affecting uptake &adherence to ACTs
- Qualitative
- Baseline data ended in 2010 and coding to end in December, 2011

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Community and provider acceptability module cont…….

4 data collection methods

- Community Seasonal calenders
- Focus group discussions
- Illness narrative interviews
- In-depth interviews

Preliminary findings - Ghana

- **Public providers**

  -Most CHPs Compounds use RDTs (periodic shortages)

- **Private providers**

  -No use malaria diagnositics

  -Stock mono and combination therapies

  -Supplies from vending vans & big pharmacies

  -Treatment based on patients choice

Preliminary findings – Tanzania

- Knowledge and perceptions of malaria drugs
- *Mseto"* catch-all phrase for many antimalarial
- ALu and "*dawa mseto*" as two different drugs
- drug's ability to effectively treat malaria depends on an individual's body or blood group
- Availability of ALu
  - Absence of ALu in the drug shops (Rufiji HDSS)
  - Quinine used for uncomplicated malaria

Costing and cost effectiveness

- Aim: to estimate cost per clinical episode of fever(proxy for malaria) at health facility and incurred by patients

- Direct & indirect costs of seeking care
  - Before diagnosis
  - During diagnosis
  - Pre-treatment
  - treatment

- Indicator
  - Incremental financial costs of drugs policy (costs of drugs + costs of other activities required to change policy)
  - Costs per clinical outcome

Median and Mean cost per episode of Fever at household Level

Cost Items	Tanzania				Ghana					
	Ifakara		Rufiji		Dodowa		Kintampo		Navrongo	
	Mean (US$)	Median (US$)	Mean (US$)	Median (US$)	Mean (US$)	Median (US$)	Mean (US$)	Median (US$)	Mean (US$)	Median (US$)
Direct Costs										
Diagnosis & treatment	3.05	2.30	1.62	0.83	7.76	3.33	4.13	1.33	2.76	0.77
Coping costs	10.10	4.17	1.87	1.67	31.78	0.33	20.21	20.17	5.33	2.00
Total Direct cost	13.15	5.20	3.49	2.50	39.54	3.66	24.34	21.40	8.09	2.77
Indirect cost	12.80	8.33	13.18	7.5	64.3	26.67	30.65	16.67	15.89	8.00
Total Direct cost + indirect cost	**25.95**	**13.53**	**16.67**	**10.00**	**103.84**	**30.33**	**54.99**	**38.07**	**23.98**	**10.77**

Important findings and policy implication

- Out-of-pockets payments are very high in both countries despite national health insurance operates in Ghana.
- Reducing or eliminating drug costs for fever treatment would improve access.
- introduction of AMFm , households will save on average 35.1% off drug costs in Ghana and 59.8% savings in Tanzania.
- Sustaining the AMFm initiative will improve effective fever/malaria management with RDTs.
- National health and community health insurance coverage is very low in Tanzania & improving coverage reduce out-of-pockets which affect the poor disproportionately.

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Demographic Surveillance System and Health Information System data linkage

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HIS and DSS data linkage enrolment status report (Individuals) for Ghana and Tanzania January, 2010 to June 2011

	INDEPTH centre	Total pop^{n}	Number enrolled	% of total pop^{n}	% IDs distributed
Ghana	Dodowa, GH	108,459	89,119	82	54
	Kintampo, GH	136,323	117,403	86	72
	Navrongo, GH	153,000	109,856	72	51
Tanzania	Ifakara, TZ	112,521	67,802	60	81
	Rufiji, TZ	84,095	46,410	55	53
Burkina Faso	Nouna	85,000	571	0.6	not yet started

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Objective 3

To evaluate the safety of new treatments through a comprehensive pharmacovigilance in a health system context

Objectives of Safety component

- Strengthening the normal SAERS
- Following a cohort on specified anti-malarials in a defined HDSS population to ensure denominator values for incidence rates of adverse reactions
- Following a subset of patients to establish adherence to treatment & complement safety methods
- To obtain real life profile & identification of rare adverse events

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Safety cont…..

3 approaches

- *Spontaneous adverse event reporting (SAER) system.*

  -Use National Adverse Drug Reaction reporting form (TFDA & FDB)

- Active cohort event monitoring (Linked Health Information & Demographic Surveillance Systems)

- Adherence module

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Spontaneous Adverse Events for Ghana and Tanzania October 2009 to June 2011

Country	Site	Adverse events	Serious Adverse Events
Ghana	Dodowa	95	4
	Kintampo	58	23
	Navrongo	33	2
Tanzania	Ifakara	41	10
	Rufiji	29	14
	Total	**256**	**53**

Spontaneous Adverse Events for Ghana and Tanzania cont…..

- 256 drug event associations
- Few required verification action
- Regulatory action in Ghana (Misoprosol deaths)

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List of spontaneous adverse events reported in Ghana and Tanzania

Ghana		Tanzania	
Abdominal crumps	Nausea	Blisters	Rashes on male organ
Bleeding	oedema	Blurred vision	Reaction on face
Body pains	Palpitations	Body Itching	Severe pain during menstruation
Cardiac arrest	Rashes/Blisters	Body rashes	Skin pilling
Cold/Chills	Skin rashes	Body swelling	Skin Rashes
Convulsion	Skin swellings	Body tightening	Sore and body rashes
Diarrhoea	Sleeplessness	Body weakness	Upper swelling
difficulty hearing	Sore	General Body	Vomiting
Dizziness	Steven Johnson syndrome	Chest tightness	
Drowziness	Stomach pains	Difficulty breathing	
Drug interaction	Sweating	Eyes swelling	
Epileptic fit	swellings	Fever	
Eruptions on trunk limbs	Swollen/itching eye	General body malaise	
Fever	Tongue paralysis	Headache	
Headache	Vomiting	High Fever	
Heartburns	Weakness	Increase in Heartbeat	
Internal Body pains		Itching	
Itching/rashs		Loss of sense	
Limbs rash		Muscle tightening	
Lip inflammation		Nausea	
Loss of appetite		Nightmare	

Cohort event monitoring (CEM)

- Active follow up of 10 000 exposures
  - To detect events 1 in 3000
  - Determine factors underlying observed reactions
  - Drug utilization, diagnosis, concomitant illness
- Follow up 5-10 days after ASAQ/ALU administration
- All events are recorded
- Local safety team review all reports
- Safety panel will review all SAEs

Cohort event monitoring for Ghana (ASAQ) and Tanzania (AL) October 2009 to June 2011

Country	Site	Number of Patients Treated	Number of Patients Reporting Adverse Events
Ghana	Dodowa	4,165	1,117
	Kintampo	3,879	283
	Navrongo	3,335	577
	Total	11,379	1977
Tanzania	Ifakara	3,658	15
	Rufiji	6,034	3
INDEPTH Network INESS	Total	9692	18

Signs and symptoms reported by patients after starting ACT for Ghana October 2009 to June 2011

DODOWA		KINTAMPO		NAVRONGO	
Nasal Congestion	7 (0.4)	Catarrh	3 (0.9)	Urinating	5 (0.5)
Fatigue	6 (0.3)	Eye Problem	3 (0.9)	Difficult Breathing	4 (0.4)
Measles	6 (0.3)	Mouth Sore	3 (0.9)	Swollen Limbs	4 (0.4)
Sore Mouth	6 (0.3)	Palpitation	3 (0.9)	Bloated Stomach	3 (0.3)
Sleeplessnes s	6 (0.3)	Skin Rashes	3 (0.9)	Feeling Cold	3 (0.3)
Bitterness In Mouth	5 (0.3)	Convulsion	2 (0.6)	Restlessness	3 (0.3)
Body Itching	5 (0.3)	Heart Beat	2 (0.6)	Weakness	3 (0.3)
Other	125 (7.5)	Other	18 (6.3)	Other	25 (2.7)
Total	1722	Total	348	Total	921

Important observation on CEM

- 1995 reported cases with 2088 adverse drug events
- Highest ever collected for ACTs
- Substantial contribution to global safety database on ACTs
- Pregnant women being monitored for birth outcomes
- Known denominator for calculating incidence rates
- Marked difference in reporting rates among sites (needs careful examination)

Adverse events from the Adherence study for Ghana and Tanzania, October 2009 to June 2011

Country	Site	Patients recruited	Patients with side effects
Ghana	Dodowa	430	343 (79.8)
	Kintampo	238†	72 (13.4)
	Navrongo	429	141 (32.9)
	Total	**1097**	**556 (50.7)**
Tanzania	Ifakara	311	18(5.8)
	Rufiji	400	5 (1.3)
	Total	**711**	**23 (1.3)**

Summary findings from Safety

- Routine SAER was NOT ENCOURAGING
- Thorough training and capacity building led to Sharp increase in reports (186 in Ghana & 70 in Tanzania)
- Forms readily available
- Event associated drug investigated by national regulatory authorities (eg Mesoprosol , quinine, ACT use in Ghana)

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Summary findings from Safety cont…..

- CEM showed recruitment and follow up of large cohorts for safety evaluation in real life settings
- Ability to detect and record several adverse events in patients
- Phone follow up possible for follow up of very large cohorts & is flexible
- Possible to use phones for SMS any adverse events post-drug exposure and reminders for drug intake.

Summary findings from Safety cont…..

- CEM study represent huge dataset on safety information for ACTs use
- One of the biggest post-marketing safety studies ever conducted
- WHO database of adverse drug reactions (vigibase) contains ONLY 464 reports on all ACTs

INESS Team

- Tanzania
  - Salim Abdulla, Rashid Khatib, Irene Masanja, Baraka Amuri, Majige Selemani, Msomhe Sadick, Mahmoud Kamusi
- Ghana
  - Margaret Gyapong, Christine Clerk, Elizabeth Awuni,
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  - Eusebio Macete, & team
- Burkina Faso
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INDEPTH NETWORK EFFECTIVENESS AND SAFETY SURVEILLANCE PLATFORM IN AFRICA (INESS)

Gyapong M., Abdulla S. Owusu-Agyei S., Atuguba F, de Savigny D., Skarbinski J., Akweongo P., Dodoo A., Allen D. and Binka F. on behalf of the INESS Team. INDEPTH Network, Accra.

Background

There is a huge gap between licensure and introduction of new malaria drugs in developing countries. The main goal of the INESS Platform is to minimize the time gap between licensure and introduction of new antimalarial drugs by providing objective endemic country safety and effectiveness data that will help inform national policy and practice.

INESS is set up in 7 Health and Demographic Surveillance Systems (HDSS) sites in Ghana (Dodowa, Kintampo and Navrongo), Tanzania (Rufiji and Kilombero/Ulanga), Burkina Faso (Nouna) and Mozambique (Manicha) under the auspices of the INDEPTH network. INESS is currently being implemented in Ghana and in Tanzania. The framework enhances Africa's capacity to document safety of drugs and to monitor local health systems in order to track costs, effective coverage and thereby provide evidence-based assessment of registered antimalarial drugs in real life settings.

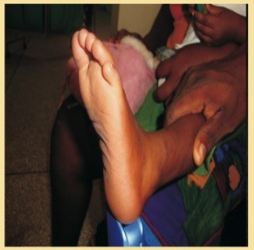
Objectives

- Develop and maintain a phase IV - effectiveness studies platform for antimalarials in Africa
- Assess effectiveness of new malaria treatments and its determinants in real-life settings
- Evaluate the safety of new malaria treatments through a comprehensive pharmacovigilance platform

Methods

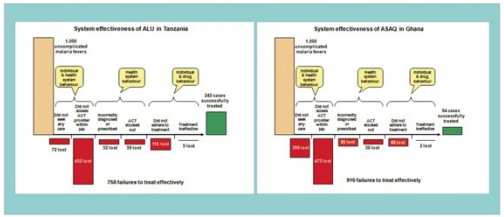
Health Systems Effectiveness: Household, community and provider surveys, population surveillance, and therapeutic efficacy studies were conducted under the following modules; I) Access to Antimalarials ii) Targeting Accuracy and Provider Compliance, iii) Patient Adherence, iv) Household Costs and Cost-effectiveness.

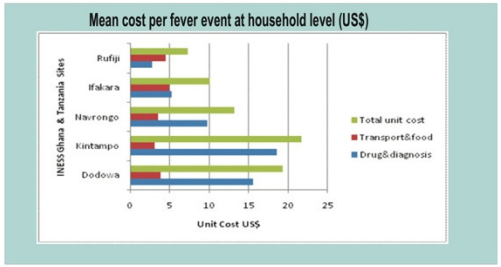
Safety of antimalarials: Strengthening the National Spontaneous Adverse Events Reporting System (SAERS), Patient Adherence and created a Cohort Event Monitoring System within the HDSS.



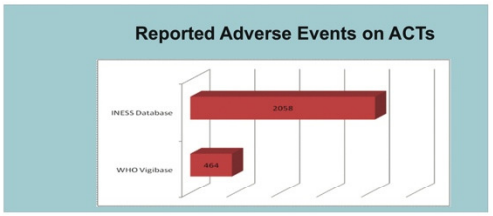
Results

a) *Health Systems Effectiveness*





b) *Safety of Antimalarial drugs*



Key Outcomes

- Effectiveness of highly efficacious drugs is determined largely by individual patient behaviour and health system factors and is unacceptably low (less than 25% in Tanzania and less than 10% in Ghana)
- Significant efforts directed to health system strengthening and behaviour change are required to achieve the full potential benefits of new ACTs for malaria control.
- The INESS Safety data contributes substantially to the National & Global safety information on ACT use
- The platform is now ready to evaluate new antimalarials and other interventions such as vaccines

Acknowledgments: NESS Consortium members: HDSS sites Ghana (Kintampo, Navrongo and Dodowa) ; Tanzania (Rufiji and Ifakara; Burkina Faso (Nouna); Mozambique (Manicha); INESS Task Team leaders: Swiss TPH, University of Ghana School of Public Health, CDC); ,INESS Governance Council and Scientific Advisory Board, INDEPTH Secretariat and the Bill & Melinda Gates Foundation