Malaria case management: from presumptive treatment to definitive diagnosis

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Overview

1. Review rationale for moving from presumptive treatment to confirmed diagnosis for malaria (fever) case management

2. Review highlights of Uganda's progress in expanding parasite-based diagnosis of malaria

3. Review current activities and identify some remaining challenges in moving toward confirmed diagnosis for all patients with suspected malaria in Uganda

Presumptive case management

- Based on symptoms/signs only, e.g. fever (omusujja, kwaman lieth, etc), fatigue, myalgias, etc.
- Nigeria & Niger: physicians' diagnosis correct ~50% in high season, ~10% in low
- Gabon: PPV of both patients & clinicians = 38%
- Multiple studies show that attempts to improve clinical diagnosis with algorithms of specific symptoms/signs do not improve accuracy

Definitive (parasite-based) malaria diagnosis: microscopy and RDTs

- Microscopy
  - If performed by well-trained, motivated lab personnel using good-quality equipment, gives accurate diagnosis at low cost
  - Not available to all patients with suspected malaria – e.g. in Uganda, available only at hospitals, Health Centers IV, and some Health Centers III

Definitive (parasite-based) malaria diagnosis: microscopy and RDTs

- Rapid diagnostic tests (RDTs)
  - Simple to use, do not require special equipment or laboratory personnel – ideal for settings where microscopy is not available
  - Some logistical challenges remain for effective implementation

Health care in malaria-endemic areas at a crucial tipping point

- Increased commitment to and funding for malaria control → large-scale efforts to improve access to effective antimalarials
- Improved access to antimalarials without improved diagnostic capacity → misuse of drugs, mistreatment of many patients, pressure toward resistance, diversion of funds
- Thoughtful implementation of malaria diagnostics has potential for broad public health benefit

Rationale for moving from presumptive to definitive diagnosis (1 of 5)

1) Evidence of poor outcomes for patients who receive antimalarial treatment for non-malarial disease

- Bacterial, viral and other febrile illnesses cannot be distinguished from malaria without diagnostic testing – e.g. respiratory infections, sepsis, meningitis

- Non-malarial febrile illnesses have high mortalities in Africa; mortality increases with delays caused by wrong diagnoses and inappropriate treatment

Rationale for moving from presumptive to definitive diagnosis (2 of 5)

2) Better targeting of ACT (Coartem) preserves medicine for patients who truly need it

- Uncertainty in global artemisinin supply
- Delays in procurement of ACT due to supply and funding issues
- Stock-outs at health facilities reported in many countries, including Uganda

Rationale for moving from presumptive to definitive diagnosis (3 of 5)

3) Better targeting of ACT may help to preserve drug efficacy

- May improve adherence to treatment by giving patients clear evidence of malaria infection
- Reduce exposure of malaria parasites to low levels of artemisinins in communities
- No new antimalarials to replace ACT if resistance develops, so maintaining ACT lifespan is critical

Rationale for moving from presumptive to definitive diagnosis (4 of 5)

4) Accurate diagnosis is essential to monitor trends in malaria prevalence

- Monitor impact of malaria control interventions
- Target malaria control resources to areas with true need
- Sustain enthusiasm and funding for malaria control programs

Rationale for moving from presumptive to definitive diagnosis (5 of 5)

5) Economics: better targeting of antimalarial treatment → less waste of resources

- Studies show that misdiagnosis and over-diagnosis of malaria drain resources at household level, with worst impact on poorest families
- ACT remains relatively expensive, even with subsidies
- Targeting treatment to true malaria cases allows more efficient use of health care resources

The real world:
From presumptive treatment to definitive malaria diagnosis in Uganda

Presumptive vs definitive malaria diagnosis in Uganda (2006-07)

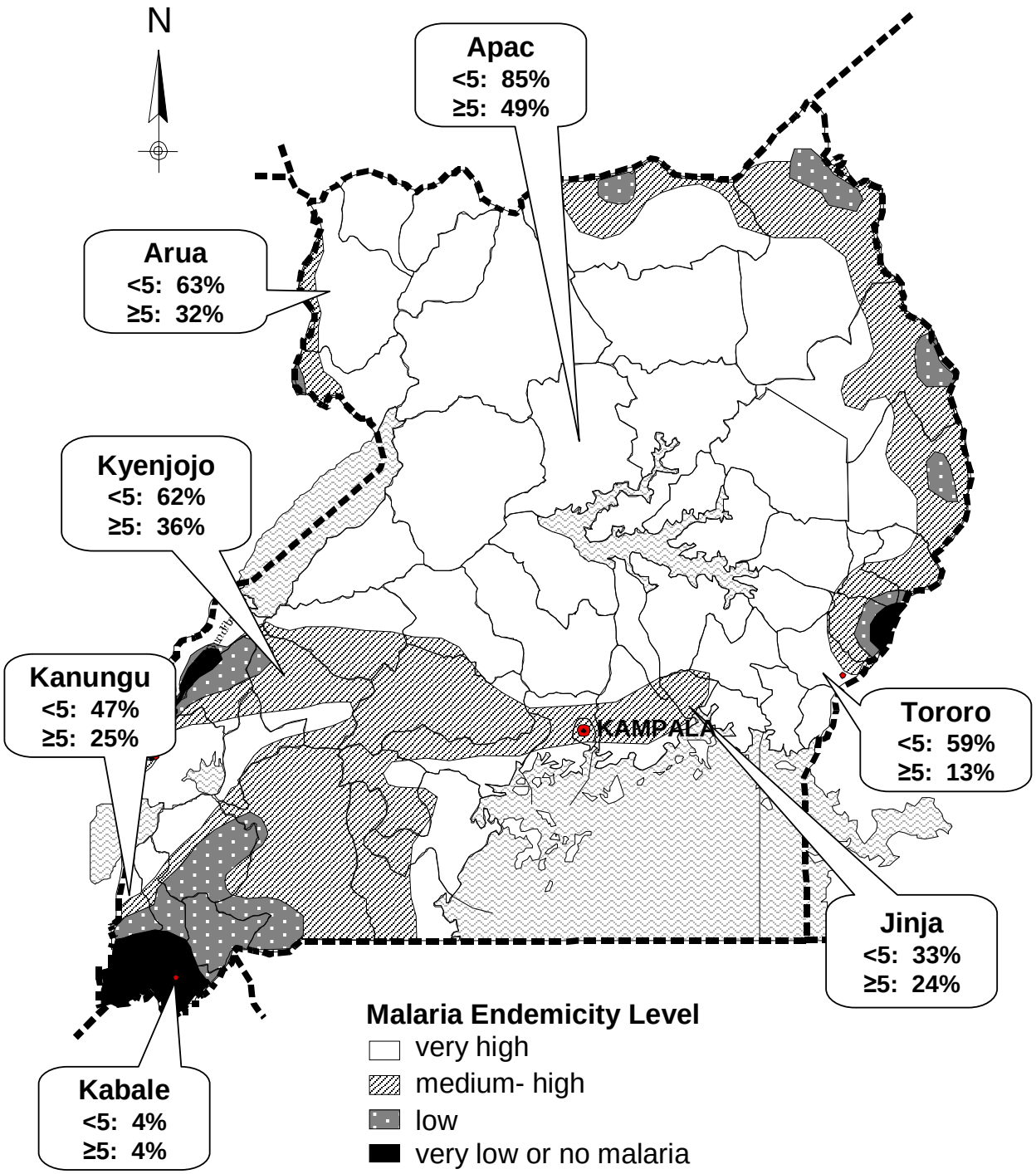
7 UMSP sites of varied transmission intensity

x 1000 patients per site

= 7000 fever cases evaluated

Figure shows proportions positive by expert microscopy

Hopkins et al, *Journal of Infectious Diseases* 2008



Current status of malaria diagnosis in Uganda

- Microscopy diagnosis available in hospitals, Health Centers IV, some Health Centers III
- RDTs in early stages of roll out and scale up in Health Centers II and III in some districts
- At the moment, most cases still diagnosed presumptively (by patients and health workers)…
- BUT – new national policy and policy guidelines nearing approval, stating commitment to improved diagnostic capacity and treatment of malaria based on confirmed diagnosis

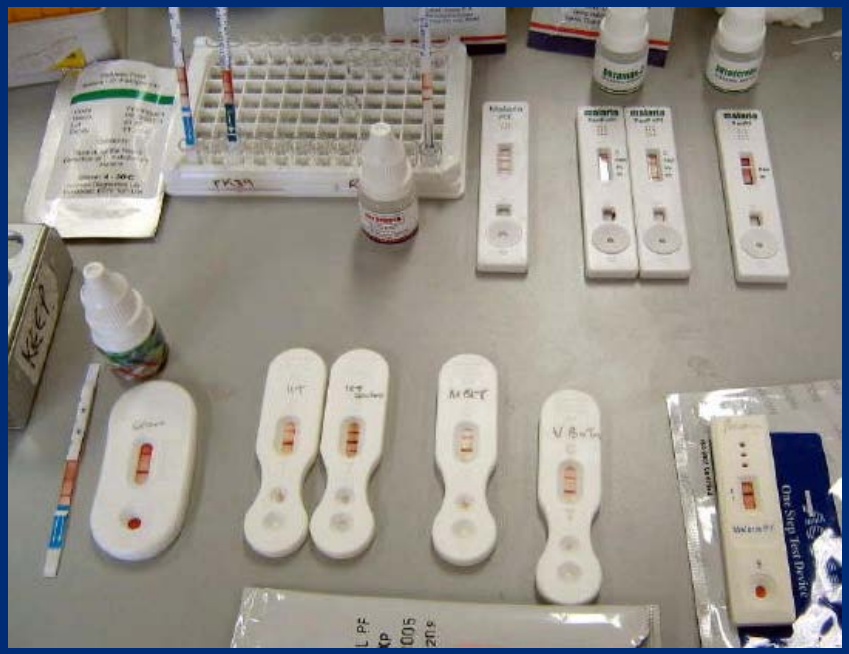
Malaria microscopy in Uganda

- Efforts underway to improve QA/QC, microscopist training, health workers' use of results
- Challenges in ensuring access (availability and morale of lab personnel, supply of reagents)
- Thoughtful training and support supervision → better impact of microscopy on case management:
  - From ~35% to >50% patients with suspected malaria referred to lab
  - From 40-48% to <20% patients w negative smear given antimalarial

(Ssekabira et al, *AJTMH* 2008)

Brief background and chronology:

Toward evidence-based implementation of malaria RDTs (rapid diagnostic tests) in Uganda



Data on RDT accuracy in Uganda

- Research demonstrates good accuracy of RDTs in range of geographic and transmission zones across Uganda:
  - Evaluation of original HRP2 test, Kabarole district, Kilian et al, *Acta Tropica* 1999
  - Comparison of 5 versions of HRP2 tests in Mbarara, Guthmann et al (MSF/Epicentre), *Trans R Soc Trop Med Hyg* 2002
  - Comparison of HRP2 and pLDH tests in Kampala, Hopkins et al (MU-UCSF), *Am J Trop Med Hyg* 2007
  - Accuracy of HRP2 tests, Kyabayinze et al (Malaria Consortium), *Malaria Journal* 2008
  - Comparison of new pLDH tests in Mbarara, Fogg et al (MSF/Epicentre), *TRSTMH* 2008
  - Comparison of HRP2 and pLDH tests in Kampala, Hopkins et al (UMSP), *J Infect Dis* 2008

Uganda's RDT timeline: key policy steps

- Feb '07: RDT workshop and data review in Kampala → consensus on "step-wise implementation":
  - Begin with HRP2-based tests
  - Begin in areas with low-to-medium transmission intensity, and areas where large-scale interventions are expected to decrease transmission in the near future
  - Begin in Health Centers II and III, where microscopy is not currently available
- Dec '07, Feb '08: Follow-up meeting identified policy areas requiring consensus
- Current: New policy guideline on malaria diagnosis nearing approval in MoH

Uganda's national RDT implementation components

PROCUREMENT & DISTRIBUTION

QUALITY ASSURANCE/ QUALITY CONTROL SYSTEM

TRAINING (HEALTH WORKERS & COMMUNITIES)

MONITORING & EVALUATION

Challenge: Health worker training for effective RDT use

- Appropriate training is critical:
  - Experience in Zambia, Tanzania, and Kenya shows that basic training alone (i.e. teaching only the mechanics of RDT use) did not have desired impact on treatment practices
- Models and data show that poor targeting of RDTs, and poor adherence to test results, dramatically decreases their utility and cost-effectiveness
- Not just correct and safe use of RDTs, but appropriate fever case management for Ugandan context

Development of the RDT curriculum and training materials for Uganda

- In mid-2007, Uganda MoH requested development of training program to help with effective and safe roll-out of RDTs
- Collaborative effort to develop first draft
- Revision through series of national stakeholders' meetings
- Pilot evaluation of impact on health worker behavior and patient outcomes (brief results presented here)
- Current activities: Further refinement of materials and early national roll-out

Content of curriculum

- Session 1: How to select patients for testing with RDTs
- Session 2: Performing and reading an RDT
- Session 3: Management of a patient with fever and a positive RDT
- Session 4: Management of a patient with fever but a negative RDT
- Session 5: Recognition and referral of patients with severe illness
- Session 6: Patient education
- Session 7: RDT storage and stock management

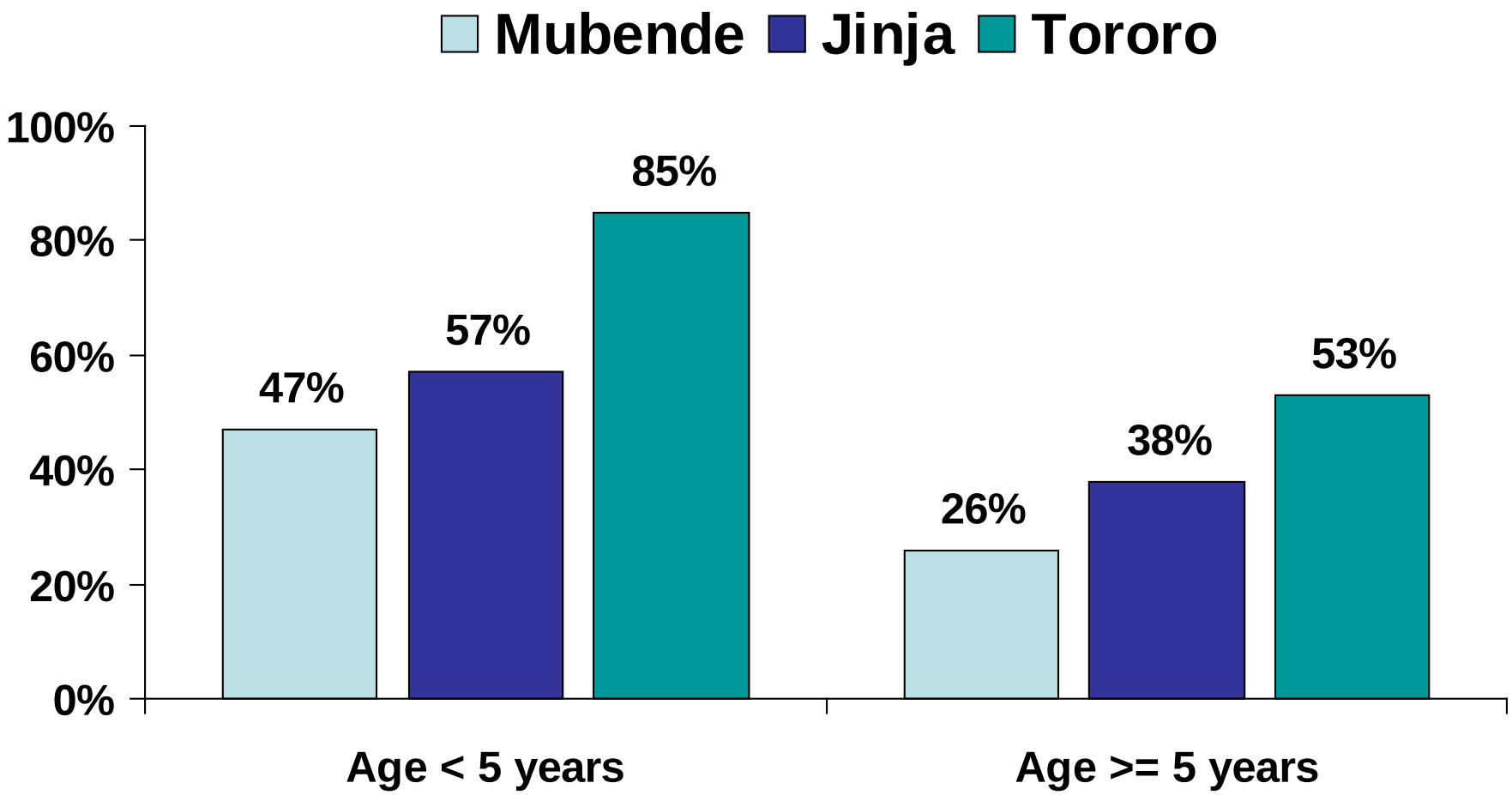
Points kept in mind during curriculum development

- Most health care at Health Centers II and III is delivered by personnel with little formal training: nursing assistants, midwives, sometimes even volunteers
- Clear algorithms likely most appropriate especially for lower-level health facility staff
  - Selection of patients for testing with RDTs
  - Management of patients with positive and negative tests
- As much as possible, integrate with IMCI guidelines, other MoH guidelines, and earlier training messages

Dr Jane Nabakooza of the national Malaria Control Program demonstrates how to evaluate for signs of anemia (Paya Health Center III, Tororo, Uganda)

Alex Ojaku of the JUMP team describes the mode of action of RDTs to health workers at Wakitaka Health Center III (Jinja, Uganda).

Pilot training evaluation: RDT results by patient age



Antimalarial prescribing by RDT result (1)

Characteristic	Site		
	Tororo (n = 1308)	Jinja (n = 487)	Mubende (n = 191)
Patients with **positive** RDT who received antimalarial prescription	**99%**	**99%**	**100%**

Antimalarial prescribing by RDT result (2)

Characteristic	Site		
	Tororo (n = 513)	Jinja (n = 616)	Mubende (n = 409)
Patients with **negative** RDT who received antimalarial prescription	**0.8%**	**0.2%**	**0.5%**

Impact of RDT training intervention on antimalarial prescribing

Site	Relative change in proportion of patients prescribed antimalarial		**Antimalarial doses saved per 1000 patients**
	RR (95% CI)*	p-value	
Mubende	0.32 (0.29 – 0.36)	<0.001	**420**
Jinja	0.44 (0.39 – 0.50)	<0.001	**358**
Tororo	0.73 (0.70 – 0.77)	<0.001	**183**

***Generalized estimating equations controlling for history of fever and age, adjustment for repeated measures on the same day.**

Summary

- At three representative health centers in Uganda, training and RDTs led to virtually “perfect” targeting of antimalarial prescriptions
- At two sites, patient satisfaction with illness outcome was equivalent at centers with and without RDTs
- At one site, a significant number of patients with negative RDTs, who did not receive antimalarials, went on to seek care elsewhere

On-going RDT training activities

- Dec ’08 – Official training and hands-on practice sessions for national RDT training team
- Dec ’08 to Mar ’09 – On-site trainings for staff at Health Centers II and III in Rukungiri, Kisoro, Kanungu and (hopefully soon) Kabale districts
- Basic M&E of early training impact, coordinated by UMSP and JUMP, will help to gauge likely impact of national roll-out
- RDT training program formally approved by MoH, to be printed and available for general use

Martin Shibeke of MoH explains aspects of RDT use in patient management to health workers at Nagongera Health Center III (Tororo, Uganda) during a practice session for national training team.

Uganda's national RDT implementation components

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Some challenges remaining in improving malaria diagnostic capacity

- In general:
  - Clear guidance for management in special populations: under 5s, pregnant women, recently treated patients, severe illness
  - Training and sensitization of health workers and patients to improve adherence to test results
  - Coordination with private sector
- For microscopy:
  - Improve and maintain skills of laboratory personnel
  - Maintain reagent supplies through efficient distribution
- For RDTs:
  - Regulation of procurement and distribution
  - Design and implementation of sustainable QA/QC system
  - High quality training across all districts
  - Design and implementation of sustainable M&E

Patients awaiting care at Paya Health Center III (Tororo, Uganda).

Some next steps for research:

Planned FIND field studies for malaria diagnostics

- Positive control wells (PCWs) as QA/QC component
  - Initial pilot in Uganda to evaluate training messages and health worker response to PCWs
  - Multi-country trials to evaluate utility and stability in the field
- Blood transfer devices for RDTs
  - Evaluation of accuracy and consistency, safety, and ease of use of various devices
- Utility of RDTs in detecting asymptomatic placental malaria in pregnant women
  - Possible alternative to IPTp as SP resistance rises
- Field evaluations of new tests as appropriate

Thank you!

Effective RDT implementation:
Experience in other African countries (slide 1 of 2)

- **TANZANIA, Reyburn et al, *BMJ* 2007:**
  - **Outpatient clinic staff received training on RDT use, and reviewed national guidelines on malaria diagnosis and treatment.**
  - **Of patients with a negative RDT result, 54% were treated with an antimalarial drug; of those with negative blood smear, 51% received an antimalarial.**
  - **In a low-moderate transmission setting, over 90% of antimalarial prescriptions were for patients with a negative lab test.**
  - **Authors conclude that "use of [RDTs], with basic training for clinical staff, did not in itself lead to any reduction in over-treatment for malaria. Interventions to improve clinicians' management of febrile illness are essential but will not be easy."**

Effective RDT implementation:
Experience in other African countries (slide 2 of 2)

- **ZAMBIA, Hamer et al, *JAMA* 2007:**
  - **One year after RDTs were introduced nationally, assessment of association between use of microcopy and RDTs and antimalarial prescription.**
  - **Of patients with negative RDT, 35.5% were prescribed antimalarial; of patients with negative blood smear, 58.4% received an antimalarial.**
  - **Of patients with fever who did not have diagnostic tests done, 65.9% were also prescribed antimalarials.**
  - **Authors conclude that "provision of new tools to reduce inappropriate use of new expensive antimalarial treatments must be accompanied by a major change in clinical treatment of patients presenting with fever but lacking [laboratory] evidence of malaria infection."**