Answering key questions on malaria

ACT Consortium research from 2007 to 2015... and future directions

This booklet describes the main findings from our studies so that they can be applied to malaria control efforts.

Funded by the Bill & Melinda Gates Foundation through a grant to the London School of Hygiene & Tropical Medicine.
**What is the ACT Consortium?**

The ACT Consortium is an international research collaboration working to answer key questions on malaria drug delivery.

- **Started in 2007**
- **25 projects in 10 countries in Africa and Asia**
- **20+ partner institutions**
- **Completed in 2015**

Work included formative research, cluster randomised trials, cohort and descriptive studies, impact evaluations, economic and anthropological assessments.

**Why did we start this work?**

- Many people with malaria can't access effective malaria treatment, increasing the risk of severe disease and death.
- The safety profiles of ACTs need to be established in their routine use in the general population and in vulnerable populations.
- Many people who receive malaria treatment don't actually have malaria, resulting in poor antimalarial targeting and wastage.
- Poor quality antimalarial medicines in the market and surveillance systems are not yet ready to address this challenge.

**What is ACT?**

Artemisinin-based Combination Treatment

The recommended treatment for uncomplicated malaria caused by Plasmodium falciparum, the most dangerous malaria parasites.

**What is an RDT?**

- Rapid Diagnostic Test
- Allows for the rapid diagnosis of malaria at a community level
- Requires limited training, simple to perform and interpret
- Can improve the quality of management of malaria infections, especially in remote areas with limited access to good quality microscopy services.

**INFECTED & TREATED**

- There are poor quality antimalarial medicines in the market and surveillance systems are not yet ready to address this challenge.
- The safety profiles of ACTs need to be established in their routine use in the general population and in vulnerable populations.
- Many people who receive malaria treatment don't actually have malaria, resulting in poor antimalarial targeting and wastage.
- Many people with malaria can't access effective malaria treatment, increasing the risk of severe disease and death.

*25 projects in 10 countries: Afghanistan, Cambodia, Cameroon, Ghana, Equatorial Guinea, Kenya, Nigeria, South Africa, Tanzania, Uganda*
How does the ACT Consortium fit into the global malaria context?

From 2000–2015 there was significant and rapid progress in the fight against malaria; however, the burden is still high, especially in sub-Saharan Africa.

Both documents lay out concrete targets to accelerate progress for malaria control by 2030, encouraging the development of tailored country programmes.

Where do patients seek care?

Patients with a fever seek health care in a variety of settings:

- **Public Health Facilities**
  - Government-supported public health facilities, including hospitals and health centres — the source of health care for many patients
  - Facilities run by non-governmental organisations, including missionaries

- **Community Health Workers**
  - Village-based extension of the public health care services
  - Ranges from small drug shops and street vendors to licensed pharmacies, private health clinics and hospitals

- **Private Health Care Sectors**
  - Scope and size vary greatly from country to country
  - Ranges from small drug shops and street vendors to licensed pharmacies, private health clinics and hospitals

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But how do these goals affect patients?

1. How can we improve the management of patients with fever in all health care sectors?
2. Diagnosis before treatment is a critical part of good quality patient care, and is now policy from the WHO and most endemic countries

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Therefore...
What influences the uptake of RDTs?

Our research showed that all these factors influence RDT uptake.

**Health care provider willingness to participate in the RDT intervention**
**The proportion of trained health care providers in a given setting**
**The relationship between health care providers and authorities**
**Provider confidence in RDT supplies**
**Provider and patient familiarity with malaria testing**
**The priorities of health care providers**
**Evaluation and data collection methods used**

Malaria control programmes should consider these factors when designing RDT implementation and training programmes for various settings in their countries, taking into account providers’ and patients’ expectations of care. Authorities should also communicate with local communities about malaria diagnosis and treatment, to encourage their understanding and acceptance of new health care practices.

![Diagram](https://example.com/diagram.png)

Our research showed that all these factors influence RDT uptake.

**www.actconsortium.org/diagnosis**

Do health providers prescribe according to RDT results?

![Diagram](https://example.com/diagram.png)

Often, but not always - it varies across settings. Here are some factors identified in ACT Consortium studies to affect prescribing behaviour.

**Test result is positive, but patient does NOT receive an ACT**
- Which treatment do patients prefer?
- How willing were providers to participate in the RDT intervention?
- Is ACT supply adequate and reliable?
- What is the cost of ACTs to patients?
- Did proportions of positive and negative RDT results fit with expectations?

**Test result is negative, but patient RECEIVES an ACT**
- How willing were providers to participate in the RDT intervention?
- How aligned were providers with the idea of test-based care?
- How acceptable were non antimalarial treatments?

Malaria control programmes should consider these factors when designing RDT implementation and training programmes for various settings in their countries, taking into account providers’ and patients’ expectations of care. Authorities should also communicate with local communities about malaria diagnosis and treatment, to encourage their understanding and acceptance of new health care practices.

When a patient comes in and then you see that the patient hasn’t money you just go straight to giving the treatment rather than sending the patient to the lab, while when coming back from the lab he will not be able to buy drugs.

(Bamenda, public facility nurses, Cameroon)

![Diagram](https://example.com/diagram.png)

**www.actconsortium.org/REACTCameroon**
Compared to instances where a definitive diagnosis is unavailable, patients with a negative RDT are less likely to receive ACTs and other antimalarials, which:

- Reduces ACT wastage
- Encourages alternative diagnoses
- Often increases patient referrals for further care; particularly where providers do not have alternative treatments (community health worker programmes)

Importantly, we did not find evidence of poor health outcomes when patients with a negative RDT result did not receive antimalarials.

Patient adherence to treatment is another important step in ensuring ACT effectiveness. Patient and provider-related and circumstantial factors can influence patient adherence.

What are the effects of RDTs on...

... the HEALTH CARE SYSTEM and the PATIENT

On the other hand...

- No evidence of difference in patient-reported health outcomes (typically asked at day 14), regardless of RDT availability
- In many cases, providers prescribe more antibiotics when RDTs are available—especially when test results are negative
- In some cases, patients continue to “shop around” for further care, particularly when RDTs are negative
- Impact on economic costs and household finances are mixed

On the other hand...

- Quality assurance and general standards of care in the private sector
- Patient advocacy programmes to reinforce the importance of patients receiving the correct diagnosis and subsequent treatment, and thus enhance the acceptability of RDTs.
The cost-benefit of introducing RDTs is only one factor influencing the use of the tests. However, an economic modelling project, based on data from ACT Consortium and other sources, provides a picture of economic consequences of introducing RDTs in different settings.

RDTs improve the targeting of ACTs:
- In all African settings, fewer patients without malaria received ACTs, reducing the wastage of antimalarial drugs
- Improvements vary widely across health care settings

However, not all patients who had malaria received an ACT.

NEW QUESTION: How can we improve the management of patients with fever in all health care sectors?

A) Accurate diagnosis is key — and context matters

We were able to identify several broad patterns in our findings:

- RDTs improve the targeting of ACTs: In all African settings, fewer patients without malaria received ACTs, reducing the wastage of antimalarial drugs
- Improvements vary widely across health care settings

However, not all patients who had malaria received an ACT.

NEW QUESTION: How do we balance the reduced wastage of ACTs against the possibility of failing to treat some malaria cases?

NEW QUESTION: What is the longer term impact on health (and health care systems) of introducing RDTs? What can we learn from malaria RDTs for introduction for other points of care?

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NEW QUESTION: How can we improve the targeting of antibiotics?

NEW QUESTION: Nonetheless, we are also aware of differences in the performance and accuracy of RDTs.

• RDTs can help to identify patients with non-malarial illnesses. However, where RDTs are used, health workers increase their prescription of antibiotics, which are not likely needed by most patients.

NEW QUESTION: What are the longer term implications of varied performance of RDTs?

NEW QUESTION: How can we improve the targeting of antibiotics?
ACT Consortium researchers examined what treatment patients received when they tested positive for malaria, and when they did not. Where RDTs were available, health workers tended to prescribe more antibiotics, particularly in patients who didn’t have malaria.

If it’s not malaria, what is it?

Every patient with fever imagines they have malaria... we try to advise that not every fever is malaria. We try to explain other causes of fever like tonsilitis, ear infection and urinary tract infection (UTI).

Health worker, Zanzibar

In Tanzania, we found that fewer than 1% of outpatients who tested negative for malaria had a bacterial illness (i.e. a minority of patients who did not have malaria required antibiotics).

Together with our partner institutions, we have developed an interactive, open-access map showing published data on causes of fever.

Access the tool at:
www.wwarn.org/surveyor/NMFI/index.html

What are other common, preventable and/or treatable illnesses that cause fever, besides malaria?

Answers to this question will help to inform the development of more rational treatment guidelines and appropriate diagnostic tests.

www.actconsortium.org/NMFI

Access the tool at:
www.wxrm.org/surveyor/NMFI/index.html

The management of patients presenting with a fever must be seen in the context of global public health, and requires multi-disciplinary action.

www.actconsortium.org/ROTZanzibar

...increasingly, patients and providers recognise that not all fevers are caused by malaria

...most fevers do not need a specific treatment — but some do. It’s important to identify these more serious conditions

...antimicrobial resistance is likely to increase with the indiscriminate use of antimicrobials. There is growing global recognition of the need to better target antimicrobials to patients who truly need them

www.who.int/mediacentre/factsheets/fs194/en/

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The management of patients presenting with a fever must be seen in the context of global public health, and requires multi-disciplinary action.
A complex intervention improved malaria case management, communication between health workers and patients, and community perceptions of care offered at the intervention health centres. But these improvements were small, and did not affect the health outcomes of the children in the community.

To maximise the impact of investment in malaria control, we must influence not just local factors — we must also address broader systems and political issues.

Comparing RDT implementation across 3 health care sectors in Uganda: A case study enabled by our consortium approach

WHAT DID WE LEARN?

Public Health Facilities

- A complex intervention improved malaria case management, communication between health workers and patients, and community perceptions of care offered at the intervention health centres.
  - But these improvements were small, and did not affect the health outcomes of the children in the community.
  - To maximise the impact of investment in malaria control, we must influence not just local factors — we must also address broader systems and political issues.

Community Health Workers (CHW)

- CHW use of RDTs improved malaria diagnosis and helped to ensure that patients received malaria treatment appropriately.
- Community members understood that not all fever was caused by malaria, and accepted RDT testing.
- As a result, the inappropriate prescription of ACTs reduced dramatically.
- CHWs referred more patients to health facilities.

Private Health Care Sectors

- RDTs were popular in the private retail sector; reducing the over-prescription of ACTs by 70%.
- Patients were willing to buy RDTs at subsidised prices.
- Trained drug shop vendors used RDTs correctly.
- Training drug shop vendors to use RDTs can improve the quality of care and change the reputation of drug shops.

Visit www.actconsortium.org/diagnosis to learn about our cross-study analysis in Uganda.
Recognising this, in 2013 ACT Consortium members and partners conducted a systematic review of available evidence. While the evidence base continues to build, the ACT Consortium is part of a global conversation to answer the question: How can countries best scale up malaria RDTs in their private health care sectors?

How can we ensure consistent, affordable access to quality assured ACTs in the private health care sector?

Fever case management in the private health care sector is an important area, but evidence to inform public health practices is lacking.

Can the private sector be engaged effectively, and cost-effectively, to improve malaria treatment?

Can drug shop vendors be trained in effective and safe fever case management?

**CONCLUSIONS:**

- Experience in Ghana and Uganda showed that prescribers in the retail sector were able and eager to use RDTs to improve the appropriate use of ACTs
- However, uptake in Nigeria was less enthusiastic, showing that approaches to RDT introduction need to be tailored for different settings
- It is also important to consider wider consequences of introducing RDTs in the private sector — e.g. general quality of care in drug shops, and potential impact on the status of the shops in public perceptions

**CONCLUSIONS:**

- Experience in Afghanistan and in Uganda showed that CHWs were able to use RDTs to improve the appropriate use of ACTs
- Both CHWs and community members understood that not all fever is caused by malaria, and accepted RDT testing
- As a result, the number of unnecessary ACT treatments can be reduced
- CHW use of RDTs can improve malaria diagnosis and help to ensure that patients receive appropriate anti-malarial treatment, even in populations that otherwise do not have good access to health services

Can community health programmes improve fever case management and targeting of ACTs?

Can CHWs in Afghanistan and in Uganda be trained to use RDTs for malaria diagnosis and treatment?

While the evidence base continues to build, the ACT Consortium is part of a global conversation to answer the question: How can countries best scale up malaria RDTs in their private health care sectors? How can we ensure consistent, affordable access to quality assured ACTs in the private health care sector?
How safe are ACTs in vulnerable populations?

We conducted four studies to answer this question.

Repeated use of ACTs in children with malaria

In Malawi we assessed whether ACT drugs are safe and effective in young children receiving repeated weight-based treatments over time as part of standard care.

- Some antiretrovirals interacted with antimalarials; meaning that they increased or decreased the levels of malaria medicines in the patients’ bodies.
- However, there was no evidence of harm from combining these medicines and the efficacy of the antimalarials was not affected.

How can we collect and monitor safety data in real-world environments?

Our teams in malaria-endemic countries developed standardised data collection tools, which were used to collect data from more than 3000 patients, within and beyond ACT Consortium studies.

These patient groups were diverse: young, old, children, pregnant women, healthy adults, HIV-positive patients, and people taking other medications.

We collected data from a variety of sources — including trained clinicians and community health systems.

Data on adverse events allow us to weigh up the benefits and harms of malaria medicines, and identify how these harms can be minimised.

The observed drug interactions were not found to be clinically important.

In Tanzania and two in South Africa assessed whether specific HIV and malaria medicines interact when taken simultaneously.

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Repeated use of ACTs did not cause serious adverse events.
What is the quality of ACTs in the market?

Poor quality medicines: different causes, all dangerous

- **Falsified**
  - Fake medicines which do not contain any stated API and may carry false representation of their source of identity. A falsified drug could signal a potentially counterfeit product, which does not comply with intellectual property rights or may infringe trademark law.

- **Substandard**
  - Medicines produced by authorised manufacturers which do not have the correct amount of API. This can result from inadequate quality control in the manufacturing process. In addition, well-manufactured medicines may become degraded if they are stored in inappropriate conditions, such as high heat and humidity.

- **Counterfeit**
  - Medicines that do not comply with intellectual property rights or that infringe trademark law.

- **Substandard ACT medicines not only leave patients with malaria undertreated, which could be fatal, but they may also contribute to the development of drug resistance.**

Our data from three independent laboratories showed that, although falsified antimalarials are a persistent problem, they are not as common as previously reported elsewhere.

Substandard drugs are relatively common and may be an even bigger threat to malaria control than anticipated. Also, artemisinin monotherapy tablets were still available in some areas.

Counts were collected using the following methods:

- **Convenience**
  - Convenience sampling strategies may effectively identify “hot spots” where poor quality drugs are common. However, to understand the true scale of the problem more representative large-scale sampling is required.

- **Representative**
  - Representative sampling strategies require more resources, but allow changes in drug quality to be tracked with confidence over time.

Overall, our studies showed that drug quality is an ongoing issue, and that there is no room for complacency.

Previous reports suggested that up to 1/3 of antimalarials in malaria-endemic countries were fake. We purchased and analysed the quality of over 10,000 ACT samples from six countries: Cambodia, Equatorial Guinea, Ghana, Nigeria, Rwanda and Tanzania.

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Overall, our studies showed that drug quality is an ongoing issue, and that there is no room for complacency.

It is important to establish affordable, long-term surveillance systems that sample medicines in a representative way and analyse them regularly with reliable laboratory techniques. This is not just a health problem, but a problem that requires involvement from partners across different sectors, including law, customs, industry and pricing.
In summary

Over the past decade, enormous strides have been made in the fight against malaria. But much remains to be done.

Results from the ACT Consortium contribute to the evidence base to guide further improvements in malaria control through enhanced access, targeting, safety and quality of ACTs, and better malaria and fever case management.

This booklet summarises the key results of dozens of projects, the product of the efforts of hundreds of committed people over the past decade. We thank them for their contributions.

We look forward to continuing the progress toward a malaria-free future.

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*The ACT Consortium works with many other partner institutions worldwide

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