



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



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& 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



What is ACT?
Artemisinin-based Combination Treatment

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



*25 projects in 10 countries:

Afghanistan
Cambodia
Cameroon
Ghana
Equatorial Guinea
Malawi
Nigeria
South Africa
Tanzania
Uganda

Why did we start this work?



Many people with malaria can't **access** effective malaria treatment, increasing the risk of severe disease and death



Many people who receive malaria treatment don't actually have malaria, resulting in poor antimalarial **targeting** and wastage



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.



The **safety** profiles of ACTs need to be established in their routine use in the general population and in vulnerable populations



There are poor **quality** antimalarial medicines in the market and surveillance systems are not yet ready to address this challenge

www.who.int/malaria/areas/diagnosis/rapid_diagnostic_tests/en/



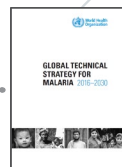
How does the ACT Consortium fit into the global malaria context?

A

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



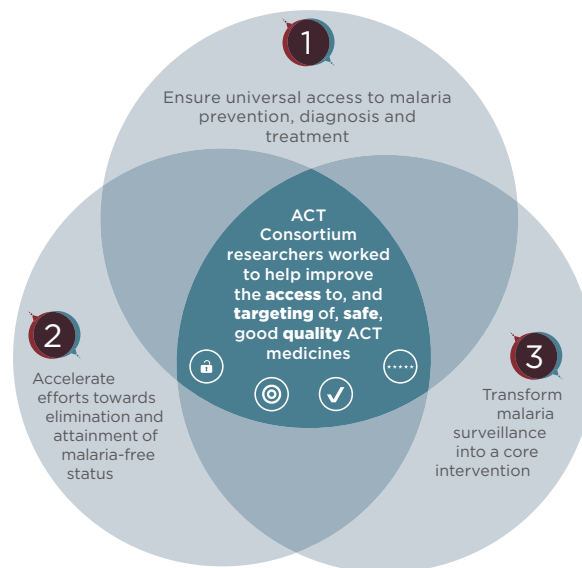
Roll Back Malaria Partnership's **Action and Investment to Defeat Malaria (AIM) 2016–2030** — For a Malaria-Free World



WHO **Global Technical Strategy (GTS) for Malaria 2016–2030**

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

The 3 pillars of the GTS



QUESTION

But how do these goals affect patients?



Where do patients seek care?

A

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
- Endorsed by some governments to reach patients with poor access to public health facilities

Private Health Care Sectors

- Scope and size varies greatly from country to country
- Ranges from small drug shops and street vendors to licensed pharmacies, private health clinics and hospitals

QUESTIONS



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



Therefore...

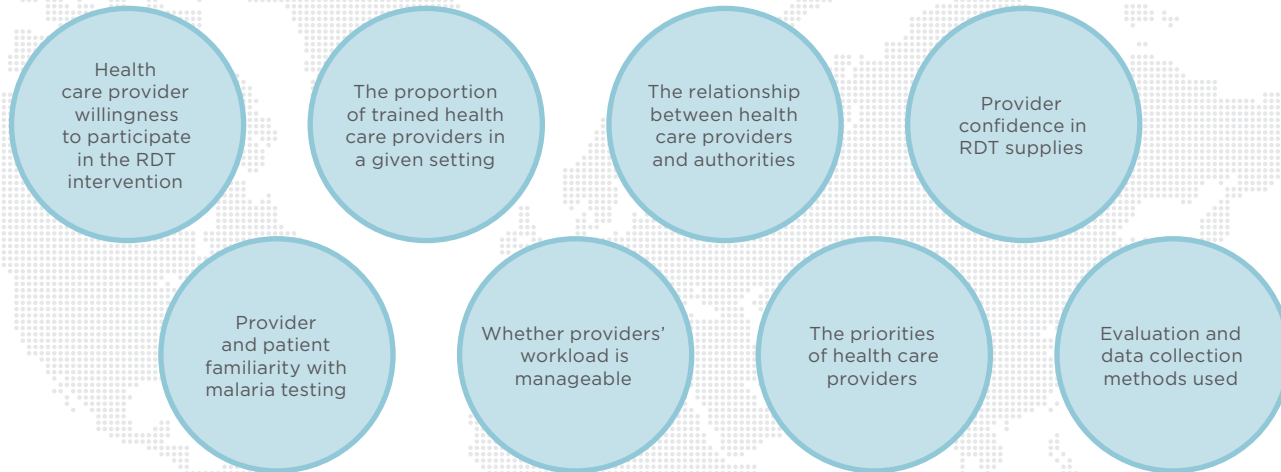


...How can we optimise the use of malaria diagnostics? For example,

What influences the uptake of RDTs?



Making rapid diagnostic tests available is just one part of effective testing and treating strategies. Other considerations, to encourage appropriate use by health care providers and patients, include:



Our research showed that all these factors influence RDT uptake.



www.actconsortium.org/diagnosis



Do health providers prescribe according to RDT results?



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?



Test result is **negative**, but patient **RECEIVES** an ACT

How willing were providers to participate in the RDT intervention?

Did proportions of positive and negative RDT results fit with expectations?

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)

www.actconsortium.org/REACTCameroon



SEEKING HEALTH CARE ASSESSMENT TREATMENT OUTCOME



... the HEALTH CARE SYSTEM and the PATIENT

What are the effects of RDTs on...



On the other hand...

A 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)

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

A No evidence of difference in patient-reported health outcomes (typically asked at day 14), regardless of RDT availability

A In many cases, providers prescribe more antibiotics when RDTs are available - especially when test results are negative

A In some cases patients continue to "shop around" for further care, particularly when RDTs are negative

A Impact on economic costs and household finances are mixed

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



What else happens when RDTs are introduced?



SEEKING HEALTH CARE ASSESSMENT TREATMENT OUTCOME

Wider consequences of RDT introduction should be considered:

Patients' treatment seeking behaviour may change

Quality assurance and general standards of care in the private sector

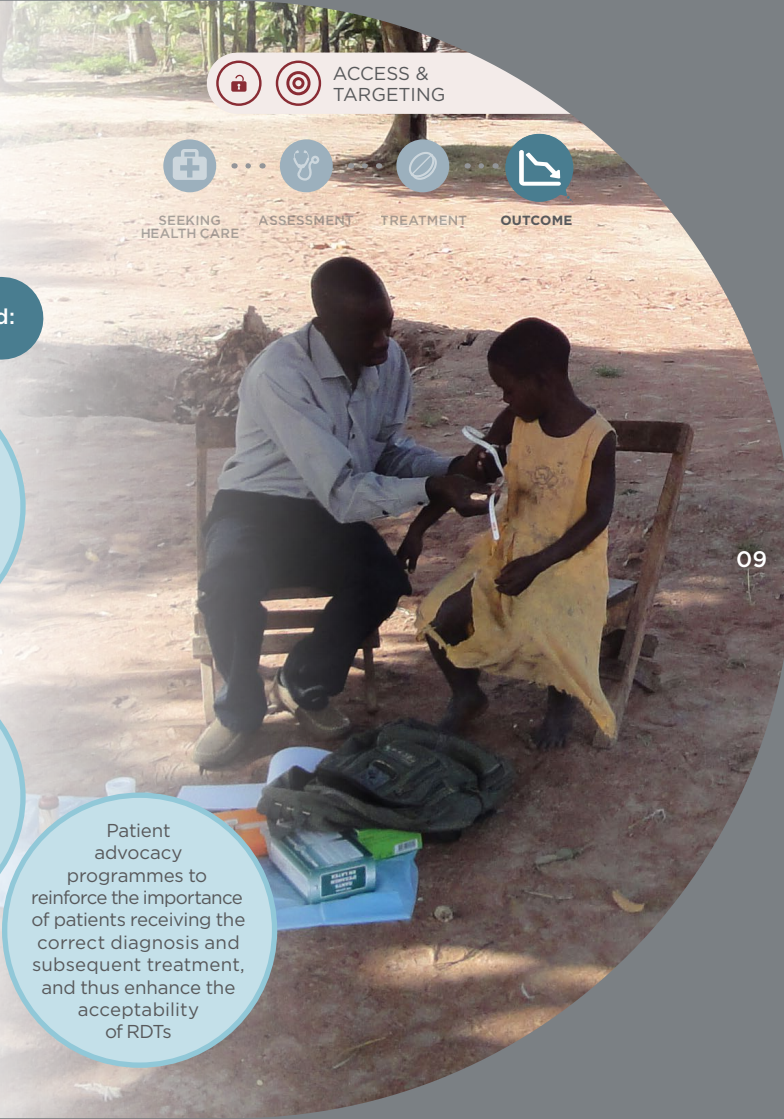
Establishing clear referral policies, so patients are able to access the care they need

Guidelines for the management of patients with a negative RDT need to be developed and implemented

Increased need for other treatments, including antipyretics, antibiotics, and other antimicrobials, with implications for the supply chain

A system to capture patient data to help quantify the success of any public health interventions and identify resurgence

Patient advocacy programmes to reinforce the importance of patients receiving the correct diagnosis and subsequent treatment, and thus enhance the acceptability of RDTs





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

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.

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?



SEEKING
HEALTH CARE



ASSESSMENT



TREATMENT



OUTCOME

- In general, our evidence does not show that introducing RDTs is beneficial to individual health outcomes; but it also does not appear to be harmful

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?

- Nonetheless, we are also aware of differences in the performance and accuracy of RDTs

NEW QUESTION

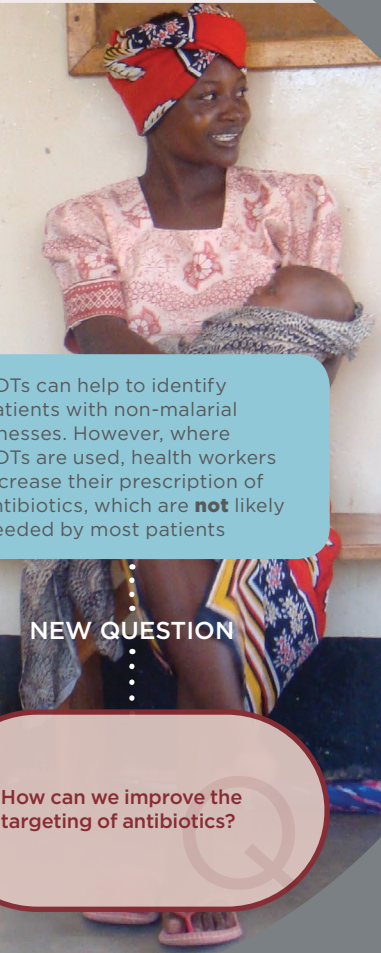
What are the longer term implications of varied performance of RDTs?



- 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

How can we improve the targeting of antibiotics?





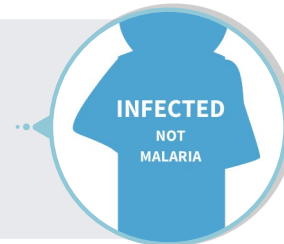
If it's not malaria, what is it?

A



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 tonsillitis, ear infection and urinary tract infection (UTI)

Health worker, Zanzibar



- 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/



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/RDTZanzibar



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.



1 2

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)

1 2

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

NEW QUESTION

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.wwarn.org/surveyor/NMFI/index.html



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

www.actconsortium.org/PRIME



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

www.actconsortium.org/RDThomemanagement



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

www.actconsortium.org/RDTdrugshops



UGANDA





RDT implementation across 3 health care sectors:

Examples and broader findings from our studies



Public Health Facilities

- A randomised study in Tanzania evaluated alternative approaches to RDT introduction and training, with the goal of improving adherence to Tanzania's national guidelines for ACT use
- Ranged from basic training only for health workers, to more intensive messages and supervision for health workers, to sending additional educational messages to the community

CONCLUSIONS

- Comparing findings of this study with a previous study in Tanzania suggests that over-use of malaria drugs may reduce over time, perhaps as familiarity/experience with RDTs grows
- Training, emphasising learning through experience and reflection, as well as motivational SMS to health workers can improve prescribing practices in some contexts
- Providing explanations about testing for patients may improve health workers' use of RDTs and further encourage adherence to RDT results

www.actconsortium.org/TACT



Community Health Workers (CHW)

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

CONCLUSIONS

- CHWs in Afghanistan and in Uganda 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

www.actconsortium.org/CHWs



Private Health Care Sectors

- 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

www.actconsortium.org/privatesector



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

Recognising this, in 2013 ACT Consortium members and partners conducted a systematic review of available evidence.

NEW QUESTION

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 “real-world” use?



All medicines have benefits and risks. Antimalarials, like most medicines, are evaluated for safety in clinical trials

They then go on the market for health care providers to treat patients. ACTs were widely introduced in Africa after 2005. Data on their use in ‘real life’ is limited

After medicines go on the market, they still need to be monitored for adverse events to detect those which may be rare but potentially serious and related to the medicine

- Adverse events may or may not be caused by a medicine
- A media story or a village rumour about experiences with antimalarials could lead to public concern
- People may decide not to take the medicine, or do not take the correct dose, causing treatment failures

How can we collect and monitor safety data in ‘real life’ environments?

Establishing whether a medicine has a good safety profile often requires different research methods and large sample sizes

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

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. We also investigated how the methods used to collect data influenced our findings

Our centralised antimalarial safety database in the UK monitors the data for potential safety issues. We have not identified new safety concerns relating to ACTs. However, monitoring is ongoing



Our data collection forms are available to anyone conducting drug safety assessments and surveillance. The forms have been developed for use by health workers with or without formal clinical training. Our drug safety database is also available for reference and use.

www.actconsortium.org/safety



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

- 838 children aged <5 years
- Followed over time for episodes of fever and repeatedly treated with the same ACT when they had malaria

Repeated use of ACTs did not cause serious adverse events

www.actconsortium.org/ACTia



ACTs in people living with HIV

One study in **Tanzania** and two in **South Africa** assessed whether specific HIV and malaria medicines interact when taken simultaneously

- 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

The observed drug interactions were not found to be clinically important

www.actconsortium.org/InterACT

www.actconsortium.org/SEACAT



Further work on this area, especially in areas of lower malaria transmission and immunity, will also be valuable.



What is the quality of ACTs in the market?

A

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

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

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.



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.

Counterfeit

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



www.actconsortium.org/drugquality

www.actconsortium.org/antimalarials

Sampling medicines representatively is a challenge

Samples 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.



Mystery shoppers: Actors pretended to be patients with malaria or their carers, and bought any medicines offered to them



REPRESENTATIVE



Overt sampling: Researchers told vendors that they were going to analyse the quality of their medicines

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

NEW QUESTION

How can we move from data in six countries to ongoing surveillance of drug quality?



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.





What did we learn from developing our projects?



All public health interventions are complex, with multiple, interconnected components

Little attention has been paid to the process of developing such interventions, and how their different components are expected to work together.



We worked with multidisciplinary teams to design and evaluate interventions on malaria case management, including why they did or did not work.



Guidance notes on qualitative research methods, health economics and RDT programme evaluation, as well as training manuals used in the ACT Consortium studies, are available on our website.



www.actconsortium.org/resources



We encourage investigators and implementers to report the **processes of designing interventions**, as well as the way the intervention is finally delivered.

This promotes clear understanding of how to assess the internal validity of findings, and the potential for transferring an intervention to other contexts — as well as preventing repeated mistakes and recreating interventions that already exist or that may have already proven unsuccessful.



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.

The ACT Consortium Directorate

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*The ACT Consortium works with many other partner institutions worldwide

actconsortium.org