SURE Rapid Response

What is the appropriate malaria treatment for a low income endemic country like Uganda?

May 2010

This rapid response was prepared by the Uganda country node of the Regional East African Community Health (REACH) Policy Initiative.

Key messages

- The WHO recommends the use of Artemisinin-based combination therapies (ACTs) in order to ensure high cure rates of *Plasmodium falciparum* malaria and to reduce the spread of drug resistance.
- ACTs are now generally considered the best current treatment for uncomplicated falciparum malaria in both adults and children
- Care should be taken that Artemisinin and its derivatives are not used as monotherapy.
- For severe or complicated malaria in children and adults, parenteral artesunate is recommended with Quinine as an acceptable alternative if parenteral artesunate is not available.
- Malaria in pregnancy: 1st trimester - quinine plus clindamycin to be given for 7 days with an ACT indicated only if this it is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails
- Lactating women should receive standard antimalarial treatment (including ACTs) except for dapsone, primaquine and tetracyclines.
- While patients of sickle cell disease benefit from the standard treatment of malaria, it is beneficial for them to receive routine malaria chemoprophylaxis in areas where malaria is endemic.
- Several combinations of chemoprophylaxis including atovaquone-proguanil, are recommended for travellers from non-malaria endemic regions.

Who requested this rapid response?

This document was prepared in response to a specific question from a policy maker in Uganda.

! This rapid response includes:

- Key findings from research
- Considerations about the relevance of this research for health system decisions in Uganda

X Not included:

- Recommendations
- Detailed descriptions

What is SURE Rapid Response?

SURE Rapid Responses address the needs of policymakers and managers for research evidence that has been appraised and contextualised in a matter of hours or days, if it is going to be of value to them. The Responses address questions about arrangements for organising, financing and governing health systems, and strategies for implementing changes.

What is SURE?

SURE – Supporting the Use of Research Evidence (SURE) for policy in African health systems - is a collaborative project that builds on and supports the Evidence-Informed Policy Network (EVIPNet) in Africa and the Regional East African Community Health (REACH) Policy Initiative (see back page). SURE is funded by the European Commission's 7th Framework Programme.
www.evipnet.org/sure

Glossary

of terms used in this report:
www.evipnet.org/sure/rr/glossary

Background

Treatment of malaria in endemic areas which are also usually low income countries has been partially complicated by increasing resistance to anti-malarial medicines and access to the medicines both physically and financially. Despite this, the Government of Uganda is committed to providing universal access to treatment for the population for malaria as stipulated in the goals of the Uganda National Malaria Control Plan and Strategy (2009/10-2014/15). This strategy is based on the principles and aims of the global Roll Back Malaria partnership, the Abuja Declaration, and the Millennium Development Goals, and the World Health Organization recommendations (WHO).

WHO has made guidelines (and recently modified these) for the treatment of malaria for different groups basing on research evidence from different areas of the world. This paper will use the WHO guidelines to outline the appropriate treatment for malaria in a low income endemic country like Uganda. Focus will be on malaria caused by *Plasmodium falciparum* species.

Summary of findings

WHO recommendations

The World Health Organization recommends the use of Artemisinin-based combination therapies (ACTs) so as to ensure high cure rates of *Plasmodium falciparum* malaria infections and to reduce the spread of drug resistance.

Uncomplicated malaria

ACTs are now generally considered the best current treatment for uncomplicated falciparum malaria. The following ACTs are recommended:

artemether plus lumefantrine, artesunate plus amodiaquine, artesunate

How this Response was prepared

After clarifying the question being asked, we searched for systematic reviews, local or national evidence from Uganda, and other relevant research. The methods used by the SURE Rapid Response Service to find, select and assess research evidence are described here:

www.evipnet.org/sure/rr/methods

What the quality of evidence (GRADE) means

The quality of the evidence is a judgement about the extent to which we can be confident that the findings of the research are correct. These judgements are made using the GRADE framework, and are provided for each outcome. The judgements are based on the type of study design (randomised trials versus observational studies), the risk of bias, the consistency of the results across studies, and the precision of the overall findings across studies. For each outcome, the quality of the evidence is rated as high, moderate, low or very low using the definitions below.

⊕⊕⊕⊕
High: We are confident that the true effect lies close to what was found in the research.

⊕⊕⊕◯
Moderate: The true effect is likely to be close to what was found, but there is a possibility that it is substantially different.

⊕⊕◯◯
Low: The true effect may be substantially different from what was found.

⊕◯◯◯
Very low: We are very uncertain about the effect.

For more information about GRADE:

www.evipnet.org/sure/rr/grade

plus mefloquine, artesunate plus sulfadoxine-pyrimethamine.

The choice is based on the level of resistance of the second drug in the combination.

It is essential that healthcare providers and policymakers ensure that Artemisinin and its derivatives are not used as monotherapy.

Below are two examples of summaries of systematic reviews of ACT based drug combinations used for malaria treatment, that is artemether plus lumefantrine (AL) and dihydroartemisinin plus piperaquine (DHA+PPQ), both compared to amodiaquine plus sulfadoxine-pyrimethamine combination.

Is AL superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa?

Patients or population: Adults and children with acute uncomplicated malaria with asexual P. falciparum

Settings: Sub-Saharan Africa

Intervention: Artemether plus lumefantrine combination

Comparison: Amodiaquine plus sulfadoxine-pyrimethamine

Outcomes	**Impact**			**Number of studies**	**Quality of evidence**
	AL	**AQ + SP**	**Absolute change**		
Total failure by day 28 PCR adjusted	17 per 1000 people	146 per 1000 people	129 people fewer per 1000	3	+++ Moderate
Total failure by day 28 PCR unadjusted	147 per 1000 people	410 per 1000 people	263 people fewer per 1000	4	+++ Moderate
Gametocyte carriage day 14	11 per 1000 people	25 per 1000 people	14 people fewer per 1000	4	+ Low
Serious adverse events	12 per 1000 people	13 per 1000 people	1 person less per 1000	3	+ Low

Is DHA+PPQ superior to AQ+SP for treating uncomplicated *P. falciparum* malaria in Africa?

Patients or population: Adults and children with acute uncomplicated malaria with asexual P. falciparum

Settings: Sub-Saharan Africa

Intervention: Dihydroartemisinin plus piperaquine combination

Comparison: Amodiaquine plus sulfadoxine-pyrimethamine

Outcome	**Impact**			**Number of studies**	**Quality of Evidence**
	DHA+PPQ	**AQ+SP**	**Absolute change**		

Total failure by day 28, PCR adjusted	30 per 1000 people	110 per 1000 people	80 people fewer per 1000	2	**+++** Moderate
Total failure by day 28, PCR unadjusted	60 per 1000 people	180 per 1000 people	120 people fewer per 1000	2	**+++** Moderate
Gametocyte development (in those negative at baseline)	30 per 1000 people	50 per 1000 people	20 people fewer per 1000	1	**+** Very low
Serious adverse events including deaths	0 per 1000 people	0 per 1000 people	Not estimatable	1	**+** Very low

For second-line antimalarial treatment, the following is recommended:
Any alternative ACT known to be effective in Uganda and the choice may include;

- Artesunate plus tetracycline or doxycycline or clindamycin; any of these combinations to be given for 7 days;
- Quinine plus tetracycline or doxycycline or clindamycin; any of these combinations should be given for 7 days.

Severe malaria

For severe or complicated malaria in adults, according to WHO guidelines, Intravenous IV or Intramuscular IM artesunate is recommended; (IV) artesunate should be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults. Quinine has been an acceptable alternative if parenteral artesunate is not available, however a recent study still under review shows that use of Quinine as monotherapy for second-line treatment is worse than using Artemether-Lumefantrine combination. For children (especially in the malaria endemic areas like Uganda) WHO recommends the following antimalarial medicines: parenteral artesunate preferably IV; quinine (IV infusion or divided IM injection); artemether IM (should only be used if none of the alternatives are available as its absorption may be inconsistent).
It is recommended that if parenteral anti-malarials are used in the treatment of severe malaria they should be given for a minimum of 24 hours once started (irrespective of the patient's ability to take oral medication earlier) and, thereafter, complete treatment by giving a complete course of an ACT; or artesunate plus clindamycin or doxycycline; or quinine plus clindamycin or doxycycline. Below is a systematic review comparing artesunate and quinine for the treatment of severe malaria in endemic areas.

Is artesunate superior to quinine for treating severe malaria in endemic areas?					
Patients or population: Adults and children with severe malaria **Settings:** Africa **Intervention**: Artesunate **Comparison:** Quinine					
Outcomes	**Impact**			**Number of studies**	**Quality of evidence**
	Artesunate	**Quinine**	**Absolute change**		
Death	13 per 100 people	22 per 100 people	9 people fewer per 100	6	++++ High
Neurological sequelae at discharge	10 per 1000 people	5 per 1000 people	5 people more per 1000	2	+ Very low
Time to hospital discharge	59	54		1	+ Very low
Hypoglycemia routine monitoring	12 per 100 people	27 per 100 people	15 people fewer per 100 people	2	++ Low

If complete treatment of the severe or complicated malaria is not possible at the given facility, it is recommended that patients be given pre-referral treatment and referred immediately to an appropriate facility for further management. The following are recommended as options for pre-referral treatment: rectal artesunate, quinine IM, artesunate IM, artemether IM.

Special groups

Malaria in pregnancy

Although it is acknowledged that women are more vulnerable to malaria during pregnancy, and that malaria may have harmful effects on the unborn and eventually born baby, consistent research regarding the benefits and risks of treatments for malaria in pregnancy is scarce. Furthermore choices of treatment are becoming more restricted because the malaria parasite is developing resistance to existing drugs and due to concerns about whether drugs may harm the baby. The WHO recommends the following treatments during pregnancy.

1st trimester:

- Quinine plus clindamycin to be given for 7 days (artesunate plus clindamycin for 7 days is indicated if this treatment fails);
- An ACT is indicated only if this is the only treatment immediately available, or if treatment with 7-day quinine plus clindamycin fails or uncertainty of compliance with a 7-day treatment.

Second and third trimesters:

ACTs known to be effective in the country/region or artesunate plus clindamycin are recommended and these should be given for 7 days, or quinine plus clindamycin given for 7 days. Below is a table showing several alternative treatments for malaria treatment in preganancy and the findings from systematic studies comparing them.

Alternative treatments	Findings
Artesunate plus atovaquone-proguanil versus quinine	• Fewer treatment failures by day 63 in artesunate plus atovaquone-proguanil group • Median parasite clearance time was shorter in the artesunate plus atovaquone-proguanil group than in the quinine group • Anaemia not statistically significantly different in the two groups
Artesunate plus mefloquine versus quinine	• Fewer treatment failures at day 63 with artesunate plus mefloquine • Performance at day 28: approximately 97%of the artesunate plus mefloquine group and 88% of the quinine group were without parasite recrudescence; • fever and parasite clearance times shorter with artesunate plus mefloquine (4.47 days and 3.46 days, respectively) than quinine (8.04 days and 7.03 days) • Anaemia on admission was similar in both treatment groups in but by day seven more women in the artesunate plus mefloquine group had anaemia
Artesunate plus sulfadoxine-pyrimethamine versus azithromycin plus sulfadoxine-pyrimethamine	• The proportion of treatment failures at delivery or day 40 was similar in both treatment groups
Artesunate plus sulfadoxine-pyrimethamine versus sulfadoxine-pyrimethamine	• Treatment failure at delivery (or day 40) was statistically significantly reduced by adding artesunate to sulfadoxinepyrimethamine • Maternal anaemia was similar in both groups
Quinine plus spiramycin versus quinine	• Equal distribution of treatment failures between the two groups by day 28. • No statistically significant difference for mean parasite clearance time in this small trial
Artesunate versus quinine plus clindamycin	• More treatment failures reported at 48 hours in the quinine plus clindamycin group but by day 42 all women in both treatment groups were cured. • The mean parasite clearance time was shorter in the artesunate group than the quinine plus clindamycin group • Median haematocrit was similar in the two groups on admission but

	by day seven there were more participants with anaemia in the artesunate group; • his difference did not persist at later time points.
Artemether plus mefloquine versus artemether	• All women treated with artemether plus mefloquine were aparasitaemic on day 28, and those treated with artemether were aparasitaemic on day 14 • The mean fever clearance time was similar in both groups as was the mean parasite clearance time • Mean haematocrit did not change dramatically in either group between the first day of treatment and day seven.
Amodiaquine plus sulfadoxine-pyrimethamine versus chloroquine	• Fewer treatment failures at day 28 with amodiaquine plus sulfadoxine-pyrimethamine
Amodiaquine versus chloroquine	• Fewer treatment failures at day 28 with amodiaquine
Azithromycin plus sulfadoxine-pyrimethamine versus sulfadoxine-pyrimethamine	• Treatment failure at delivery (or day 40) was statistically significantly reduced by adding azithromycin to sulfadoxinepyrimethamine • Maternal anaemia was similar in both groups
Sulfadoxine-pyrimethamine versus chloroquine	• There was no statistically significant difference in treatment failure in either trial at day 14 • At day 28 there were fewer treatment failures with sulfadoxinepyrimethamine
Chloroquine plus clindamycin (for three or five days) versus chloroquine	• At day 14 there were more treatment failures in the chloroquine group than in the chloroquine plus clindamycin groups, but this difference was not statistically significant • All treatment failures were cured with chloroquine plus clindamycin.

Lactating mothers:

Lactating mothers should receive standard antimalarial treatment (including ACTs) except for dapsone, primaquine and tetracyclines.

Sicklers

For treatment in sickle cell disease, sicklers benefit from the standard treatment of malaria. However in addition it is recommended and is beneficial for this group of patients to receive routine malaria chemoprophylaxis in areas where malaria is endemic.

Malaria chemoprophylaxis in sickle cell disease			
Patients or population: Patients (adults and children) with sickle cell disease **Settings:** Malaria endemic regions (Sub-Saharan Africa) **Intervention:** Malaria chemoprophylaxis given for a minimum of 3 months **Comparison:** Placebo			
Outcomes	Impact	Number of studies	Quality of evidence

	Malaria chemoprophylaxis	Placebo	Absolute change		
Sickle cell painful crises	29 per 1000 people	172 per 1000 people	143 people fewer per1000	1	+++ Moderate
Blood transfusion (severe anemia)	44 per 1000 people	276 per 1000 people	232 people fewer per 1000	1	+++ Moderate
Malaria infection	347 per 1000 people	739 per 1000 people	392 people fewer per 1000	2	++ Low
Hospital admissions	103 per 1000 people	379 per 1000 people	276 people fewer per 1000	1	+++ Moderate

Non-immune travellers

For travellers from non-malaria endemic regions and returning to non-endemic countries the following combinations are recommended by WHO:

- atovaquone-proguanil;
- artemether-lumefantrine;
- quinine plus doxycycline or clindamycin.

Drugs for preventing malaria in travelers: Atovaquone-proguanil compared to Mefloquine for Non immune child and adult travellers

Patient or population: Non immune child and adult travellers
Settings: International travel
Intervention: Atovaquone-proguanil
Comparison: Mefloquine

Outcomes	**Impact**			**Number of studies**	**Quality of evidence**
	Mefloquine	**Atovaquone-proguanil**	**Relative (absolute) change**		
Any adverse effect	422 per 1000	302 per 1000	40% reduction 120 events less per 1000	1	++ Low
GI adverse effect	288 per 1000	156 per 1000	84.6% reduction 132 events less per 1000	1	++ Low
Neuropsychiatric adverse event	771 per 1000	663 per 1000	16.3% reduction 108 events less per 1000	1	+++ Moderate
Neuropsychiatric adverse effect	288 per 1000	141 per 1000	100% reduction 147 events less per 1000	1	++ Low
Total mood		7.2 lower		1	++

disturbance scores	Low

Conclusion

To treat malaria effectively and avoid drug resistance, ACTs are the current recommended treatment in both uncomplicated and complicated malaria, a choice of the combination (non-artemisinin) drug depending on the sensitivity patterns in the region. In addition special groups like pregnant mothers, sicklers and travellers do benefit from a given combination of drugs too. It is crucial that the treatment chosen, ACT or otherwise be used in combination and not as monotherapy.

References

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This summary was prepared by
Dr. Rhona Mijumbi, Supporting Use of Research Evidence for Policy (SURE Project), Office of the Principal, College of Health Sciences, Makerere University, New Mulago Hospital Complex, Administration Building, 2nd Floor, P.O Box 7072, Kampala, Uganda

Conflicts of interest

None known.

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For more information contact

Rhona Mijumbi, mijumbi@yahoo.com