WHO Malaria Guidelines: Treatment of Malaria

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Dr. Peter OLUMESE,
Global Malaria Programme
WHO, Geneva, Switzerland.

Global **Malaria** Programme

World Health Organization

Malaria Diagnosis

5.1 Diagnosing malaria

Good practice statement

Diagnosing malaria (2015)

All cases of suspected malaria should have a parasitological test (microscopy or RDT) to confirm the diagnosis.

Both microscopy and RDTs should be supported by a quality assurance programme.

- The results of parasitological diagnosis should be available within less than two hours of the patient presenting. In the absence or delay, patients with suspected severe malaria, and other high-risk groups, should be treated on clinical grounds.

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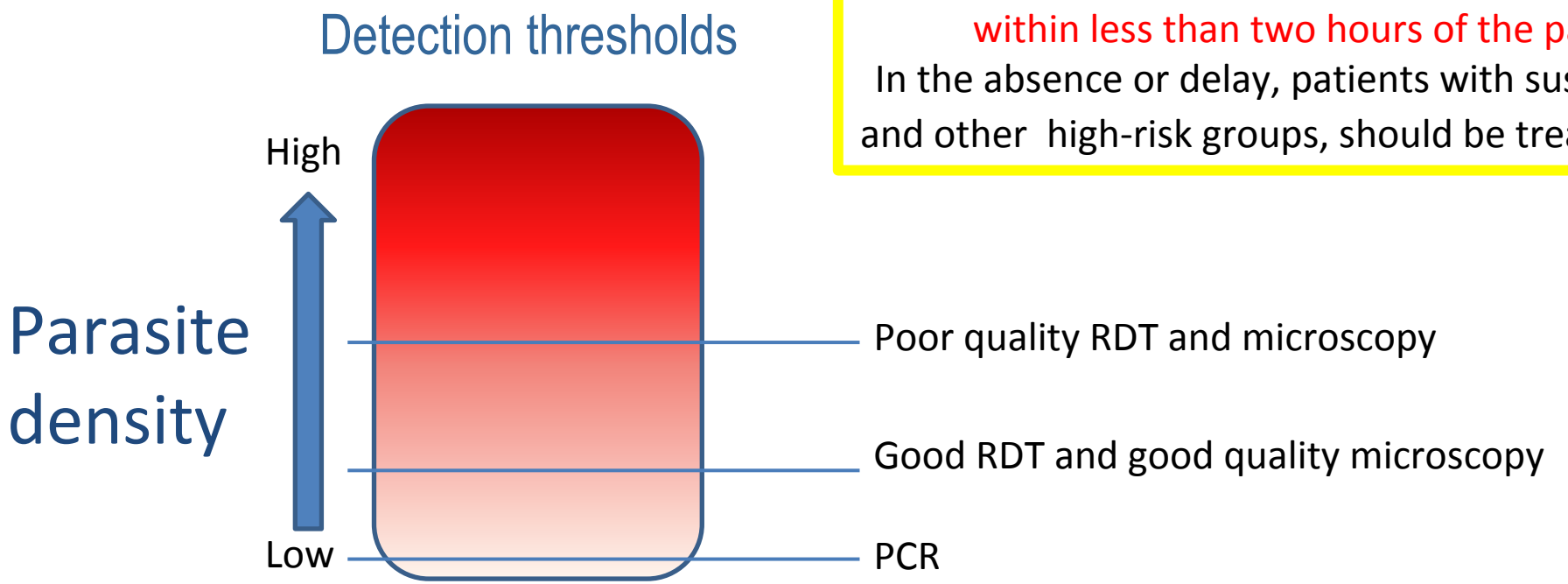


Selection of malaria diagnostic test

Criteria	Clinical settings	RDT	Microscopy
Parasite density	Uncomplicated malaria	YES	YES
	Severe malaria at admission	Not alone	YES
	Follow-up of hospitalized severe malaria	NO	YES
Antigen persistence	Treatment failure of confirmed malaria	NO	YES
	Incomplete antimalarial treatment and/or unconfirmed malaria diagnosis	YES	YES
Electricity supply	Hospitals and health centers	YES	YES
	Health Posts and CHWs	YES	NO
Test duration	Heavy patient load	YES	Not alone
Technical skills	Limited training and supervision	YES	NO

Treatment of uncomplicated falciparum malaria

5.2.1 Treating uncomplicated malaria

5.2.1.1 Artemisinin-based combination therapy

Strong recommendation for , High certainty evidence

Artemisinin-based combination therapy (2015)

Children and adults with uncomplicated *P. falciparum* malaria should be treated with one of the following ACTs*:

- artemether-lumefantrine (AL)
- artesunate-amodiaquine (AS+AQ)
- artesunate-mefloquine (ASMQ)
- dihydroartemisinin-piperaquine (DHAP)
- artesunate + sulfadoxine-pyrimethamine (AS+SP)
- artesunate-pyronaridine (ASPY) (2022)

*Artesunate + sulfadoxine-pyrimethamine and artesunate-pyronaridine are not recommended for use in the first trimester of pregnancy. For details of treatment using ACTs in the first trimester of pregnancy, see 5.2.1.4.1 below.

Treatment of uncomplicated falciparum malaria

5.2.1.1.1 Duration of treatment

Strong recommendation for , High certainty evidence

Duration of ACT treatment (2015)

ACT regimens should provide 3 days' treatment with an artemisinin derivative.

5.2.1.3 Reducing the transmissibility of treated P. falciparum infections in areas of low-intensity transmission

Strong recommendation for , Low certainty evidence

Reducing the transmissibility of treated *P. falciparum* infections (2015)

In low-transmission areas, a single dose of 0.25 mg/kg bw primaquine should be given with an ACT to patients with *P. falciparum* malaria (except pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months) to reduce transmission. G6PD testing is not required.

Treatment of Malaria in special populations : 1st trimester of pregnancy

5.2.1.4.1 Pregnant and lactating women

Strong recommendation for , Low certainty evidence

Treatment in the first trimester of pregnancy (2022)

Pregnant women with uncomplicated *P. falciparum* malaria should be treated with artemether-lumefantrine during the first trimester.

Remark:

- Limited exposures to other ACTs (artesunate-amodiaquine, artesunate-mefloquine and dihydroartemisinin-piperaquine) suggest that the current evidence is insufficient to make a recommendation for routine use of these other ACTs in the first trimester of pregnancy. However, consistent with the previous WHO recommendation that provided for limited use of ACTs if the first-line recommended medicine was not available, these other ACTs may be considered for use where artemether-lumefantrine is not a recommended ACT for uncomplicated malaria or is not available, given the demonstrated poorer outcomes of quinine treatment, along with the challenges of adherence to a seven-day course of treatment.
- Antifolates are contraindicated in the first trimester of pregnancy. Therefore, ACTs containing sulfadoxine-pyrimethamine are contraindicated during the first trimester of pregnancy.
- There is currently no documented record of the use of artesunate-pyronaridine during the first trimester of pregnancy.

Treatment of falciparum Malaria in special populations

- Treat infants weighing less than 5 kg with an ACT dosed at the same mg/kg target as for children weighing 5 kg
- In people who have HIV/AIDS avoid AS+SP if on treatment with co-trimoxazole and avoid AS+AQ if on treatment with efavirenz.
- Treat travelers returning to non-endemic settings with uncomplicated *P. falciparum* malaria with an ACT

Treatment of uncomplicated non-falciparum Malaria

Strong recommendation for , High certainty evidence

Blood stage infection (2015)

In areas with chloroquine-susceptible infections, adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria should be treated with either an ACT or chloroquine.

In areas with chloroquine-resistant infections, adults and children with uncomplicated *P. vivax*, *P. ovale*, *P. malariae* or *P. knowlesi* malaria should be treated with an ACT.

* For details of treatment using ACTs in the first trimester of pregnancy, see section 5.2.1.4.1.

Strong recommendation for , High certainty evidence

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

To prevent relapse, children and adults (except pregnant women, infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency) should be treated with a 14-day course of primaquine in all transmission settings.

PREVENTING RELAPSE: Short-course standard dose primaquine treatment

Strong recommendation for , Very low certainty evidence

Short-course standard dose primaquine treatment (2022)

To prevent relapse, an additional treatment option of using primaquine 0.5 mg/kg/day for seven days is recommended to treat *P. vivax* or *P. ovale* malaria in children and adults (except pregnant women, infants aged < 6 months, women breastfeeding infants aged < 6 months, women breastfeeding older infants unless they are known not to be G6PD deficient, and people with G6PD deficiency).

Conditional recommendation against , Very low certainty evidence

Short-course standard high-dose primaquine treatment (2022)

To prevent relapse, an additional treatment option of using primaquine 1.0 mg/kg/day for seven days to treat *P. vivax* or *P. ovale* malaria is not recommended.

PREVENTING RELAPSE: others

Conditional recommendation for , Very low certainty evidence

Preventing relapse in people with G6PD deficiency (2015)

In people with G6PD deficiency, primaquine base at 0.75 mg/kg bw once a week for 8 weeks can be given to prevent relapse, with close medical supervision for potential primaquine-induced haemolysis.

Good practice statement

Preventing relapse in *P. vivax* or *P. ovale* malaria (2015)

When G6PD status is unknown and G6PD testing is not available, a decision to prescribe primaquine should be based on an assessment of the risks and benefits of adding primaquine.

Conditional recommendation for , Moderate certainty evidence

Pregnant and breastfeeding women (2015)

In women who are pregnant or breastfeeding, weekly chemoprophylaxis with chloroquine can be given until delivery and breastfeeding are completed, then, on the basis of G6PD status, primaquine can be given to prevent future relapse.

Severe Malaria

- Therapeutic objectives
  - Main objective is to prevent the patient from dying
  - Secondary objectives are to prevent disabilities and prevention of recrudescent infection
- Death from severe malaria often occurs within hours of onset of symptoms or admission to hospital
  - Essential that therapeutic concentrations of a highly effective antimalarial are achieved as soon as possible
- Management of severe malaria comprises four main areas
  - Clinical assessment of patient
  - Specific antimalarial treatment
  - Additional treatments (managements of other complications), and
  - Supportive care

Treatment of severe malaria

5.2.2 Treating severe malaria

5.2.2.1 Artesunate

Strong recommendation for , High certainty evidence

Treating severe malaria (2015)

Adults and children with severe malaria (including infants, pregnant women in all trimesters and lactating women) should be treated with intravenous or intramuscular artesunate for at least 24 h and until they can tolerate oral medication. Once a patient has received at least 24 h of parenteral therapy and can tolerate oral therapy, treatment should be completed with 3 days of an ACT.

Strong recommendation for

Treating severe malaria in children (2015)

Children weighing < 20 kg should receive a higher dose of artesunate (3 mg/kg bw per dose) than larger children and adults (2.4 mg/kg bw per dose) to ensure equivalent exposure to the drug.

*Not evaluated using the GRADE framework; recommendation based on pharmacokinetic modelling

5.2.2.2 Parenteral alternatives when artesunate is not available

Conditional recommendation for , Low certainty evidence

Parental alternatives when artesunate is not available (2015)

If artesunate is not available, artemether should be used in preference to quinine for treating children and adults with severe malaria.

Treatment of severe malaria

5.2.2.3 Pre-referral treatment options

Strong recommendation for , Moderate certainty evidence

Pre-referral treatment options (2015)

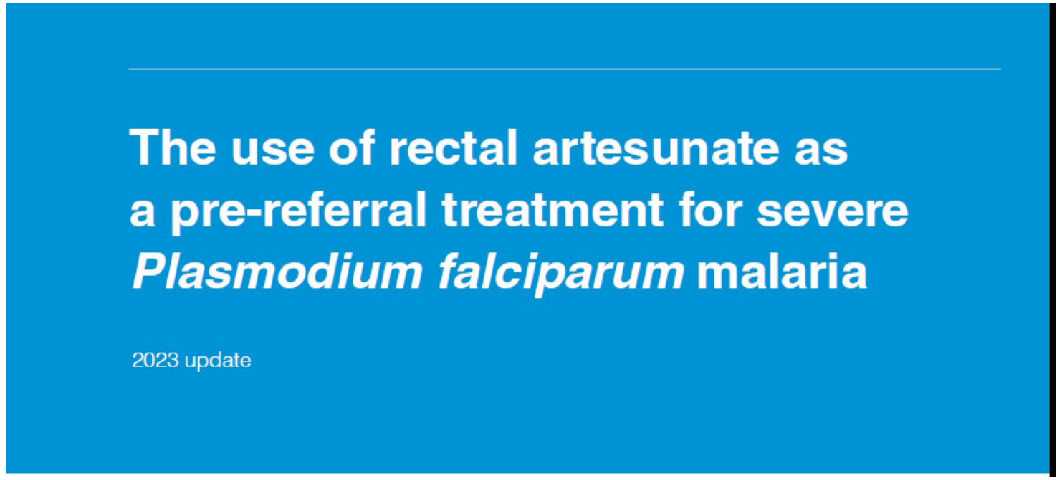
Where complete treatment of severe malaria is not possible, but injections are available, adults and children should be given a single intramuscular dose of artesunate, and referred to an appropriate facility for further care. Where intramuscular artesunate is not available, intramuscular artemether or, if that is not available, intramuscular quinine should be used.

Where intramuscular injection of artesunate is not available, children < 6 years should be treated with a single rectal dose (10mg/kg bw) of artesunate, and referred immediately to an appropriate facility for further care. Rectal artesunate should not be used in older children and adults.

WHO Information Note - 2023 update: The use of RAS as pre-referral treatment….

- In October 2022, WHO convened a technical consultation of independent experts to conduct a formal evidence review of the data from the CARAMAL project, as well as data from other studies evaluating the deployment of pre-referral RAS at programmatic level

- The outcomes of the review, including results of additional analyses undertaken by the WHO-appointed experts, form the basis of this 2023 update on the use of RAS as a pre-referral treatment for severe Plasmodium falciparum malaria.



4 July 2023
https://www.who.int/publications/i/item/9789240075375

From Efficacy to Effectiveness

- The technical review identified several issues in the design of the CARAMAL study, which have left it susceptible to several biases and made the results difficult to interpret, particularly in terms of the impact of RAS on mortality and referral completion.
  - The CARAMAL project, however, highlighted many challenges and deficiencies along the cascade of care, revealing health system weaknesses and inadequate quality of care.
- Implementation research on scaling up the use of RAS for treatment of severe malaria at the community level in Zambia showed that the CFR decreased from 3.1% to 0.1% in the two high-intensity intervention districts and from 10.7% to 1.4% in the other districts

WHO Information Note - 2023 update: The use of RAS as pre-referral treatment….

Artemisinin resistance

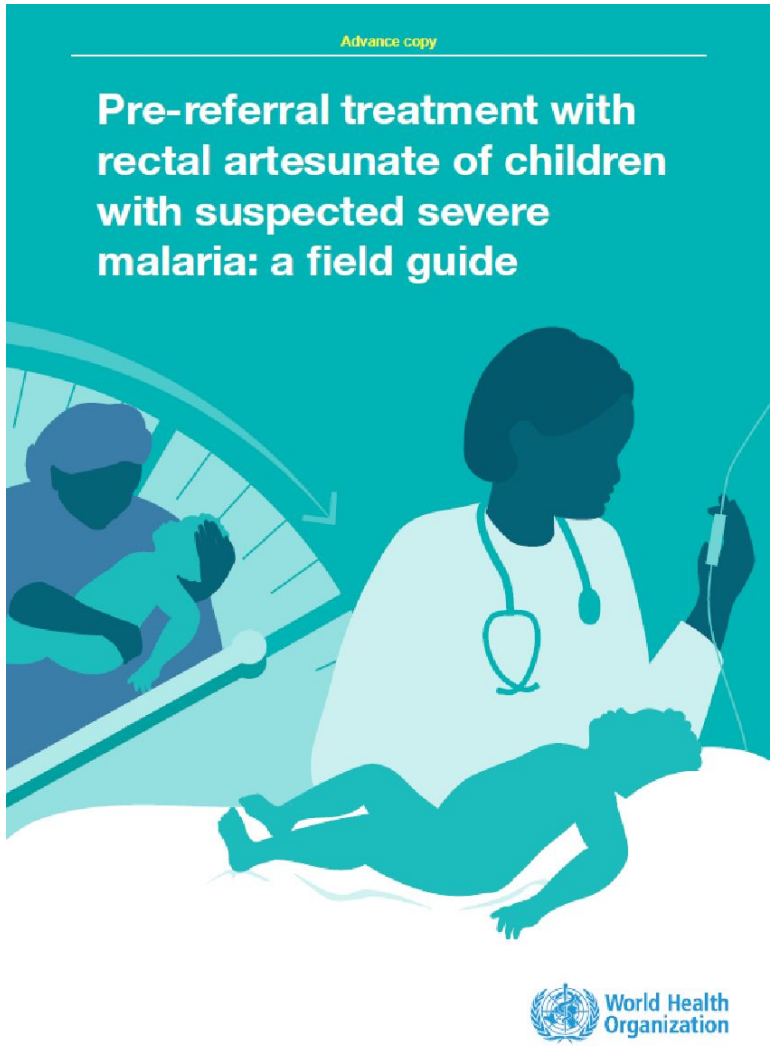
- In a sub study in Uganda, the CARAMAL project reported that the prevalence of the kelch 13 (K13) C469Y marker for partial artemisinin resistance increased at day 28 post-RAS in children who failed to complete referral treatment (20%) compared to on day 0 in children directly presenting at a referral health facility, without receiving RAS (6.2%).
  - This finding is difficult to interpret, as it was based on a relatively small number of children and convenience sampling was used.
  - K13 C469Y molecular markers for partial artemisinin resistance were present in Uganda before RAS was deployed and were widely present and increasing in the northern provinces – in some CARAMAL districts and in other districts where RAS was not deployed.
- Despite the limitations noted above, this study provides a signal that RAS alone, when not followed by referral and complete treatment with a full course of ACT, may select partial artemisinin-resistant parasites with the K13 C469Y mutation.

WHO Information Note - 2023 update: The use of RAS as pre-referral treatment….

Risk mitigation

- Countries that are already implementing or considering implementation of RAS for pre-referral treatment of severe malaria need:
  - to strengthen all aspects of the continuum of care for a severely sick child – from community health workers being adequately trained and stocked for giving RAS in the areas where it is most needed, to ensuring rapid transfer and access to referral facilities where a complete course of post-referral treatment is given following WHO recommendations for the treatment of severe malaria;
  - to ensure support for adequate supply chain management and referral systems from community health workers and health facilities to referral treatment centres, which is essential for achieving the intended impact of RAS;
  - to address barriers to referral completion, as this will improve outcomes not only for severe malaria but also for other severe diseases; and
  - to ensure effective community sensitization to increase understanding of severe malaria, its causes, how dangerous it is for children, how to recognize danger signs and the need to promptly seek care if such signs are present.

RAS as pre-referral treatment…. Implementation field guide

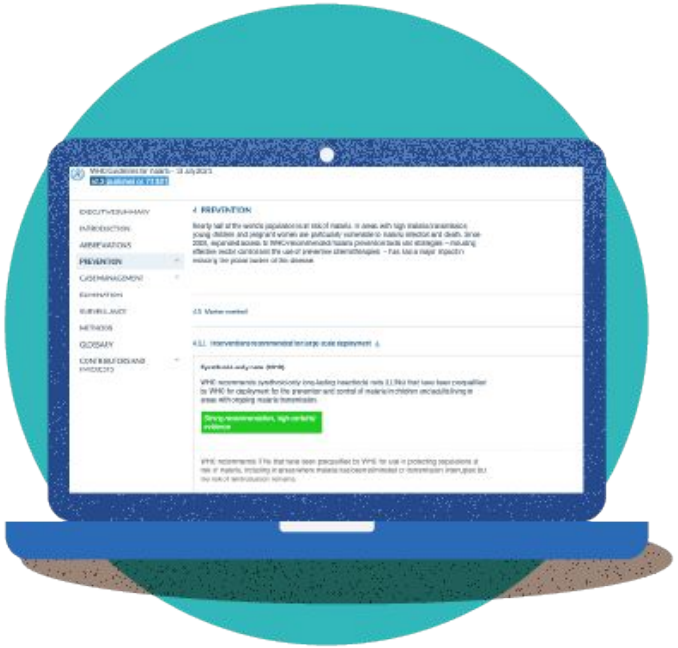


- Implementation field guide
  - The purpose of the field guide is to support the effective deployment of rectal artesunate as a pre-referral treatment of suspected severe malaria in line with the guidelines.
  - Expected date of publication: October 2023

Community Case Management of Malaria

- CCM of malaria delivered as part of integrated CCM (iCCM), which includes the treatment of pneumonia and diarrheal diseases.
- Trained community providers (CHWs, Medicine Sellers or Retailers) should be provided with:
  - Rapid Diagnostic Tests (RDTs)
  - ACTs for treatment of uncomplicated malaria.
  - Rectal artemisinin suppositories for pre-referral treatment of severe malaria.
  - Information, Education and Communication materials.
  - simple patient registers and reporting forms.

How to access WHO malaria guidance

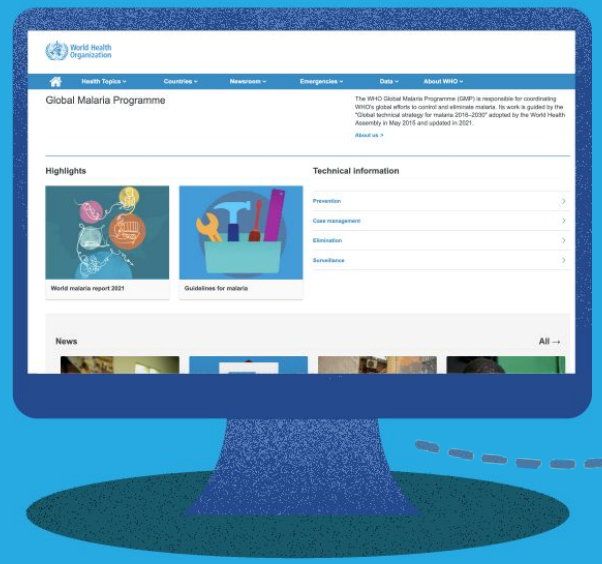


1 [WHO Global Malaria Programme website]

2 [MAGICapp]

3 [WHO Malaria Toolkit app]

Ways to access WHO malaria guidance



1

The [WHO Global Malaria Programme website](#) is the main gateway through which national malaria programmes and partners can access the most up-to-date malaria guidance.

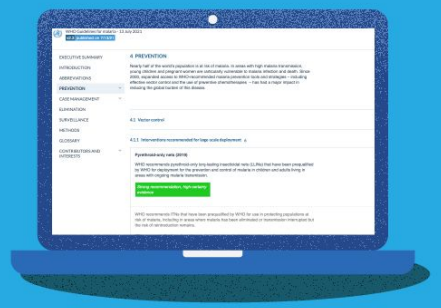
The new consolidated *[WHO Guidelines for malaria](#)* bring together all current WHO recommendations on malaria in one easy-to-navigate web-based platform.

They are a living resource that will be updated periodically as new evidence becomes available.

Ways to access WHO malaria guidance

WHO's malaria guidance can also be found on 2 digital platforms:

2



Through MAGICApp, you can access a consolidated set of all WHO malaria guidance, including:

- All official WHO recommendations
- Operational manuals
- Handbooks
- Frameworks
- And links to other resources

3

All WHO recommendations can also be accessed through an easy-to-navigate mobile "Malaria Toolkit app".

The app is available for iOS devices and Android devices.

In addition to the WHO recommendations, it provides the latest data and trends from the *World malaria report*.

Keep our eye on the prize: a world free of malaria

Thank you