WHO Malaria Technical Updates

- Case management and preventive chemotherapy

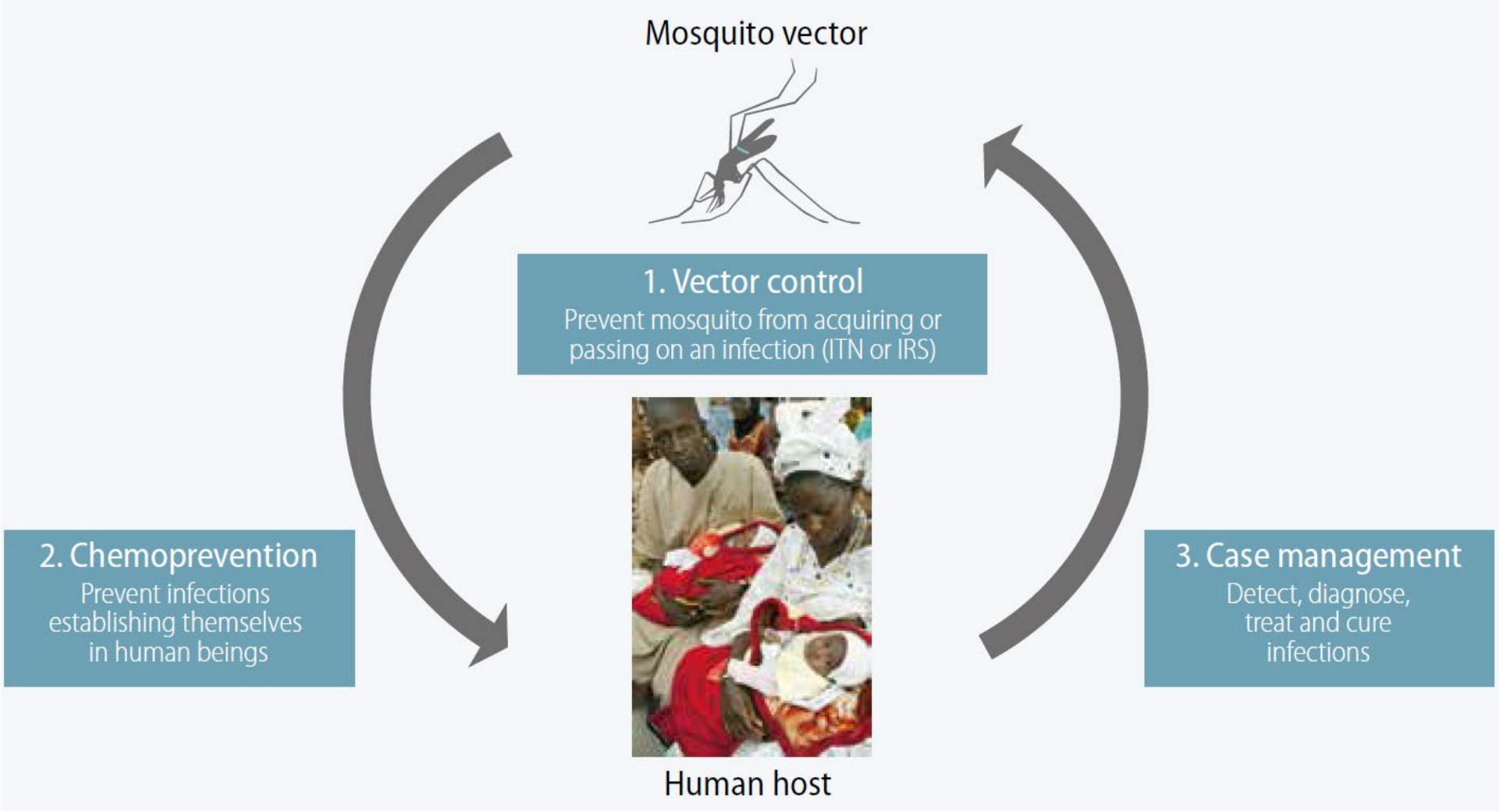
August 2023

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

Global **Malaria** Programme

World Health Organization

Main malaria prevention and treatment strategies



Key antimalarial interventions & strategies

Prevention

- Insecticide-treated mosquito nets
- Indoor Residual Spraying

Preventive Chemotherapy

- IPT in pregnancy (IPTp)
- Perennial Malaria Chemoprevention (PMC /IPTi+)
- SMC
- IPT in School Children
- Post Discharge malaria chemoprevention
- MDA

Malaria vaccine

Diagnosis & Treatment

- Parasite based diagnosis
  - Microscopy
  - Rapid Diagnostic Tests
- Artemisinin-based combination therapies (ACTs)
- Severe Malaria
  - Artesunate

Case management service delivery areas::

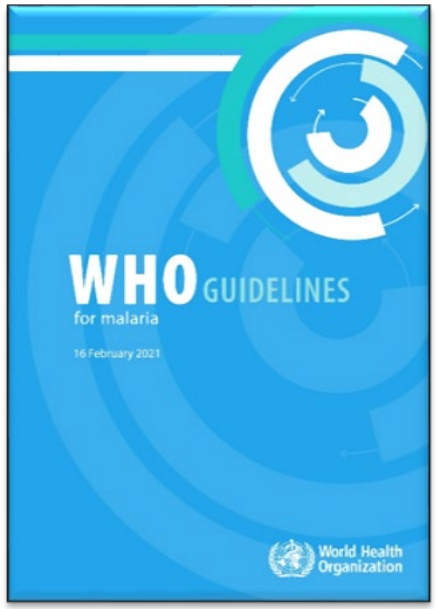
- Health facilities
- Community Case Management
- Private sector

Surveillance, M & E

- Routine HMIS
- Malaria surveillance and response systems
- Household surveys
- Health Facility Surveys

Strengthening health systems in endemic countries

Main malaria prevention and treatment strategies



- WHO Guidelines for Malaria (2021)
  - These consolidated guidelines replace 2 guideline documents on the WHO website: the Guidelines for the treatment of malaria, 3rd edition and the Guidelines for malaria vector control.
  - The sections in the WHO Guidelines for malaria includes
    - Prevention (Vector control, preventive chemotherapies and Vaccine)
    - Case Management
    - Elimination and prevention of re-introduction
    - Surveillance
  - As new evidence becomes available, the recommendations will be reviewed and updated, where appropriate, **using WHO's transparent and rigorous guideline development process.**
- Published in February 2021;
- Latest update – 14th March 2023, and will be updated on a continuing basis
- Available online: https://www.who.int/publications/i/item/guidelines-for-malaria

Malaria Case Management

Global **Malaria** Programme

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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.

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.

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: 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 a number of 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

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: The use of RAS as pre-referral treatment...

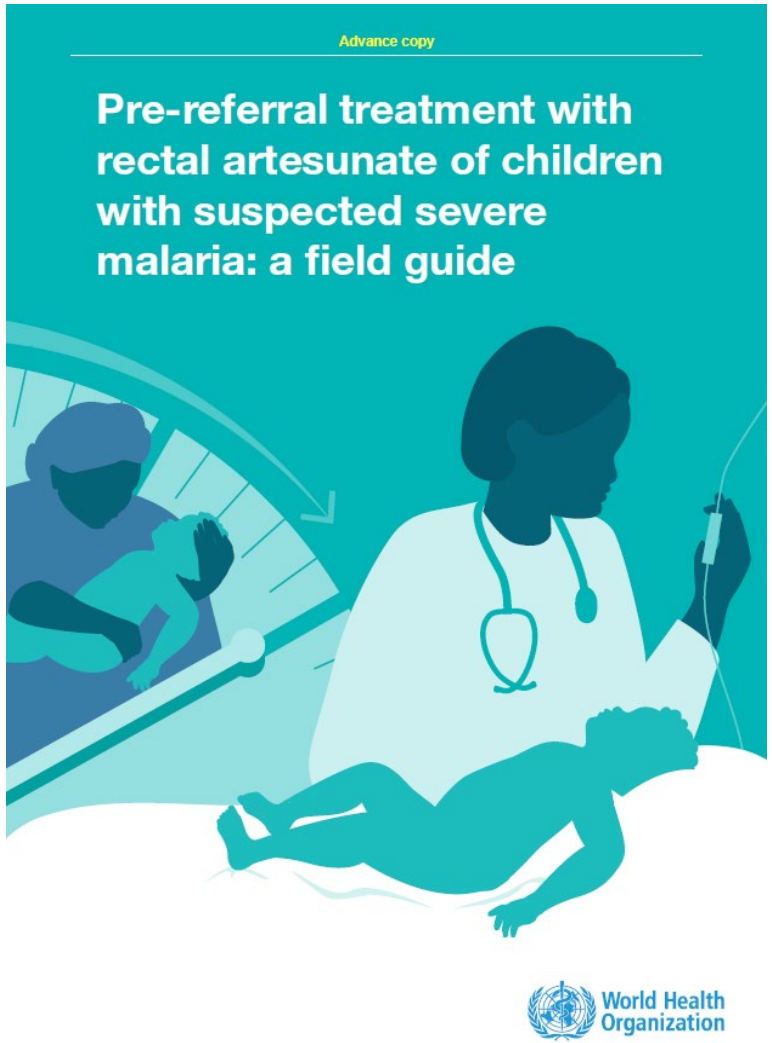
Risk mitigation

- 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.

Risk mitigation (contd)

- Malaria programmes and their partners should ensure that health providers adhere strictly to malaria treatment guidelines and make sure that caregivers of children with severe malaria are aware of the importance of completing treatment courses. Intense efforts should be made to ensure that:
  - artemisinin-based monotherapies (both rectal and parenteral) are used only for treating severe malaria cases as per WHO guidelines;
  - referral facilities treat severe malaria patients with parenteral artesunate and a full course of an effective ACT;
- Antimalarial resistance surveillance should be strengthened at the population level across Africa, and most urgently in East Africa, with:
  - prioritization of interventions to holistically address the drivers of resistance selection;
  - prompt response in line with the WHO Strategy to respond to antimalarial drug resistance in Africa when resistance is detected.

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: August 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.

Preventive Chemotherapies

Global **Malaria** Programme

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Intermittent preventive treatment of malaria in pregnancy (IPTp)

4.2.1 Intermittent preventive treatment of malaria in pregnancy (IPTp)

Strong recommendation for , Moderate certainty evidence

Intermittent preventive treatment of malaria in pregnancy (2022)

In malaria-endemic areas, pregnant women of all gravidities should be given antimalarial medicine at predetermined intervals to reduce disease burden in pregnancy and adverse pregnancy and birth outcomes.

- Antenatal care (ANC) contacts remain an important platform for delivering IPTp. Where inequities in ANC service and reach exist, other delivery methods (such as the use of community health workers) may be explored, ensuring that ANC attendance is maintained and underlying inequities in ANC delivery are addressed.

Perennial Malaria Chemoprevention (former IPTi)

4.2.2 Perennial malaria chemoprevention (PMC) - formerly intermittent preventive treatment of malaria in infants (IPTi)

Conditional recommendation for , Moderate certainty evidence

Perennial malaria chemoprevention (2022)

In areas of moderate to high perennial malaria transmission, children belonging to age groups at high risk of severe malaria can be given antimalarial medicines at predefined intervals to reduce disease burden.

PMC: Practical information

- Medicines for PMC should be different from that used for first-line malaria treatment.
- Evidence is limited on other medicines besides SP; including potential cumulative toxicity, efficacy, adherence to multi-day regimens, and cost-effectiveness in the context of PMC in young children.
- The EPI platform remains important for delivering PMC, especially in the first year of life, and it may be possible to make use of the EPI or other routine health visits or establish new contacts to reach children over 1 year of age. Research on alternative approaches for PMC delivery beyond the EPI schedules may be warranted.

Seasonal Malaria Chemoprevention

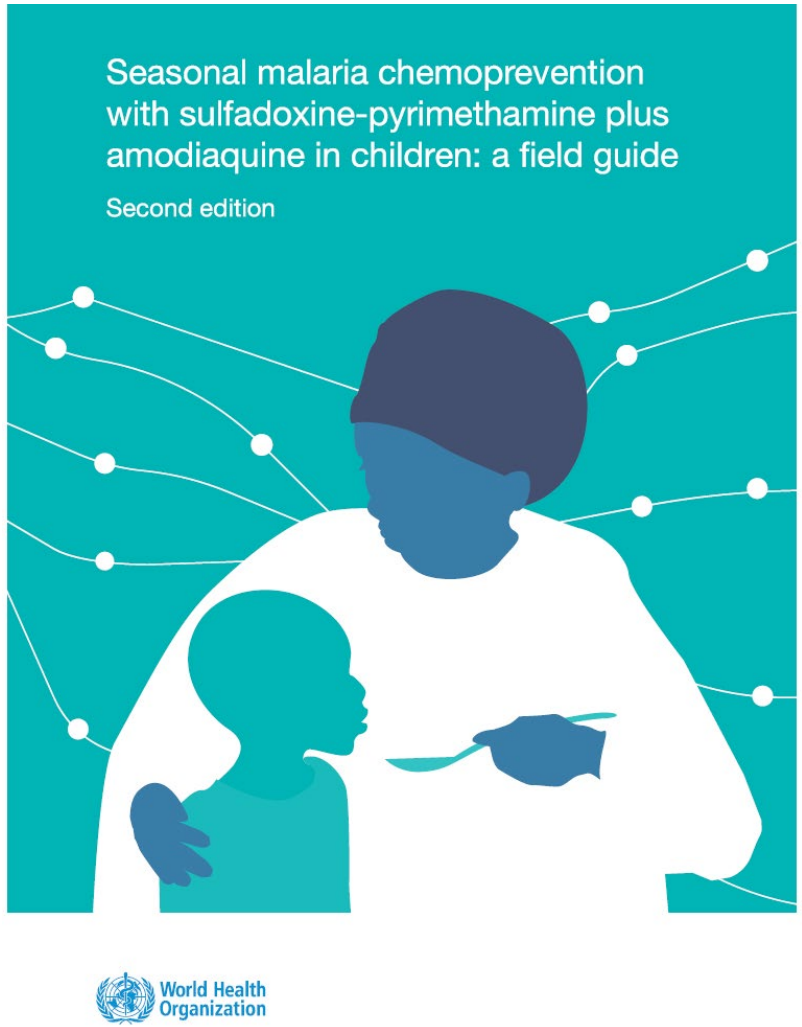
4.2.3 Seasonal malaria chemoprevention (SMC)

Strong recommendation for , Moderate certainty evidence

Seasonal malaria chemoprevention (2022)

In areas of seasonal malaria transmission, children belonging to age groups at high risk of severe malaria should be given antimalarial medicines during peak malaria transmission seasons to reduce disease burden.

Implementation field guide



- Update implementation field guide (2013) to reflect current Guidelines recommendation
  - specify age groups, transmission intensity thresholds, numbers of doses or cycles, or specific drugs.

26 May 2023

https://www.who.int/publications/i/item/9789240073692

further guidance (Field Guide 2nd ed, 2023)

- Target area:
  - malaria transmission is highly seasonal and the majority (>60%) of clinical malaria cases occur within 4 consecutive months
  - the clinical attack rate of malaria (without SMC) is at least 0.1 episodes per child during the transmission season in the target group

- Target population
  - Children in age groups at high risk of severe malaria are eligible. In most countries with intense seasonal malaria transmission, these are children below 5 years of age.

further guidance (Field Guide 2nd ed, 2023)

- Number of cycles
  - SMC courses should be given at 28-day intervals, beginning at the start of the transmission season and continuing for 3–5 cycles, depending on the local context.
    - In some settings, three cycles may be sufficient.
    - Add a fifth cycle if a month on either side of the 4-month season contributes more than 10% of the annual burden
    - Gains from adding a sixth SMC cycle appear to be minimal and not cost effective
- Recommended medicines
  - The combination of SP+AQ is currently recommended for SMC.

Intermittent preventive treatment of malaria in school-aged children (IPTsc)

4.2.4 Intermittent preventive treatment of malaria in school-aged children (IPTsc)

Conditional recommendation for , Low certainty evidence

Intermittent preventive treatment of malaria in school-aged children (2022)

School-aged children living in malaria-endemic settings with moderate to high perennial or seasonal transmission can be given a full therapeutic course of antimalarial medicine at predetermined times as chemoprevention to reduce disease burden.

Post-discharge malaria chemoprevention (PDMC)

4.2.5 Post-discharge malaria chemoprevention (PDMC)

Conditional recommendation for , Moderate certainty evidence

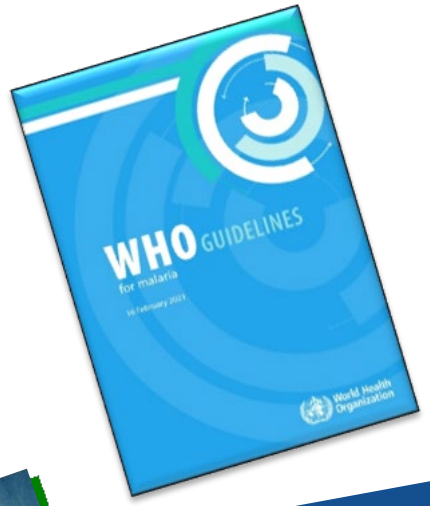
Post-discharge malaria chemoprevention (2022)

Children admitted to hospital with severe anaemia living in settings with moderate to high malaria transmission can be given a full therapeutic course of an antimalarial medicine at predetermined times following discharge from hospital to reduce re-admission and death.

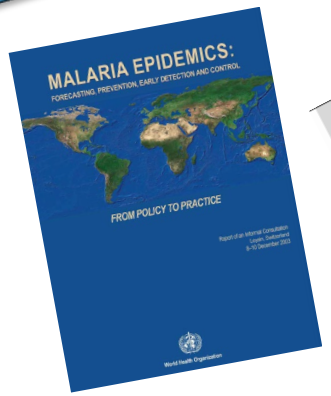
Adoption and Implementation of Chemoprevention Recommendations

Adoption and adaptation of the chemoprevention recommendations will be guided by specificities provided through implementation field manuals, based on current available evidence.

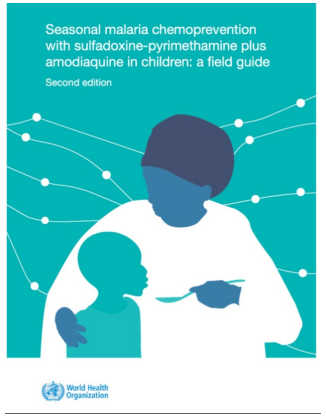
- SMC
  - Implementation Field manual 2nd edition *(26 May 2023)*
- IPTp at community level
  - New field manual *(in process)*
- PMC
  - Projects and early implementation underway to provide the evidence required for expansion of IPTi beyond the current recommendation and transition to PMC. – Development of updated implementation field manual – *(planned)*.
- IPTsc and PDMC
  - Deployment studies and experience required to develop implementation guidance documents
  - Implementation Guidance – *(planned)*


WHO GUIDELINES
for malaria
World Health Organization


Technical Expert Group meeting on Preventive chemotherapy
Report of the Technical Consultation on Intermittent Preventive Treatment in Infants (IPTi)
World Health Organization


MALARIA EPIDEMICS:
FORECASTING, PREVENTION, EARLY DETECTION AND CONTROL
FROM POLICY TO PRACTICE


DISEASE SURVEILLANCE FOR MALARIA CONTROL
AN OPERATIONAL MANUAL


Seasonal malaria chemoprevention with sulfadoxine-pyrimethamine plus amodiaquine in children: a field guide
Second edition
World Health Organization

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

Thank you