

THE UNITED REPUBLIC OF TANZANIA



**MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT,
GENDER, ELDERLY AND CHILDREN**

NATIONAL GUIDELINES FOR MALARIA DIAGNOSIS, TREATMENT AND PREVENTIVE THERAPIES 2020



National Malaria
Control Programme

NATIONAL MALARIA CONTROL PROGRAMME

DECEMBER, 2020

THE UNITED REPUBLIC OF TANZANIA



**MINISTRY OF HEALTH, COMMUNITY DEVELOPMENT,
GENDER, ELDERLY AND CHILDREN**

NATIONAL GUIDELINES FOR MALARIA DIAGNOSIS, TREATMENT AND PREVENTIVE THERAPIES 2020



National Malaria
Control Programme

**National Malaria Control Programme
December, 2020**

Table of Contents

Foreword.....	vii
Acknowledgements.....	viii
List of abbreviations.....	x
Justification for 2020 National Guidelines for Malaria Diagnosis and Treatment.....	xii
1 Malaria Diagnosis, Treatment and Preventive Therapies in the Context of Malaria Risk Stratification.....	1
1.0 Positioning Malaria Diagnosis, Treatment and Chemoprevention in the current control strategic plan....	1
1.1 The changing malaria epidemiological context of malaria in Tanzania.....	1
1.2 The Role of National Guidelines for Malaria Diagnosis Treatment and Preventive Therapies in the Strategic Context of Malaria Control in Tanzania	4
2 Management of Malaria and Health Care Delivery in Tanzania.....	8
2.0 Health Care Delivery Categories in Tanzania.....	8
2.1 Community.....	8
2.2 Dispensary.....	9
2.3 Health centre.....	10
2.4 Hospital.....	11
3 Case Definition, Classification and Diagnosis of Malaria.....	13
3.0 The Rationale of Malaria Case Definition, Classification and Diagnosis under the Current Epidemiological Transition.....	13
3.1 Malaria Case Definition.....	13
3.2 Malaria Case Detection.....	15
3.3 Malaria Case Classification.....	16
3.4 Clinical diagnosis of malaria.....	17
3.5 Differential diagnoses of malaria.....	18
3.6 Parasite-based malaria diagnosis: confirmed malaria.....	19
3.7 Choosing a Diagnostic Strategy.....	21
4 Management of Uncomplicated malaria.....	24
4.0 The objectives of uncomplicated malaria case management.....	24
4.1 Clinical features of uncomplicated malaria.....	24
4.2 Treatment of uncomplicated malaria using combination therapy.....	25
4.3 Treatment of uncomplicated malaria with medicine of choice: Artemether-Lumefantrine.....	25
4.4 Other ACT options for the treatment of uncomplicated malaria.....	28
4.5 Treatment of Malaria using ACT plus Primaquine.....	34
4.6 Management of fever.....	35
4.7 Recommendations to be given to uncomplicated malaria patient/caretakers.....	35
5 Management of Severe Malaria.....	36
5.0 The primary objectives of Severe Malaria Management.....	36
5.1 Principles for the management of severe malaria.....	36
5.2 Clinical features and conditions related to severe malaria	37
5.3 Treatment of severe malaria.....	40
5.4 Adjunctive management of severe malaria.....	43
5.5 Management of severe malaria by levels of health facility.....	44
5.6 Monitoring of patients with severe malaria.....	48
5.7 Emergency management of severe malaria.....	49
6 Anaemia in relation to Malaria.....	52
6.0 The relationship between malaria and anaemia.....	52
6.1 Clinical presentation and classification of anaemia.....	53
6.2 Management of malarial anaemia.....	54
7 Management of Malaria in Special Situations and Groups.....	57
7.0 Special groups and special situations that need specific case management interventions.....	57
7.1 Management of malaria in pregnancy.....	57

7.2	Management of malaria in neonates.....	60
7.3	Malaria and HIV/AIDS.....	62
7.4	Malaria case management in epidemics and complex emergency.....	64
7.5	Management of malaria in special groups.....	66
8	Preventive Therapies for Special Risk Group.....	69
8.0	The needs of Targeted Preventive Therapies.....	69
8.1	Intermittent Preventive Treatment in pregnancy (IPTp).....	69
8.2	Chemoprophylaxis options for special risk groups.....	72
8.3	Non-immune traveller's and malaria chemoprophylaxis.....	74
8.4	Malaria chemoprophylaxis in sickle cell disease.....	75
8.5	Targeted approaches in preventive therapies that need to be further explored.....	75
9	Management of Commodities for Malaria Diagnosis and Treatment.....	80
9.0	The Rationale for Malaria Commodities and Logistic Management.....	80
9.1	Logistic Management of Malaria Case Management Commodities.....	80
9.2	Quality assurance for malaria diagnostics.....	82
9.3	Malaria therapeutic and laboratory devices quality assurance procedures.....	85
9.4	Pharmacovigilance.....	85
9.5	Restrictions of SP use in ANC only.....	89
10	ACT Resistance Mitigation Strategy.....	90
10.0	Emergence of ACT resistant malaria and mitigation strategies.....	90
10.1	Role of parasitological diagnosis for all malaria suspected patients in artemisinin resistance.....	90
10.2	Access to quality-assured ACTs for confirmed cases and adherence to treatment.....	90
10.3	Enforced ban on the use of ACT-based monotherapies.....	90
10.4	Exploring the introduction of multi ACT policy.....	91
11	Social Behaviour Change for Malaria Diagnosis, Treatment and Preventive Therapies.....	93
11.0	The needs of Social Behaviour Change for Sustainable Malaria Control Interventions.....	93
11.1	Key Social Behaviour Change (SBC) issues for diagnosis and treatment of malaria.....	93
12	Malaria Surveillance, Monitoring and Evaluation in Relation to Malaria Diagnosis, Treatment and Preventive Therapies.....	95
12.0	The Malaria Surveillance Monitoring and Evaluation Framework.....	95
12.1	Reporting malaria cases and malaria related rates.....	95
12.2	Malaria Surveillance.....	100
12.3	Malaria Services and Data Quality Improvement Framework.....	103
12.4	Programmatic Monitoring of the Efficacy of ACT and mRDT.....	104
Appendix.....	108
Appendix A:	Choice of Malaria Rapid Diagnostic Tests (mRDTs).....	109
Appendix B:	Reporting of blood smear results.....	110
Appendix C:	Integrated Management of Childhood Illness algorithm for child with fever.....	111
Appendix D:	Time schedule for 1st, 2nd and 3rd dose of Artemether-Lumefantrine.....	112
Appendix E1:	Appendix E1: Preparation and administration of Injectable Artesunate.....	112
Appendix E2:	Artesunate injectable dose chart.....	113
Appendix F:	Coma scales.....	114
Appendix G:	Classification and management of anaemia by severity in children one week up to 5 years of age according to IMCI.....	115
Appendix H:	Adverse Medicine Reaction Reporting Form.....	116
References.....	128

List of Tables

Table 1:	Treatment indication, medicine options and reference in the Guidelines.....	7
Table 2:	Common target antigens for commercially available mRDTs devices.....	21
Table 3:	Strategic framework for selection of routine malaria test to be used at different levels and in different clinical settings.....	23
Table 4:	Clinical features of uncomplicated malaria and expected frequency in children below 5 years of age and adults.....	24
Table 5:	Dosage schedule of Artemether 20mg & Lumefantrine 120 mg (AL) (number of tablets recommended at approximate timing of dosing).....	27
Table 6:	Dosage schedule of Artemether 80mg & Lumefantrine 480 mg 'AL 40/480' (number of tablets recommended at approximate timing of dosing).....	28
Table 7:	Dosage schedule for DP: 4 mg/kg/day Dihydroartemisinin and 18 mg/kg/day Piperaquine once a day for 3 days.....	30
Table 8:	Dosing Schedule for Artesunate-Amodiaquine.....	31
Table 9:	Dosing Schedule for Artesunate-Mefloquine.....	32
Table 10:	Dosage regimen for Pyronaridine tetraphosphate 60mg and Artesunate 20 mg granular paediatric formulation.....	33
Table 11:	Dosage regimen for Pyronaridine tetraphosphate 180 mg and Artesunate 60 mg.....	33
Table 12:	Dosage of Primaquine single dose (0.25mg/kg).....	34
Table 13:	Treatment schedule for paracetamol (500mg) tablets dosage for children: 10 mg/Kg bwt.....	35
Table 14:	Features of severe malaria.....	37
Table 15:	Clinical features of severe malaria and expected frequency by age group.....	38
Table 16:	Common conditions observed in severe malaria cases.....	39
Table 17:	Artesunate for injection package by strength.....	40
Table 18:	Quantity for dilution of Artesunate for injection.....	41
Table 19:	Artemether Injectable dosage by weight.....	42
Table 20:	dosage regimen for Artesunate suppositories for different age groups (10mg/kg body weight).....	43
Table 21:	Immediate clinical management of complications due to severe malaria.....	44
Table 22:	Investigations of severe malaria at hospital level.....	47
Table 23:	Important clinical observations and their implications during treatment of severe malaria.....	48
Table 24:	Important observations and their implications during treatment of severe malaria: laboratory parameters.....	49
Table 25:	Normal Hemoglobin concentration levels by ages and sex.....	52
Table 26:	Classification of anaemia by severity and risk group.....	53
Table 27:	Medicines indicated for chemoprophylaxis.....	72
Table 28:	Main activities for malaria diagnosis QA system.....	83
Table 29:	Malaria case management communication gaps and needs.....	93
Table 30:	Framework for implementing malaria diagnosis and treatment BCC/IEC.....	94

List of Figures

Figure 1:	Malaria burden Stratification at regional (upper map) and council (lower map) level (2020).....	3
Figure 2:	Malaria case definition.....	14
Figure 3:	Case detection diagram.....	16
Figure 4:	Case classification diagram.....	16
Figure 5:	Reported malaria cases based on the malaria case definition.....	96
Figure 6:	Snapshot of Interactive malaria dashboard into national health data warehouse (DHIS2).....	99
Figure 7:	The six MCBS steps.....	102
Figure 8:	Criteria for changing the national treatment policy for <i>P. falciparum</i> based on therapeutic efficacy studies results (WHO, GMP Status report, 2018).....	105

Foreword

These National Guidelines for Malaria Diagnosis, Treatment and Preventive Therapies (NGMDT&PT) continue to advocate a WHO policy of 3Ts; “Test, Treat and Track”. In the WHO ‘test, treat and track’ initiative, it is recommended that every suspected malaria case should have a confirmatory test undertaken, either by microscopy or malaria rapid diagnostic test (mRDT); all confirmed cases should be treated with antimalarial recommended by the country treatment policy guidelines for uncomplicated and severe malaria; and the disease should be tracked through records in the national surveillance system. Artemether Lumefantrine remains the medicine of choice for the treatment of confirmed uncomplicated malaria because its efficacy is still high. On the other hand, injectable Artesunate will remain the first-choice medicine for the treatment of severe malaria as in the previous 2014 NGMDT.

The Supplementary Malaria Strategic Plan (SMSP) for the period 2018-2020 introduced the concept of malaria risk stratification in the country and defined corresponding tailored interventions to address a) the reduction of disease burden in moderate and high transmission areas and b) specific interventions targeting disease elimination in very low transmission areas. Following the way opened by the 2018-2020 SMSP, the new National Malaria Strategic Plan (NMSP) for the period 2021-2025 provides the roadmap for national malaria technical guidelines including this National Guidelines for Malaria Diagnosis Treatment and Preventive Therapies. Some innovative interventions that are currently explored for their efficacy, effectiveness and feasibility under implementation research, such as Intermittent Preventive Treatment in infancy and Seasonal Malaria Chemoprophylaxis, are also included in these guidelines, to reduce malaria burden in vulnerable groups in moderate and high malaria risk areas. In the same transmission areas, where access to health care is a challenge as per national established criteria, malaria related package for Community Health Volunteers is streamlined to increase access to the services. Malaria Case Based Surveillance framework has been developed to operate in very low transmission areas targeted for elimination. When indicated, as part of case investigation of the passively detected patients, active case detection and further assessment of surroundings for vector control interventions are conducted. Strategic reorientation of the NMSP also provides a roadmap for effective vector control interventions tailored for high and low transmission settings. Use of long-lasting insecticide treated nets, indoor residual spraying complemented by larval source management where breeding sites are few, fixed and findable. All these interventions combined with an effective case management strategy and large-scale deployment of artemisinin-based combination treatment is expected to greatly reduce malaria burden and transmission in the country.



Prof. Mabula D. Mchembe
PERMANENT SECRETARY,

Acknowledgements

The preparation of the 2020 National Guidelines for Malaria Diagnosis, Treatment and Preventive therapies was done through technical meetings, led by the Ministry through National Malaria Control Program with planned technical collaboration from Swiss Tropical and Public Health Institute and technical guidance from the Global Malaria Programme in WHO/HQ and the WHO Country Office. The meeting benefited from sound technical presentations of published evidence and discussion by invited experts. The Ministry acknowledges the technical experts who through meetings prepared updates to formulate 2019 guidelines in the process of reviewing the previous 2014 National malaria diagnosis and treatment guidelines:

Prof.	Omary Minzi,	Muhimbili University of Health and Allied Sciences (MUHAS)
Dr.	Abdallah Lusasi	National Malaria Control Programme, MoHCDGEC
Dr.	Ally Mohamed	Manager, National Malaria Control Programme, MoHCDGEC
Dr.	Amina Mgunya	Muhimbili University of Health and Allied Sciences (MUHAS)
Ms.	Anna David	National Malaria Control Programme, MoHCDGEC
Dr.	Andrea Bosman	Global Malaria Programme, World Health Organization, Geneva
Dr.	Billy Ngasala,	Muhimbili University of Health and Allied Sciences (MUHAS)
Dr.	Celine Mandara	National Institute for Medical Research (NIMR), Tanga
Mr.	Constatine Mzava	Regional Laboratory Technologist; Regional Administrative Secretary (RAS), Dar-es-salaam
Mr.	Daniel Mbwambo	National Malaria Control Programme, MoHCDGEC
Mr.	Dedan Jonas	Regional Pharmacist; Regional Administrative Secretary (RAS), Lindi
Dr.	Fabrizio Molteni	Swiss Tropical and Public Health Institute, Dar es salaam
Dr.	Felix Bundala	IMCI Unit
Dr.	Geofrey Makenga	National Institute for Medical Research (NIMR), Tanga
Dr.	Grace Shayo	Muhimbili University of Health and Allied Sciences (MUHAS)
Dr.	Samwel Nhiga	National Malaria Control Programme, MoHCDGEC
Ms.	Jeniva Jasson	Tanzania Medicine & Medical Devices Authority (TMDA)
Mr.	Joakim Chacha	Laboratory Technology, District Executive Director (DED) Ruangwa District Council
Ms.	Martha Kikwilu	Pharmaceutical supply Managements Unit (PSM)
Dr.	Mercy Chiduo	National Institute for Medical Research (NIMR), Tanga
Ms.	Orsolina Tolage	Community Based Health Program (CBHP), MoHCDGEC
Mr.	Richard Silumbe	Clinton Health Access Initiative (CHAI), Dar-es-salaam
Dr.	Ritha Njau	World Health Organisation (WHO), Tanzania
Mr.	Samir Saitoti	Benjamin Mkapa Hospital
Dr.	Sigsbert Mkude	Ifakara Health Institute (IHI), Dar es Salaam
Ms.	Ssanyu Nyinondi	RTI International, Dar-es-salaam
Dr.	Theodora Kazimoto	Muhimbili University of Health and Allied Sciences (MUHAS)
Mr.	Theophil Malibiche	Mloganzila Hospital, Dar-es-salaam
Ms.	Vera Nelson	Health Laboratory Practitioner Council (HLPC).
Dr.	Vito Baraka	National Institute for Medical Research (NIMR), Tanga
Dr.	Zahra Mkomwa	USAID Boresha Afya, Lake and Western Zone
Dr.	Zainabu Nyangumi	Pharmacy Council

The Ministry also commends the following meeting participants and guidelines reviewers: Inputs to the key issues was provided by Dr Andrea Bosman (WHO- GMP Geneva). The

contribution and facilitation of Dr Fabrizio Molteni (Swiss TPH), Dr Sigsbert Mkude (IHI), Professor Omary Minzi (MUHAS) and Dr Abdallah Lusasi (NMCP) were particularly important for preparation of summary of published evidence, facilitation and coordination of guidelines development technical meetings and editorial works.

We gratefully acknowledge the support of Global Fund to fight HIV/AIDs, Tuberculosis and Malaria who funded meetings to prepare and to publish these guidelines.



Prof. Abel N. Makubi
CHIEF MEDICAL OFFICER

List of abbreviations

ACT	Artemisinin based Combination therapy
ADDO	Accredited Drug Dispensing Outlet
ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
AL	Artemether-Lumefantrine
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase (Alanine transaminase)
AMFm	Affordable Medicine Facility for malaria
ANC	Ante Natal Clinic
AO	Acridine Orange
AQUAMAT	African Quinine vs. Artesunate Malaria Trial
ASAQ	Artesunate Amodiaquine
ARV	Antiretroviral
AST	Aspartate aminotransferase
BS	Blood Smear
CHMTs	Council Health Management Teams
CHW	Community Health Workers
CPT	Co-trimoxazole Preventive Therapy
CSF	Cerebro-spinal Fluid
DIC	Disseminated intravascular coagulation
DHIS2	District Health Information Software Version 2
DLDM	<i>Duka la Dawa Muhimu</i> (Accredited Drug Dispensing Outlet)
DOT	Direct Observed Treatment
DP	Dihydroartemisinin-Piperaquine
EIR	Entomological Inoculation Rate
EQA	External Quality Assurance
FEFO	First Expiry, First Out
G6PD	Glucose-6-phosphat-dehydrogenase deficiency
Hb	Haemoglobin
HF	Health Facility
HIV	Human Immunodeficiency Virus
HLPC	Health Laboratory Practitioners Council
HMIS	Health Management Information System
HRP2	Histidine-rich Protein-2
HW	Health Workers
ICCM	Integrated Community Case Management
IDSR	Integrated Disease Surveillance and Response
IHI	Ifakara Health Institute
IM	Intra muscular
IMCI	Integrated Management of Childhood Illness
IPC	Interpersonal communication
IPD	In Patient Department
IPTi	Intermittent Preventive Treatment of infancy
IPTp	Intermittent Preventive Treatment of Pregnant Women
IPTSc	Intermittent Preventive Treatment of school Children
IQC	Internal Quality Control
IRS	Indoor Residual House-spraying
IV	Intravenous

LLINs	Long Lasting Insecticide treated Nets
M&E	Monitoring and Evaluation
MDA	Mass Drug Administration
MFT	Mass Fever Treatment
MMTSP	Malaria Medium Term Strategic Plan
MoF	Ministry of Finance
MoHCDGEC	Ministry of Health, Community Developments, Gender, Elderly & Children
mRDTs	malaria Rapid Diagnostic Tests
MSaT	Mass Screening and Treatment
MSD	Medical Stores Department
MTCT	Mother To Child Transmission
MTAT	Malaria Test and Treatment
MTPR	Malaria Test Positivity Rate
MTR	Malaria Test Rate
NHLQATC	National Health Laboratory and Quality Assurance Training Centre
NMCP	National Malaria Control Programme
OPD	Out Patient Department
ORS	Oral Rehydration Salts
ORT	Oral Rehydration Therapy
PHLB	Private Health Laboratory Board
pLDH	Plasmodium Lactate Dehydrogenase
PR	Pulse Rate
QA	Quality Assurance
QAACT	Quality Assured ACT
QAMRDT	Quality Assured MRDT
RCH	Reproductive and Child Health
RR	Respiratory Rate
SCD	Sickle cell disease
SMC	Seasonal malaria Chemoprevention
SME	Surveillance, Monitoring and Evaluation
SOP	Standard Operating Procedures
SP	Sulfadoxine-Pyrimethamine
Swiss TPH	Swiss Tropical and Public Health Institute
TDHS	Tanzania Demographic and Health Survey
THMIS	Tanzania HIV/AIDs and Malaria Indicator Survey
TMDA	Tanzania Medical and Medical Devices Authority
TRA	Tanzania Revenue Authority
UNICEF	United Nations Children's Fund
USAID	United States of America International Development Agency
VC	Vectorial Capacity
WHO	World Health Organization

Justification for 2020 National Guidelines for Malaria Diagnosis and Treatment

The supplementary malaria strategic plan (SMSP) for the period 2018-2020 introduced tailored interventions to address the reduction of disease burden in moderate and high transmission areas and specific interventions targeting disease elimination in very low and low transmission areas. This information has now been included in the draft National Malaria Strategic Plan (NMSP) – 2021-2025.

The development of the 2020 National Guidelines for Malaria Diagnosis, Treatment and Preventive therapies (NGMDT& PT) is the product of the review of approaches, technical updates and justifications from strategic recommendations contained in the SMSP 2018-2020. It is also aligned to the Global Technical Strategy (GTS) for malaria – 2016-2030.

New evidences in traditional approaches to diagnosis and treatment

Area	Updated approach	Evidence
Treatment of uncomplicated malaria in pregnancy	AL is the medicine of choice for the treatment of confirmed uncomplicated malaria to pregnant women in all trimesters and lactating women. Therefore, oral Quinine medications do not have any further recommendation in the guidelines	There is now enough evidence that Artemisinin are not associated with an increased risk of; (a) miscarriage, (b) stillbirths and (c) major congenital malformations compared to non-artemisinin regimens.
Treatment of severe malaria	The medicine of choice for treatment of severe malaria remains Injectable Artesunate. The alternative treatments for severe malaria is Injectable Artemether. Quinine is no longer a recommended option for treatment of severe malaria.	The largest randomized trial conducted in Africa children with severe malaria showed a significant reduction in mortality (22.5%) in the artesunate group when compared to the quinine group
Treatment of severe malaria in children	The use of revised dose of injection Artesunate. Children weighing less than 20kg should receive the higher dose of Artesunate (3mg/kg bw per dose) instead of the usual 2.4 mg	Evidence presented in 3 rd edition WHO treatment guidelines recommendations. Revised dosage to children in this weight category ensure equivalent exposure to the drug
Treatment of severe malaria in pregnancy	The use of Injection Artesunate as a first choice for treatment of severe malaria in the 1st trimester during pregnancy. Quinine is no longer a recommended option for treatment of severe malaria.	The main therapeutic objective of the treatment of severe malaria is to prevent the patient from dying. Secondary objective are prevention of disabilities and prevention of recrudescence infection

Innovative approaches to malaria diagnosis and treatment according to country malaria risk stratification

Area	Updated approach	Evidence
Malaria diagnosis and malaria case definition	Broaden definition for a 'malaria case': occurrence of malaria infection (symptomatic or asymptomatic) in a person in whom the presence of parasites in the blood has been confirmed by parasitological testing.	Malaria case definition will include asymptomatic malaria positive diagnosed in the communities through Active Case Detection as a response to the established Malaria Case Based Surveillance in low transmission risk
Treatment in very low transmission areas	The addition of a single 0.25mg base/kg low dose of Primaquine (PQ) for P.falciparum confirmed malaria with ACT treatment in very low transmission areas targeted for elimination.	Primaquine Single Low Dose (SLD) clears gametocytes that persist after treatment with ACTs, including those at a sub-microscopic level and is unlikely to cause serious toxicity in subjects with any of the G6PD variants
Active case detection	Active case detection is done by facilities or community health workers directly in the community, among population groups who are considered to be at high risk or within case based surveillance.	The aim of case based surveillance is to determine whether an infection was acquired locally and the likely location of infection, and therefore whether there is indigenous malaria transmission or factors that may lead to onward transmission.
Increasing access to malaria testing	The strategic directions for the next NSP period will emphasize the improvement of quality of testing in the existing points of care and will try to expand the services beyond the operational facilities in order to increase the access to malaria testing services.	With the current malaria testing services, mainly depending on operational healthcare facilities, it is unlikely to achieve universal access to appropriate malaria diagnosis, treatment and, if indicated, preventive therapies.
Increase Testing in Health Facility in low and very low transmission	Testing ratio in the health facilities within the very low and low malaria risk is largely and consistently below the national average.	The reasons of low testing should be investigated, and appropriate actions should be put in place to optimize passive detection among patients presenting with fever.
Increasing access to malaria treatment	The strategic directions for the next NSP period will emphasize the improvement of quality of treatment in the existing points of care and will try to expand the services beyond the operational facilities to increase the access to essential malaria case management services.	Universal access to appropriate, quality and timely treatment has not been achieved in the implementation of previous NSP 2015 -2020 periods. Alternative additional service delivery mechanisms are needed to attempt reaching the objective.
Increasing access to severe malaria pre referral management	Rectal Artesunate can be administered as a pre-referral medication of severe malaria in children under 6 years of age in places where parenteral artemisinin administration is not possible.	As the progression of severe malaria from severe illness to death can be very rapid, prompt access to pre-referral treatment can save lives
Increasing access to malaria case management in	Special initiatives will target: a) resurgence of malaria transmission, b) incumbent malaria epidemics, c) identified persistent transmission foci in areas of low transmission; and d) specific population segments with	The changed epidemiology of malaria in Tanzania presents a few scenarios where malaria case management should be delivered with different
special group and special situation	high occupational and socio economical exposure to the disease.	modalities compared to the conventional, individual-based approaches:

Innovative approaches for preventive therapies according to country malaria risk stratification to be further explored through implementation research

Area	Updated approach	Evidence
IPTi in very high transmission areas	Use the co-administration of SP for IPTi with Pentavalent 2, Pentavalent 3 and Measles-Rubella 1 immunization to infants through routine EPI. Explore the use of alternative IPTi medicine in case of SP failure.	SP-IPTi provides an overall protection in the first year of life against clinical malaria [30.3%], anaemia [21.3%], hospital admissions associated with malaria parasitaemia [38.1%], and all-cause hospital admissions [22.9%]. SP-IPTi remains effective in areas where resistance to SP is not high
Seasonal malaria chemoprevention	Use of full treatment of antimalarials during the malaria season to prevent malarial illness in very seasonal in moderate to high transmission geographical areas for children aged between 3 and 59 months. The recommended medicine is currently SP AQ. Explore alternative medicine in case of SP failure	The evidence suggests that SMC using AQ+SP monthly for up to 4 months during the transmission season in children less than 5 years of age a) prevents up to 75% of malaria episodes; b) prevents up to 75% of severe malaria episodes; and may be associated with reduction of mortality (risk ratio 0.66).
IPTp in very low transmission areas	Withdrawing of routine IPTp intervention in very low transmission areas engaged in to be established Malaria Case Based Surveillance (mCBS)	WHO recommends continued IPTp-SP implementation until the area approaches interruption of transmission.
Mass drug administration	Provide Mass Drug Administration (MDA) as an optional intervention response where Malaria Case Based Surveillance will be established in very low malaria transmission areas targeted local malaria elimination (zero incidence) and in other areas potential for rapid decrease in transmission	MDA rapidly reduces the prevalence and incidence of malaria. The general recommendation is not to start MDA unless case management, vector control and surveillance are well implemented, reintroduction risk is low and there is a good chance that elimination is feasible in the area where it is being administered.
Preventive therapies in high risk groups	Provision of targeted antimalarial drug administration is recommended as a measure to decrease burden of infection in population living in malaria high risk area and to increase effectiveness of malaria case management. NGMDT&PT includes different chemoprophylaxis and chemoprevention options for vulnerable and non-immune population.	Parasite prevalence is progressively shifting from early childhood (children 1-5 years of age) to late childhood and early teenage stages (children 6-15 years of age), especially in high transmission areas. Recent observations have shown that over 50% of school going age children in high malaria risk areas are infected by malaria parasites and have some degree of anaemia.
Strategies to mitigate ACT resistance	Explore and evaluate mechanisms to reduce resistance pressure to currently recommended 1 st line ACT through rotation of 1 st line-treatment, sequential ACT treatments or multiple first-line therapies.	After over 10 years of implementation of AL as treatment of choice it is recommended to intensify therapeutic efficacy studies.

1 Malaria Diagnosis, Treatment and Preventive Therapies in the Context of Malaria Risk Stratification

1.0 Positioning Malaria Diagnosis, Treatment and Chemoprevention in the current control strategic plan

Key technical interventions which are recommended by WHO for the control of malaria are the use of insecticidal treated nets (ITNs) or indoor residual spraying (IRS) supported by larviciding where appropriate for vector control, and **prompt access to diagnosis and treatment of clinical malaria**.

Since the publication of the “National Guidelines for Malaria Diagnosis and Treatment (NGMDT) 2014” new malaria diagnosis and treatment strategic approaches and recommendations have been made. The 2020 National Guidelines for Malaria Diagnosis, Treatment and Preventive Therapies contains updated approaches and recommendations in line with WHO Global Technical Strategy (GTS) 2016–2030 and has been adopted to the country context in the National Malaria Strategic Plan (NMSP) 2021-2025. The major re-orientation of the new strategic plan is stratification of the malaria burden which aligns to corresponding targeted intervention packages. The strategic adjustments facilitate burden reduction in moderate to high transmission areas and advance towards malaria elimination in very low transmission settings. Development of SMSP 2018 - 2020 necessitate parallel revision and updating of NGMDT 2014 to the agreed new recommended approaches and intervention packages. The NMSP promotes **universal access to early malaria diagnosis and prompt treatment** in all transmission settings, to prevent the occurrence of mortality related to malaria infection. In addition, the NMSP intends to widen and extend the scope for **provision of preventive treatments** to more biological and socio-economic vulnerable groups, further than pregnant women, especially in areas with high disease burden. Currently, WHO recommended malaria preventive chemotherapies include Intermittent Presumptive Therapy for pregnant women (IPTp), Intermittent Presumptive Therapy for infants (IPTi) and Seasonal Malaria Chemoprevention (SMC). The main objective of chemotherapies is to prevent malaria illness by maintaining therapeutic drug levels in blood throughout the period of greatest risk. Although, preventive chemotherapies are not expected to have major impact on the reduction of malaria transmission. they are expected to contribute to the reduction of malaria morbidity and mortality in the most vulnerable population groups. In the course of implementation of the NMSP, targeted chemopreventive options will be explored, and eventually scaled up to other vulnerable groups, including infancy, children below 5 years of age, older children in school going age, sickle cell patients, HIV pregnant women, non-immune internal travellers, and complex emergency situations.

1.1 The changing malaria epidemiological context of malaria in Tanzania The Epidemiology of Malaria

Malaria is a disease caused by the protozoan parasite of the genus *Plasmodium* and is transmitted by the bite of an infected female anopheline mosquito. Among the four major *Plasmodium* species that cause malaria in humans; three are endemic in Tanzania, *P. falciparum*, *P. ovale*, and *P. malariae*, There are no conclusive evidences of transmission of *P. vivax*, and its variant *P. simiovale*, in the country, though they should be considered for diagnosis in travellers infected outside the country. The remaining plasmodium specie, *P. knowlesi* has limited transmission in South-East Asia, In addition, molecular analysis indicates that *P. ovale* and *P. malariae* have morphological variants that are as divergent as distinct species (*P. o. curtisi*, *P. o. wallikeri* and *P. brasilianum*)¹, though, there is no evidence of

their transmission in Tanzania. *P.falciparum* is the most common species and predominates across sub-Saharan Africa. *P. vivax* predominates in the subtropics and coexists with *P. falciparum* in Asia, the tropical Americas and the Horn of Africa. *P.ovale* is found in Africa and sporadically in South-East Asia and the western Pacific. *P.malariae* has a similar geographical distribution to *P.falciparum* but its distribution is patchy.²

Plasmodium falciparum is the most virulent species and can be fatal. The case fatality rate of severe falciparum malaria can reach up to 10% even in well-equipped hospitals. *P. vivax* malaria on the other hand is an acute but not life-threatening illness and is associated with anaemia and splenomegaly. Furthermore *P. vivax* and *P. ovale* can stay dormant in the liver as hypnozoites for up to several months or even years after inoculation by the anopheline mosquito and generate relapses. Plasmodium falciparum is the main parasite responsible for 96% of malaria infections in Mainland Tanzania, the remaining being attributed to other plasmodia, mainly *P. malariae* and *P. ovale*. The principal malaria vectors are the *Anopheles gambiae* complex and *Anopheles funestus*.

The transmission of the diseases is influenced by a number of factors:

- Distribution of the mosquito vector species
- Vectorial capacity of the mosquito vector species
- Temperature and humidity
- Patients' immunity status
- Incidence and prevalence of *Plasmodium species*
- Presence of other co-morbidities e.g. Malnutrition, HIV/AIDS

The vectorial capacity (VC) is the expression of the efficiency of the mosquito vector in transmitting infective parasites to humans. This is important as the interventions which are used to reduce the mosquito's daily survival rate will also affect the vectorial capacity. Another important factor in the epidemiology of the disease is the Entomological Inoculation Rate (EIR), defined as the number of infectious mosquito bites received per person per unit time, this depends on both the efficiency of the mosquito vector and the magnitude of infective parasites in the area.

In situations where the EIR <10 per year malaria transmission is unstable and is considered to be low-to-moderate in intensity. In situations where rates of EIR are > 10 per year, malaria transmission is high and stable.

The epidemiology of malaria in Tanzania

Malaria remains a major public health challenge. However, Tanzania is in malaria epidemiological transition. Malaria prevalence in children aged 6 -59 months has declined from an average of 18.1% in 2008 to 7% in 2017. The country decline in malaria burden has a wide geographical diversity. Over the last 10 years, approximately one third (31%) of the country consistently showed a 'very low' (<1%) malaria prevalence in children under 5 years of age. In the second third (32%), the transmission has remained 'low' (1 - <10%). During the same period, in the last third of the country, the transmission has remained in 'moderate to high' (10% and above). In areas where malaria transmission has remained constant moderate to high or even increased, half of burden is borne by children below 5 years of age. Climatic conditions are favourable for transmission almost throughout the entire country in over 80% of the mainland Tanzania. Over 93% of the mainland Tanzanian population lives in areas where malaria is transmitted. The Supplementary Malaria Strategic Plan (SMSP) 2018 -2020 used local community prevalence and routine health facility malaria data for the previous three years to stratify Tanzania malaria burden into four epidemiological classes; 'very low',

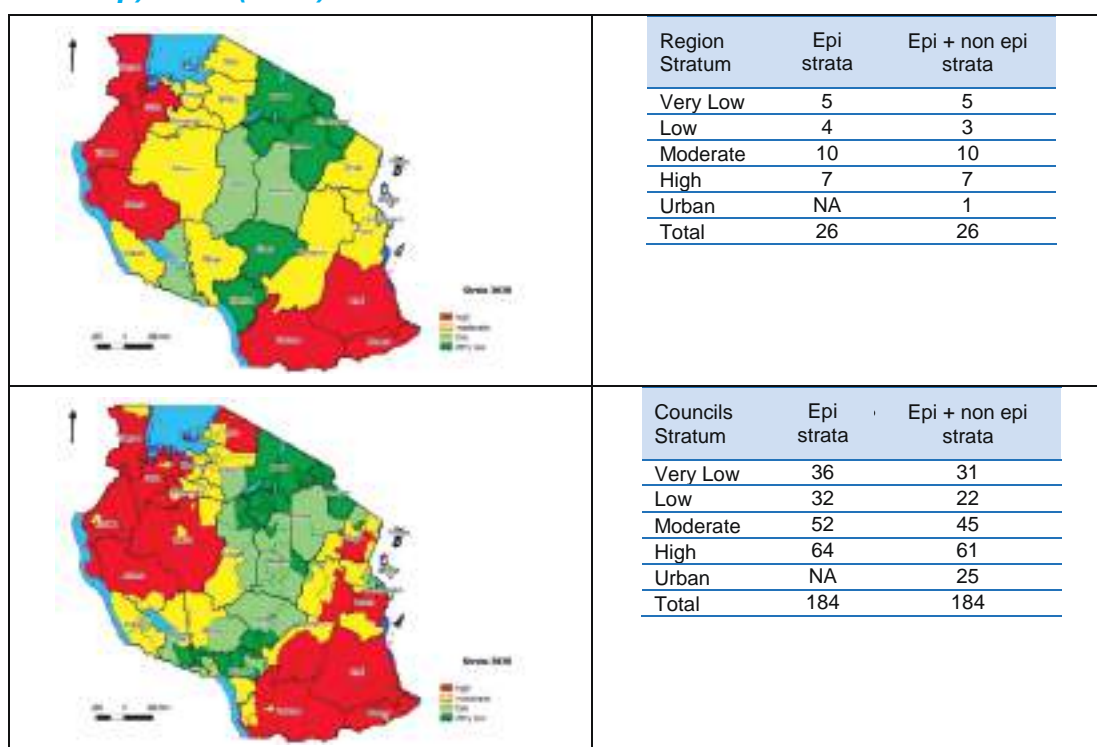
‘low’, ‘moderate’ and ‘high’ malaria risk strata and one operational strata; ‘urban’(see Figure 1). These strata are matched with stratified interventions.

High malaria risk: This indicates an area where transmission is mostly perennial. Malaria is stable with severity of the disease occurring in children under the age of five. The councils in this stratum have been consistently demonstrating more than 30% prevalence and a high case load of more 150 cases per 1000 population per annum. In first malaria burden stratification (2018), high transmission areas had a total of 73 councils accounting for 35% of country population.

Moderate malaria risk: Areas where there is intense year round transmission, with periods of no transmission during the dry season; these areas are referred to as stable transmission. The councils in this stratum have been consistently demonstrating more than 5% and less than 30% prevalence and a case between 50 and 150 per 1000 population per annum. In first malaria burden stratification for the period of 2018 -2020, the total number of councils in this stratum is 49 accounting for 19% of country population

Low malaria risk: Areas with regular but seasonal transmission; referred to as unstable malaria transmission. The councils in this stratum have been consistently demonstrating between 1% to less than 5% prevalence and a quite low case load of less than 50 cases per 1000 population per annum. In first malaria burden stratification for the period of 2018 -2020 the total number of councils in this stratum was 34 accounting for 12% of country population. Very low malaria risk: Areas where transmission is intermittent and very low. Vector species are difficult to find. The councils in this stratum have been consistently demonstrating less than 1% prevalence and a very low case load of less than 15 cases per 1000population per annum. In first malaria burden stratification for the period of 2018 -2020, the total number of councils in this stratum was 28 accounting for 11% of country population. This stratum is unstable malaria transmission and is considered prone to malaria epidemics.

Figure 1: Malaria burden Stratification at regional (upper map) and council (lower map) level (2020)



1.2 The Role of National Guidelines for Malaria Diagnosis Treatment and Preventive Therapies in the Strategic Context of Malaria Control in Tanzania

The strategic context

NEW!

Malaria Diagnosis, treatment and preventive therapies needs to be calibrated according to epidemiological and operational strata

The Supplementary Malaria Strategic Plan (SMSP) 2018 -2020 reoriented the road map for malaria control strategies in the country. SMSP 2018 – 2020 has three core strategies :

- Malaria Diagnosis and Treatment
- Integrated Vector Management
- Surveillance Monitoring and Evaluation

The strategic objective for malaria diagnosis and treatment is to prevent the occurrence of mortality related to malaria infection through promotion of universal access to appropriate early diagnosis, prompt treatment

and provision of preventive therapies in vulnerable groups

The 2020 National Guidelines for Malaria Diagnosis, Treatment and Preventive Therapies are expected to guide the National Malaria Control Programme (NMCP) to achieve this strategic objective. The guiding principle of the national antimalarial treatment policy is to promote safe, effective, good quality, affordable and accessible antimalarial treatment.

Updating antimalarial treatment policies is the culmination of efforts on several levels;

- a) analysis of the technical, social and economic issues related to malaria control;
- b) consensus building on antimalarial drug efficacy and best diagnostic options;
- c) review of new recommendations from the global level on updated evidence for malaria treatment; and
- d) selection of options among policy makers, researchers, regional and health personnel and other relevant stakeholders.

Rationale of guidelines update

The Global Technical Strategy (GTS) 2016 – 2030 is providing several scientific sound technical recommendations and is promoting a call for countries to review their national plans. Tanzania responded by developing the SMSP 2018-2020 which adopted global recommendations in local context. It became increasingly clear that after country strategic reorientation next step was updating guidelines to the agreed new recommended technical interventions including the previous 2014 NGMDT.

Furthermore, both updated global level WHO guidelines on the diagnosis and treatment of malaria and local level evidence was taken on board during the revision process.

The epidemiology of malaria in the country is changing, malaria prevalence has declined from an average of 18.1% in 2008 to 7% in 2017 but has a wide geographical diversity. Over the last 10 years, one third of the country consistently showed a 'very low' (<1%) malaria prevalence. In the second third, the transmission has remained 'low' (1 - <10%). While in the last third of the country, the transmission has remained or even increased in 'moderate to high' (10% and above).

Stratification of country malaria burden and establishment of Malaria Case Based Surveillance (MCBS) for very low malaria transmission strata will in practice raise surveillance to core

intervention. MCBS track location of health facility diagnosed malaria positive patient to their place of residence in the community. While in the community malaria case management response to MCBS is house hold members or community testing and treatment referred to as Active Case Detection (ACD).

ACD of asymptomatic (non-clinical) participants reorient the definition of malaria case in this revised guideline to include all malaria infection (malaria test positive) regardless of their status of clinical symptoms.

Evidence from therapeutic efficacy monitoring studies conducted in sentinel sites in the country reveal that *P. falciparum* remains highly sensitive to the first line drug: Artemether Lumefantrine (AL)⁶. However, in very low transmission areas it is recommended to provide as Direct Observed Therapy (DOT) a single low dose 0.25 mg/kg body weight Primaquine with ACT to patients with *P. falciparum* malaria to reduce the transmissibility of malaria infection.

The evidence from multi-centre study (AQUAMAT.⁷) still remains that injectable Artesunate is superior in efficacy to quinine for the treatment of severe malaria. However, its dosage has been revised to children weighing less than 20kg should receive the higher dose of Artesunate of 3mg/kg BW per dose instead of the usual 2.4mg/kg. This is a WHO treatment recommendation. The revised dosage to children in this weight category ensure equivalent exposure to the drug.

The incidence of convulsions, coma and hypoglycaemia after leaving the hospital was also significantly reduced in the artesunate group compared to those treated with quinine. It was also observed that there was no significant difference in the incidence of severe neurological sequelae. From this evidence, WHO has recommended injectable artesunate to be used in preference to quinine for the treatment of severe *P. falciparum* malaria in adults and children. Artesunate also has a number programmatic and logistical advantages over quinine, as it does not require rate-controlled infusion or cardiac monitoring.⁸

Hence, these guidelines continue to promote the use of injectable artesunate as the medicine of choice in the treatment of severe malaria. Injectable Artemether is the alternative treatment where injectable artesunate is contraindicated or not available.

Specific to high burden areas of moderate to high transmission, this updated version introduces the evaluation under implementation research of chemo-preventive treatment in vulnerable groups to further reduce malaria morbidity and mortality in the most vulnerable groups.

Current WHO recommended malaria chemo-preventive treatment include IPTp, IPTi and SMC. The objective of malaria preventive chemotherapy is to prevent malaria illness by maintaining therapeutic drug levels in blood throughout the period of greatest risk. Preventive chemotherapies do not have as primary objective the reduction of malaria transmission but rather, reduce the burden of malaria morbidity and mortality in the most vulnerable groups.

Mass Drug Administration (MDA) is among the added preventive chemotherapy interventions in this 2nd version of the National Guidelines for Diagnosis and Treatment of Malaria in Tanzania. In contrast to preventive treatment, MDA rapidly reduces the prevalence and incidence of malaria in the short term. The objectives of MDA is to reduce or interrupt transmission in very

low transmission areas targeted for local malaria elimination, and to rapidly reduce malaria morbidity and mortality in malaria epidemics and complex emergencies.

In very low transmission areas in the country, malaria has been reduced substantially. Pregnant women residents to these areas test mRDT negative to routine screening during their 1st ANC visits. Malaria case based surveillance (mCBS) and its technical response is currently established in very low transmission areas to interrupt malaria transmission. These guidelines recommend stopping routine use of SP for IPTp to all pregnant women residents in areas with very low transmission risk.

Broad objective

The broad objective of these guidelines is to provide standard management reference for the care of suspected malaria patients, provide the indications to treatment for both asymptomatic and symptomatic malaria cases in the public and private sectors.

Specific objectives

- To stipulate the definition and classification of malaria case
- To promote prompt and accurate malaria diagnosis
- To clearly specify the best and efficacious therapeutic options for treatment of uncomplicated and severe malaria
- To stipulate at what level of health care delivery, specific antimalarial drugs should be made available at all times
- To promote proper management and accountability of quality assured malaria case management commodities
- To provide consistent guidance to prescribers and users on the potential of the recommended and evidence based malaria preventive chemotherapy for specific at risk groups and the need for well conducted implementation research
- To provide information to health care managers and service providers on the detection of antimalarial drug resistance

Choice of antimalarial medicines

The following antimalarial medicines are recommended for treatment of malaria in Tanzania.

Table 1: Treatment indication, medicine options and reference in the Guidelines

	Indication	Medicine	Reference in the Guidelines
1.	Medicine of choice for the treatment of uncomplicated malaria remains	Artemether-Lumefantrine (AL)	<i>chapter 4 Management of Uncomplicated malaria, page 49</i>
2.	Alternative medicines for the treatment of uncomplicated malaria, where there is no response to Artemether-Lumefantrine or it is contraindicated	Artesunate-Amodiaquine (ASAQ) and Dihydroartemisinin-Piperaquine (DP)	<i>chapter 4 Management of Uncomplicated malaria, page 49</i>
3.	Medicine of choice for treatment of severe malaria	Injectable Artesunate,	<i>chapter 5 Management of Severe malaria, page 64</i>
4.	Alternative treatments for severe malaria	Injectable Artemether	<i>chapter 5 Management of Severe malaria, page 64</i>
5.	Medicine of choice for treatment of uncomplicated malaria in pregnant women in all trimesters	Artemether-Lumefantrine (AL)	<i>Section 7.1, Management of malaria in pregnancy Page 89</i>
6.	Medicine of choice for severe malaria in pregnant women	Injectable Artesunate. Artemether Injectable can be used in case there Artesunate Inj is not available	<i>Section 7.1, Special groups and special situations that need specific case management interventions, Page 89</i>
7.	Medicine for Intermittent Preventive Treatment in pregnancy (IPTp) at each scheduled antenatal care visit and, in infancy (IPTi) at the time of Pentavalent 2, Pentavalent 3 and Measles Rubella 1 immunization. IPTi is indicated only in high malaria risk areas and where there is evidence of optimal SP efficacy.	Sulfadoxine-Pyrimethamine (SP)	<i>chapter 8, Preventive Therapies for Special Risk Group, page 104</i>
8.	Medicine of choice for more research on malaria preventive therapies in different risk groups	Dihydroartemisinin-Piperaquine (DP)	<i>chapter 8, Preventive Therapies for Special Risk Group, page 104</i>
9.	Medicine for malaria patients in settings with very low transmission	single dose low dose Primaquine as DOT in addition to ACT	<i>Section 4.5, Treatment of Uncomplicated Malaria using ACT plus Primaquine, page 61</i>
10.	Malaria chemoprevention or chemoprophylaxis indication for risk groups	depends on specific situations;	<i>chapter 8, Preventive Therapies for Special Risk Group, page 104</i>

2 Management of Malaria and Health Care Delivery in Tanzania

2.0 Health Care Delivery Categories in Tanzania

These guidelines categorise health care delivery as follows:

- Category I: Community - Home, Village/Community Primary Health Care Post, Pharmacy, Accredited Drug Dispensing Outlet (Duka la Dawa Muhimu or ADDO)
- Category II: Dispensary
- Category III: Health Centre
- Category IV: Hospital

The categories mentioned above should not be viewed as a rigid sequence of referral from category I - II - III - IV. Instead, a well-trained health worker should be able to recognize the severity of malaria and refer the patient directly to the most appropriate category of care consistent with that condition.

2.1 Community

Community based management of malaria is one of the recommended strategies for improving access to prompt and effective treatment of malaria episodes, which makes use of trained community members living as close as possible to where the patients live. Community awareness on the importance of early care of malaria patients is a crucial aspect for appropriate and prompt malaria treatment.

NEW!

Community malaria case management is a major contribution for the achievement of universal access to malaria diagnosis and treatment

Community based providers are adequately trained, equipped and supported to give health education on malaria prevention, encouraging early health care seeking behaviour and, in selected areas, diagnosis using mRDT, treatment of uncomplicated malaria, pre-referral management.

Providers and caregivers

The following are involved in management of malaria at the community level

- Community members/household
- Community owned resource persons, Community Health Volunteers
- Dispensing staff of Accredited Dispensing Drug Outlets (ADD0, or *duka la dawa muhimu*) and community pharmacies

- Use of mRDTs to support clinical diagnosis and Active Case Detection (ACD)
- Treatment of malaria cases; symptomatic and asymptomatic infections identified through ACD
- Pre-referral treatment for severe malaria
- Supportive care (fanning-kupepea and antipyretics)
- Encourage early health care seeking behavior and referral to the nearest facility

Community Malaria Case Management

Diagnosis and types of services provided should include the following:

- Health education and promotion
- Identification of signs and symptoms of uncomplicated and severe malaria

Where referral is made, a referral note should be written and where ACD is conducted, the register should be filled

Commodities for Community based Malaria Management by trained CHVs and ADDO providers

- mRDTs
- Artemether-Lumefantrine (AL) tablets
- Paracetamol tablets/syrup
- Sharp safety disposal box
- Examination gloves
- Oral rehydration salt (ORS)
- Rectal Artesunate

2.2 Dispensary

At the dispensary a more detailed history should be taken and a more extensive clinical examination should be performed. Laboratory investigations for malaria parasites should be available throughout. This level of health care is critical to promote appropriate management of uncomplicated malaria and for pre-referral care of severe malaria cases.

Where applicable in very low transmission areas targeted for elimination initiate immediate ACD follow up of malaria case index.

All dispensary staff, should be able to competently perform mRDT and correctly administer antimalarial medications including parenteral, when indicated

Staffing

- Clinical Officers
- Assistant Clinical Officers
- Trained Nurses/Public Health Nurses
- Pharmaceutical Assistants
- Medical attendants
- Laboratory Assistants

Diagnosis is based on

- Clinical history and physical examination
- Malaria RDT and/or blood smear for malaria parasites

Types of services provided

- Treatment of uncomplicated malaria
- Pre-referral treatment of severe malaria cases with intra-muscular artesunate
- Treatment of severe malaria cases where urgent referral is not possible
- Patient education and promotion
- Identification of patients with anaemia for the purpose of treatment and/or referral
- Identification of patients with severe disease and treatment failures for referral with the case summary
- Detection of hypoglycaemia (where possible)
- Measurement of haemoglobin (where possible)
- Exposure and Fanning (kupepea)

Type of treatment provided

- Antimalarials:

Artemether-Lumefantrine (AL) tablets

Injectable antimalarials (Artesunate)

SP tablets for Intermittent Preventive Treatment of pregnant women and infants (in high malaria risk areas and where there is evidence of optimal SP efficacy)

- Analgesics/antipyretics: Paracetamol and Aspirin
- Anticonvulsant medicines: Diazepam and Phenobarbitone (injectable/tablets)
- Oral Rehydration Salt (ORS)
- Correction of hypoglycaemia: Sugar solution, Dextrose 10% solution (where available)

2.3 Health centre

At the health centre, better resources for differential diagnosis and patient monitoring are available. Therefore, a more detailed history should be taken, more extensive clinical investigation should be performed; mRDT and/or a blood smear for malaria parasites should be done. This level of care is critical for the care of severe malaria cases referred from lower level.

Where applicable in very low transmission areas targeted for elimination, after case classification and investigation, initiate immediate ACD follow up to malaria case index.

Health centre staff are equipped to perform mRDT, microscopic diagnosis of malaria and to administer antimalarial medication intramuscularly and/or intravenously, when indicated

Staffing

Staffing with case summary

- Identification of patients with anaemia for the purpose of treatment and/or referral
- Detection and correction of hypoglycaemia
- Detection and correction of anaemia
- Pre-referral treatment
- Exposure and fanning (kupepea)

Type of treatment available

- Antimalarials

Artemether-Lumefantrine (AL) tablets

Injectable antimalarials (artesunate)

SP tablets for Intermittent Preventive Treatment of pregnant women and infants (in high malaria risk areas and where there is evidence of optimal SP efficacy)

Other recommended antimalarial medicines may be available i.e Artemether Injection as alternative medicines in case of unavailability of Artesunate Inj

- Analgesics/anti-pyretics: paracetamol, aspirin (not for children under 12 years of age)
- Anticonvulsants medicines: diazepam and phenobarbitone (Injectable/tablet)
- Oral rehydration salts (ORS)
- Intravenous fluids: dextrose 5%, sodium chloride 0.9% (normal saline), sodium lactate compound (Ringer lactate/Hartmann's solution) and dextrose saline
- Dextrose 10%, 25% and 50% solutions for correction of hypoglycaemia

2.4 Hospital

At the hospital, better resources for differential diagnosis, patient monitoring and advanced care services are available. Therefore, a more detailed history should be taken, more extensive clinical investigation should be performed; mRDT and/or a blood smear for malaria parasites should be done. This level of care is critical for the care of severe malaria cases referred from lower levels.

Where applicable, in very low transmission areas targeted for elimination, after case classification, initiate immediate ACD follow up to all malaria cases.

Blood transfusion services should be available in all hospitals

Staffing:

- Medical Officers
- Assistant Medical Officers
- Nursing Officers
- Assistant Nursing Officers
- Public Health Nurses A and B
- Nurse Midwives
- Medical Attendants
- Laboratory Scientist and/or Laboratory
- Technicians/Assistants
- Pharmacists and/or Pharmaceutical Technicians
- Other Medical Cadres

Diagnosis

At this level there is sufficient clinical expertise for diagnosis of severe malaria and its complications and adequate differential diagnosis. There should also be greater efficiency and accuracy in mRDT and microscopic diagnosis of malaria including identification of species, sexual and asexual forms and performance of quantitative parasite counts. Diagnosis is based on:

- Clinical history and physical examination
- Laboratory tests, radiology and other supportive tests

Laboratory tests available include:

Urgent test for suspected severe malaria patients:

- Blood smear for malaria parasites
- Blood glucose
- Lumbar puncture for CSF examination
- Full blood picture including Haemoglobin

Other supportive tests:

- Urinalysis including haemoglobinuria
- Basic biochemical tests
- Liver function tests - including bilirubin, ALT, AST and ALP
- Serum creatinine and blood urea
- Electrolytes including sodium, potassium, chloride, bicarbonate and lactate
- Cultures – blood, CSF and urine

Type of services provided

- Treatment of uncomplicated and severe malaria cases
- Health education and promotion
- Identification of patients with complicated conditions that cannot be managed at district/regional hospitals (e.g. renal failure, uncontrollable convulsions, etc.) for treatment at consultant hospitals
- Identification of patients with anaemia for the purpose of treatment
- Patient monitoring
- Blood transfusion services
- Intensive care
- Exposure and fanning (kupepea)

Type of treatment available

- Antimalarials

Artemether-Lumefantrine (AL) tablets

Injectable Artesunate

SP tablets for Intermittent Preventive Treatment of pregnant women and infants (in high malaria risk areas and where there is evidence of optimal SP efficacy)

Other recommended antimalarial medicines may be available both for oral or parenteral treatment: e.g. Dihydroartemisinin-Piperaquine (DP) tablets, alternative antimalarial: Injectable e.g. Artemether

- Analgesics/antipyretics: paracetamol, aspirin (not for children under 12 years of age)
- Anticonvulsant medicines: Injectable Diazepam and Phenobarbitone (injectable / tablet)
- Oral rehydration salts (ORS)
- Intravenous fluids: Dextrose 5%, sodium chloride 0.9% (normal saline), sodium lactate compound (Ringer Lactate/Hartmann's solution) and dextrose saline
- Blood transfusion services
- Correction of hypoglycaemia: dextrose 10%, 25% and 50% solution

3 Case Definition, Classification and Diagnosis of Malaria

3.0 The Rationale of Malaria Case Definition, Classification and Diagnosis under the Current Epidemiological Transition

In the current epidemiological transition (see section 0: The epidemiology of malaria in Tanzania, page 18) the case definition and classification of malaria needs some adjustment compared to the previous 2014 National Guidelines for Malaria Diagnosis and Treatment. Prompt, accurate and adequate diagnosis of both symptomatic and asymptomatic malaria is part of effective disease management and control in relation to different malaria risk setting. The two recommended methods in routine use for parasitological diagnosis are malaria microscopy and malaria Rapid Diagnostic Tests (mRDT). Quality microscopy remains the gold standard for parasitological diagnosis of malaria.

The diagnosis of malaria in symptomatic cases is based on clinical suspicion and on the detection of parasites in the blood (parasitological or confirmatory diagnosis). The aim of malaria diagnosis for a symptomatic patient is to assist in the treatment of the disease. A positive clinical identification of malaria is based on exclusion diagnosis, therefore, symptoms and signs of other common febrile illness have to be elicited through history and examination. The results of parasitological diagnosis should be available within a short time (<2 hours) of the patient presenting.

The benefit of parasitological diagnosis to a symptomatic patient depends entirely on health care providers adhering to the results when managing the patient. Clinical diagnosis without parasitological confirmation should be a rare exception justified by a) prompt management of severe illness and b) temporary unavailability of diagnostics. In the symptomatic cases, confirmation of malaria diagnosis improves the quality of patient care by

- Ensuring that only malaria positive cases receive treatment,
- Improving management of non-malarial febrile illnesses, and
- Improving malaria disease surveillance by recording true cases only.

On the other hand, in the Country it is expected a progressively increase in detection of asymptomatic malaria cases during: a) routine testing in health facility (e.g. ANC), b) community surveys (e.g. SMPS); c) active case detection within case based surveillance; and d) focal screening and testing. All these cases should be promptly managed and reported irrespectively from the epidemiological setting.

3.1 Malaria Case Definition

A malaria case is a person with malaria infection, confirmed by microscopy or RDT, regardless of whether fever and other clinical symptoms are present.

NEW!

In the current epidemiological transition both symptomatic and asymptomatic malaria infected people should be defined as malaria cases

In very low transmission areas where MCBS has been established targeting local elimination (zero incidence), all malaria infections asymptomatic and symptomatic are important because they may lead to onward transmission. Therefore, all patients with parasitaemia are considered “malaria cases”, regardless of whether clinical symptoms are present. In these mentioned areas, Active case detection (ACD) by health workers in the community and in households, sometimes among population groups who are considered to be at high risk such as people living with HIV (PLHIV), pregnant women, sickle cell patients, etc.

Not all cases of malaria receive a diagnostic test. Thus, it is necessary to distinguish between suspected malaria cases, probable cases and confirmed cases . The relationship between these categories is shown diagrammatically in Figure 2 :Based on clinical symptoms malaria is further defined as;

- **Suspected malaria case**

This is a patient suspected of having malaria. The criteria for recognizing suspected malaria is recent history of fever or fever measured by a healthcare worker. If measured, axillary temperature more than 37.5 °C or rectal temperature more than 38 °C. All suspected cases of malaria should be given a diagnostic test either by microscopy or rapid diagnostic test (RDT).

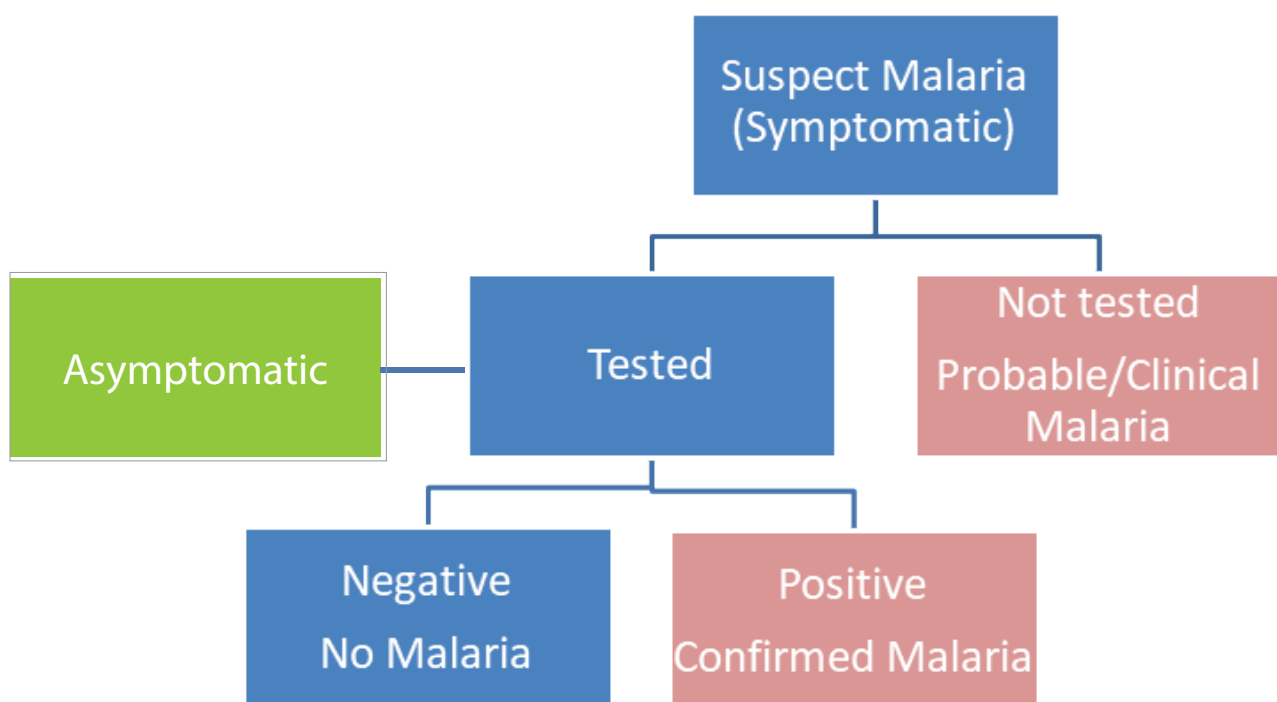
- **Clinical/probable (not tested) malaria case**

These are suspected malaria cases that did not receive a diagnostic test for malaria but were nevertheless treated as malaria. The terms “clinical” and “probable” are interchangeable and were widely used in the past.

- **Confirmed malaria (malaria test positive)**

A suspected malaria case in which malaria parasites have been demonstrated by microscopy or a rapid diagnostic test, the definition implies that the case displayed symptoms of malaria as well as the presence of parasites. It should be noted that for some suspected cases with a positive test, particularly in populations that have acquired immunity to malaria, febrile illness may in fact be due to other causes. Nevertheless, in such instances, a diagnosis of confirmed malaria is still given. If a concurrent disease is suspected, it should be further investigated and treated.

Figure 2: Malaria case definition



Uncomplicated and severe malaria cases

Symptomatic malaria cases can be split into uncomplicated or severe cases.

Uncomplicated malaria: is defined as symptomatic malaria without signs of severity or evidence (clinical or laboratory) of vital organ dysfunction.

Severe malaria: Is a symptomatic patient with *P. falciparum* asexual parasitaemia and no other obvious cause of symptoms the presence of one or more of features (listed in chapter 5: management of severe malaria) classifies the patient as suffering from severe malaria.

In general, uncomplicated malaria cases are treated as out-patient cases while severe malaria is managed as in-patient. Therefore, out-patient and in-patient malaria cases are considered as proxies for uncomplicated and severe malaria cases, respectively¹²

3.2 Malaria Case Detection

NEW!

Malaria cases need to be detected both actively and passively

Cases can be detected across the malaria transmission continuum by Passive Case Detection (PCD), when patients seek care for their illness from health workers, and/or by Active Case Detection (ACD), which includes testing for malaria or screening for symptoms followed by testing in high-risk groups or locations in the community (see Figure 3).

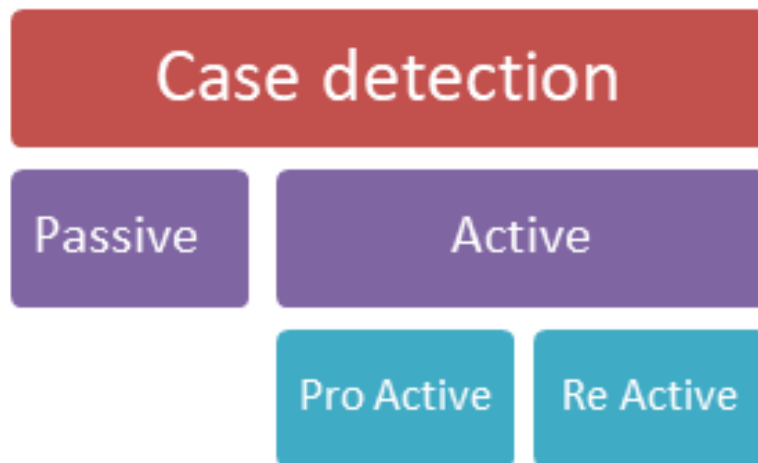
- Passive case detection (PCD) is detection of malaria cases among people who go to a health facility or a CHV on their own initiative to get treatment, usually for fever.
- Active case detection (ACD) is detection by health workers of malaria cases in the community and in households, sometimes among population groups who are considered to be at high risk. ACD can be conducted as fever screening followed by parasitological examination of all febrile patients or as direct parasitological examination of the target population.

Active case detection (ACD)

ACD is further classified into reactive case detection (Re ACD) and proactive case detection (Pro ACD).

- Re ACD is undertaken in immediate follow up response to an index case, to health facility predefined caseload cut point in very low transmission areas. The immediate follow up trigger additional ACD, in which a household or a population potentially linked to the index case is tested before treatment. Index cases are usually seen at a health facility.
- Re ACD is only for villages targeted for elimination, which implies that all cases reported at health facility should be investigated at the community level
- Pro ACD is where communities at risk, based on predefined criteria, are screened and positive cases treated. The aim of doing proactive surveillance is to find community members who could be asymptomatic carriers of the parasite without feeling sick.

Figure 3: Case detection diagram



3.3 Malaria Case Classification

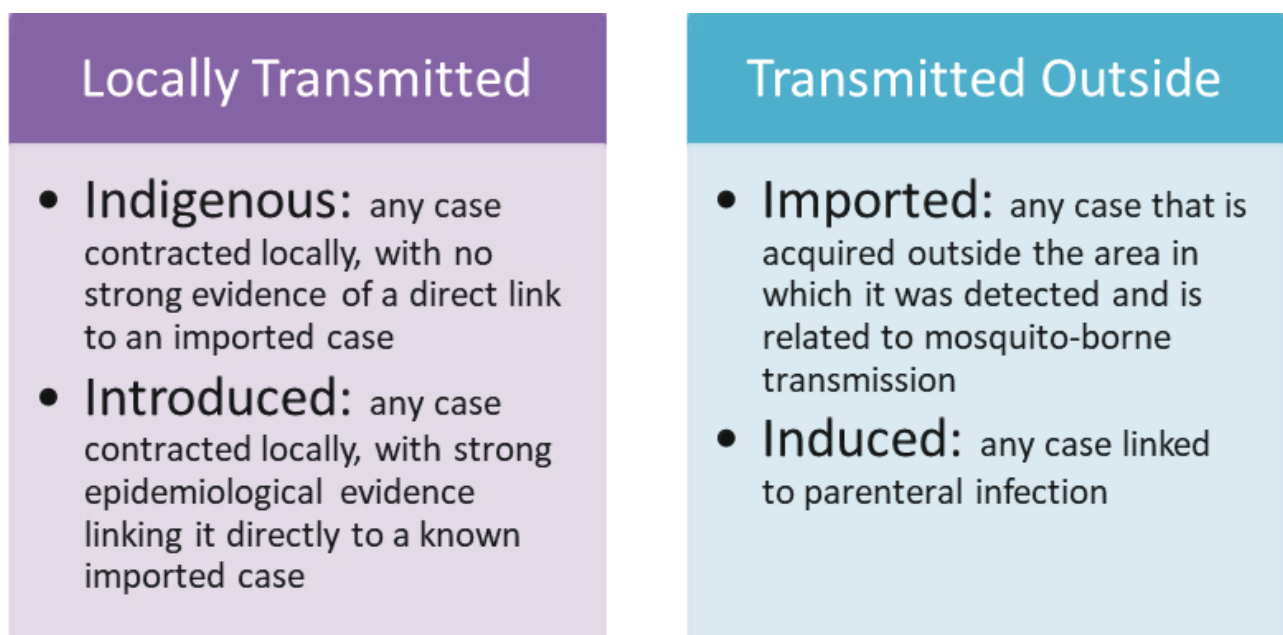
NEW!

Classifying where the people are infected by malaria parasites is necessary to interrupt transmission or to avoid re-introduction

Case classification becomes important especially in the context of implementation of malaria Case Based Surveillance in very low malaria risk strata of the Country. Case classification is a primary reason for further case investigations in the index case household or neighbourhood.

Once a case has been detected it is classified into one of the broad category as locally acquired, imported or induced (see Figure 4).

Figure 4: Case classification diagram



Locally acquired cases

A locally acquired case is one that is due to mosquito-borne transmission and is acquired within the area of detection. The two types of locally acquired malaria cases are:

- indigenous: any case contracted locally, with no strong evidence of a direct link to an imported case; and
- Introduced: any case contracted locally, with strong epidemiological evidence linking it directly to a known imported case (first generation from an imported case; i.e. the mosquito was infected by a patient classified as an imported case). There is limited practical value in classifying cases as introduced in areas of known transmission.

It is difficult to differentiate between introduced and indigenous cases. Both indicate local transmission, showing that malaria control was not strong enough to interrupt transmission. Indigenous transmission is more serious, because it indicates that neither prevention nor treatment contained the spread of malaria.

If the evidence is unclear, the classification that reflects local transmission should be assigned. This conservative classification ensures that local malaria elimination initiatives are more responsive to possible renewed transmission on their foci

Imported cases

An imported case is one that is due to mosquito-borne transmission and is acquired outside the area in which it was detected, in a known malarious area to which the patient has travelled outside the elimination area.

In this protocol, “imported” is a locally imported cases, that is, cases in which infection occurred in areas outside the focus (village) but within the country. Countries listed for elimination global WHO reporting, imported are classified as only if the infection was acquired in another country. Currently, Tanzania mainland is not in global WHO list of countries for malaria elimination.

In endemic countries with ongoing local transmission, local elimination initiatives for all cases occurring during the transmission season, it is sensible to assume a local origin of the infection, unless there is strong evidence to suggest otherwise.

A common mistake especially during transmission season, is to make a general assumption that a case is imported because the local patient visited an council or region known to have low or moderate or high transmission. Most regions or councils with low to high transmissions, however, contain areas in which there is no risk of transmission and therefore, no transmission takes place. Detailed history should be obtained on place of stay in relation to malaria transmission and duration spent in the place of visit. If such detailed information is not available, it is effective to assume a local origin of the infection.

3.4 Clinical diagnosis of malaria

Malaria is an acute disease which exhibits non-specific signs and symptoms. Malaria is clinically suspected mostly on the basis of fever or a history of fever. Diagnosis based on clinical features alone, especially in low and moderate malaria transmission settings, has very low specificity and results in low malaria diagnosis accuracy.

As noted above, early symptoms of malaria are non-specific and similar to the symptoms of a minor systemic viral illness. They comprise: headache, fatigue, abdominal discomfort,

muscle and joint aches, usually followed by fever, chills, perspiration, anorexia vomiting and worsening of malaise. Malaria is, therefore, frequently over-diagnosed on basis of symptoms (clinical diagnosis) alone. At this early stage of disease, if it is malaria, clinically it is classified (diagnosed) as uncomplicated malaria.

However, if the disease progresses to severe form it is diagnosed as severe malaria, the usual cause being delayed treatment or the use of ineffective treatment. Vital organ dysfunction is an indication of severe malaria. Severe malaria usually manifests with one or more of the following: coma (cerebral malaria), severe anaemia, metabolic acidosis, hypoglycaemia, acute renal failure or pulmonary oedema. By this stage of the disease, the case fatality in people receiving treatment is typically 10-20%. However, if left untreated, severe malaria is fatal in the majority of cases. In Tanzania the most common presentations of severe malaria are severe anaemia and cerebral malaria.

Malaria clinical diagnosis at Community level

Management of malaria at the community level is still a big challenge, mainly due to the lack of capacity to correctly diagnose malaria and appropriate regulatory framework. Therefore, selected community members should be adequately trained and empowered to identify symptoms and encourage appropriate management of uncomplicated malaria including testing. The same selected community resources persons will be trained to identify severe malaria symptoms for immediate pre-referral management and referral to the nearest health care facility. The ideal approach for the introduction of community diagnosis and treatment component is the Integrated Community Case Management (iCCM managed by community health volunteers (CHV) for the management of malaria, and when is possible, pneumonia, diarrhoea and malnutrition in children under 5 years of age.

Malaria diagnosis at health facility level

In a health facility, detailed history should be taken and a thorough physical examination made in order to diagnose malaria. A careful assessment of a patient with suspected malaria is essential in order to differentiate between uncomplicated and severe disease.

In children under five years of age, IMCI practical algorithms for management of sick child should be used to ensure full assessment and appropriate case management of children, in particular in the primary level health facilities.

Laboratory investigations should always be done in all health facilities, to confirm malaria clinical diagnosis

3.5 Differential diagnoses of malaria

Malaria features may mimic other disease, therefore, care should be taken when diagnosing malaria and other diseases that may have similar clinical presentation should also be considered. Apart from malaria, the most common causes of acute fever (in approximate descending order of frequency) are :

- Upper respiratory tract infections, including otitis media and tonsillitis (mostly of viral origin)
- Viral diseases (influenza, dengue, human herpes virus 6, parvovirus B19, Epstein-Barr virus, cytomegalovirus, SARS CoV-2, Chikungunya)
- Pneumonia
- Gastroenteritis
- Urinary tract infection

- Typhoid fever
- Skin infection (abscess, cellulitis)
- Sepsis due to bacteremia
- Meningitis

3.6 Parasite-based malaria diagnosis: confirmed malaria

The two recommended diagnostics tests for routine confirmation of malaria diagnosis are quality malaria microscopy and quality mRDT.

According to MoHCDGEC policy, malaria microscopy is a diagnostic investigation based in an established health laboratory. It requires a well-trained skilled staff to perform it, with a minimum qualification of Laboratory Assistant. Malaria microscopy needs an energy source preferable electricity to power the microscope.

mRDTs have made accurate malaria diagnosis potentially accessible to virtually all suspected patients; previously such diagnosis was restricted to people close to clinics or laboratories at which microscopy-based diagnosis could be maintained.

mRDTs are diagnostic investigations which are not necessarily be performed in a health laboratory facility. The testing site should be certified by Quality Assurance Unit under MoH and, in the private sector, by the delegated authority (Private Health Laboratories Board-PHLB). The policy allows the testing site for mRDT to be outside the established registered and approved health laboratory facilities, as long as it is performed by a trained, certified person and given license of practice by Health Laboratory Practitioners Council (HLPC).

To increase access to malaria diagnostics, it is proposed that CHV and ADDO¹⁴ providers should be trained, certified and given license to perform malaria tests using RDT.

Thus, malaria laboratory investigations may be performed depending on the capacity of the facility and the clinical indications. Malaria tests should be made available to all health care services managing malaria suspected cases. For referral cases, additional supportive urgent laboratory investigations should be made available for patients to support patient management.

The role of laboratory in malaria diagnosis

Under the current epidemiological and clinical settings, malaria laboratory investigations are essential to:

- Improve the quality of patient care by confirming parasite-positive patients
- Improve the quality of patient care by identifying parasite-negative patients in whom another diagnosis must be looked for
- Prevent unnecessary use of antimalarials, reducing frequency of adverse effects, especially in those who do not need the medicines, and medicine pressure selection for resistant parasites
- Improve malaria disease surveillance by reporting confirmed cases
- Confirmation of treatment failure by malaria microscopy
- Improve the quality of testing methods through Validation, IQC and EQA performances

Malaria Rapid Diagnostic Tests

Conventional Malaria Rapid Diagnostic Tests

Malaria Rapid Diagnostic Tests (mRDTs) are qualitative techniques which specifically detect antigens (proteins) produced by malaria parasite. The tests can be done by minimally trained personnel, and results can be obtained within 15 to 30 minutes (according to manufacturer instructions). Conventional mRDT have sensitivity and specificity similar to quality assured microscopy. The level of detection of mRDT (and microscopy as well) is between 100-200 parasites per μL .

There are two main groups of commercially available mRDTs:

- Specific antigen mRDT; detects one species of human malaria parasites
- Pan specific antigen mRDT; detects all human species of malaria parasites

The common malaria antigens detected by mRDTs are:

- Histidine-Rich Protein-2 (HRP2). This antigen is expressed by cell membrane of red blood cells parasitized by *P. falciparum*, hence heat stable. It is a highly sensitive antigen for *P. falciparum* only
- Plasmodium Lactate Dehydrogenase (pLDH). This antigen is an enzyme with antigenic properties produced by all Plasmodium species. There are multiple target pLDH antigens, specific for *P. falciparum* only (Pf-pLDH), *P. vivax* only (Pv-pLDH), all non-falciparum malaria species (Pvnm-pLDH) and all malaria species (Pan-pLDH). It is heat unstable
- Aldolase is an enzyme with antigenic properties, produced by all Plasmodium species. It is heat unstable

The above antigens are component of available mRDTs. They can be presented alone or in combination in the same device.

High Specific Malaria Rapid Diagnostic Tests (HS-RDT)

Recently, next-generation highly sensitive rapid diagnostic tests (HS-RDTs) for Plasmodium falciparum have become commercially available. These tests claim a limit of detection that is 10-fold more sensitive than that of conventional rapid diagnostic tests.

The sensitivity of conventional rapid diagnostic tests for malaria is largely adequate in the clinical context for diagnosis of symptomatic malaria suspect patients but might be inadequate for detecting low-density, often asymptomatic infections. The indications for use of next gen malaria diagnostics, including HS-RDT, are investigated worldwide under operational research¹⁵.

In areas where malaria prevalence has decreased, a significant portion of infected individuals may have low-density parasite infections with none or few symptoms. These low-density cases can still transmit infection. The challenge is in identifying such cases, which are not readily detected using conventional rapid diagnostic tests and standard microscopy. The next generation of diagnostics for malaria are supposed to be sensitive enough to detect low-density cases at the point of care so that patients can be treated, and the cycle of transmission broken.

Therefore, in Tanzania the only possible field application, that need further exploration, of HS-RDT is for active case detection (ACD) in very low malaria transmission strata to increase the detection rate of the index case close contacts as indicated in the NMCP case based surveillance¹⁶.

3.7 Choosing a Diagnostic Strategy

The choice of diagnostic strategy on whether to use mRDT or microscopy depends on the local availability of skilled personnel, patient case load, epidemiology of malaria and the use of microscope for diagnosis of other diseases. In areas where case load is high, implementing high quality microscopic testing may be operationally less feasible. Microscopy may have advantage including accurate parasite counting and thus identification of high parasite density, prognostication in severe malaria, speciation of other malaria species and sequential assessment of response to antimalarial treatment.

The target antigens for mRDTs and the detected plasmodium species are summarized in Table 2.

Table 2: Common target antigens for commercially available mRDTs devices

Antigen Device/Species	HRP-2	pLDH	Aldolase
<i>P. falciparum</i> specific	√	√	
<i>P. vivax</i> specific		√	
Pan-specific (all species)		√	√
Non falciparum specific		√	

In Tanzania the recommended mRDT in public health facilities is a combination RDT which is able to detect two antigens: HRP2 and Pan-pLDH

The criteria for choice of mRDTs are explained in Appendix A.

Malaria microscopy

Malaria microscopy is a skilled exercise requiring great care at each step of the standard operating procedures (SOPs) and precise visual and differential skills.

Microscope for detection of malaria parasites

A reliable and well maintained binocular microscope is essential for accurate malaria diagnosis. A binocular microscope with a x7 or x10 eyepiece, a quality immersion oil (refractive index of 1.5) and lens (x100) with a built-in electrical light source is the “**gold standard**”¹⁷.

Stains for detecting malaria parasites

Many stains have been developed for the detection of malaria parasites. The Romanowsky stains have proved the most adaptable and reliable for routine work.

Routine malaria blood smears are judged to be of good quality if smeared and stained as recommended.

Giemsa stain:

The **Giemsa stain** is one of the Romanowsky stains. The alcohol based stain is the “**gold standard**”. It is recommended for routine diagnosis due to its applicability to both thick and thin blood films, its stability during storage and its constant and reproducible staining quality over a range of temperatures.

Quality Giemsa stain used in a reliable and well maintained binocular microscope is the recommended “gold standard” for routine parasite-based malaria diagnosis in health laboratories

For reporting of results of thick and thin blood smears for malaria parasites, see Appendix B.

Which routine malaria test to use at health facility

All patients suspected of having malaria must be confirmed by malaria microscopy or mRDT. It improves the accuracy of malaria diagnosis and ensures that ACT treatment is given to those who really need it.

Treatment solely on the basis of clinical suspicion should only be considered when a parasitological diagnosis is not feasible.

All patients suspected of having malaria must be confirmed by quality malaria microscopy or mRDT. The two malaria parasite-based investigations complement each other to ensure 24-hours access to all suspected patients

- A quality assurance programme for microscopy and mRDT is a prerequisite to implementing appropriate malaria diagnostic services and consequently, to improving malaria case management (see chapter 12)
- For the management of a new suspected uncomplicated malaria case both quality microscopy and quality mRDT have adequate sensitivity for the diagnosis of malaria
- The results of parasitological diagnosis should be available within the short time (<2hrs) of the patient presenting
- In all suspected severe malaria cases microscopy is recommended. For severe malaria management there is the need to assess parasite density for monitoring of treatment response. However, mRDT should also be performed at admission to guide treatment due to possible operational delays of malaria microscopy results. In cases where malaria non-response to treatment (treatment failure) is suspected in-patients who initially tested positive, microscopy is the recommended laboratory procedure. In this instance, mRDT are not recommended because parasite antigens persist up to 4 weeks after parasitaemia has cleared
- HS-RDT use should be restricted for ACD in areas with extremely low malaria transmission under malaria case based surveillance

To maximise the benefits of malaria diagnosis at different levels of health care and in different clinical settings, the strategic framework outlined in Table 3 below should be adhered to

Table 3: Strategic framework for selection of routine malaria test to be used at different levels and in different clinical settings

Health facility level	Clinical setting	• Condition/Remarks	Microscopy	mRDT
Community (CHV, ADDO)	Screening of suspected patients	<ul style="list-style-type: none"> community member received adequate training and supervision regular commodity supply proper storage compliance with blood safety procedures 	NA	Yes *
Dispensary without lab facilities	Screening of suspected malaria patients at OPD	<ul style="list-style-type: none"> non lab trained testers (health care workers to be trained) 	NA	Yes
	Follow up of patients previously tested positive and with persistent malaria symptoms between 4-14 days (suspect drug failure)	<ul style="list-style-type: none"> mRDTs not to be used due to persistent antigenaemia. 	NA*	No*
	Screening of Severe illness before referral		NA*	Yes*
Dispensary with lab facility	Screening of suspected malaria patients at OPD	<ul style="list-style-type: none"> non lab trained testers (health care workers to be trained) 	No	Yes
		<ul style="list-style-type: none"> registered and Certified ** personnel available low workload quality assurance in place electricity available 	Yes	Yes
Health Centre and Hospital with lab facilities	Screening of suspected malaria patients at OPD	<ul style="list-style-type: none"> low workload quality assurance in place, registered and certified ** personnel available electricity available 	Yes	No
	Screening of suspected malaria patients at OPD	<ul style="list-style-type: none"> high workload peak hours quality assurance not in place, registered and certified ** personnel not available, electricity not available 	No	Yes
	Severe malaria cases upon admission	<ul style="list-style-type: none"> Parasite density needed 	Yes	Yes
	Follow up of admitted patients	<ul style="list-style-type: none"> Parasite density needed 	Yes	No
	Follow up of patients previously tested positive and with persistent malaria symptoms (suspect drug failure)	<ul style="list-style-type: none"> mRDTs not to be used due to persistent antigenaemia 	Yes	No
Malaria outbreak investigation		<ul style="list-style-type: none"> Competent and trained personnel 	Yes	Yes
Malaria epidemic follow up		<ul style="list-style-type: none"> Blood smears are taken in the field for later examination by registered and qualified personnel mRDTs not to be used due to persistent antigenaemia 	Yes	No
Areas targeting 0 (zero) local transmission	Actively and passively patients tested with mRDT and pan antigen positive needs to confirm speciation	<ul style="list-style-type: none"> If competent lab personnel are available perform thin BS and report species If competent lab personnel is NOT available BS (or dry Blood spot - DBS) taken and stored for supervisor action 	Yes	Yes
Community surveys		<ul style="list-style-type: none"> Blood smears are taken in the field for later examination by registered and qualified Lab personnel 	Yes	Yes
Malaria testing at first antenatal attendance		<ul style="list-style-type: none"> Competent and trained personnel or non lab trained testers (health care workers to be trained) for mRDT 	Yes	Yes
Active case detection	In very low transmission risk settings targeting malaria elimination under malaria case based surveillance	<ul style="list-style-type: none"> In this epidemiological setting high sensitive mRDTs provide larger detection rate (below 100-200 parasite per μL) 	No	Yes
* use of RDTs for household malaria management depends on availability of appropriate supportive strategic framework at this level				
** Microscopist should be certified after attending special training on malaria microscopy under NMCP supervision				
* Patient should be referred for microscopic examination at another facility				

4 Management of Uncomplicated malaria

4.0 The objectives of uncomplicated malaria case management

This chapter of the guidelines intends to stipulate the standard therapeutic regimens to be adhered by clinicians at all level of health care within the public and private system.

The ultimate objective of appropriate management of malaria cases is to limit progression of malaria infection into severe disease and eventually death.

4.1 Clinical features of uncomplicated malaria

NEW!

In the current epidemiological transition clinical features are related to biological and environmental vulnerability

Diagnosis of malaria begins with clinical assessment of patients, through detailed history taking and recording of signs and symptoms. Malaria signs and symptoms are non-specific and may mimic symptoms of systemic viral illnesses or other disease conditions. The occurrence of malaria signs and symptoms may differ in children and adults and in population living in different malaria risk strata according to the immunity status. The main features of malaria are included in Table 4.

Table 4: Clinical features of uncomplicated malaria and expected frequency in children below 5 years of age and adults

Features	Broad age group		Malaria risk setting	
	< 5 years	>5 years and adults	Very low and low	Moderate and high
Fever	+++	+	+++	+
Vomiting/Diarrhea	+++	+	+++	+
Pallor	+++	+	+++	+
Poor appetite	++	++	++	++
Body weakness	++	++	++	++
Enlarged spleen	++	+	++	+
Headache	+	++	+	++
Joint pains	+	++	+	++
Malaise	+	++	+	++
Body ache	+	++	+	++

Note: +++ - most frequent; ++ - intermediate/moderate; + - Least frequent

4.2 Treatment of uncomplicated malaria using combination therapy

Artemisinin and semisynthetic derivatives, including artesunate, artemether and dihydroartemisinin, are short-acting antimalarial agents that kill parasites more rapidly than conventional antimalarials and are active against both the sexual and asexual stages of the parasite cycle. Artemisinin fever clearance time is shortened to 32 hours as compared with 2–3 days with older agents. To delay or prevent emergence of resistance, artemisinins are combined with one of several longer-acting drugs which permit elimination of the residual malarial parasites. ACTs combine the rapid schizontocidal activity of an artemisinin derivative with a longer-half-life partner drug. Combinations of chemotherapeutic agents can accelerate therapeutic response, improve cure rates and protect the component drugs against resistance. The artemisinin component provides a well-tolerated drug with a unique mode of action that clears asexual forms quickly and has gametocidal activity. The partner drug should be one that is also well tolerated and non-toxic, but which is present in the blood at therapeutic concentrations for at least several times the duration of the parasite lifecycle (48 hours in the case of *P. falciparum*).

Treatment of the uncomplicated malaria is accomplished by using a fixed dose **combination therapy** of two or more blood schizontocidal medicines with independent modes of action to improve therapeutic efficacy and delay the development of resistance to the individual components of the combination.

Artemisinin-based combination treatments (ACTs) are recommended by WHO to be used for the treatment of uncomplicated malaria. ACTs are combinations in which one of the components is Artemisinin derivatives (e.g. Artesunate, Artemether, and Dihydroartemisinin etc.); and other component is an antimalarial medicine with a known good efficacy profile (e.g. Lumefantrine, Piperaquine, Mefloquine, Amodiaquine).

The Artemisinin compounds are active against all four species of malaria parasites that infect humans and are generally well tolerated.

Artemisinin and its derivatives (Artesunate, Artemether, and Dihydroartemisinin) should not be used as monotherapy.

For the ACTs to eliminate at least 90% of the parasitaemia, a 3-day course of the Artemisinin is required. This ensures that only about 10% of the parasitaemia is present for clearance by the partner medicine (e.g. Lumefantrine, Piperaquine, Mefloquine, Amodiaquine etc.).

Uncomplicated malaria treatment should include at least 3 days with an Artemisinin derivatives (ACT) for an optimum effect

In Tanzania, the ACT of choice for the treatment of uncomplicated malaria is Artemether-Lumefantrine (AL). The alternative medicines for the treatment of uncomplicated malaria, where there is no response to Artemether-Lumefantrine or it is contraindicated, are Dihydroartemisinin-Piperaquine (DP) and Artesunate-Amodiaquine (ASAQ).

4.3 Treatment of uncomplicated malaria with medicine of choice: Artemether-Lumefantrine

Artemether-Lumefantrine (AL) is the medicine of choice for the treatment of uncomplicated malaria. Its therapeutic efficacy, remains above 90% (evaluated at Day 28, with PCR correction, following WHO standard protocol)

An added advantage of this combination is that Lumefantrine is not available as a monotherapy for the treatment of malaria.

Medicine description:

Artemether-Lumefantrine (AL) is an oral fixed combination tablet of 20mg Artemether, and 120mg Lumefantrine.

Artemether is effective against all four human malaria parasites species and has rapid schizonticidal action against *Plasmodium falciparum*. However, recrudescence is frequent when it is used as a monotherapy. Lumefantrine is an aryl amino alcohol with a long elimination half-life of up to 10 days and is associated with a low recrudescence rate but it has a slow onset of action. AL has high cure rate as it combines the benefits of the fast onset of action of Artemether with the long duration of action of Lumefantrine in a single oral formulation. It is highly efficacious even against multi medicine resistant malaria parasites with clearance of the parasites from the blood within 2 days.

Available formulations:

Standards Tablets:

NEW!

The new formulation of Artemether 80mg Lumefantrine 480mg might improve compliance in adults.

- Fixed formulation Artemether 20mg, Lumefantrine 120mg; 6, 12, 18 and 24 tablets blister
- Fixed formulation Artemether 80mg, Lumefantrine 480mg; 6 tablets blister Dispersible tablets: Fixed formulation for children.
- Artemether 20mg, Lumefantrine 120mg 6 tablets blister (5–14kg): 1 tablet; 15–24 kg: 2 tablets)
- Artemether 20mg, Lumefantrine 120mg 12 tablets blister (15–24 kg: 2 tablets)

Indications:

AL is the treatment of choice for uncomplicated malaria in all age groups and all trimesters during pregnancy.

NEW!

Artemether Lumefantrine is safe in first trimester of pregnancy and is the recommended therapeutic option

Contraindications:

Hypersensitivity to either Artemether or Lumefantrine

Adverse effects of Artemether-Lumefantrine (AL)

While the overall incidence of side effects to AL is low, the common adverse effects reported include sleep disorders, headache, dizziness, nausea, anorexia, abdominal pain, pruritus, rash, cough, palpitation, arthralgia and myalgia. Lumefantrine does not cause prolongation of Q-T intervals and therefore it is safe in patients with cardiac illness.

Medicine interactions:

The manufacturer of AL recommends avoiding the following: grapefruit juice; antiarrhythmics, such as amiodarone, disopyramide, flecainide, procainamide and quinidine; antibacterials, such as macrolides and quinolones; all antidepressants; antifungals such as imidazoles and triazoles; terfenadine; other antimalarials; all antipsychotic drugs; and beta blockers, such as metoprolol and sotalol.

AL administration:

- The first dose of AL should preferably be administered at the health service delivery point, as direct observed treatment (DOT)
- If the medicine is vomited or spat out within 30 minutes, the dose should be repeated
- AL should be taken with fat meals to enhance its absorption

Dosage regimen:

The recommended treatment is a 6-dose regimen over a 3-day period.

The dosing of the standard “20/120” formulation (Artemether 20mg, Lumefantrine 120mg) is based on the number of tablets per dose according to pre-defined weight bands (5–14 kg: 1 tablet; 15–24 kg: 2 tablets; 25–34 kg: 3 tablets; and > 34 kg: 4 tablets), given twice a day for 3 days.

The dosing of the “80/480” formulation (Artemether 80mg, Lumefantrine 480mg) for patient weighting > 34 kg: is 1 tablet given twice a day for 3 days.

The above recommended regimen approach is more convenient, rather than the use of extrapolates to 1.7/12 mg/kg body weight of Artemether and Lumefantrine, respectively, per dose, given twice a day for 3 days, with a therapeutic dose range of 1.4–4 mg/kg of Artemether and 10–16 mg/kg of Lumefantrine.

Treatment on the basis of clinical suspicion alone should only be considered when parasitological diagnosis is not accessible

The recommended dosing schedule for AL (strength 20/120 mg) is reported in Table 5.

Table 5: Dosage schedule of Artemether 20mg & Lumefantrine 120 mg (AL) (number of tablets recommended at approximate timing of dosing)

Kg	Dose	Day 1		Day 2		Day 3	
		1 st	2 nd	3 rd	4 th	5 th	6 th
	Hours	0 (*)	8	24	36	48	60
	Age (years)	tablets	Tablets	tablets	Tablets	Tablets	Tablets
5 up to 15	0 to 3	1	1	1	1	1	1
15 up to 25	3up to 8	2	2	2	2	2	2
25 up to 35	8up to 12	3	3	3	3	3	3
35 and above	12 and above	4	4	4	4	4	4
(*) 0 hours means the time of starting medication (see appendix D for time schedule for 1 st and 2 nd dose)							

For practical purposes, a simpler dosage regimen is recommended in order to improve compliance: the first dose should be given as DOT; the second dose should strictly be given after 8 hours; subsequent doses could be given twice daily (morning-evening) in the second and third day of treatment until completion of 6 doses

The recommended dosing schedule for AL strength 80/480 mg is reported in Table 6.

Table 6: Dosage schedule of Artemether 80mg & Lumefantrine 480 mg 'AL 40/480' (number of tablets recommended at approximate timing of dosing)

Kg	Dose	Day 1		Day 2		Day 3	
		1 st	2 nd	3 rd	4 th	5 th	6 th
	Hours	0 (*)	8	24	36	48	60
	Age (years)	tablets	Tablets	tablets	Tablets	tablets	Tablets
35 and above	12 and above	1	1	1	1	1	1
(*) 0 hours means the time of starting medication (see appendix D for time schedule for 1 st and 2 nd dose)							

Non response to AL may be due to:

- Vomiting the medicine
- Inadequate dose and dosage regimen
- Poor quality of the medicine
- Fever/symptoms from a cause other than malaria
- Parasite resistance to the medicine
- Drug interaction(s)
- Individual pharmacogenomics

Management of non-response to malaria treatment with AL

Treatment failure within 14 days of receiving an ACT in malaria confirmed patient is unusual. When a confirmed patient returns between 4 to 14 days after treatment with AL complaining of continued symptoms of malaria, non-response should be considered, and the following recommendations followed after a full history, examination and laboratory tests:

- Where laboratory facilities are not available and malaria is still suspected, treatment with DP should be started immediately after thoroughly assessment for other causes of identified symptoms, provide referral if necessary, and do strict follow-up.
- Where laboratory facilities are available, a blood smear (and not mRDT) should be examined. If parasites are found, treatment with DP should be started and treatment failure recorded. If parasites are not found, other causes for the symptoms should be sought and treated accordingly

Health providers should instruct the patient, or caretaker, to return to the health service delivery points in 2 days if symptoms persist or immediately if condition worsens

Health workers should immediately refer cases that fail to respond to the recommended medicine regimen for further investigations and appropriate management

4.4 Other ACT options for the treatment of uncomplicated malaria

Recommended ACT options for the treatment of uncomplicated malaria are those with a minimum 3-day course.

The partner medicines in an Artemisinin based combination must, independently, be sufficiently efficacious in treating malaria. Reported resistance to a partner medicine is a significant factor, thus, the higher rates of resistance to a partner medicine the lower the recommendation for the ACT in question.

Efficacious combinations improve treatment outcomes; in parasites resistant to one of the medications in the combination, then the other antimalarial medicine by ensuring that parasites are killed. This mutual protection is thought to prevent or delay the emergence of resistance especially to Artemisinin compounds.

The most recommended regimens are fixed dose combination regimens. These ensure that patients take both medicines together in the right dose. Patient adherence to treatment is also a major determinant of the response to antimalarial medicines, as most treatments are taken at home without medical supervision.

Dihydroartemisinin-Piperaquine (DP)

Medicine description

The recommended formulation is an oral fixed combination tablet of Dihydroartemisinin- a derivative of Artemisinin and Piperaquine.

Dihydroartemisinin is the main active metabolite of the Artemisinin derivatives. It has cure rates, toxicity and medicine interaction close to those of other oral Artemisinin derivatives.

Piperaquine is an antimalarial compound belonging to the 4-aminoquinolines.

NEW!

For children weighting <25 kg, the target doses are: 4 mg/kg bw per day of Dihydroartemisinin and 24 mg/kg bw per day of Piperaquine given once a day for 3 days

The exact mechanism of action of Piperaquine is still unknown. It is reasonable to assume that the compound has similar targets as chloroquine considering the close structural resemblance.

Piperaquine is highly active in vitro against both chloroquine-sensitive and chloroquine-resistant isolates of *P. falciparum*.

Piperaquine is less toxic than chloroquine or Amodiaquine. However similar cardiovascular side-effects could be seen manifesting such as sinus bradycardia, asymptomatic prolongation of QT interval, which correlates with the food-dependent plasma levels of Piperaquine. Due to this finding Piperaquine should be administered with water without food to minimize these side effects.

The prolonged duration of post-treatment of the Piperaquine combination is evidence for the benefit of Piperaquine as a partner medicine in ACTs.²¹

Available formulation

- Fixed-dose combination with tablets containing Dihydroartemisinin (DHA) and Piperaquine (PPQ)
- Two strengths for the above formulation:
40 mg DHA + 320 mg PPQ
20 mg DHA + 160 mg PPQ (for paediatric formulation)

Indications

- Alternative medicine of choice for the treatment of uncomplicated malaria
- Treatment of uncomplicated malaria where AL is contraindicated
- Treatment of uncomplicated malaria where AL has failed
- Medicine of preventive treatment where applicable

Contraindications

- Hypersensitivity to either Dihydroartemisinin or Piperaquine

Adverse effects

- DP does cause sinus bradycardia and asymptomatic prolongation of QT interval. Therefore, it is to be given with caution in patients with cardiac illness
- Other known adverse effects related to treatment are, nausea, anorexia, body weakness (asthenia), dizziness and headache

Dosage regimen

For children weighting <25 kg, the target doses are: 4 mg/kg bw (range 2.5-10) per day of Dihydroartemisinin and 24 mg/kg bw (range 20-32) per day of Piperaquine given once a day for 3 days.

For adults and children weighting >25 Kg, a target dose of 4 mg/kg (range 2-10) per day of Dihydroartemisinin and 18 mg/kg (range 16-27) per day of Piperaquine given once a day for 3 days.

Table 7 below gives guidance on dosage schedule for malaria treatment using two different strength DP tablets for different pre-defined groups of body weights.

Table 7: Dosage schedule for DP: 4 mg/kg/day Dihydroartemisinin and 18 mg/kg/day Piperaquine once a day for 3 days,

Body Weight (kg)	Daily dose (mg)		Tablet strength	Number of tablets per dose
	Dihydro artemisinin	Piperaquine		
5 to <8	20	160	20mg / 160mg	1 tablet x 3 days
8 to <11	30	240	20mg / 160mg	1 ½ tablet x 3 days
11 to <17	40	320	40mg / 320mg	1 tablet x 3 days
17 to <25	60	480	40mg / 320mg	1 ½ tablet x 3 days
25 to <36	80	640	40mg / 320mg	2 tablets x 3 days
36 - <60	120	960	40mg / 320mg	3 tablets x 3 days
60 to <80	160	1,280	40mg / 320mg	4 tablets x 3 days
>80	200	1,600	40mg / 320mg	5 tablets x 3 days

Artesunate-Amodiaquine

Available formulations

- Fixed –dose formulation with tablets containing 25/67.5 mg, 50/135 mg or 100/270 mg of Artesunate and Amodiaquine respectively

- Separate tablets: containing 50 mg of Artesunate and 135 mg base of Amodiaquine respectively

Indications:

- Treatment of uncomplicated malaria
- Alternative medicine of choice for the treatment of uncomplicated malaria when AL is contraindicated where AL has failed

Adverse Events

ASAQ is generally well tolerated but is associated with higher incidence of gastrointestinal disturbances than other ACT. Other commonly reported adverse events include cough, anorexia, insomnia, fatigue and weakness. Serious adverse events associated with amodiaquine are neutropenia and hepatotoxicity. Long term use of amodiaquine is associated with agranulocytosis. ASAQ is generally well tolerated in children, and no serious adverse events have been reported.

Dosage regimen

A target dose artesunate: 4 mg/kg/day and 10 mg/kg/day Amodiaquine once a day for 3 days (see Table 8).

Table 8: Dosing Schedule for Artesunate-Amodiaquine

Body weight ranges (age ranges)	Co-blistered 50mg Artesunate (AS) and 135mg Amodiaquine (AQ) Number of tablets	Fixed dose combination artesunate / amodiaquine	
		Formulation strength	Number of tablets
≥4.5kg to < 9 kg (2 to 11 months)	½ tablet of AS and ½ tablet of AQ per day for 3 days	25mg artesunate/67.5mg amodiaquine	1 tablet per day for 3 days
≥9kg to <18kg (1 to 5 years)	1 tablet of AS and 1 tablet of AQ per day for 3 days	50mg artesunate/135mg amodiaquine	1 tablet per day for 3 days
≥18kg to <36kg (6 to 13 years)	2 tablets of AS and 2 tablets of AQ per day for 3 days	100mg artesunate/270mg amodiaquine	1 tablet per day for 3 days
≥ 36kg (14 years and above)	4 tablets of AS and 4 tablets of AQ per day for 3 days	100mg artesunate/270mg amodiaquine	2 tablets per day for 3 days

Artesunate - Mefloquine

Available formulations

This is currently available as blister packs with separate scored tablets containing 50 mg of Artesunate and 250 mg base of Mefloquine, respectively.

Adverse effects

Mefloquine is associated with an increased incidence of nausea, vomiting, dizziness, dysphoria and sleep disturbance in clinical trials, but these are seldom incapacitating. Where this ACT has been deployed it has been well tolerated.

Indications

Treatment of uncomplicated malaria.

Dosage regimen

The target dose is Artesunate 4 mg/kg/day given once a day for 3 days, and 25 mg/kg of Mefloquine split over 2 days as 15 mg/kg and 10 mg/kg. See Table 9.

Table 9: Dosing Schedule for Artesunate-Mefloquine

Age	Dose in mg (no. of tablets)					
	Artesunate			Mefloquine (base)		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5–11 months	25 (½)	25	25	–	125 (½)	–
1–6 years	50 (1)	50	50	–	250 (1)	–
7–13 years	100 (2)	100	100	–	500 (2)	250 (1)
>13 years	200 (4)	200	200	–	1000 (4)	500 (2)

**Alternatively, the total dose of mefloquine may be split into three, with one third of the dose being taken on days 1, 2 and 3*

Artesunate-Pyronaridine

Considering recent positive scientific opinion of EMA under Art. 58 and registration by Tanzanian MDA, Artesunate-Pyronaridine is recently available for use in the private sector in Tanzania. Deployment should be conducted under a pharmacovigilance system as required for the introduction of all new medicines .

NEW!

Artesunate Pyronaridine is the new comer in the ACT family

Composition

Each tablet contains 180 mg Pyronaridine tetraphosphate and 60 mg Artesunate.

Pharmaceutical Formulation

Film-coated tablet Round, biconvex, orange coloured tablet.

A granule formulation is available for children weighing between 5 kg to under 20 kg.

Therapeutic indications

Artesunate-Pyronaridine (AP) tablets are indicated in the treatment of acute, uncomplicated malaria infection caused by *Plasmodium falciparum* or by *Plasmodium vivax* in adults and children weighing 20 kg or more.

Method of administration

The dose should be taken orally once a day for three days with or without food.

Posology

Dosage in adults and children Artesunate-Pyronaridine tablets should be taken orally as a single daily dose for three consecutive days.

In the event of vomiting within 30 minutes of administration after the first dose, a repeat dose should be given. If the repeat dose is vomited, the patient should be given an alternative

antimalarial drug. In the event of non-severe diarrhoea normal dosing should be continued. If a dose is missed, it should be taken as soon as realised and then the recommended regimen continued until the full course of treatment has been completed.

Contraindications

- Known hypersensitivity to pyronaridine or artesunate or any component of the formulation.
- Patients with clinical signs or symptoms of hepatic injury (such as nausea and/or abdominal pain associated with jaundice) or known severe liver disease
- Severe renal impairment

Adverse Effects

AP has been associated, in some patients, with transient increases in liver enzymes without clinical signs. If a patient is already known to have elevated transaminases the use of AP is not recommended.

Table 10: Dosage regimen for Pyronaridine tetraphosphate 60mg and Artesunate 20 mg granular paediatric formulation

Body weight	Number of sachets	Regimen
5- < 8 kg	1 sachet	Daily for 3 days
8 - < 15 kg	2 sachets	Daily for 3 days
15 - < 29 kg	3 sachets	Daily for 3 days

Table 11: Dosage regimen for Pyronaridine tetraphosphate 180 mg and Artesunate 60 mg

Body weight	Number of tablets	Regimen
20 - < 24 kg	1 tablet	Daily for 3 days
24 - < 45 kg	2 tablets	Daily for 3 days
45 - < 65 kg	3 tablets	Daily for 3 days
≥ 65 kg	4 tablets	Daily for 3 days

4.5 Treatment of Malaria using ACT plus Primaquine

NEW!

To reduce transmissibility of treated malaria infection, in very low transmission areas, give a Single Low Dose (SLD) of 0.25 mg/kg/BW Primaquine with ACT to malaria patients

In contrast to other antimalarial medicine groups, the Artemisinin have marked effects on all stages of the parasite, the parasite viability declining soon after the start of treatment leading to quick patient recovery.

Artemisinin based medicines have the effect on mature gametocyte stage (gametocytocidal effects) on *P. falciparum*, and this help to reduce transmission.

Though ACTs reduce gametocyte carriage and transmission markedly, this effect is limited to early stage immature gametocytes hence not complete.

The addition of a low single dose of Primaquine (0.25mg/kg maximum of 15mg in adults) to ACTs

treatment should be given to all eligible patients because it affects the transmissibility of mature gametocytes of *P. falciparum* by minimizing further transmission of the disease.

Formulation: Primaquine is available in the formulation of tablets 7.5 mg and 15 mg.

Dosage: A single 0.25 mg base/kg Primaquine dose (Table 12) should be given to all patients with parasitological confirmed malaria, (see exceptions under 'not recommended').

Not recommended

In pregnant women, women in the first 6 months of breastfeeding and children less than 6 months of age.

Adverse Events

Haemolytic Anemia, especially in G6PD individuals, is the major adverse event reported. Although, single low dose of Primaquine is considered to be safe.

Indications

Primaquine should be given on the first day of treatment in addition to an ACT, preferably under Directly Observed Therapy (DOT).

Primaquine alone has no clinical cure effect and should always be associated, when indicated, to an efficacious ACT

Table 12: Dosage of Primaquine single dose (0.25mg/kg)

Weight	Age (Months/Years)	Single dosage (tablets)	
		7.5 mg	15 mg
	< 6 months	Contraindicated	
≤ 10 kg	6 <12 months (Infants)	¼ tablet	
10-20 kg	1-6 years (Young Children)	1/2 tablet	
21-40 kg	7-13 years (Children)	1 tablet	½ tablet
>40 Kgs	Adults 14 years and above	2 tablets	1 tablet

4.6 Management of fever

Patients with high fever (38.5°C and above) should be given an anti-pyretic medicine like paracetamol (Table 13) or aspirin every 4 to 6 hours (maximum 4 doses in 24 hours) until symptoms resolve, usually after two days. Children below 12 years should not be given aspirin because of the risk of developing Reye's syndrome.

Table 13: Treatment schedule for paracetamol (500mg) tablets dosage for children: 10 mg/Kg bwt

Weight	Age (Months/Years)	Single dosage (tablets)	
		7.5 mg	15 mg
	< 6 months	Contraindicated	
≤ 10 kg	6 <12 months (Infants)	¼ tablet	
10-20 kg	1-6 years (Young Children)	1/2 tablet	
21-40 kg	7-13 years (Children)	1 tablet	½ tablet
>40 Kgs	Adults 14 years and above	2 tablets	1 tablet

4.7 Recommendations to be given to uncomplicated malaria patient/caretakers

The time of consultation, testing and prescription is a unique and critical opportunity for the health care provider to counsel and advise the patient or the caretaker. In this occasion health education messages should focus on the following:

- Importance of compliance to the parasitological results, antimalarial treatment if test positive, and further investigation if test negative
- Doses, schedules and route
- When to return immediately; worsening conditions especially when fever remains high, excessive vomiting and extreme weakness
- Continue with feeding and fluid intake
- When to return for follow up to the health facility; If symptoms persist after completing correct treatment
- Personal protection measures especially use of long lasting insecticide treated nets

The benefit of parasitological diagnosis depends entirely on health providers adhering to the results when managing patients with uncomplicated malaria

5 Management of Severe Malaria

5.0 The primary objectives of Severe Malaria Management

Severe *Plasmodium falciparum* malaria is a medical emergency. Delay in diagnosis and provision of appropriate treatment may lead to serious complications and even death. In Tanzania the most common presentations of severe malaria are severe anaemia and cerebral malaria.

***The primary objectives of treatment of severe malaria are:
a) prevent death and, b) prevent further complications and disabilities***

5.1 Principles for the management of severe malaria

In the management of all cases of severe malaria, concerns about prevention of recrudescence, use of Injectable monotherapy in the first 24 hours instead of combination therapies and avoidance of minor side effects are not primary objectives.

Death from severe malaria often occurs within hours of admission to hospital or clinic, so it is essential that highly effective management be achieved as soon as possible.

Management of severe malaria comprises of four main areas; rapid clinical assessment, management of emergency condition, specific antimalarial treatment and supportive care.

Rapid clinical assessment of the patient

Severe malaria is a potentially fatal medical emergency; thus, assessment of the patient's condition must be conducted with minimum loss of time. An open airway should be secured in unconscious patients and breathing and circulation assessed. The patient should be weighed or body weight estimated, so that medicines, including antimalarial and fluids, can be given accordingly. Differential diagnosis must be made, malaria tests and relevant supportive investigation performed, see section 3.4.

Management of emergency conditions

After the rapid assessment, open airway should be secured in unconscious patients, providing respiratory support, if necessary, and circulation maintained. Convulsions and coma should be managed and severe dehydration corrected.

Specific antimalarial treatment

After above rapid clinical assessment and provisional diagnosis, while waiting for parasite-based confirmatory investigation results, parenteral antimalarial treatment should be started without delay with whichever first available recommended effective antimalarial.

Supportive care

In an attempt to reduce the high mortality of severe malaria caused by complications, supportive treatments should be provided for any complication which appears. Supportive treatment is determined by level of health care delivery and existing capacity.

5.2 Clinical features and conditions related to severe malaria

Features of severe malaria

If the disease progress to a severe form it is diagnosed as severe malaria. Categorisation of a case as severe malaria is due to evidence of vital organ dysfunction. One or more of the features in Table 14 indicate severe malaria.

Table 14: *Features of severe malaria*

Clinical features	Description/criteria
Prostration/extreme weakness	Unable to stand or sit up without support
Impaired consciousness	Altered level of consciousness Coma
Change of behaviour	Hallucinations, delusions, agitation Acute state of confusion
Convulsions	Repetitive abnormal muscular movements
Respiratory distress (due to lactic acidosis and/or pulmonary oedema)	<i>Acidotic breathing</i> : deep and laboured breathing <i>Pulmonary oedema</i> : laboured breathing, restlessness, blood stained frothy sputum
Bleeding tendency/DIC	Easy/prolonged bleeding
Jaundice	Yellow colouration of mucus membranes
Circulatory collapse/shock*	Low systolic BP ** and fast pulse rate ***
Vomiting everything	Throwing up after every feed/drink
Inability to drink or breast feed	Not able to swallow
*Shock: cold extremities, capillary refill delayed for ≥ 3 seconds (when a nail of the thumb is pressed); weak and fast pulse;	
** Low systolic BP <50 mmHg in children and <90 mmHg in adults;	
*** Fast pulse rate ≥ 150 per minute in children and ≥ 100 beats per minute in adults;	

The occurrence of features associated to severe malaria are related to the age of the patient and are summarised in Table 15.

Table 15: Clinical features of severe malaria and expected frequency by age group

Clinical features- severe malaria	<5 years	>5 and adults
Duration of illness	Short (1-2 days)	5-7 days
Behavioural Changes	+	+++
Prostration/Extreme weakness	+++	+++
Posturing (decorticate/decerebrate and opisthotonic rigidity)	+++	+
Coma	+++	++
Resolution of coma	1-2 days	2-4 days
Neurological sequelae after cerebral malaria	++ (5-30%)	+ (1%)
Respiratory distress	+++	++
Metabolic acidosis	++	++
Convulsions	+++ (30%)	+ (12%)
Hypoglycaemia	++	+
Vomiting everything	++	+
Inability to drink or breast feed	++	+
Circulatory collapse/Shock	+	++
Pulmonary oedema	+	+
Bleeding tendency /DIC	+	++ (up to 10%)
Jaundice	+	+++
Acute Renal Failure	+	++
Haemoglobinuria	+	++
Invasive Bacterial co-infection	++ (10%)	+ (<5%)
+ = less common, ++ = common, +++ = Very common		

Conditions related to severe malaria

Malaria infection may cause vital organ dysfunction and death. The common conditions associated with severe malaria and the corresponding laboratory indices are listed in Table 16.

Table 16: Common conditions observed in severe malaria cases

Condition	Corresponding Laboratory Indices	Frequency of condition by agegroup	
		<5 years	>5 and adults
Severe malarial anaemia	Hb <5g/dl in children or 7g/dl in pregnant women	+++	+
Haemoglobinuria	Dark brown or Positive Hb on dipstick urine	+	++
Pulmonary oedema	Chest X-ray findings	++	++
Metabolic acidosis	Arterial pH <7.3, Plasma lactate > 5 mmol/L or Plasma bicarbonate < 15 mmol/L	+++	++
Acute renal failure	Oliguria urine output <0.3 ml/kg/hr in children and <17ml/hr in adults Raised serum creatinine >265 mmol/L	+	+++
Hypoglycaemia	Glucose <2.5 mmol/L	+++	++
Uraemia	BUN >6.7 mmol/L	+	+++
Hyponatraemia	<130 mmol/L	+	+

Hyperparasitaemia

Hyperparasitaemia refers to a parasite density of over 200,000 parasites per μL . This level of parasitaemia might be present in patients with no signs of severity (uncomplicated hyperparasitaemia). However, a high density of parasites in the blood increases the risk of deterioration of uncomplicated to severe malaria and of subsequent treatment failure. The risk varies in different endemic areas according to the level of malaria transmission. In low transmission settings, mortality begins to increase when the parasite density exceeds 100,000/ μL . In higher transmission settings the risk of developing severe malaria in patient with hyperparasitaemia is lower, but uncomplicated hyperparasitaemia is associated with high rate of treatment failure. Close monitoring and admission are recommended to patients with hyperparasitaemia even with no signs of severity.

Supportive investigations for suspected severe malaria ill patients

Laboratory diagnosis of malaria can be complemented with other laboratory tests such as:

- Blood glucose estimation in patients with altered consciousness
- Haematocrit and/or haemoglobin estimation
- Lumbar puncture (LP) to exclude meningitis at hospital and health centre levels (if facilities for LP assessment are available)

The following investigations, if available, are also helpful in the management of severely ill patient suspected of having severe malaria:

- Serum creatinine or urea- to assess Kidney function
- Electrolytes- for early detection of acute renal failure
- Full blood cell count and differential white cell count for additional diagnosis of other infectious diseases
- Blood gases, pH and anion gap- to diagnose acidosis

N.B. Plasma and cerebrospinal fluid lactate concentrations. These are raised in metabolic acidosis. High levels are associated with a poor prognosis

Radiological investigation:

- Chest X-ray; look for pulmonary oedema or lobar consolidation

5.3 Treatment of severe malaria

The medicine of choice for treatment of severe malaria is Artesunate Injectable. Artemether injectable is to be used when Artesunate is not indicated or is not available.

Give Injectable antimalarials for the treatment of severe malaria for a minimum of 24 hours, even if the patient can tolerate oral medication earlier than 24 hours. Complete treatment by giving a complete course of Artemether-Lumefantrine.

Artesunate for injection

Description of medicine

Artesunate is a water-soluble derivative of Artemisinin. The only Artemisinin analogue that can be given intravenously, it produces rapid parasite clearance in falciparum malaria.

Available formulations

Three formulations are available: 30mg, 60mg and 120mg of Artesunate for injection.

The recommended formulation for public sector is 60mg.

Package details are in Table 17.

Table 17: Artesunate for injection package by strength

Strength	30 mg	60 mg	120 mg
Artesunate for injection	1 vial of 30 mg	1 vial of 60 mg	1 vial of 120 mg
Sodium bicarbonate 5%	1 ampoule of 0.5 ml	1 ampoule of 1 ml	1 ampoule of 2.5 ml
Sodium chloride	1 ampoule of 2.5 ml	1 ampoule of 5 ml	1 ampoule of 10 ml

NEW!

Artesunate Injectable is the recommended treatment for severe malaria in all trimester of pregnancy

Indications

Medicine of choice for treatment of severe malaria in all age groups and all trimesters during pregnancy.

Dosage

Artesunate for injection should be administered in a dose of 2.4 mg/kg body weight IV or IM given on admission (time = 0 hour), then at 12 hours and 24 hours.

Children weighting less than 20 kg should receive a higher dose of Artesunate: 3 mg/kg/dose with the same schedule (0, 12, 24 hours). The higher dose will ensure a drug exposure equivalent to older children and adults.

If the patient can tolerate oral medication after 24 hours provide a full treatment course of AL. Initiate the first dose of AL 8 hours after the last injection.

Add Single Low Dose Primaquine (except when is contraindicated, e.g. pregnant women) in areas of very low malaria transmission. (See section 4.5, page 55).

Administration and dosage (60 mg strength)

Injectable Artesunate has 2-steps dilutions.

Step 1: The powder for injection should be diluted with 1ml of 5% sodium bicarbonate solution (provided in each box) and shaken vigorously 2-3 minutes for better dissolving till the solution becomes clear.

Step 2:

- For slow intravenous infusion (3-4 minutes), add 5 ml of 5% dextrose or normal saline, to obtain a Artesunate concentration of 10 mg/ml
- For deep intra-muscular injection, add 2 ml of 5% dextrose or normal saline to obtain a Artesunate concentration of 20 mg/ml

Dilution

The quantity for reconstitution and dilution of different strength are shown in Table 18.

Table 18: Quantity for dilution of Artesunate for injection

Route	IV injection			IM injection		
Strength	30 mg	60 mg	120 mg	30 mg	60 mg	120 mg
Sodium bicarbonate 5%	0.5	1	2	0.5	1	2
Normal saline	2.5	5	10	1	2	4
Total (ml)	3	6	12	1.5	3	6
Artesunate concentration (mg/ml)	10	10	10	20	20	20

The powder form for injection is difficult to dissolve, care should be taken to ensure that it is completely dissolved before parenteral administration. If the solution is cloudy or a precipitate is present, the parenteral preparation should be discarded. Dissolved Artesunate should always be used immediately after 2nd dilution. Never store diluted Artesunate for further use

See also Appendix Ea and Eb; Artesunate injection dilution, administration and dosage.

Alternative medicine for treatment of severe malaria: Injectable Artemether

NEW!

There are no more indications for using parenteral Quinine for treatment of severe malaria due to its inferiority in treatment outcomes compared to artemisinin parenteral medicines

Artemether is a lipid soluble Methyl ether of Dihydroartemisinin
Formulation

Formulation advised by the WHO are ampoules of injectable solutions for intramuscular injection containing 80 mg Artemether in 1ml oil solution for adults or 40 mg Artemether in 1ml oil solution for paediatric use.

Administration and Dosage:

Artemether should be administered in a dose of 3.2 mg/kg body weight loading dose IM stat then 1.6mg/kg body weight (time = 0h then at 24 hrs and 48 hrs). See Table 19 for reference.

If the patient can tolerate oral medication after 24 hours provide a full treatment course of AL. Initiate the first dose of AL 8 hours after the last injection.

Add Single Low Dose Primaquine in areas of very low malaria transmission (except when is contraindicated, e.g. pregnant women). (See section 4.5, page 55).

Injectable Artemether is to be used when Artesunate is contraindicated (in case of allergy, medicine interaction or non-response) and when not available

Table 19: Artemether Injectable dosage by weight

Loading dose			Second and subsequent doses	
0 hrs			24, 48, ..., hrs	
	Dose	Strength	Dose	Strength
Weight	3.2 mg/Kg	80 mg/ml	1.6 mg/kg	80 mg/ml
Kg	mg	ml	mg	ml
<5	16	0.2	8	0.1
5-8	26	0.3	13	0.2
9-12	38	0.5	19	0.2
13-16	51	0.6	26	0.3
17-20	64	0.8	32	0.4
21-25	80	1.0	40	0.5
26-29	93	1.2	46	0.6
30-33	106	1.3	53	0.7
34-37	118	1.5	59	0.7
38-41	131	1.6	66	0.8
42-45	144	1.8	72	0.9
>45	160	2.0	80	1.0

Artemether injections need additional supplies such as tuberculin syringes.

Artemether injectable can be deployed effectively in malaria epidemics (see section 7.5).

Rectal Artesunate

NEW!

As the progression of severe malaria from severe illness to death can be very rapid, prompt access to pre-referral treatment can save lives. When parenteral artesunate formulations are not readily available or in operational conditions that they are not viable, rectal formulations are a suitable alternative

The risk of children for death from severe malaria is greatest in the first 24 h. The interval between the appearance of the first signs of severe illness and reaching a health facility where the appropriate parenteral treatment can be administered is usually long in the most “hard to reach” areas where access to operational health facility is sub-optimal due to long distance, walking time, and geographical barriers.

Rectal artesunate formulations are a suitable alternative to injectable artemisinin formulation for pre-referral treatment of severe malaria in

children under 6 years of age, when parenteral formulations are not available or in operational conditions that they are not viable due to inadequate skills (e.g. administered by relatives, caretakers or community health resource persons) or unconducive site of administration (e.g. outside health facilities, household or community level).

Available formulation:

Suppositories/Recto-capsules 100 mg

Dosage

10 mg / kg of body weight (see Table 20) as soon as a presumptive diagnosis of severe malaria has been made

Indication:

Rectal Artesunate can be administered as a pre-referral medication in places where parenteral artemisinin administration is not possible.

Table 20: dosage regimen for Artesunate suppositories for different age groups (10mg/kg body weight)

Weight (Kg)	Age	Artesunate (mg)	Suppositories
<10 kg	<12 months	100 mg	1
10-19 kg	1-5 years	2 x 100mg	2

Intra-rectal administration, immediate referral and completion of full treatment

To administer the medicine, remove the suppository from the wrapper and insert it rectally; then, cover the buttocks of the child for 1–2 min.

If the suppository slips out and is still intact, reinsert the same one. If it bursts or has partially melted, insert a new suppository.

If the suppository is expelled from the rectum within 30 min of insertion, insert a new suppository and hold the buttocks together for 10 min to ensure retention of the dose.

After administration of rectal artesunate, the child should be immediately transported to a higher-level facility where i.m. or i.v. artesunate can be given.

If referral is impossible, rectal treatment could be continued until the patient can tolerate oral medication.

As soon as the child can tolerate oral medication, he or she should receive a full 3-day treatment course of AL to ensure complete cure.

5.4 Adjunctive management of severe malaria

In an attempt to reduce the unacceptably high mortality of severe malaria, patients require intensive care. Clinical observations should be made as frequently as possible. See Table 21).

Table 21: Immediate clinical management of complications due to severe malaria

Condition	Immediate management
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis)
Hyperpyrexia	Fanning and antipyretic medicines. Paracetamol is preferred over other medicines
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or Intramuscular paraldehyde. Check blood glucose
Hypoglycaemia	Check blood glucose, correct hypoglycaemia and maintain with glucose containing infusion
Severe anaemia	Transfuse with screened fresh whole blood
Acute pulmonary oedema	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids
Acute renal failure	Exclude pre-renal causes, check fluid balance, if in established renal failure consider renal replacement therapy hemofiltration or haemodialysis
Spontaneous bleeding and Coagulopathy	Transfuse with screened fresh whole blood and give vitamin K injection
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe, add or refer for hemofiltration or haemodialysis
Shock	Suspect septicaemia, take blood for cultures; give parenteral broad-spectrum antimicrobials, correct haemodynamic disturbances

5.5 Management of severe malaria by levels of health facility

The transit time between referral and arrival at appropriate health facilities is usually prolonged thus delaying the commencement of appropriate antimalarial treatment.

During this time the patient may deteriorate or die. It is recommended that patients are treated with the first dose of one of the recommended parenteral treatments before referral (unless the referral time is very short). This could be intramuscular Artesunate, Artemether, Management of severe malaria at community level (Home, Community Malaria Case Management and ADDO providers)

Management should include

- Early recognition of symptoms and signs defining severe malaria with appropriate early health care seeking behaviour
- Control of fever by the use of antipyretics and fanning (kupepea)
- Continued feeding and fluid intake
- Malaria testing using a mRDT (if available and resource person been trained)
- Pre-referral Artesunate suppository (if available and resource person been trained)
- Immediate referral to the nearest health care facility

Management of severe malaria at dispensary level

Management should include

- Early diagnosis of severe malaria based upon a complete history, physical examination
Taking and reporting of blood smear/mRDT must not be allowed to delay treatment unduly
- Provision of pre-referral treatment with i/m Artesunate
- Immediate referral with clinical summary, to the nearest health care facility where resources for the continuing care of patients with severe malaria are available

General management

Assessment and resuscitation

- Airway – ensure airway is open with no foreign objects
- Put the patient in semi prone position
- Breathing – ensure there is adequate respiratory movement
- Circulation – measure pulse rate and blood pressure
- Blood smear for malaria parasites (do not wait for results)
- Blood glucose estimation by glucose strips
- Hb estimation

Pre-referral treatment

- Administration of i/m Artesunate
- In suspected severe malaria where meningitis and septicaemia cannot be ruled out, a broad-spectrum antibiotic should be administered
- Correction of hypoglycaemia by using oral sugar-water
- Control fever with antipyretics and fanning (kupepea)
- Control convulsion with diazepam

Management of severe malaria at health centre level

Management should include

- Early diagnosis of severe malaria based upon a complete history, physical examination and blood smear/RDT for malaria parasites. Taking and reporting of blood smear must not be allowed to delay treatment unduly
- Provision of appropriate treatment intravenously/intramuscularly. Artesunate injection should be given on admission (time = 0 hour), then at 12 hours and 24 hours (in the first 24 hours irrespective of the patient's ability to tolerate oral medication earlier) and, thereafter, complete treatment by a full course of AL. Initiate the first oral dose 8 hours after the last injection
- Treatment of hypoglycaemia. Hypoglycaemia remains a major problem in the management of severe malaria especially in young children and pregnant women. It should be deliberately looked for and treated accordingly
- Referral with clinical summary to the nearest hospital when clinical need dictates (e.g. blood transfusion or intensive care)

General management

Assessment and resuscitation

- Airway – ensure airway is open with no foreign objects
- Put the patient in semi prone position
- Breathing – ensure there is adequate respiratory movement
- Circulation – measure pulse rate and blood pressure
- Blood smear for malaria parasites (do not wait for results)
- Blood glucose estimation by glucose strips/glucometer
- Hb estimation

Insert intravenous cannula

- Blood samples for random blood glucose (RBG), full blood picture (FBP), serum creatinine, liver function tests (bilirubin, AST, ALT, ALP) and serum electrolytes
- Start dextrose-saline or dextrose 5% infusion

Insert nasogastric tube (if indicated)

- For feeding and medication

Insert urethral catheter (if indicated)

- Urine for dipstick
- Urinary output measurement

Nursing care and monitoring

- Fluid input and output chart
- Level of consciousness
- Temperature, PR, RR and BP
- Feeding
- Changing position every 2 hours

Investigations

- Hb, Glucose, Creatinine, Electrolytes if indicated

Management of severe malaria at hospital level

Management should include:

Early diagnosis of severe malaria based upon a complete history, physical examination and blood smear/RDT for malaria parasites. Taking and reporting of blood smear and other investigations must not be allowed to delay treatment unduly.

- Provision of appropriate treatment intravenously/intramuscularly. Artesunate injection should be given on admission (time = 0 hour), then at 12 hours and 24 hours (in the first 24 hours irrespective of the patient's ability to tolerate oral medication earlier), and thereafter, complete treatment by a full course of AL. Initiate the first oral dose 8 hours after the last injection
- General management, nursing care and monitoring
- Treatment of complications e.g. blood transfusion
- Treatment of hypoglycaemia. Hypoglycaemia remains a major problem in the management of severe malaria especially in young children and pregnant women. It should be deliberately looked for and treated accordingly
- Laboratory investigations for other complications where indicated

General management

Assessment and resuscitation

- Airway – ensure airway is open with no foreign objects
- Put the patient in a semi prone position
- Breathing – ensure there is adequate respiratory movement
- Circulation – measure pulse rate and blood pressure
- Blood smear for malaria parasites (do not wait for results)
- Blood glucose estimation by glucose strips/glucometer
- Hb estimation
- Insert intravenous cannula
- Blood samples for random blood glucose (RBG), full blood picture (FBP), serum creatinine, liver function tests (bilirubin, AST, ALT, ALP) and serum electrolytes
- Start dextrose-saline or dextrose 5% infusion

Insert naso-gastric tube (if indicated)

- For feeding and medication

Insert urethral catheter (if indicated)

- Urine for dipstick
- Urinary output measurement

Nursing care and monitoring

- Fluid input and output chart
- Level of consciousness
- Temperature, PR, RR and BP
- Feeding
- Changing position every 2 hours

Investigations

Investigations of severe malaria at hospital level are shown in Table 22.

Table 22: *Investigations of severe malaria at hospital level*

Essential	If indicated
Blood film for malaria parasites/RDT	Blood culture and sensitivity
Blood glucose estimation	Chest radiograph
Full blood picture	Cerebrospinal fluid analysis
Urinalysis (including detection of Hb)	Urine culture and sensitivity
Biochemical tests:	Serum lactate, serum bicarbonate, serum creatinine, liver function tests (bilirubin, AST, ALT, ALP) arterial pH and serum electrolytes

5.6 Monitoring of patients with severe malaria

All patients with severe malaria should be closely monitored clinically as described in Table 23.

Table 23: Important clinical observations and their implications during treatment of severe malaria

Regularly observe	Possible observation	Appropriate action
Breathing	<p>Increased respiratory rate:</p> <ul style="list-style-type: none"> • < 2 months: 60 or more per minute • 2 up to 12 months: 50 or more per min • 1 yr up to 5 yrs: 40 or more per min • 5 yrs and above: 20 or more per min <p>Or difficulty in breathing</p>	<ul style="list-style-type: none"> - Check position of the patient - Put the patient in semi-prone (Fowler's) position - Give oxygen if there is respiratory distress - Review urine output - Examine lung, heart and size of the liver - Chest X ray if available - If pulmonary oedema is demonstrated, or seems likely treat appropriately
Axillary temperature	<p>$\geq 38.5^{\circ}\text{C}$ If temperature remains high or rises despite 24 hours of Artesunate therapy</p>	<ul style="list-style-type: none"> - Give paracetamol if not given within the past 4 hours - Fanning (<i>kupepea</i>) - Reassess and investigate for other possible causes while continuing treatment
Shock	<p>Cold extremities, capillary refill delayed for ≥ 3 seconds (when a nail of the thumb is pressed); weak and fast pulse; BP Falls:</p> <ul style="list-style-type: none"> • <90 mmHg systolic in an adult • < 50 mmHg in infants and children (using paediatric cuff) 	<ul style="list-style-type: none"> - Review fluid balance, urine output, and haematocrit - If hypovolemic/dehydrated give saline infusion - Evidence recommends not to give bolus (rapid) infusion to severely ill children in shock if not dehydrated, it is associated with increased mortality - Look for haemorrhage - Take blood for bacteriological culture and sensitivity if facilities are available - Give broad spectrum antibiotic (for possible gram negative bacteraemia) if confirmed or sepsis suspected
Urine output	<p>Oliguria:</p> <ul style="list-style-type: none"> • <17 ml/hr in an adult or • <0.3 ml/kg/hr in infants and children 	<ul style="list-style-type: none"> - Review fluid input and status of hydration - Correct fluid deficit if necessary - Prevent or manage acute renal failure if suspected - Catheterize if acute renal failure
Coma score	<p>Deterioration See appendix F for Glasgow and Blantyre coma scale</p>	<ul style="list-style-type: none"> - Reassess and investigate for other possible causes while continuing treatment - Immediately check blood glucose (correct hypoglycaemia if suspected) - Lumbar puncture

Convulsions	These can recur, or develop for the first time during treatment and may be due to fever, abnormal blood glucose or electrolyte imbalance or other causes	<ul style="list-style-type: none"> - Check axillary temperature if $\geq 38.5^{\circ}\text{C}$, treat as above - Check blood glucose (correct hypoglycaemia if suspected) - Check fluid balance - Check electrolytes if possible (to detect hyponatraemia) - Give anticonvulsant medicines
Bleeding from venepuncture sites or spontaneous haemorrhage	Prolonged bleeding time suggesting <i>Disseminated intravascular coagulopathy</i> (DIC)	<ul style="list-style-type: none"> - Check bleeding time - Grouping and cross matching blood - Give whole fresh blood as needed to correct blood loss and bleeding tendency (20 ml/kg for children, 2 units in adults)

Laboratory indices should be also frequently monitored to establish the appropriate actions to be taken (see Table 24).

Table 24: Important observations and their implications during treatment of severe malaria: laboratory parameters

Regularly observe	Possible observation	Appropriate action
Blood glucose	Falls below 2.5 mmol/L (<45 mg/dl) OR <3.0 mmol/L (54mg/dl) in malnourished children	<ul style="list-style-type: none"> - Ask when last fed. A child will become hypoglycaemic if deprived of glucose for more than 12 hours - Give IV 10 or 25% glucose bolus - Review infusion - Maintain feeding
Haematocrit	Falls to 12% or below	<ul style="list-style-type: none"> - Grouping and cross-matching blood - Give blood transfusion 10 ml/kg body weight of packed cells - Repeat haemoglobin and haematocrit at regular intervals - Consider transfusion if in cardiac failure even if Hb is >4g/dl
Haemoglobin	Falls to 4g/dl or below	
Parasitaemia	Remains high 2-3 days or remains positive for >5 days Parasitaemia commonly remains at the initial level for 12-24 hours even if medicines are fully effective	<ul style="list-style-type: none"> - Take BS for malaria parasites daily until the results are negative - Review adequacy of antimalarial dosage - Consider alternative medicine (Quinine)

5.7 Emergency management of severe malaria

Convulsions

Convulsions are common in children with severe *P. falciparum* malaria but are relatively rare in adults. The general principles for the care of patients with convulsions should be as follows:

- Maintenance of a clear airway
- Monitoring of vital signs: temperature, pulse rate, respiratory rate and blood pressure
- Nurse the patient in a semi-prone position
- Check blood glucose where possible, or give IV dextrose

Administer anticonvulsant medicines:

- Diazepam 0.15 mg/ kg (maximum 10 mg for adults.) slow bolus IV injection
- In children, diazepam rectal route should be used. Give a dose of 0.5-1.0 mg/ kg. Draw the IV preparation into a small syringe and remove the needle. Insert 5 cm of a nasogastric tube into the rectum. Inject the diazepam into the nasogastric tube and flush it with 5 ml of water. If a nasogastric tube is not available, use a syringe without a needle. Hold buttocks together for few minutes to ensure retention and absorption of the medicine
- If convulsions persist after 10 minutes repeat rectal diazepam treatment as above. Should convulsions continue despite a second dose, give a further dose of rectal diazepam or phenobarbitone 20 mg/ kg IM or IV after another 10 minutes

Diazepam should not be used in infants below 1 month of age. Instead use phenobarbitone 20mg/kg IM or IV. If convulsions persist, repeat phenobarbitone 10 mg/ kg after 30 minutes

Hypoglycaemia

Check blood glucose every 4 hours. If blood glucose level falls to < 2.5mmol/L or level of consciousness deteriorates.

In children

- Give 5 ml/kg of 10% dextrose OR 2.5 ml/kg of 25% dextrose as bolus
- If 50% dextrose solution is available, it should be diluted to make 25% by adding an equal volume of water for injection or normal saline

In adults

- Give 125mls of 10% dextrose OR 50mls of 25% dextrose as bolus

Where dextrose is not available, sugar water should be prepared by mixing 20 gm of sugar (4-level tea spoons) with 200 ml of clean water. 50 ml of this solution is given ORALLY or by nasogastric tube if unconscious

Hypotension

Give colloid fluids (plasma expander) or blood if haemoglobin is less than 5g/dl.

Pulmonary oedema

Check for

- Restlessness
- Frothy sputum
- Basal crepitation
- Low oxygen saturation (< 95%)

Give

- Oxygen
- IV furosemide
- Mechanical ventilation may be needed

Metabolic Acidosis

Metabolic acidosis in malaria patients, is attributed to lactic acidosis.

Check for

- Respiratory distress, deep and laboured breathing

Give

- Oxygen and
- Correct hypovolaemia

6 Anaemia in relation to Malaria

6.0 The relationship between malaria and anaemia

The aetiology of anaemia in malaria endemic areas is often multi-factorial, with different causes interacting in a vicious cycle of nutritional deficiencies, infections and inherited red blood cell disorders. However, malaria remains one of the main contributors. Anaemia in malaria occur more frequently among children and pregnant women.

In endemic areas, malaria clinical diagnosis is based on a history of fever in the previous 24 hours and/or the presence of anaemia, for which pallor of the palms appears to be the most reliable sign in young children. In the same settings, malaria in pregnancy is associated with increased anaemia.

Anaemia can result from repeated or persistent malaria infections, due to delayed treatment, inadequate treatment, parasite resistance or no treatment at all. Anaemia, weakness and febrile episodes are characteristic of these cases. Anaemia due to malaria may develop rapidly following an acute malaria attack or insidiously over a period of time as described above. However, cases of post treatment haemolytic anaemia due to Artesunate have been reported between 7-14 days after treatment. The prevalence varies from 1%-10% according to population groups. The risk was higher in patients who had hyperparasitaemia.

On the other hand, severe anaemia in young children is the most frequent principal manifestation of severe falciparum malaria. Severe malaria is associated with rapid development of anaemia as infected and uninfected erythrocytes are removed from the circulation by the spleen, intravascular haemolysis or bone marrow suppression.

Mortality as a direct result of anaemia rises at lower haemoglobin levels.

Children commonly present with severe anaemia and hyperventilation (sometimes termed “respiratory distress”). In the past this was ascribed to “anaemic heart failure” (i.e. pulmonary oedema), and sometimes diuretics were administered. It is now clear that this syndrome is not a result of anaemic heart failure, but results from severe metabolic acidosis and anaemia, and so should be treated by blood transfusion.

Anaemia is defined as reduction of red blood cells or haemoglobin (Hb) concentration or both below the normal range for the age and sex of the individual (see Table 25).

Anaemia due to malaria is usually normocytic and normochromic in nature. If the findings are different, e.g microcytic hypochromic or megaloblastic, the patient should be investigated for other causes of anaemia and treated accordingly.

Table 25: Normal Hemoglobin concentration levels by ages and sex

Category	Hb g/dl
New-born	13.5 - 20
Children less than 6 years	11 – 13
Adult females, not pregnant	12 - 16
Adult females, pregnant	11 – 15
Adult male	13 - 17

6.1 Clinical presentation and classification of anaemia

Clinical presentation of anaemia

In areas of high malaria endemicity the association between malaria and anaemia is strong. However, patients presenting with anaemia and malaria are frequently not treated correctly because their symptoms and signs are often missed. All patients, especially pregnant women and young children, presenting to health facilities with malaria should be checked carefully for anaemia. This should be done by asking about anaemia related symptoms and checking for physical signs.

Ask for (symptoms):

- Tires or is fatigued easily
- Inability to feed and drink (Infants and children)
- Dizziness and breathlessness on exertion in pregnant women
- History of eating soil (especially in children or pregnant women)

Look for (signs):

- Pallor (palms, soles, nails beds, conjunctivae and tongue)
- Signs of respiratory distress (nasal flaring, chest in-drawing and deep breathing or grunting)
- Signs of congestive heart failure (dyspnoea, tachycardia, gallop rhythm, basal crepitation, oedema, puffy eyes, raised jugular venous pressure and enlarged tender liver)

6.1.2 Classification of anaemia according to severity

A classification based on severity of anaemia provides an ideal approach on its management is provided in Table 26. The classification is based on IMCI protocol (see Appendix G).

Table 26: *Classification of anaemia by severity and risk group*

	children	pregnant
Mild to moderate anaemia	7-11	8.5-11
Severe anaemia	5-7	Below 8.5
Very Severe anaemia	Below 5	

Mild/moderate anaemia, Hb 8.5-11 g/dl

- Some pallor

Severe anaemia, Hb <8.5 g/dl

- Severe palmar pallor
- Excessive tiring
- Dyspnoea or breathlessness
- Warm hands
- Peripheral oedema: pedal pitting
- Tachycardia, collapsing pulse, wide pulse pressure and gallop rhythm
- Ejection systolic murmur ('flow' murmur)

Life threatening anaemia, Hb<5g/dl

Respiratory distress

- Nasal flaring
- Chest in-drawing
- Deep breathing or grunting

Congestive heart failure

- Pulmonary oedema: basal crepitations
- Peripheral oedema: pedal, periorbital and sacral.
- Circulatory congestion: raised jugular venous pressure and enlarged tender liver
- Tachycardia
- Gallop rhythm

6.2 Management of malarial anaemia

Management of mild/moderate anaemia (8.5 up to 11 g/dl) associated with malaria

Features

- Some pallor, body weakness

Management

Patients with some pallor or moderate anaemia (Hb 8.5 - 11 g/dl) need to be treated for malaria, as persistent parasitaemia is a cause of anaemia by dyserythropoiesis and haemolysis. Iron and folic acid speed up haematological recovery after malaria and should be given at least for three months. It is also important to treat hookworm infestation in children, as this is a common cause of iron deficiency anaemia.

Folic acid tablets administration

- Start a 3 months treatment course (5 mg daily)

Ferrous sulphate tablets administration

- Start a three months course at dose of 6 mg/kg of elemental iron daily
- Adults need 200mg ferrous sulphate (one tablet) three times daily

Management of severe anaemia (Hb 5 up to <8.5g/dl) associated with malaria

Features

- Severe palmar pallor, excessive tiring, dyspnoea or breathlessness, warm hands, peripheral oedema, pedal pitting, tachycardia, collapsing pulse, wide pulse pressure and gallop rhythm, ejection systolic murmur ('flow' murmur)

Management

This condition can be managed through outpatient services with close monitoring OR can be admitted depending on the severity of the above features

- Test and eventually treat malaria (see chapter 3 and 4)
- Perform full blood count to investigate morphological type
- Do other investigations to identify other underlying causes of anaemia e.g. stool sample for hookworm and treat accordingly

- Give oral haematinics for at least three months
- Advise to return immediately if condition worsens
- Follow up after 15 days

Life threatening anaemia (Hb < 5g/dl) associated with malaria

Features

- Respiratory distress
- Congestive heart failure

Treatment

This is a medical emergency.

- Admit the patient
- Treat malaria as severe malaria with parenteral antimalarials (see management of severe malaria)
- Prop the patient up with pillows or clothing
- Administer oxygen (2.5 L/min in adults, 1.0-2.0 L/min in children) to improve oxygen delivery
- Draw blood for grouping and cross matching

Indications for urgent blood transfusion

- Hb equal or less than 4 g/dl and/or
- Signs of heart failure
- Signs of respiratory distress

Administration of blood

- Use packed cell (10 ml/kg in children) if not available consider whole blood 20 ml/kg body weight
- Transfuse slowly (4-6 hours per unit)

$$\text{Drip: drops/min} = \frac{\text{volume to be transfused in ml} \times 20(\text{or } 15) \text{ drop factor}}{\text{time of transfusion in hours (4-6 hours)}} \times 60 \text{ minutes}$$

**N.B. 1ml whole blood= 20 drops
1ml packed cell= 15 drops**

- Where blood is not available, give pre-referral treatment and refer urgently to a health facility with blood transfusion services
- Diuretics: Furosemide (IV/IM) for an adult 40 mg or 1 mg/kg bodyweight for children

Children with malarial anaemia are hypovolemic

Follow-up after discharge

- Start folic acid and ferrous sulphate (do not give ferrous sulphate to sickle cell patients)
- Review after 14 days to check on haemoglobin or haematocrit level
- Continue treatment for at least three months

- Provide monthly chemoprevention with long lasting ACT (e.g. DP) for 4-6 months
- Encourage patients to protect themselves from being bitten by mosquitoes by sleeping under an Insecticide Treated Net (ITN)
- Caution should be taken for patient treated with Artesunate, due to reported events of Artesunate induced haemolytic anaemia

Management of anaemia associated with malaria in pregnancy

In anaemic pregnant women, even if there are no signs or symptoms of malaria, perform malaria test preferably mRDT, if positive give an effective antimalarial (see section 8.2.4); if negative investigate for other causes of anaemia (see section 8.2.4).

7 Management of Malaria in Special Situations and Groups

7.0 Special groups and special situations that need specific case management interventions

The risks related to malaria infections differ among the population according to their biological and socio-economic vulnerability. The major biological vulnerable groups are **neonates, infants, childhood, pregnant women, sickle cells** and people with **inadequate immunity** (e.g. HIV). The risk of malaria infection is also higher in the population with high behavioural risk (**children in school going age**), **low wealth** or with **impaired access** to health services. Emergency situation, (**outbreaks, complex emergency, refugees**) might also require targeted malaria case management interventions. Other population groups need alternative or additional health care delivery approaches due to their occupational or livelihood exposure to malaria infection (non-immune **seasonal labourers, migrants, nomads**, etc).

7.1 Management of malaria in pregnancy

Malaria is an important cause of morbidity and mortality for the pregnant woman, the foetus and the new-born.

During pregnancy, the naturally acquired partial immunity to malaria declines. The decline in immunity is most pronounced during the first and second pregnancy. The reasons for the decline in immunity are yet to be determined. Pregnant women, especially primigravidae, are more susceptible to malarial infection than non-pregnant women.

Malaria infection is often covert during pregnancy. Pregnant women with symptomatic acute malaria are a high-risk group, and they must promptly receive effective antimalarial treatment. In primigravidae, malaria tends to be more frequent and the attacks more severe.

Effects of malaria in pregnancy

The effects of malaria in pregnancy to the foetus and new-born are related to malaria endemicity, with abortion or stillbirth more common in areas of low endemicity and intrauterine growth restriction more common in areas of high endemicity²⁵.

In high-transmission settings, though usually asymptomatic, the adverse effects of malaria to the pregnant woman include anaemia. Conversely, in low-transmission areas, malaria is common to be clinically evident and pose an increased risk of severe malaria and death.

Table 27: Effects of malaria on morbidity among pregnant woman, fetus and new born

Pregnant Woman	Fetus	New born
Severe malaria (especially cerebral malaria and pulmonary oedema)	Intrauterine growth restriction	Low birth weight
Anaemia	Congenital malaria	Prematurity
Premature labour	Abortion Stillbirth	Congenital /neonatal malaria Anaemia

Management of uncomplicated malaria in pregnancy

Early diagnosis and effective case management of malaria illness in pregnant women is crucial in preventing the progression of uncomplicated malaria to severe disease and death. Clinical features of uncomplicated malaria

The clinical presentation of malaria during pregnancy is often hidden. Some pregnant women will present with the suggestive features of uncomplicated and/or severe malaria (see chapters 4 and 5). However, in others, anaemia may be the only recognizable clinical feature.

Diagnosis of uncomplicated malaria in pregnancy

Diagnosis should follow the general principles of diagnosis of malaria based on accurate history taking, complete physical examination and appropriate laboratory tests as in any other malaria patients.

Treatment of uncomplicated malaria

NEW!

**Artemether/
Lumefantrine(AL) is the
recommended treatment
of choice of a confirmed
uncomplicated malaria to
all patients including
pregnant women in all
trimesters.**

In reality, women often do not declare their pregnancies in the first trimester or are not yet aware that they are pregnant; therefore, all women of child bearing age should be asked about the possibility of being pregnant before being given antimalarials, a standard practice for the administration of any medicine in potentially pregnant women, should be observed.

During history taking and physical examination, it is particularly important to elicit signs and symptoms of uncomplicated malaria. Whenever malaria is suspected, laboratory confirmation of malaria parasites should be performed. A negative peripheral blood smear result

does not rule out the presence of placental parasitaemia.

Evidence have shown that pregnant women who had been exposed to artemisinin based combination therapies (ACT) in the first trimester, did not have an increased risk of miscarriage, stillbirths and major congenital malformations compared to Quinine regimens.

^{26 27},

See section 4.3, Treatment of uncomplicated malaria with medicine of choice: Artemether-Lumefantrine, page 46

Management of severe malaria in pregnancy

Pregnant women infected with malaria are at increased risk developing severe malaria. Mortality due to severe malaria is higher than in non-pregnant women. Foetal death and premature labour are common.

Clinical features of severe malaria in pregnancy

Women in the second and third trimesters of pregnancy are more likely to develop severe malaria than other adults, often complicated by pulmonary oedema and hypoglycaemia.

The following are commonly presenting features:

- high fever
- hyperparasitemia

- low blood sugar
- severe haemolytic anaemia
- cerebral malaria
- pulmonary oedema

Diagnosis of severe malaria in pregnancy

NEW!

**Intramuscular/
intravenous Artesunate is
the drug of choice for
treatment of severe
malaria in all trimesters**

Diagnosis of severe malaria in pregnancy should follow the general principles of diagnosis of malaria based on accurate history taking, complete physical examination and appropriate laboratory tests.

Treatment of severe malaria in pregnancy

The primary objective of antimalarial treatment in severe malaria is to prevent death. In the treatment of severe malaria in pregnancy, saving the life of the mother is the primary objective. See section 5 Management of Severe Malaria, page 58.

Anaemia associated with malaria in pregnancy

A Pregnant woman with haemoglobin (Hb) level of <11 g/dl (or haematocrit <33%) is considered anaemic. The aetiology of anaemia in pregnancy is multi-factorial. In primigravidae, malaria is the major contributor to anaemia. Malaria infection in pregnancy worsens pre-existing conditions of anaemia; the risk of maternal mortality, especially in the face of complications such as abortion and haemorrhage, is increased by anaemia and which can be a direct cause of mortality due to cardiac failure. Anaemia can also contribute to stillbirth and low birth weight.

In Tanzania, **the major** causes of anaemia in pregnancy are:

- Malaria
- Hookworm and schistosomiasis infestation (due to increased blood loss)
- Iron and folate deficiency (due to poor dietary intake and increased demand due to pregnancy)
- Chronic infection including TB, HIV/AIDS
- Deliveries at short intervals (less than 3 years)

There are three approaches for addressing the maternal anaemia problem:

- Early diagnosis
- Treatment
- Prevention

Management of mild/moderate anaemia (Hb 8.5 up to 11 g/dl) in pregnancy

Perform appropriate investigations (malaria test (BS/mRDT), peripheral blood film, RBC indices, WBC total and differential, urinalysis, and stool examination)

Treat the cause of anaemia if determined

Give the following medicines

- Full course of AL in all trimesters if the patient is positive for a malaria test
- Combined ferrous sulphate 200mg + folic acid 0.25mg twice daily for three months
- Anthelmintics (e.g. mebendazole from second trimester)
- Treat schistosomiasis if the patient lives in areas with high schistosomiasis transmission (after delivery)

Monitor response to treatment

- Clinical response
- Haemoglobin measurement is recommended every 2 weeks until Haemoglobin reaches 11 g/dl
- Reticulocyte count

For non-responding patients, other investigations should be considered e.g. bone marrow aspiration.

Management of severe anaemia (Hb < 8.5 g/dl) in pregnancy

Severe anaemia has to be aggressively treated before the woman goes into labour. During labour, a patient may go into cardiac failure because of the increased work of the heart. Likewise, the shunting of the blood to the circulation from the placental bed after delivery may overload the circulation and precipitate cardiac failure.

Aims of treatment

- Correct anaemia and improve Haemoglobin concentration to a safe level (> 8.5 g/dl) before the patient goes into labour
- Avert congestive cardiac failure by increasing the oxygen carrying capacity

Management of severe anaemia

Gestational age should determine the appropriate approach for the management of severe anaemia in pregnancy. Before 36 weeks of gestational age and if the patient is not in cardiac failure the treatment should be as for the above moderate anaemia. If in failure and after 36 weeks of gestational age with or without failure:

- Treat the cause if determined
- Give blood transfusion (preferably packed cells)
- Continue with combined iron and folic acid up to 3 months after delivery
- Follow up the patient every 2 weeks until Hb reaches 11 g/dl

Prevention of anaemia during pregnancy

Prevention of anaemia is part of the routine antenatal care. During the scheduled ANC visits the following services are offered to pregnant women:

- Combined ferrous sulphate 200mg + folic acid 0.25mg once daily
- Intermittent Preventive Treatment with SP
- Early detection of anaemia (Haemoglobin screening)
- Thorough history taking and physical examination
- De-worming as indicated in the antenatal care guidelines
- Treatment of any underlying infection

All women should be advised on appropriate diet during pregnancy and on personal malaria protection using long lasting insecticide treated nets (LLINs).

7.2 Management of malaria in neonates

Though rare, congenital and neonatal malaria does occur. A significant proportion of neonates with malaria may be missed in the wards on the assumption that the disease condition is rare. Neonatal malaria is defined as symptoms attributable to malaria with evidence of ring forms of malaria parasite in the blood of an infant within the first twenty-eight days (4 weeks) of life.

Congenital malaria is defined as symptoms attributable to malaria with evidence of ring

forms of malaria parasite in the blood of an infant within the first seven days (1 week) of life. Congenital or acquired malaria in this age group is life threatening and requires immediate treatment.

The signs and symptoms resemble those seen in the new-born with septicaemia.
Clinical features of malaria in the neonatal period

The clinical features of malaria in the new-born include:

- Fever
- Lethargy
- Unable to breastfeed
- Vomiting
- Irritability
- Respiratory distress
- Seizures
- Jaundice
- Pallor
- Hepatosplenomegaly

Laboratory findings will include the presence of malaria parasites, hyperbilirubinemia, anaemia (Hb<13.5 g/dl), hypoglycaemia and acidosis.

Management of neonatal malaria

- Neonatal malaria should always be considered as severe malaria
- Neonates with suspected malaria should be admitted to hospital immediately as they can deteriorate quickly and die at home
- Symptoms and signs of neonatal malaria mimic serious bacterial infection. Therefore, a thorough investigation should be done

Assessment and resuscitation

- Airway: ensure airway is open
- Breathing: ensure there is adequate respiratory movements, give oxygen if indicated
- Circulation: measure pulse rate

Investigations

- Full blood picture
- blood sugar
- blood culture and sensitivity, blood smear for malaria parasite, serum electrolytes
- CSF for analysis

Treatment

- Broad spectrum antibiotic as provided in the Standard Treatment Guidelines (STG)
- Parental Artesunate is recommended treatment of choice for neonates and infant. Injectable Artemether can be used as an alternative if Artesunate is not available
- If a neonate is not able to breast feed, give 10% glucose IV 60ml/kg/bw/24hours
- Give blood transfusion if HB is <10g/dl

Nursing care and monitoring

- Monitor vital signs (PR, RR & Temperature)
- Monitor input/output
- Check BS for malaria parasite daily
- Ensure feeding
- Advise on use of LLINs

7.3 Malaria and HIV/AIDS

Malaria and HIV infections are both endemic in Tanzania and co-infection is common. The two diseases are the most important health problems in the country, being among the high ranking causes of morbidity and mortality.

Recent studies have documented in detail the consequences of HIV infection on malaria ; observing that HIV infection is associated with increased prevalence and severity of clinical malaria and impaired response to antimalarial treatment. One review emphasises that this is dependent on; age, immune-depression and previous immunity to malaria²⁹.

Patients infected with HIV are often on medications which include cotrimoxazole as prophylaxis and antiretroviral (ARVs). However, there is limited information on drug interactions between ARVs and ACTs (see section 0 below).

In HIV-infected pregnant women, the adverse effects of placental malaria on birth weight are reported to increase, and all pregnancies are at risk, not only primigravidae and secundigravidae³¹ .

Clinical features of malaria in HIV/AIDS

Worsening HIV-related immunosuppression may lead to more severe manifestations of malaria. In stable endemic areas, HIV-infected patients with partial immunity to malaria may suffer more frequent and higher density infections; while in areas of unstable transmission, HIV infection is associated with an increased risk of severe malaria and malaria-related deaths.

Clinical features of uncomplicated malaria in HIV/AIDS

Fever

Fever is a major symptom of both AIDS related opportunistic infections and malaria. Patients with AIDS often present with fever, which may be intermittent or continuous. The acute fever due to malaria could be masked with the prolonged fever due to existing opportunistic infections. In stable transmission areas, patients may suffer fever more frequent.

One should always consider a possibility of malaria in AIDS patients presenting with fever. However, in severe immunosuppressed patient fever may be absent due to failure to mount an immune response.

Anaemia

Anaemia in HIV may be present due to multiple factors (nutritional deficiencies, drugs, HIV itself) and therefore malaria coinfection may worsen the anaemia.

Headache

Headache in HIV patient may be due to cerebral toxoplasmosis, meningitis and intracranial tumours or malaria.

Central nervous system symptoms

It is important to note that the manifestation of cerebral malaria such as altered level of consciousness, prostration and convulsions resembles the CNS manifestation of HIV/AIDS

Other constitutional symptoms

Diarrhoea, joint aches and general body weakness can manifest in both, AIDS and malaria. These symptoms tend to be chronic in AIDS and acute in malaria, hence the risk of malaria symptoms being masked by AIDS related symptoms is significant.

Clinical features of severe malaria in HIV / AIDS

HIV infection is associated with an increased risk of severe malaria and malaria-related deaths, especially in low transmission areas.

Severe malaria in HIV/AIDS patients frequently presents as cerebral malaria or severe anaemia³².

Diagnosis of malaria in HIV/AIDS

Diagnosis should follow the general principles of diagnosis of malaria based on accurate history taking, complete physical examination and appropriate laboratory tests as in any other malaria patient.

Consider the possibility of malaria in HIV/AIDS patients presenting with fever, pallor, headache and the other constitutional symptoms. More extensive work up should be performed to exclude other infective causes of fever and other HIV related constitutional symptoms.

In stable malaria transmission areas where resident population has partial immunity to malaria, the attacks may be frequent with higher density infections.

In suspected cerebral malaria in a HIV/AIDS patient, cerebrospinal fluid (CSF) examination to rule out other life threatening conditions such as bacterial and cryptococcal meningitis

Treatment of uncomplicated and severe malaria in HIV /AIDS

If malaria is diagnosed, depending on classification of the malaria diagnosis, a full treatment with antimalarial should be given according to the guidelines (see chapter 4 and 5).

However, it should be noted that, clearance of parasitaemia may not necessarily be accompanied by clearance of symptoms (fever) due to the presence of other underlying opportunistic infections. HIV/AIDS infected adults with low CD4 cell counts may be more susceptible to treatment failure of anti-malaria drugs³³.

Malaria and HIV/AIDS in pregnancy

HIV infected pregnant women are at an increased risk of infection with malaria parasites and are more likely to develop clinical malaria. Their parasite density is increased compared to non-HIV infected pregnant women and they tend to have a diminished response to antimalarial treatment. HIV and malaria co-infected pregnant women are also at very high risk of anaemia and placental malaria. Pregnant women with dual infection have poorer birth outcomes (foetal loss, pre-term delivery, low birth weight)³⁴. A considerable proportion of children born to women with HIV and malaria are of low birth weight and are more likely to die during infancy. Malaria infection during pregnancy may be associated with increased risk of mother to child transmission (MTCT) of HIV.

Effect of malaria on HIV infected children

The effects of malaria on HIV infected children include increased risk of illness and anaemia. All clinical outcomes such as severity of anaemia, transfusion, hospitalization rates, coma and hypoglycaemia were higher in HIV-infected children than in HIV-negative children in a study carried out in Kenya³⁵. Although HIV infection increases the prevalence and severity of clinical malaria in children, it does not undermine the response to treatment with antimalarial medicines in uncomplicated malaria³⁶. In one particular study it was observed that although treatment of uncomplicated malaria with Artesunate plus Amodiaquine was highly effective in patients on antiretroviral therapy (ARV) there was a significant 7-8 fold increased risk of neutropenia 14 days after initiation of treatment among HIV-infected children compared to uninfected children³⁷. WHO therefore recommends that treatment of malaria in HIV-infected patients receiving Zidovudine or Efavirenz should as much as possible avoid Amodiaquine containing ACT regimens³⁸.

Treatment in HIV-infected patients on zidovudine or efavirenz should, if possible, avoid Amodiaquine-containing ACT regimens

7.4 Malaria case management in epidemics and complex emergency

A malaria epidemic is defined as the occurrence of new cases of malaria clearly exceeding the number expected at that particular time and place. Malaria epidemics should be clearly differentiated from area with high intensity seasonal transmission that occurs in several areas of Tanzania.

High morbidity and mortality usually occurs during an epidemic. In Tanzania the numbers of admissions, blood transfusions and deaths during malaria outbreaks have been found to be 4-5 times higher in epidemic than in non-epidemics years.

Generally, there is an inverse relationship between the usual intensity of malaria transmission and the risk of epidemics. Unstable malaria transmission areas, such as fringe highlands and semi-arid zones, are more prone to malaria epidemics.

In Tanzania, about 1/4 of the councils are classified as malaria epidemic prone and people living in those areas are at a higher risk of malaria epidemics. The 2017 MIS suggests that malaria transmission is decreasing. If greatly reduced; it will be followed in time by a corresponding change in the population malaria immunological and, consequently, clinical epidemiological profile, malaria transmission instability, and consequent increased risk of epidemics, especially if control measures are not sustained.

Factors associated with unexpected increases in malaria transmission include:

- Failure of malaria control measures; impaired antimalarial medicine supply or efficacy, may contribute to the occurrence of outbreaks
- Movements of non-immune population to areas with sustained malaria transmission (refugees, seasonal labourers)
- Man-made (environmental modification) or natural (climatic)

Measures to be considered during malaria epidemics

- Prompt diagnosis and treatment
- Indoor residual house spraying
- Community mobilization and participation

- Community health education about malaria control in the epidemic area
- Enhance use of LLINs
- Mass Drug Administration (MDA) can be considered for a confirmed malaria epidemic as part of the initial response intervention. (refer to section 0, page 104)

Malaria diagnosis and treatment in epidemic situations

In epidemic situations, facilities for malaria tests may be unavailable or inadequate to cope with the case load. In such circumstances, it may be impractical and unnecessary to demonstrate presence of parasites before treatment in all cases of fever. Once a malaria epidemic has been confirmed, and if case numbers are high, treatment based solely on the presence of fever is appropriate in most cases, using a full treatment course.

It is also useful to monitor the proportion of parasitologically confirmed cases during an epidemic, the Malaria Test Positivity Rate (mTPR). As the epidemic wanes, the proportion of fever cases investigated for parasites can be increased. It is important to monitor the clinical response to treatment wherever possible; bearing in mind that other causes of fever may be involved.

However, parasite-based diagnosis is essential to:

- Diagnose and confirm the cause of an epidemic of febrile illness both in health facilities and communities. Rapid diagnostic tests (mRDTs) offer the advantage of simplicity and speed in epidemic situations
- Follow up the progress of the epidemic and confirm the end. In this case microscopy is preferred since HRP2 may be positive for several weeks after the parasitological clearance
- Microscopy may be needed also to follow progress in admitted severe malaria cases

Treatment of uncomplicated malaria cases during a malaria outbreak

Malaria epidemics are emergencies in which populations at risk are mainly non-immune or only partially immune. The aim of malaria case management in such situation is to prevent the occurrence of severe disease and, ultimately, deaths.

All suspect cases of malaria should be given a full therapeutic dose of antimalarial medicines according to the guidelines (see chapter 4 or 5).

Use of preventive therapies

- Mass Drug Administration (MDA): Malaria epidemics present as a sudden and unexpected increase of malaria cases and deaths (in the case of falciparum malaria) in time and space. They differ from the increase in transmission caused by seasonal fluctuations. Once the epidemic of malaria is confirmed, MDA can be considered as part of the immediate response to reduce morbidity and mortality while other interventions – notably case management, vector control and surveillance – are put in place. The role of MDA in the context of an epidemic would be rapid reduction in malaria morbidity and mortality, while concurrently alleviating burden on treatment centres. (See section 0, page 104).

Management of severe malaria cases

Management of severe malaria in epidemic situations will often take place in temporary clinics or situations in which staff shortages and high workloads make intensive care monitoring difficult. Medical treatment should therefore be as safe as possible, with simple dosing schedules and a minimum need for monitoring.

Due to the high workload and to facilitate care of the patients, the medication of choice for pre-referral management and for treatment of severe cases during a malaria epidemic is intramuscular Artemether. Artemether injectable is an oil solution and offers some advantages compared to the other injectable antimalarials. It doesn't require the two steps reconstitution and dilution of Artesunate. Hence, its administration during emergencies, where numerous patients are expected to be managed for severe malaria at the same time, offers several advantages. However, Artesunate is acceptable alternative treatments in case Artemether is not available. The principles of treatment of severe malaria are described in chapter 5, page 58.

Malaria epidemic preparedness and commodities stock management

It is essential to ensure that adequate supplies of diagnostics and antimalarial medicines are available by establishing and maintaining stocks at national and district level to deal with the eventuality of an epidemic. These stocks will need to be continuously rotated to ensure that commodity shelf-lives do not expire. Replenishment assumes prompt release, transport and customs clearance of commodities (see section 9.0).

Prevention of malaria during epidemics

During malaria epidemics there is an increased risk of malaria infection for the whole population. Therefore, all the population should be protected by vector control intervention such as IRS.

7.5 Management of malaria in special groups

Malaria case management in refugees

Diagnosis using preferably mRDT (section 0, page 38), treatment of uncomplicated malaria with the recommended ACT (section 4.3, page 46) and treatment of severe malaria with Artesunate (section 0, page 58) are recommended in all refugees camps.

Preventive therapies are mostly recommended according to the epidemiological situation: among them IPTp with SP for pregnant women is highly prioritized in high malaria risk areas: (section 8.1, page 93). Some innovative interventions that are currently explored for their efficacy, effectiveness and feasibility under implementation research include IPTsc (section 0, page 105), MDA (section 0, page 104) and IPTi (section 8.2, page 96).

Other vector control interventions are recommended and routinely implemented in refugees camps: LSM, LLIN distribution and IRS.

Malaria Case Management in Population with Inadequate Health Care Access

Hard to reach areas are defined as human settlements (villages, hamlets) with: a) long walking (expressed in minutes) or physical (expressed in Km) distance from an operational health facilities and b) geographical barriers limiting the access from settlement and health facility (rivers, water bodies, islands, hills and mountains, poor road infrastructures). Ideally users of a health care facility should live within 5 km and/or 1 hour walking distance. The outcome of long distance or impaired access to health care services is poor or delayed utilization of diagnosis and treatment services.

Inadequate health care access is also determined by large catchment population size. Typically, a dispensary caters between 5 to 10 thousand people living in the service area. Long waiting time and poor quality of health services are the outcomes of excessive population due to limitation in health care due to lack of skilled providers and scarcity of commodities.

The proposed option for overcoming inadequate access to health care services is to improve the engagement of the respective communities in provision of malaria community case management (mCCM). A platform for introducing mCCM within the integrated CCM has been developed by NMCP ready for the introduction of following services, in High and Moderate malaria risk strata, through the utilization of community health volunteers (CHV):

- a) Health education and promotion;
- b) Identification of signs and symptoms of uncomplicated and severe malaria;
- c) Use of mRDTs to test for confirmatory malaria diagnosis;
- d) Treatment of uncomplicated malaria in children;
- e) Supportive care (fanning-kupepea and antipyretics);
- f) Pre-referral treatment for severe malaria and
- g) Where referral is made, a referral note should be written.

In Low and Very Low strata together with above assignments, the CHVs will conduct case base surveillance including testing and treatment of index patient's contacts.

A modified version, according to the respective settings, of the malaria community case management approach might be useful to improve access to malaria case management for other segments of the population that for occupational reasons are mobile and living temporarily or permanently far from operational health facilities: among them: fishermen, nomads, seasonal labourers, workforce in large civil construction projects, and miners. Other alternative and specific approaches should also be explored such as outreach, regular testing and treatment, establishment of temporary health facilities.

Malaria Case Management in Population with low wealth status

All Malaria Indicators Surveys have shown that population with low wealth status has a) increased malaria risk; b) low access to testing and treatment services and c) low coverage of preventive services. Most of the times this segment of population lives in rural areas with some degree of impaired access to operational health services.

Free of charge, or highly subsidized, access to malaria commodities is key for improving malaria diagnosis and treatment among the poorest strata of the population. Poverty and low education level are frequently going together. Special targeted SBCC efforts should be put in place to address the needs of better knowledge on malaria prevention and care among this high risk population.

Malaria Case Management in Population Living in Urban Areas

All Malaria Indicators Surveys have shown that population living in urban settings has

- a) low malaria risk level;
- b) high access to testing and treatment services and
- c) higher coverage of preventive services.

Urban population usually enjoy a better wealth status, higher education level, access to SBCC messages, improved housing and optimal access to operational health care. In many urban areas malaria diagnosis and treatment is sub-optimal. The main reasons are

- a) overcrowded public health facilities with long waiting time;
- b) low quality private sector premises;
- c) insufficient access to health insurance schemes;
- d) expensive premium private health care;

- e) sub-standard malaria case based commodities in private outlets;
- f) influence of social media and advertisements; and
- g) inappropriate health information.

Fever prevalence in urban communities is consistently high, at least at the same level of rural communities, but the distribution of diseases contributing to febrile illnesses is completely different. Risk of periodical epidemics of dengue, chikungunya, and other viral conditions is higher than in more rural areas.

Malaria case management in urban areas should be improved by concerted efforts in providing quality assured services especially in private sector and deploying appropriate health education and information messages.

Targeted malaria vector control initiatives (e.g. bio-larviciding, environmental management) may play a role not only to decrease abundance and infectivity of anopheline mosquitoes but to control other vector borne diseases.

8 Preventive Therapies for Special Risk Group

8.0 The needs of Targeted Preventive Therapies

With the changing epidemiology of malaria, there is a progressive paradigm shift from a “one size fits all” approach, to the targeting of malaria control strategies to specific populations and/or locations for maximal effectiveness. In keeping with this approach WHO is recommending preventive treatments

The objective of preventive treatment is to prevent malaria illness by maintaining therapeutic drug levels in blood throughout the period of greatest risk⁴⁰. Current WHO recommended malaria preventive therapies include intermittent preventive treatment in pregnancy (IPTp), intermittent Preventive treatment in infants (IPTi) and seasonal malaria chemoprevention (SMC). Country specific context for preventive services is as follows:

- IPTp with SP is recommended for all pregnant women except in very low transmission councils in councils according to the malaria risk stratification and engaged in Malaria Case Based Surveillance (mCBS)
- IPTi with SP is recommended in all high transmission areas where there is optimal SP resistance profile. However, new preventive treatment options are being investigated under research settings
- SMC is indicated only in a restricted number of councils with high seasonality and high malaria risk. The WHO recommended SMC medicine, SP-AQ, is not the best option for Tanzania. Hence, alternative treatment options are currently investigated under research settings

Other innovative chemo-preventive approaches (MDA, MTAT) are currently investigated, globally and in the country, under operational and implementation research. Other chemopreventive options recommended in these guidelines also need careful monitoring (e.g. sickle cell and post-discharge prophylaxis). The targeted use of the above initiatives will be implemented according to the evidence of their efficacy, safety, effectiveness and feasibility.

8.1 Intermittent Preventive Treatment in pregnancy (IPTp)

Controlling the effects of malaria infection on the pregnant woman and the foetus requires a balanced programme of effective case management of malaria illness and prevention of the consequences of asymptomatic infection. Interventions on malaria prevention during pregnancy consists of intermittent preventive treatment and use of insecticide treated nets.

Administration of SP as Intermittent Preventive Treatment in pregnancy

Intermittent preventive treatment (IPT) is the administration of antimalarials in full therapeutic doses at predetermined intervals during pregnancy even if individuals have no symptoms and/or signs of malaria. IPT should not be considered as chemoprophylaxis; the woman is not protected from infection and still could be infected after taking IPT.

The aim of IPT is to prevent adverse effects of malaria on both mother and foetus, including maternal anaemia, foetal loss, premature delivery, intrauterine growth restriction, and delivery of low birth-weight infants.

The medicine of choice for IPT is Sulfadoxine-Pyrimethamine (SP)

SP remains the medicine of choice for IPT. It is particularly important that medicines used in pregnancy are known to be safe. Sulfadoxine-Pyrimethamine is a medicine with a long half-life and still effective when used as IPT.

There is convincing evidence⁴¹ showing that it is beneficial for both the pregnant woman and her baby to receive 3 or more doses of SP (IPTp), and that as many as 4 or 5 doses of SP are safe in pregnancy.

Where IPTp with SP is recommended, at each scheduled antenatal care visit the first IPTp-SP dose should be administered as early as possible during the 2nd trimester of gestation and repeated at four weekly intervals until the time of delivery

IPTp with SP is recommended for all pregnant women EXCEPT in councils with very low malaria risk and where malaria case based surveillance has been established

Pregnant women coming from those areas should be recommended to use insecticides treated nets and they will be issued a LLIN at the time of their first ANC attendance
Special considerations for SP administration for IPT in pregnancy

Special considerations for SP administration for IPT in pregnancy

- Sulfadoxine-Pyrimethamine in the last four months of pregnancy is not associated with kernicterus (jaundice in the new-born) as previously thought; therefore, it is safe to give SP right up until the time of delivery.
- SP can be given either on an empty stomach or with food
- SP can be administered safely with combined ferrous sulphate 200 mg + folic acid 0.25 mg
- In exceptional cases where a pregnant woman is taking folic acid at a daily dose equal or above 5 mg, she should not take it together with SP as this counteracts its efficacy and therefore suspension of folic acid for up to two weeks is recommended after taking SP.
- SP should not be administered to women receiving Cotrimoxazole prophylaxis

IPT should be administered as direct observed treatment (DOT) during an antenatal care visit

- If mRDT test positive for malaria in a routine ANC screening or if symptomatic malaria is confirmed by mRDT or microscopy before administration of IPT with SP, a full treatment with antimalarials should be given according to the guidelines
- If malaria is diagnosed after administration of IPT with SP a full ACT treatment course should be given according to the severity of the disease (see chapter 4 or 5)
- If a woman is treated for malaria with an ACT, IPTp should be given after a month in the next ANC visit and continue as scheduled
- IPT is not a contraindication to tetanus toxoid injection and the two can be administered simultaneously

- Pregnant women who are known to have hypersensitivity to sulphonamides (most commonly skin rashes) should not receive IPTp-SP. No other medicine should be used for IPT. Currently, operational researches are ongoing to identify the alternative medicine for IPT apart from SP

Withdrawing SP as IPTp in very low malaria risk areas

NEW!

IPTp is strongly indicated in areas with moderate and high risk of malaria transmission. IPTp with SP might be safely withdrawn in areas with very low transmission

IPTp is recommended by WHO GMP in areas with moderate and high malaria transmission. NMCP recommends a careful withdraw of IPTp in some areas of the country with very low malaria risk where ANC malaria positive attendances are extremely rare and mainly imported.

A mitigation plan should be put in place to mitigate adverse effect of the withdrawing by:

- continue testing of ANC first attendance;
- establish case based surveillance to include history of travel and classification;
- administer SP as IPTp if positive history of travel from low transmission areas to an area with moderate to high malaria risk;
- monitor positivity rate trends monthly and report immediately to direct supervisor abnormal increase of locally transmitted positive cases and e) pregnant women should be recommended to use insecticides treated nets and they will be issued a LLIN at the time of their first ANC attendance.

Preventive treatment in HIV infected pregnant women

Pregnant women who are infected with HIV and receiving co-trimoxazole preventive therapy (CPT), do not need to receive concurrent treatment with SP for IPTp⁴².

HIV positive pregnant women should be referred to PMTCT services and should always be protected by LLINs

Co-trimoxazole preventive therapy according to the PMTCT guidelines is recommended for all pregnant women infected with HIV, regardless from the clinical stage, to prevent malaria, Pneumocystis carinii pneumonia and toxoplasmosis

Prevention for the people living with HIV/AIDS

As people living with HIV/AIDS in areas of high transmission are particularly vulnerable to malaria, their protection using Long Lasting Insecticide Treated Nets (LLINs) is a high priority.

HIV infected individuals with advanced immunosuppression (CD4 T-cell count \leq 350 μ l) should receive co-trimoxazole prophylaxis until their CD4 count is above 350 μ l to prevent them from respiratory tract infections and malaria

8.2 Chemoprophylaxis options for special risk groups

The term chemoprophylaxis is used to describe the administration of an antimalarial drug or drug combination in such a way that blood levels are maintained above the inhibitory level of survival of the local strains of parasite for the whole of the period at risk and, in the case of travellers, for an appropriate period afterwards in order to kill emerging liver forms. The recommended chemoprophylaxis options are atovaquone-proguanil, doxycycline, and mefloquine.

Table 27: Medicines indicated for chemoprophylaxis

	Indications	Adult	Children	Pregnancy	Start	Finish
Mefloquine	Non-Immune Stay <3 months	250 mg weekly	5 mg/kg weekly	Yes	4 weeks before	4weeks after
Proguanil/ Atovaquone	Up to 28 days	1 tab daily	See 8.6.2	Contraindicated	1-2 days before	1week after
Doxycycline	Up to 6 months	100 mg daily	>12 years	Contraindicated	1week before	4weeks after

Chemoprophylaxis for non-immune pregnant women

Non-immune pregnant women should ideally not travel to malarious areas unless absolutely necessary. Mefloquine prophylaxis may be taken even in the first trimester. Doxycycline is contraindicated during pregnancy. Data on the safety of exposure to atovaquone–proguanil during pregnancy are limited and this combination is therefore not recommended for use in pregnancy.

Chemoprophylaxis is currently not recommended for pregnant women living in malaria endemic areas.

Mefloquine

This medicine is structurally similar to quinine. It is a potent long acting blood schizonticide effective against all malaria parasites including *P.falciparum* parasites resistant to 4 aminoquinolines (chloroquine and amodiaquine), SP and quinine. However, resistance to mefloquine develops very fast.

Available formulation

Tablet 250mg mefloquine base.

Indications

Prophylaxis against malaria.

Contraindications

- History of allergy to mefloquine
- Pre-existing neurological or psychiatric disease including epilepsy
- Concomitant use of halofantrine, SP, quinine, anti-convulsants and beta blockers e.g propranolol

- Treatment with mefloquine in the previous 4 weeks
- Pregnancy during the first trimester
- Persons undertaking fine co-ordination and spatial discrimination e.g. drivers, pilots, machine operators

Use in pregnancy and lactation

If travel to a malaria endemic area cannot be avoided, good preventive measures should be taken, including prophylaxis with Mefloquine where this is indicated.

Adverse effects

Dizziness, sinus bradycardia, sinus arrhythmia, neuropsychiatric disorders

Dose for chemoprophylaxis

- Adult: 250 mg weekly
- Children: 5mg/kg weekly

Doxycycline

Indications

Prophylaxis for malaria

Dose for prophylaxis

Adult dose is 100 mg daily. To be given from 12 years of age and above.

Can normally be used continuously for a period of at least 6 months (professional guidance is required).

A trial course should be taken before departure if this regimen is being used for the first time; it can be used to detect the likelihood of developing allergic reactions. Doxycycline needs to be started one week before exposure and continued throughout exposure and for 4 weeks after return from malaria endemic area.

Contraindications

Doxycycline is contraindicated during pregnancy, breastfeeding, and in those with systemic lupus erythematosus, porphyria and children aged less than 12 years because permanent discolouration of teeth can occur.

It should be used with caution by women on oral contraceptive pills as it may reduce the effectiveness of the pills.

Adverse effects

Occasionally the medicine causes anorexia, nausea and diarrhoea. Long term use may lead to super-infections such as candida infection and sore tongue (glossitis) and on rare occasions hepatitis, colitis and blood dyscrasias.

Exposure to UV light can lead to skin photosensitivity. Sunscreens can be used to counter this effect, and if the reaction is severe, alternative prophylaxis should be used. Heartburn is a common side effect, so the capsule should be taken with a full glass of water.

Proguanil Hydrochloride/Atovaquone

Indications: Prophylaxis of malaria particularly where resistance toward other antimalarial medicines is suspected.

Contraindications

Contraindications include renal impairment, diarrhoea or vomiting. The medication should be avoided in pregnancy and during breastfeeding. Concomitant administration with tetracycline, rifampicin, indinavir and metoclopramide is also not advised, due to reduced plasma concentration of atovaquone.

Side effects

Some side effects: Nausea, vomiting, mouth ulcers, stomatitis, diarrhoea, abdominal pain, anorexia, fever, headache, dizziness, insomnia, cough, visual disturbance, angioedema, blood dyscrasia, and hair loss.

Caution: operating machinery and other activities, which require full attention and fine motor coordination, should be avoided when using this medication.

Formulation and strength available

Adult strength formulation (tablets):

- Proguanil hydrochloride 100 mg
- Atovaquone 250 mg

Paediatric formulation (tablets):

- Proguanil hydrochloride 25 mg
- Atovaquone 62.5 mg

Dose for chemoprophylaxis

Adult dosage—one tablet, started 1-2 days before travel, taken daily during exposure, and for 7 days after leaving the malarious region.

Child dosage—Paediatric-strength tablet (25 mg Proguanil with 62.5 mg Atovaquone) is available.

The dosage is based on weight:

- 10 kg-20 kg 1 paediatric-strength tablet
- 21-30 kg 2 paediatric-strength tablets
- 31-40 kg 3 paediatric-strength tablets
- More than 40 kg 1 adult-strength tablet

8.3 Non-immune traveller's and malaria chemoprophylaxis

Prevention of malaria among healthy, non-immune persons who travel to a malarious area involves multiple strategies such as mosquito avoidance (by use of insecticide bed nets and repellents) and use of antimalarials medicines to kill any parasite that are contracted from residual mosquito bites.

Chemoprophylaxis is the regular use of antimalarial medicines to prevent development of malaria parasites following any possible inoculation.

All recommended primary chemoprophylaxis regimens involve taking a medicine before, during, and after travel to the malaria risk country.

The risk for travellers to acquire malaria differs substantially from region to region and from traveller to traveller, even within the same region. This variability is a function of the intensity of transmission within the various regions, duration, season and type of travel.

Travellers who have symptoms of malaria should be advised to seek medical evaluation as soon as possible but not to stop their chemoprophylaxis regimen.

8.4 Malaria chemoprophylaxis in sickle cell disease

Sickle cell disease (SCD) is an inherited condition where the sickle cell gene responsible for the production of abnormal haemoglobin S is inherited from both parents.

In areas where malaria is common, SCD patients have low risk of malaria infection⁴³. However, when they do get malaria it is associated with high risk of morbidity and mortality⁴⁴.

Malaria is the most common precipitating cause of crises in sickle cell disease in malaria-endemic countries⁴⁵.

It is recommended to give routine malaria prevention medicines (chemoprophylaxis) to individuals with SCD in areas where malaria is endemic. This helps to reduce SCD crises and all the problems that go along with it.

The recommended approaches for Tanzania are:

- Proguanil-Atovaquone: daily administration according to body weight
- Dihydroartemisinin-Piperaquine: monthly administration according to body weight⁴⁶

New!

Due to the available safe and effective pharmacological options every SCD patient that requires malaria protection must receive a suitable chemopreventive treatment

It is recommended to monitor both efficacy and safety of chemoprophylaxis in this special group. Academic and research institutions are expected to provide adequate monitoring and evaluation support on implementation of this activity before nationwide scaling up.

Malaria prevention in sickle cell disease

The emphasis of malaria prevention for people affected with SCD is on the use of Long Lasting Insecticide Nets (LLINs); access to prompt diagnosis and treatment; and health education on risks associated with malaria in SCD.

Treatment of malaria in sickle cell disease

If malaria is diagnosed, full treatment with recommended antimalarials should be given according to the guidelines on the treatment of uncomplicated and severe malaria. (See chapters 4 and 5).

8.5 Targeted approaches in preventive therapies that need to be further explored

Targeted approach 1: Intermittent Preventive Treatment in infancy (IPTi)

Intermittent Preventive Treatment in infancy (IPTi) is the administration of a full antimalarial therapeutic course delivered through the Expanded Program on Immunization (EPI) at defined intervals corresponding to routine vaccination schedules of Pentavalent 2, Pentavalent 3 and Measles.

Expected benefits

IPTi provides an overall protection in the first year of life:

- a) against clinical malaria [30.3%];
- b) against anaemia [21.3%];
- c) against hospital admissions associated with malaria parasitaemia [38.1%]; and against all-cause hospital admissions [22.9%].

Who

Infants (<12 months of age) usually at 10 weeks, 14 weeks, and ~9 months of age

NEW!

Every infant attending EPI (Penta 2, Penta 3, MR1) should receive SP as IPT in high malaria risk areas with evidence of adequate SP efficacy

What:

The WHO recommended medicine for IPTi is SP.

Protective efficacy of SP-IPTi is related to a) the half-life of the medicine and b) the susceptibility of the malaria parasite to SP.

SP-IPTi offers a personal protection against clinical malaria for a period of approximately 35 days following the administration of each dose

Parasite resistance to SP in the area should serve as a guide to use of SP-IPTi. Surveillance of molecular markers of SP resistance should be conducted to verify the distribution and prevalence of pfdhps 540 mutations

which a surrogate measure of SP therapeutic efficacy.

Where:

Intermittent Preventive treatment in infants (IPTi) is recommended in areas of moderate to high transmission provided that SP resistance markers mutations in dhps gene codons 540E are less than 50% and 581G are less than 10%.

Operational researches on alternative medicines, in case of high SP resistance, and different treatment schedule beyond the infancy, should be encouraged.

Caution

Intermittent Preventive Treatment with SP in infancy (IPTi) and SMC should not be administered concomitantly. Therefore, in target areas for SMC, IPTi should not be deployed

Targeted approach 2: Prevention of malaria reinfection after discharge for children with severe anaemia and severe malaria diagnosis

NEW!

Post-discharge malaria chemoprevention reduces severe morbidity and mortality by decreasing recrudescence of infection, re-hospitalization, and increasing Hb level

Post-discharge malaria chemoprevention (PMC) is the intermittent administration of full treatment courses of antimalarial to children recovering from severe anaemia and findings suggest that this intervention reduces recrudescence of infection, re-hospitalization, increase Hb level, and, eventually, significantly reduces severe morbidity and deaths in children.

It is recommended to prescribe to all children under five years of age discharged with a diagnosis of severe anaemia and severe malaria, a monthly treatment of ACT (preferably long term acting e.g. DP) for 6 months irrespectively from malaria risk area.

Alongside chemoprevention the patient or caretaker should be adequately counselled to use LLIN to avoid mosquitoes biting.

This chemopreventive approach needs to be further explored in the country.

Targeted approach 3: Seasonal Malaria Chemoprevention (SMC)

Seasonal malaria chemoprevention (SMC), previously referred to as Intermittent Preventive Treatment in children (IPTc), is defined as the intermittent administration of full treatment courses of an antimalarial medicine during the malaria season to prevent malarial illness with the objective of maintaining therapeutic antimalarial drug concentrations in the blood throughout the period of greatest malarial risk.

This intervention has been shown to be effective, cost-effective, safe, and feasible for the prevention of malaria among children less than 6 years of age in areas with highly seasonal malaria transmission.

Expected benefits

- Prevents approximately 75% of all malaria episodes
- Prevents approximately 75% of severe malaria episodes
- May result in a decrease in child mortality of around 1 in 1000
- Probably reduces the incidence of moderately severe anaemia
- Does not result in an increase in clinical malaria in the following malaria transmission season after one year of administration but the consequences of giving SMC for several years have not yet been evaluated.
- Serious adverse events have not been reported and are probably rare

Where:

Seasonal Malaria Chemoprevention (SMC) is recommended in areas of moderate to high transmission but highly seasonal malaria transmission.

- Malaria transmission and the majority of clinical malaria cases occur during a short period of about four months.
- the clinical attack rate of malaria is greater than 0.1 attack per transmission season in the target age group, and
- The prevalence of dhfr/dhps SP resistance markers is below the global recommended levels

What:

WHO recommends a complete treatment course of Amodiaquine plus Sulfadoxine-Pyrimethamine (AQ+SP) to be given at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season, provided both drugs retain sufficient antimalarial efficacy. This regimen is not optimal for Tanzania: In the country *P. falciparum* treatment failure to Sulfadoxine-Pyrimethamine (SP) and Amodiaquine (AQ) has been reported in early 2000s; with a mean treatment failure of 25.5% for SP and 11.5% for AQ⁵⁰. Alternative molecules (DP) are currently explored in southern Tanzania for their safety and effectiveness.

Who:

Children aged between 3 and 59 months

Caution:

Intermittent Preventive Treatment with SP in infancy (IPTi) and SMC should not be administered concomitantly. Therefore, in target areas for SMC, IPTi should not be deployed

Targeted approach 4: Mass Drug Administration (MDA)**New!**

MDA is indicated as part of foci response in Case Based Surveillance and a tool for immediate emergency and epidemic response

Mass Drug Administration (MDA) has received increasing interest in the context of malaria elimination. Modelling assisted Tanzania to predict the impact of the current and the revised (SMMSP 2018-2020) strategic plans. Modeling shows that MDA is very potential to reduce transmission drastically in very low transmission with sustained impact. It is included in this guideline as an optional response to MCBS in very low transmission areas targeted for local elimination⁵¹.

The objectives of MDA can be to reduce or interrupt transmission, to rapidly reduce malaria morbidity and mortality, or to prevent relapses and resulting malaria transmission.

Where

In very low transmission councils as targeted response to identified foci with local transmission. In emergency and epidemic situation

What and When:

As mCBS response, targeted focal MDA consists in the administration of a full dose of ACT (e.g. DP) and PQ treatment, irrespective of the knowledge of symptoms or presence of infection, to the targeted population in a given area. In MDA as part of an epidemic response, the number of rounds may depend on the epidemic curve (incidence rate and attack rate), type of medicines used and the expected duration of transmission. In MDA in complex emergencies, the rounds should be repeated to cover the transmission period to prevent morbidity and mortality.

Who

All age group or targeted community members except those with contraindication to the recommended antimalarials

Expected benefits

Provide therapeutic concentrations of antimalarial drugs to as large a proportion of the population as possible in order to

- Cure asymptomatic infections and
- To prevent re-infection during the period of post-treatment prophylaxis.
- Rapidly reduces the prevalence and incidence of malaria in the short term.

Targeted approach 5: Preventive Treatment for School-children

In the current epidemiological transition there is increasing evidence that parasite prevalence peak is progressively shifting, especially in high transmission areas, from early childhood (children below 5 years of age) to late childhood and early adolescence (children 6-15 years of age). Recent observations in the country (SMPS 2015, 2017 and 2019) have shown that school going age children in high malaria risk councils are carrying parasites up to over the prevalence rate of 50%. In the same areas half of school age going children have

New!

Schoolchildren chemoprevention in high malaria risk areas is expected to have high impact on malaria cases averted, improved Hb and better cognitive levels. Additional benefit is the reduction of the high gametocidal rate.

some degree of anemia. Several studies evaluating Intermittent Preventive Treatment for School-children (IPTsc) strategy by using ACT, have shown feasibility of conducting school based IPT programme and that the drugs were safe and effective on reducing malaria incidence and reducing anaemia^{52 53}.

The NMSP 2021-2025 encourages the implementation of targeted preventive drug administration in schoolchildren in high transmission risk areas, where. This approach is expected to have high impact on malaria cases averted and eventually transmission when implemented on top of optimal access to malaria

case management (MCM) and malaria vector control (MVC) initiatives.

Currently an evaluation of the implementation and effectiveness of intermittent preventive treatment for malaria using dihydroartemisinin-piperaquine (DP) on reducing malaria burden in school aged children in Tanzania is undergoing in the country. In the intervention areas, DP is given at an interval of four to six months, two to three times a year in liaison with school curriculum schedule and transmission seasonality. The schedule is described in page 50. After the evaluation of the above initiative, NMCP will explore the possibility to expand to further areas according to malaria risk.

Targeted approach 6: Focal and Mass Testing and Treatment

Mass/Focal Testing and Treatment (M/FTAT) involves the testing, using mRDT, of all individuals in a defined geographical area, and treating those who are positive. MTAT and

New!

Testing and treatment (TAT) is potential to rapidly reduce malaria parasitaemia in high malaria risk settings. High coverage of vector control interventions is needed to maintain the gains

FTAT provide a targeted approach to malaria control, by deploying treatment to the detected populations of parasitaemic individuals, with the aim of reducing the parasite reservoir. Since it is widely known that carriers with submicroscopic or undetectable parasitaemia by conventional mRDT, contribute to onward transmission of malaria, these methods rely on the use of highly sensitive detection tests⁵⁴.

Targeted testing and treatment interventions are encouraged as part of the Active Case Detection under malaria case surveillance in low transmission settings. Other initiatives are currently implemented and validated in moderate and high transmission settings.

9 Management of Commodities for Malaria Diagnosis and Treatment

9.0 The Rationale for Malaria Commodities and Logistic Management

Consistent availability of safe and quality assured malaria commodities and supplies at all delivery points is essential to improve the access to quality health services. The uninterrupted availability of safe, quality assured essential commodities in the service delivery points is a combination of different factors:

- a) accurate selection, quantification, and procurement system;
- b) strong inventory and logistics management practices from warehousing to distribution;
- c) appropriate data management through reinforced data culture use for decision making;
- d) strengthened workforce, infrastructure, planning process, e) robust regulatory authorities able to monitor quality and safety of the products and f) adequate financing.

9.1 Logistic Management of Malaria Case Management Commodities

Health commodities for diagnosis and treatment of malaria include pharmaceuticals, laboratory equipment and supplies. Artemisinin based combination therapy (ACT), Artesunate injection SP and Malaria Rapid Diagnostic Tests (mRDT) are the most used malaria commodities which are centrally supplied to the public sector through the Medical Stores Department (MSD).

The management procedures such as ordering, distribution, storage, inventory control, prescribing, dispensing, use and reporting must be strictly followed as prescribed in all levels to ensure uninterrupted supply. Malaria commodities should be used based on the treatment guidelines to maximise their rational use.

Quantification

Health commodities quantification for the public sector is initiated by the health facilities with technical support from the national level. Consumption based bottom up quantification is the preferred method for maintaining adequate malarial commodities in the country. In public health facilities data from the electronic logistics management system (eLMIS) supports the implementation of consumption-based bottom up quantification. From the facility level the consumption data is aggregated to the district, region and up to the national level.

Procurement and Ordering

The public procurement agency for health related commodities is the Medical Stores Department (MSD) which has a responsibility of procuring, storing and distribution of all health commodities and medical equipment including malaria commodities. NMCP provides the information on product specifications, the quantities and delivery schedules for procurement purposes. The MSD procurement system allows for emergency procurement when there is national stock-out of malaria commodities. Clearing at the port of entry of all malaria commodities for public health use is done by the delegated government authority (GPSA).

There is a system in place for ordering and procurement by health facilities. The system requires all procurement for malaria commodities to be done primarily from MSD. In the event that malaria commodities are stocked out at MSD health facilities are allowed to procure from other approved Prime Vendors (PV). Health facilities are expected to order

their requirements in accordance to their needs and ordering schedules. The order should be submitted to the relevant authorities, such as the Facility therapeutic committees for review and approval.

Storage and distribution of malaria commodities in public sector

Good storage and distribution practices require at a minimum a well-designed and managed system, stocked with constant supply of commodities; that commodities are kept in good condition throughout the distribution process; the quality of commodities is ensured and loss is minimized.

Storage and delivery of malaria commodities is coordinated from the MSD central and zonal level according to national guidelines on storage and distribution of health commodities.

Distribution of malaria commodities to the health facilities from the MSD zonal stores is managed using the Integrated Logistics Systems (ILS) according to defined delivery schedules.

Health facilities storage and distribution

Malaria commodities must be stored appropriately in accordance with Good Storage Practices (GSP) as stipulated in ILS manual to avoid deterioration and/or damage of the products. Medicines and related supplies should be issued on the basis of FEFO (First Expiry, First Out) and FIFO (First In, First Out) if the commodities are of the same batch or lot number.

Health facilities should maintain a rational and accountable distribution system through proper inventory control of malaria commodities. Tracking, stock inventory and management should follow the stipulated procedures.

Distribution chain of malaria commodities in private sector

The formal private-for-profit health sector includes hospitals, health centres, dispensaries, pharmacies, and Accredited Drug Dispensing Outlets (ADDOs). The private sector forms the cornerstone of the MOHCDGEC's home management of malaria strategy to increase access to effective treatment.

Private health facilities may obtain Artemisinin based combination therapy from approved first line buyers through co-payment mechanism.

Other malaria commodities are available in the private market including mRDTs. Frequency of orders made by private sector facilities will be on a demand-driven basis even in case of supply of subsidized malaria commodities.

Private health facilities working in collaboration with councils on a contract basis are approved to receive selected commodities through the public health system.

Malaria commodities manufacturers distribute their commodities through a range of national- and regional-level wholesalers in Tanzania. Most multinational manufacturers have selected agents' in-country who has exclusive importation rights for their products. These agents then either distribute the commodities to other areas of the country through their own networks or provide the commodities to another importer or wholesaler for distribution ("horizontal distribution").

If the product is imported, the distribution chain from manufacturer to importer includes:

- The importer who places an order with a relevant supplier
- The supplier who provides a pro-forma invoice to the importer, who forwards it to TMDA for approval and deduction specified percent (%) of the invoice value (as a regulatory fee)
- The supplier sending the consignment to the importer. Upon arrival the consignment is inspected by TMDA to ensure quality of commodities and the Tanzania Revenue Authority (TRA) for tax collection purposes.

Supportive interventions for the malaria commodities management in the private sector includes; training, supervision, medicine monitoring and spot checks, improving regulatory environment, improving access and adherence to suggested price where subsidy mechanisms are in place.

Distribution chain of malaria commodities for Community Based Malaria Management

Home malaria management is done as a basic curative service and requires an established distribution chain up to community level (community health volunteers). In this case diagnostics and medicines are managed by the nearby health facility through the standard supply chain. The health facility in charge is responsible for requisition of the products, temporary storage and distribution to the end point. Community leaders in collaboration with community health volunteers are responsible for the appropriate storage and use at the end point. Other indications on management and accountability of malaria commodities are provided in the mCCM protocol⁵⁵.

Monitoring of malaria commodities

NMCP monitors commodities from the procurement stage and in-country supply pipeline. In collaboration with MSD, NMCP may adjust the delivery schedule of commodities from suppliers depending on incoming shipments and in-country commodities' stock status.

In public health facilities PORALG is responsible for supervision of primary health facilities to ensure that commodities are managed in accordance to the set procedures to avoid over/understock. Regional/referral, specialised, zonal and national hospitals are supervised by the MOHCDGEC A verification team comprising of NMCP, PORALG and PSU should visit quarterly a sample of health facilities and the respective MSDs zonal warehouses, and produce a quarterly report which provides a snapshot of stock availability of malaria commodities. Whenever stock imbalances are detected, NMCP then conducts re-distribution to mitigate stock-outs.

In private sector NMCP conducts spot checks to First Line buyers and end user verification in private dispensing outlets to ensure that the procedures governing the mechanism and commodity management are adhered to.

9.2 Quality assurance for malaria diagnostics

Malaria tests quality assurance

The primary aim of malaria test quality assurance (QA) programme is to ensure that malaria parasite-based diagnosis services are manned by competent staff, supported by effective training and supervision that maintains a high level of staff competency and performance and by a logistics system that provides and maintains an adequate level of supply of reagents, devices and equipment.

Quality assurance involves all processes for ensuring quality of diagnostics medical devices from the manufacturer to the end user, and from the time when a specimen is collected, received in the testing site, processed, and interpreted to the time when results are dispatched to the client.

TMDA is responsible to ensure quality, safety and performance of all medical devices that are distributed in the country throughout the supply chain.

Furthermore, Health Laboratory Practitioner's Council (HLPC) in collaboration with other professional bodies ensures competence of laboratory practitioners and that quality management system in health facilities is in place and adhered to.

Objectives and framework for malaria tests quality assurance

The diagnostic unit of MoHCDGEC through NMCP is responsible for overseeing malaria parasite based diagnosis.

The long-term aim is fully functional malaria testing National QA system with the benchmarking and competency accreditation of all routine performers of malaria tests.

The malaria laboratory tests QA programme objectives are:

- Ensuring quality product supplies to both malaria RDTs and microscopy
- Improving the overall competency and performance of malaria microscopy and mRDT at all levels of the laboratory services
- Sustaining the highest level of accuracy (both in sensitivity and specificity) in confirming the presence of malaria parasites
- Systematically monitoring laboratory procedures, consumables, devices, equipment and the results of laboratory diagnosis
- Establishing a clear hierarchical reporting system for results of QA

The framework for malaria test quality assurance is included in Table 28.

Table 28: Main activities for malaria diagnosis QA system

Main activities	Malaria tests	
	mRDT	Microscopy
Ensure continuous quality product supply	Forecast, select according to established national criteria, procure from manufacturer, plan delivery schedules and perform batch (lot) test at WHO collaborator laboratory facility	Quantify, select national recommended techniques with equipment & reagent and procure from manufacturer with appropriate ISO certification
Improve competency and performance	Appropriate training and follow-ups to non and laboratory personnel on SOPs, safety precautions and proper waste disposal	Refresher trainings and follow-up for laboratory personnel on good laboratory practices with focus to SOPs
Describe QA procedures and reporting system	Description of methodology, activities, levels of implementation, management checklist/tools and lines of reporting	Description of activities, levels of implementation, management checklist/tools and lines of reporting

Laboratory quality assurance management at national level

The main functions of the National Quality Assurance system are:

- Preparation of the quality management plan
- To set quality standards for testing sites and performances
- To support the National Health Laboratory Quality Assurance and Training Centre (NHLQTC)
- Designing and updating standard operating procedures (SOP) and job aids
- To scale up the system of accreditation of points of care performing malaria tests
- To set up a system of certification of microscopist
- Perform mRDT lot testing
- Provide minimum specification for laboratory reagents and equipment for malaria microscopy
- Follow up procurement of quality equipment and reagents
- Monitoring the quality management system

The main actors and their respective functions of laboratory quality assurance management at national level are:

- NMCP case management head
- NMCP diagnostic focal person
- NMCP commodities and logistics focal person
- National Health Laboratory and Quality Assurance Training Centre (NHLQATC) malaria focal person
- National malaria quality assurance core facilitators team

Laboratory quality assurance management at district level

The main functions of the quality assurance system at district level are:

- Supervision of laboratories and points of care performing mRDT
- Monitoring competence in malaria testing
- Cross checking routine blood smear results (validation)
- Temperature monitoring of mRDT storage in health facilities

The main actors and their respective functions of laboratory quality assurance management at district level are:

- District laboratory technologist
- District malaria IMCI focal person (coordination and communication with NMCP)

Laboratory quality assessment at health facility level

The activities to be performed at points of care where malaria testing facilities are available are the following:

- Monitoring the competence of malaria tests performers (microscopes and mRDTs performers) by direct observation
- Quality control of routine BS for malaria (preparation and validation)
- Monitoring mRDTs stability
- Internal quality check (if applicable)
- Quality of mRDT performed at community level (if applicable)

9.3 Malaria therapeutic and laboratory devices quality assurance procedures

Tanzania Medicine and Medical Devices Authority (TMDA) quality control laboratory has been prequalified by WHO as a WHO quality control laboratory. TMDA implements quality assurance testing; i.e. preliminary testing upon entry and post-market surveillance

Two random sampling procedures are used, the lot or batch testing at the point of entry or post marketing surveillance.

TMDA quality assurance system for medicines and medical supplies is performed through:

- Port of Entry screening test where a sample is randomly selected from each batch of imported antimalarial agents subjected to preliminary testing; only batches that comply with screening tests are allowed into the market. This is applicable when the number of batches and the quantities per batch are reasonable for the exercise. If this is not the case, then 10% of the batches are randomly selected and samples are collected from the selected batches, if they pass the test then they are considered a representation of the entire shipment. To minimize this challenge, NMCP and MSD are working in ensuring that the numbers of batches per consignment are reasonable and manageable
- Once the products are in the market, they are again sampled during Post Marketing Surveillance. Testing and tracking of malaria commodity performance is mandatory after entry. This is a countrywide surveillance in which antimalarials are sampled according to guidelines documented in the sampling plan. Blue forms are used to report poor quality of medicines and medical devices at all service delivery points.

Procedure in case of a product failing QC testing

A recall is instituted in the case of ACT or Artesunate injection or mRDT product failing QC testing. For public health facilities, commodities are recalled through the DMO then sent to MSD. These commodities are destroyed after verification and approval from relevant authorities (TMDA and MoF). MSD will then make a claim for replacement of these commodities from the manufacturer/supplier. For the private sector, TMDA is responsible for managing a recall through the wholesalers by the distributors. These products will subsequently be disposed of in accordance with the TMDA Act.

mRDT lot testing

The quality control sampling procedure for mRDT (WHO sampling protocol) consists of a sample of 150 tests per lot for each consignment is collected from those products with a shelf-life less than 18 months and 175 tests per lot for those with more than an 18 months shelf-life and shipped to the identified WHO pre-qualified laboratory. This is done on a quarterly basis as per the procurement plan i.e. whenever a new consignment arrives.

9.4 Pharmacovigilance

Adverse drug reactions (ADRs) are inevitable consequences of pharmacotherapy. It is well known that all medicines carry the potential to produce both desirable and undesirable effects. No medicine is absolutely safe under all circumstances of use or in all patients and ADRs may occur even if a medicine is correctly selected and dosed.

All medicines undergo safety assessment during the development process, before being declared fit for human consumption. However, the populations treated once the medicine hits the market are clearly different from the ones studied during development. New safety hazards are therefore likely to be discovered once the medicine is prescribed widely also to elderly, polymorbid patients, children and women of childbearing age. Even medicines that

show no teratogenic potential in animals may cause harm to the unborn child and it is not until pregnant patients are exposed that these effects will be recognised. Patients are not followed as closely and intensively as study participants; therefore unwanted effects can go unrecognised for quite a while. Also, medication will often be prescribed for far longer periods of time than the ones studied before registration unveiling problems related to chronic use, also quality of products submitted during pre-marketing approval may differ with those supplied post-marketing. This explains the need for intensive and pro-active post-marketing surveillance applying different scientific approaches.

Importance of pharmacovigilance

The most important aspects of pharmacovigilance are:

- The continuous evaluation of medicine safety and efficacy will help to make safer and more effective treatment available to patients
- Information about rare but serious adverse reactions, chronic toxicity, use in special groups (such as children, the elderly or pregnant women) or medicine interactions is often incomplete or not available
- Monitoring after effects of accidental use of contraindicated medicines for specific groups (e.g. pregnant women in the first trimester and paediatrics)
- Data derived from the surveillance assists the regulatory authorities to make evidence-based decisions
- Early detection of ADR may prevent or reduce ADR related morbidity and mortality

Clinical presentation of adverse medicine reactions

ADRs may present with non-specific symptoms and signs and can at times mimic features of some diseases; hence, it is difficult to distinguish between ADR and clinical features of the treated condition. However, the following step-wise approach may be helpful in assessing possible medicine-related ADRs:

- Ensure that the medicine prescribed is the medicine dispensed and actually used by the patient at the dose advised
- Verify that the onset of the suspected ADR was after taking the medicine
- Determine the time interval between the beginning of medicine treatment and the onset of the event
- Evaluate the suspected ADR after discontinuing the medicines and monitor the patient's status
- Analyse the alternative causes (other than the medicine) that could on their own have caused the reaction
- Use relevant up-to-date literature on medicines and their adverse reactions and verify if there are previous conclusive reports on this reaction
- Fill in the ADR reporting form (yellow/green form/electronic reporting) and submit to the relevant authority as instructed
- Manage the patient accordingly, including referral to appropriate level
- Make all necessary arrangements for patient follow up

Reporting adverse drug reactions and medical devices adverse events

Spontaneous method using yellow/green form

The report of suspected adverse reaction to medicines or vaccines (yellow form) is the recommended form for reporting suspected ADRs. The operational challenge is the low reporting rates. It is a passive surveillance method which encourages health professionals

and others to look for adverse effects and report safety concerns and submits to the TMDA as per instructions. Reporting is entirely dependent on the initiative and motivation of the reporters. This method is commonly referred to as “spontaneous” or “voluntary” or “passive” reporting system.

Who should report?

All health care providers (specialists, medical doctors, clinical officers, pharmacists or nurses) should report ADRs as part of their professional responsibility, even if they are doubtful about the precise relationship with the prescribed medication.

What should be reported?

- All suspected adverse medicine reactions should be reported, both to common or new medicines.
- All suspected medical devices adverse events/incidents

An adverse event/incident related to a medical device that has led or may lead to mild or moderate or serious threat to public health or death or serious injury if one or more of the following events occur but not limited to;

- Malfunction or deterioration in the characteristics or performance.
- An incorrect or out of specification test result
- The discovery of a design defect during design review
- An inaccuracy in the labelling, instructions for use and/or promotional materials.
- The discovery of a serious public health threat.
- Inappropriate therapy
- Unanticipated adverse reaction or unanticipated side effect
- Use Error
- Degradation/destruction of the device (e.g. fire)
- Interactions with other substances or products
- False positive or false negative test result falling outside the declared performance of the test.
- Deficiency of a device found by the user prior to its use:
- Other information becoming available

How to report

The Tanzania Medicine and medical Devices Authority (TMDA) has developed adverse drug reaction (ADR) and medical device adverse event/incident reporting forms (copies provided in appendix H). Reporting forms are distributed by TMDA zonal offices and are available at DMO’s offices, in the TMDA website (www.tmda.go.tz) and through the mobile application TMDA Adverse Reactions Reporting Tool. At district level, the DMO is responsible for distributing forms to all health facilities both public and private. ADR form can be filled by any health care provider. The forms come with a prepaid postage stamp and once completed they should be posted to TMDA.

What happens after reporting?

Upon receipt of the forms, TMDA is responsible for sending an acknowledgement letter to the ADR reporter. In addition, TMDA is responsible for conducting causality assessment of reported ADR and taking appropriate actions such as product recall if necessary, de-registering the product, amendment of indications or summary of product characteristics.

Active pharmacovigilance method

Active (or proactive) safety surveillance means that active measures are taken to detect adverse events. This is managed by active follow-up after treatment and the events may be detected by asking patients directly or screening patient records; this is best done prospectively. The most comprehensive method is cohort event monitoring (CEM), it records all clinical events and not just suspected adverse drugs reactions. Event monitoring involves actively and systematically documenting and submitting the reports of the events.

A CEM programme is essentially an observational study of a new medicine in the early post marketing phase.

Pharmacovigilance in relation to this guideline

In this guideline new treatment strategies such as the use of single low dose primaquine, other antimalarial drugs such as pyronaridine, DP, AQ-AT and others in general population and the vulnerable groups are included. Primaquine causes hemolytic anemia in individuals with G6PD deficiency and it is not yet established in the Tanzanian population the proportion of individuals with this genetic deficiency. Primaquine is eliminated via CYP 2D6 and there may be variability in the extent of biotransformation of this drug among individuals. The drug can exhibit pharmacokinetic interaction with other drugs and cause adverse events. Furthermore, primaquine may interact with other medicines that have similar adverse events and exaggerate the side effects. Similarly, Pyronaridine which is a new drug in the current guideline has not been widely used in Tanzania. In addition, there are new preventive strategies that are currently under research that will involve the use various drug combinations. Therefore, it is important to continue monitoring and reporting the safety profiles of all drugs that are included in this guideline. Adverse events should be initially reported at the health facility so that it is evaluated and managed then reported to TMDA. TMDA has established pharmacovigilance system in the country and has provided specially designed electronic forms and hard copies to gather drug adverse events experienced by patients. Pharmacists working in all health facilities and drug outlets have a frontline role in gathering adverse events from patients they serve by directly inquiring the information from patients and not otherwise. In addition, clinicians and nurses have a role in reporting the drug related toxicity the patient experienced when managing patients during ward rounds or at clinics.

It is the role of CHMT and RHMT to ensure that TMDA tools for gathering adverse events are filled in rationally and posted to TMDA

In this guideline new treatment strategies such as the use of single low dose primaquine, other antimalarial drugs such as pyronaridine, DP, AQ-AT and others in general population and various vulnerable groups are included. Primaquine causes hemolytic anemia in individuals with G6PD deficiency and it is not yet established in the Tanzanian population the proportion of individuals with this genetic deficiency. Primaquine is eliminated via CYP 2D6 and there may be variability in the extent of biotransformation of this drug among individuals. The drug can exhibit pharmacokinetic interaction with other drugs and cause adverse events. Furthermore, primaquine may interact with other medicines that have similar adverse events and exaggerate the side effects. Similarly, Pyronaridine which is a new drug in the current national guideline has not been widely used in Tanzania. In addition, there are new preventive strategies that are currently under research that will involve the use various drug combinations. Therefore, it is important to continue monitoring and reporting the safety profiles of all drugs that are included in this guidelines. Adverse events should be initially reported at the health facility so that it is evaluated and managed then reported to TMDA.

TMDA has established pharmacovigilance system in the country and has provided specially designed electronic forms and hard copies to gather drug adverse events experienced by patients.

Reinforcement of adverse events reporting

Pharmacists and pharmaceutical technicians or other health workers involved in providing medicines in health facilities and drug outlets have a forefront responsibility in gathering adverse events from patients they serve by directly inquiring the information from patients. In addition, clinicians and nurses have a role in reporting the drug related toxicity the patient experienced when managing patients during ward rounds or at clinics. It is the responsibility of hospital directors in regional and national referral hospitals and heads of CHMT and RHMT to ensure that TMDA tools for gathering adverse events are filled in rationally and posted to TMDA as per methods mentioned in this guideline

9.5 Restrictions of SP use in ANC only

New!

SP is extensively available in drug outlets and is widely misused for malaria self-treatment. Measures to restrict its use should be emphasized

SP should be available for IPTp and IPTi in RCH clinics only. However, it has been observed that the medicine is still widely available in the private outlets and misused for the treatment of uncomplicated malaria. The following recommendations should be emphasized and implemented to restrict the use of SP for IPTp and IPTi.

- Include SP in the product list of RCH clinics delivering SP IPTp and IPTi
- Develop specific regulation and enforcements

mechanisms to restrict SP availability in public and private health facilities and drug outlets

10 ACT Resistance Mitigation Strategy

10.0 Emergence of ACT resistant malaria and mitigation strategies

The Greater Mekong sub-region (GMS) - South East Asia, has long been the epicentre of antimalarial medicine resistance. Following the initial detection of artemisinin partial resistance in the GMS, a comprehensive response combining malaria control and elimination interventions was proposed. In addition, resistance had emerged to ACT partner medicines. The Malaria Policy Advisory Committee of WHO recommended that the goal is to eliminate *P. falciparum* in the GMS. In May 2015, WHO launched a Strategy for malaria elimination in the Greater Mekong Sub-region (2015–2030), which was endorsed by all the GMS countries to guide action to eliminate malaria in the GMS before 2030.

Although in Africa, most patients are cured with limited evidence of delayed parasite clearance, routine monitoring must continue in order to ensure that the recommended ACTs are safe and effective. This will support early artemisinin resistance detection and inform national treatment policies. Assessment of validated markers, K13 propeller region mutants will facilitate the tracking of artemisinin resistance.

10.1 Role of parasitological diagnosis for all malaria suspected patients in artemisinin resistance

As the malaria transmission and malaria burden decreases in the country, the proportion of fevers due to malaria will continue to decrease. Without appropriate diagnosis, more ACTs will be wasted on non-malarial febrile illnesses, potentially increasing the risk for selecting for resistant parasites. To reduce the number of patients without malaria taking ACTs, all suspected cases of malaria should be diagnosed parasitologically before treatment.

Administering ACT to a person who does not have malaria does not, in itself, cause resistance; the problem arises when that person is later exposed to malaria. If this occurs relatively soon after the ACT were taken while therapeutic levels are adequate, the presence of the two medicines makes selection of a resistant parasite unlikely; if exposure occurs later, when only the partner medicine may be present in the blood at a sub-therapeutic level, resistant parasites may be selected.

10.2 Access to quality-assured ACTs for confirmed cases and adherence to treatment

When manufactured and administered in adherence with treatment guidelines, combination therapies are not only more effective than monotherapies, but the mutual protection provided by two medicines reduces the chance that resistance will emerge. The mutual protection of combined medicines in the ACTs is obtained through quality-assured products.

Adherence to treatment schedule as recommended in these guidelines is also important to avoid parasite exposure to sub-optimal drug concentration that can eventually lead to resistance.

10.3 Enforced ban on the use of ACT-based monotherapies

The contribution of oral artemisinin monotherapy in ACT resistance

Unlike ACTs, which require only 3 days to result in high cure rates, oral artemisinin-based monotherapies require 7 days for comparable efficacy, and many patients stop taking them after only a few days, when their symptoms have diminished significantly. When adherence is incomplete, parasites in a patient's blood are exposed to a sub curative dose; while the most sensitive parasites are eliminated, the more resistant ones can survive and be transmitted to others. As a result, the use of oral artemisinin-based monotherapies may hasten the spread of artemisinin resistance.

Enforcement of the ban on the use of antimalarial oral monotherapy.

The effective measures at country level is to:

- Ban the use of Artemisinin based oral Monotherapy
- Stop local manufacture which aims at distribution of oral artemisinin-based monotherapies
- Strengthen regulation of medicine markets to non-use of oral artemisinin-based monotherapies

New!

Due to the limited therapeutical options for treatment of uncomplicated malaria and to reduce resistance pressure rational use of alternative ACTs (ASAQ, DP and AP) should be encouraged especially through the private sector. More evidences are needed to introduce alternative ACT in public sector in different transmission areas (ASAQ and DP) alongside AL

10.4 Exploring the introduction of multi ACT policy

For the last 12 years, Artemether–lumefantrine (AL) has been the medicine of choice and, by far, the most used ACT in Tanzania. Over 180 million treatments of AL has been so far procured and distributed to public sector between 2007 and 2020. Dihydroartemisinin-Piperaquine (DP) and Artesunate–amodiaquine (AS-AQ) are also commonly used ACT, especially in the private sector. ASAQ is also the recommended antimalarial in Zanzibar. Recent data from the ongoing TES show that the three treatment options are still highly efficacious with adequate parasitological and clinical response, PCR corrected at day 28, of 98%, 97% and 97% for AL, ASAQ and DP respectively in 2019.

However, single nucleotide polymorphisms (SNPs) in the *Plasmodium falciparum* multidrug resistance 1 (*Pfmdr1*) gene may compromise sensitivity to antimalarial medicines. Fortunately, AL and AS-AQ exert opposing selective pressures in the parasite:

To reduce the resistance pressure especially to artemisinin component of the ACT, NMCP is emphasizing partner research institutions to expand the current TES for the three most used ACT and to explore innovative

initiatives to decrease the resistance pressure to the parasite. The followings are a few initiatives to improve treatment outcomes that need further exploration in the implementation of the next strategic phase:

- The most easily option to be implemented is to encourage the use of alternative ACT in the private sector through subsidized quality products (e.g. Co-paid mechanism)
- Another possible option is to introduce Alternative ACTs as first line choice in defined areas of the country (high risk and regions along international borders)
- Globally, drug cycling is one proposed option, for example countries which have used AL (and reduced the frequency of the YYY haplotype) may consider switching to ASAQ
- Several countries already recommend both AL and ASAQ as first-line therapy, although the optimal proportion of each drug provided is unclear, and might depend on relative selection strength of each drug and the levels of treatment failure after different drug–genotype combinations

- Given the importance of partner drug effectiveness in preventing ACT treatment failure as well as artemisinin resistance spread, it will be important to continue and expand monitoring not only resistance but also the rates of different ACT consumption
- Clinical trials studying the efficacy of sequential treatment with two different ACTs, and triple combination therapy are also needed

11 Social Behaviour Change for Malaria Diagnosis, Treatment and Preventive Therapies

11.0 The needs of Social Behaviour Change for Sustainable Malaria Control Interventions

Implemented Social and Behavior Change (SBC) activities through multiple approaches and channels have contributed to high knowledge and awareness on malaria in mainland Tanzania. Currently, general knowledge on malaria interventions is high and almost universal to above 90%. (MIS 2017). Exposure to malaria messages is also high especially through mass media approach and specifically radio both in urban and rural areas. Knowledge and exposure is a necessary to positive behavior change of individuals, households and communities. Apart from the high knowledge on malaria, actual behavior change is still as a little bit lagging behind, because behavior related indicators such as utilization of LLINs, treatment seeking and testing before treatment (although other factors contributes to reaching targets) have not reached the set target. Again there is still little proportion of parents/caretakers with children under five years old with fever in the last two weeks for whom advice or treatment was sought. The strategic direction for SBC is to sustain the high knowledge on malaria intervention, while increasing the coverage and intensity of community mobilization, engagement, and interpersonal communication so as to bring the actual/desired behavior change in the uptake of malaria interventions

11.1 Key Social Behaviour Change (SBC) issues for diagnosis and treatment of malaria

In the Malaria Medium Term Strategic Plan (MMTSP), Social Behaviour Change Communication is a key supporting strategy. The NMCP Communication Strategy is continued to be implemented to support the two main/core strategies that were identified in the National Malaria Strategic Plan 2015-2020 (NMSP) - Malaria prevention and case management. The communication strategy identifies the main messages to be used in addressing the challenges in each core strategy, as well as, the tools and channels to communicate these messages. Within the context of the Malaria Communication Strategy, the following issues have been identified as the key gaps in knowledge on malaria diagnosis and treatment to be addressed by the communication plan (Table 29).

Table 29: Malaria case management communication gaps and needs

Communication Gaps/Needs
a) Awareness of Signs and Symptoms of Malaria
b) Early treatment seeking behaviour (patients, especially children must receive treatment within 24 hours of detection)
c) Correct treatment of patients (both at home and at health centres with the right medicines in line with treatment guidelines)
d) Importance of completing treatment, key to fighting treatment failure and prevention of parasite developing resistance to medicines
e) Adherence to test results (health professionals and the general public)
f) Importance of pregnant mothers going promptly to the health facilities to get quality malaria management when they feel sick (safe and effective treatment based on proper diagnosis)
g) Importance of improving interpersonal communication between providers and client on diagnosis and treatment of malaria
h) Correct diagnosis of malaria at health facilities.
i) Importance of follow-up visits in the health facility in case symptoms persist or condition worsen

The framework for implementing malaria diagnosis and treatment BCC/IEC is included in Table 30:

Table 30: Framework for implementing malaria diagnosis and treatment BCC/IEC

Strategy	Communication gap	Communication objective	Main message	Message delivery channels	Desired Action
IPTp	Inadequate knowledge on IPTp	Increase knowledge among pregnant women on IPTp Increase proportion of pregnant women who take 3 or more IPT doses	IPTp ensure safety of unborn child & pregnant woman Make sure you get 3 or more doses You need 4 ANC visits to ensure safe pregnancy	Mass Media: Radio spots, TV, IPC: health providers Print Materials (leaflets, posters, brochures), Community mobilization	Pregnant women get 3 or more IPTp doses and attend all ANC appointments
Diagnosis	Low awareness of S&S of Malaria	Increase knowledge on S&S	Recognize S&S act properly Don't wait for all S&S	Mass Media: Radio spots, TV, IPC: health providers Print Materials (leaflets, posters, brochures), Community mobilization	Care takers recognize S&S and act quickly
	Poor adherence to test results	Act according to test results	Lab test are accurate More harm if results are disregarded		HW & patients treat malaria based on lab results
Treatment	Delayed treatment seeking behaviour	Increase proportion of community who seek prompt treatment	Seek treatment as soon as S&S are recognized Appropriate IPC friendly skills to patients Counselling caretakers on early seeking behaviour	Mass media: TV and Radio spots Print media IPC in health facilities CORPs: community interactions	Treatment for malaria sought within 24 h
	incorrect treatment	Increase proportion of community given correct treatment	Right ACT, right dose Complete the dosage		Correct treatment to medicine sellers & caretakers
	Failure to complete treatment		Complete the dosage Full dosage ensures recovery		Patients complete prescribed treatment

12 Malaria Surveillance, Monitoring and Evaluation in Relation to Malaria Diagnosis, Treatment and Preventive Therapies

12.0 The Malaria Surveillance Monitoring and Evaluation Framework

Monitoring is the routine tracking of the key elements of program performance through record keeping, regular reporting, surveillance systems and routine surveys. Monitoring assists decision makers and other key stakeholders to determine which areas require greater effort and may pinpoint areas that might contribute to an improved response. Monitoring is also necessary to inform any evaluation of programs conducted, as monitoring provides contextual information to assist with interpretation. Indicators selected for monitoring will be different depending on the reporting level within the health system and the epidemiological situation. At the global level, the focus of the monitoring process is outcome indicators to monitor trends in coverage of recommended interventions (as described in chapter 4, 5 and 7). At the national and sub-national levels (zonal, regional, council, health facilities and community levels), the emphasis is on utilizing programmatic records, health system data to monitor inputs, processes, outputs, and outcome.

Formal impact evaluation is required to determine and document the extent to which any expectant population-level results are attributable to an intervention or set of interventions, as measured through outcome and impact indicators. A more pragmatic definition of impact for the purposes of this plan is defined as the estimation of overall program impact on malaria morbidity and mortality brought about by all control initiatives and programs combined, irrespective of their financing source(s).

NMCP Monitoring and Evaluation plan

The focus of this plan is to provide a roadmap for monitoring and evaluating the effect of the scale-up of the Tanzania NMCP on population-level outcome coverage indicators and impact endpoints of malaria morbidity and child mortality due to malaria and all-causes. A secondary objective is to evaluate the incremental effect of the delivery systems used to distribute LLINs and social behaviour change communication messages.

12.1 Reporting malaria cases and malaria related rates

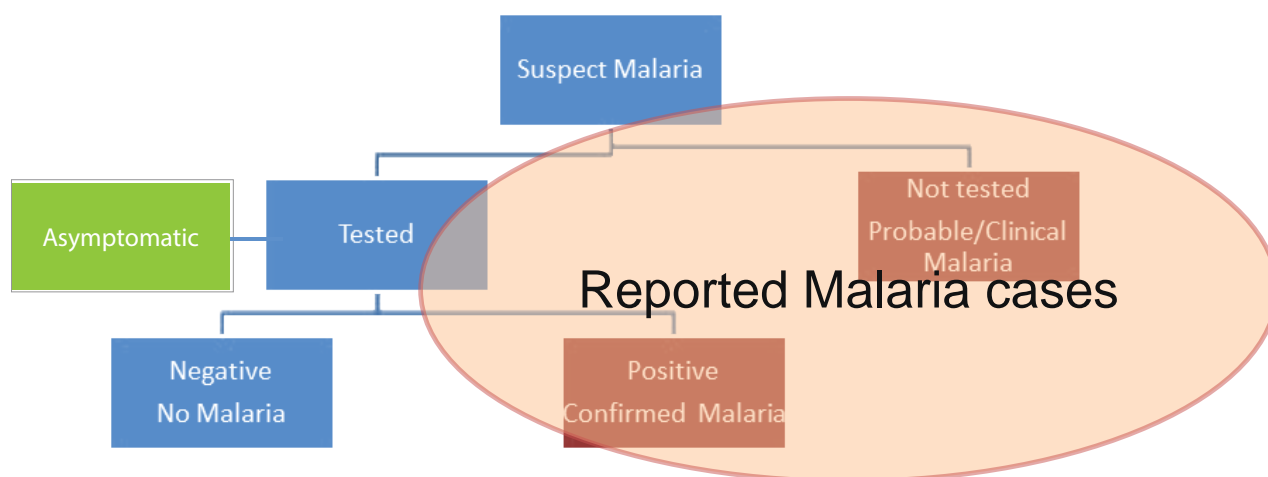
The primary focus of malaria case management is to ensure that all malaria suspected cases are tested by using mRDT or Malaria microscopy and treated using appropriate recommended antimalarial medicines. Thus, timely malaria case reporting from all health service delivery points to subnational and national levels is essential.

There are three major indicators for monitoring malaria case management:

- Suspected malaria cases: all patients having at least malaria features including fever or history of fever. All malaria suspected cases should be diagnosed with mRDT and malaria microscopy
- Confirmed malaria cases: all patients tested for malaria with a positive test result
- Clinical/probable malaria case: all patients not tested for malaria but treated with antimalarials

There are only two reported malaria cases indicators: malaria confirmed cases and malaria clinical/probable cases. Malaria suspect cases and negative malaria tests should not be reported as malaria cases (Figure 5).

Figure 5: Reported malaria cases based on the malaria case definition



Two other indicators are essential for monitoring malaria case management performances:

Annual Blood Examination Rate (ABER) is the proportion of malaria tests (mRDT and microscopy), performed annually over the population.

Malaria Test Ratio: due to the impossibility to monitor the most suitable **Malaria Test Rate** (the proportion of malaria tests either mRDT and microscopy, performed over the number of malaria suspect cases) the best proxy testing indicator to monitor the trend in testing the health facility users is the Malaria test ratio (the proportion of malaria tests either mRDT and microscopy, performed over the number outpatient visits).

Malaria Test Positivity Rate (MTPR): The MTPR is calculated by dividing the number of positive malaria tests over the total number of malaria tests performed. It can be tracked to provide information on trends in malaria. Test positivity rates can vary by season and the peak test positivity rate seen during a season may be quite different from the annual average.

For comprehensive **evaluation** of the malaria burden in communities and success of malaria control measures, confirmed reported malaria cases should be analysed against the population (malaria incidence).

Confirmed malaria cases (<5 years old and total) per 1,000 population. The number of malaria cases fluctuates with malaria transmission seasons and can be useful in assessing the success of preventive programs and demand for treatment in the public and private sectors. However, the variable is also sensitive to changes in reporting rates, diagnostic practices and utilization of health facilities. Care should be taken to ensure that there is consistency in reporting over time by examining trends in health facility reporting rates, annual blood examination rates and total outpatient attendances. If there have been changes in these variables, then it may be more informative to examine trends in test positivity rates (mRDT or malaria microscopy positivity rate), or confine analysis to a subset of health facilities that have reported consistently over time.

Annual Parasite Incidence (API): alongside the improvement of laboratory reporting, the API (number of annual positive malaria tests either by using RDT or microscopy over the population) will become a more globally accepted malaria burden indicator.

Routine HMIS reporting systems

Two primary routine reporting systems exist for malaria surveillance; the national Health Management Information System (HMIS) and Integrated Disease Surveillance and Response (IDSR) strategy. HMIS is the system used in the health sector to collect routine data from all health facilities. Malaria information collected as part of HMIS include: numbers of malaria and anaemia cases, provision of IPTi (once the intervention is scaled up in the appropriate risk areas in the country), LLIN to EPI clients, provision of IPTp, LLIN and iron/folate to ANC clients, and deaths attributes to malaria.

In addition to the health facility and district-based monitoring of malaria for timely action, health facility-based data collection and reporting through the IDSR system is implemented. The IDSR is a strategy that assists health workers to detect and respond to diseases of epidemic potential, public health importance, and those targeted for eradication and elimination. Information from this strategy is intended to enable health teams to respond quickly to outbreaks, set priorities, plan interventions, mobilize and allocate resources. However, the IDSR system, which captures data from health centres and hospitals, is usually aggregated and lacks the essential breakdown by geographical area, which is important for targeting areas at higher risk. The issue of gathering and reporting surveillance data through the IDSR system in such a way that it captures timely data from most peripheral health facilities including community based approaches needs to be strengthened.

Malaria in the Health Management Information System (HMIS)

The HMIS is the system used in the health sector to collect routine data from all health facilities. The objectives of the HMIS are to provide data for measuring/monitoring the following key impact indicators over time:

- Standardized confirmed malaria cumulative incidence per year among children < 5 years, ≥5 years, and pregnant women
- Intermittent preventative therapy uptake among pregnant women
- Standardized crude confirmed malaria death rates among < 5 years, ≥5 years, and pregnant women

Monthly data flows from the health service delivery point level up to the central level, through the National health data warehouse (DHIS2) that compiles, analyses, and provide reports to across all administrative levels. NMCP developed a DHIS2 interactive dashboard to improve and standardize data visualization for data utilization among Regional and council's health management teams.

In general, uncomplicated malaria cases are treated as outpatient cases while severe malaria cases are managed as in patients . For reporting purposes, therefore, outpatient and inpatient malaria cases are considered as proxies for uncomplicated and severe malaria cases, respectively.

The HMIS, includes a set of malaria indicators (listed below), most of them using the following categories: < 1 month, 1-11 months, 1-4 years, 5 - 60 years, 60+ years, Male and Female:

OPD reporting

- **Confirmed Malaria:** malaria cases with a positive malaria test result either mRDT or malaria microscopy;
- **Clinical Malaria:** probable malaria cases not tested but treated with antimalarials;
- **Anaemia:** clinically or laboratory diagnosed;
- **Total OPD attendances:** all cases attending OPD;

Admission reporting

- **Confirmed Malaria Admission:** malaria admission with a positive malaria test results either mRDT or blood smear;
- **Clinical Malaria Admission:** probable malaria admission not tested but treated with antimalarials and with a malaria discharge diagnosis;
- **Severe Anaemia Admission:** patients with anaemia primary discharge diagnosis either clinical or laboratory confirmed;
- **Total Admissions:** number of patients admitted;

Deaths reporting

- **Confirmed Malaria Death** deaths due to malaria, with positive malaria test results either mRDT or blood smear;
- **Presumptive Malaria Death:** probable death due to malaria, not tested but treated with antimalarials and with a malaria discharge diagnosis;
- **Severe Anaemia Death:** death due to anaemia;
- **Total Deaths:** number of patients died during the admission.

RCH

- **IPTp 1:** ANC attendances receiving first IPTp;
- **IPTp 2:** ANC attendances receiving second IPTp;
- **IPTp 3+:** ANC attendances receiving third and more IPTp;
- **Antenatal malaria test:** first ANC attendances receiving a malaria test;
- **Antenatal malaria test positive:** first ANC attendances with a positive malaria test;
- **Antenatal LLIN issued:** ANC attendances received a LLIN;

Infant LLIN issued: infant attendances received a LLIN.

Laboratory

- **Total malaria Blood Smear (BS)/Total mRDT:** The number of patients tested and the related malaria test rate is an important malaria indicator. Ideally all suspected cases of malaria, based on clinical signs and symptoms, should be tested. The number of patients tested for malaria can be affected by seasonality, availability of tests, attendances to the health facility.
 - **Malaria Blood Smear (BS)/mRDT Positives:** In areas of high malaria transmission, because of acquisition of immunity, parasitaemia is not always related to the primary cause of illness that was responsible for the patient to seek care. In low transmission settings, parasitaemia is more likely to be related to the presenting illness;
- 5 **Malaria Blood Smear Positive by *Plasmodium* species:** speciation reporting is particularly important in the areas of the country targeting elimination.

Malaria Commodities

This indicator monitors supply chain at the peripheral level (health service delivery points) and helps programmes take immediate action following the detection of stock-outs. In Tanzania, some of the indicators are included in the electronic Logistics Management Information

- AL: received and dispensed, stock status levels, by category;
- SP: received and dispensed, stock status levels;
- Artesunate Inj: received and dispensed, stock status levels;
- Artemether inj
- Alternative ACTs (e.g. DP, ASAQ etc)

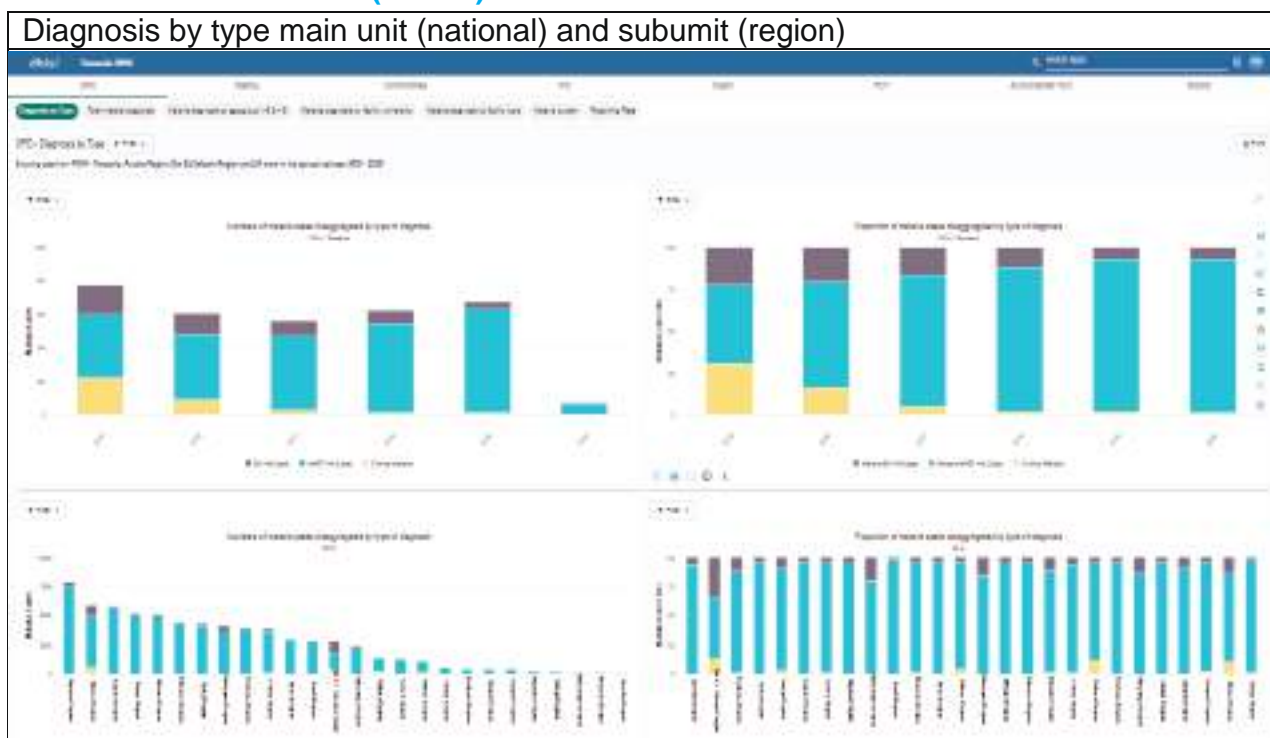
mRDT: received and dispensed, stock status levels.

Use of DHIS2 Malaria interactive dashboard

Tanzania recently developed a comprehensive malaria surveillance framework based on 4 components: disease, programmatic, transmission and quality of services surveillance system (see figure below). The framework is supported by a DHIS2 based data repository system that includes: a) DHIS2 routine information from health facilities and its interactives dashboard; b) accountability dashboard; c) malaria services and data quality improvement dashboard; and malaria composite database.

The DHIS2 outline includes all services available in different sections of health facility: OPD, Laboratory, Pharmacy, IPD, and RCH. Its outputs include interactive charts, spreadsheets, maps by indicator and functional level (national, regional, council and health facility).(Figure 6).

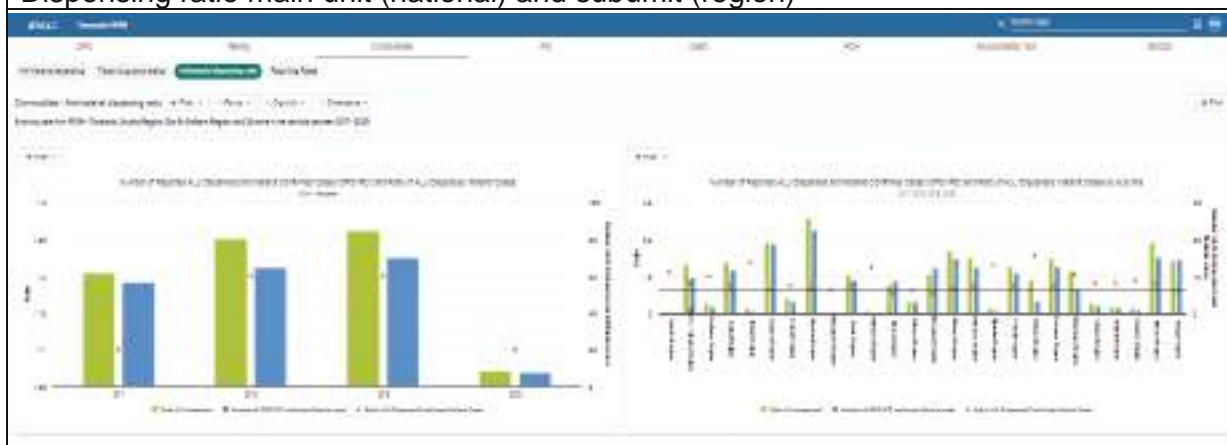
Figure 6: Snapshot of Interactive malaria dashboard into national health data warehouse (DHIS2)



Malaria positivity rate main unit (national) and subunit (region)3



Dispensing ratio main unit (national) and subunit (region)



12.2 Malaria Surveillance

Malaria passive surveillance within the Integrated Disease Surveillance and Response Strategy (IDSR)

IDSR is a strategy that assists health workers and the MoHCDGEC to detect and respond to diseases of epidemic potential, public health importance, and those targeted for eradication and elimination. Information from this strategy is collected weekly and is intended to enable health teams to respond quickly to outbreaks, set priorities, plan interventions, mobilize and allocate resources. For the NMCP, the purpose of passive weekly surveillance is to provide denominator data for measuring the proportion of malaria epidemics detected and appropriately responded to within 2 weeks of onset at the national level. Since a high proportion of suspected and probable cases are not malaria related fevers, these cases do not provide good measures for malaria surveillance; malaria surveillance is therefore based on confirmed cases. It is also important to report the different categories (suspected,

probable and confirmed malaria cases) separately - it is not helpful to aggregate these numbers (e.g. to report probable plus confirmed cases) since the final values are not comparable over time as the incidence of malaria in the community changes. To increase the timeliness electronic reporting currently developed.

The followings are the malaria indicators included in the weekly IDSR reports in Tanzania (see attached sheet):

- Total Malaria
- Malaria active surveillance (malaria case detection)

Active malaria case detection (ACD) is defined as detection by health workers of malaria infections at community and household level in population groups that are at high risk. Active case detection can be conducted as fever screening followed by parasitological examination of all febrile patients or as parasitological examination of the target population without prior fever screening. In Tanzania there are currently two indications for ACD: a) sentinel population surveillance and b) focal screen and test.

Sentinel population surveillance

Pregnant woman attending RCH clinics may be considered as a sentinel population. Although data collected through this system is not representative of malaria trends in the community, it is a useful source to monitor longitudinal malaria morbidity trends, seasonal variation and intensity of transmission in different ecological strata. : 1) there is high coverage in antenatal attendances and measles vaccination (over 90%); 2) this population represents a homogeneous group that can be followed up longitudinally; 3) this population is easily reachable; 4) these data can provide prospective/longitudinal indications of malaria trends; 5) this system does not require extensive financial resources and is easily implementable under existing routine health care delivery systems; 6) low-levels of training are required; 7) data are easily recorded and reported using a modified information system; 9) there is the potential to add Haemoglobin testing in the same facilities to monitor anaemia prevalence; and 10) this data collection system will provide a service to the target population as asymptomatic positive cases will be treated immediately.

All pregnant women attending the ANC for the first time should be tested for malaria using an RDT. If the test is positive, then the women should be prescribed a full course of antimalarial according to gestational age. If the woman is eligible IPTp, then SP should be administered as well.

Malaria Case Based Surveillance

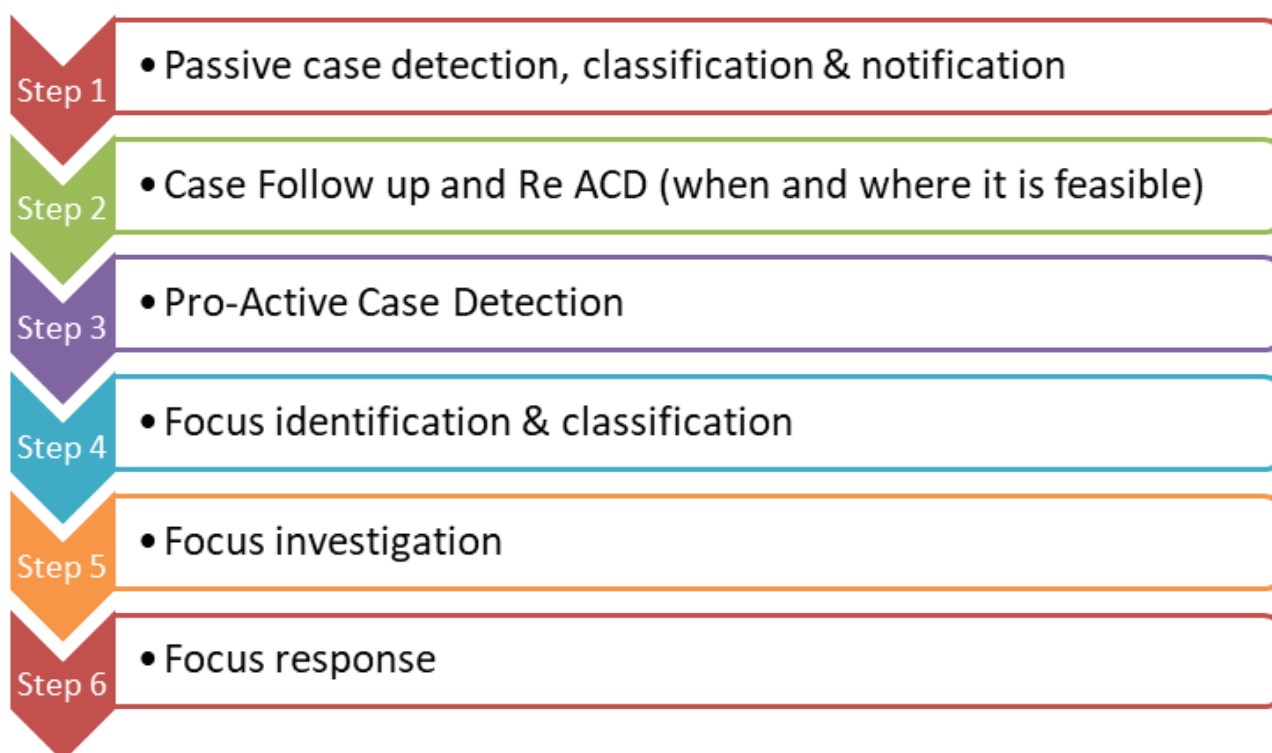
Malaria Case Based Surveillance (mCBS) is the systematic classification and investigation of malaria cases and transmission foci that enable to identify locally acquired infection and active transmission in areas where malaria risk is very low. The aim of case based surveillance is to determine whether an infection was acquired locally and the likely location of infection, and therefore whether there is indigenous malaria transmission or factors that may lead to onward transmission. The collection of a detailed history of an index case at a fixed point of care (health facility or CHV) is the basis of initial case investigation. Recording of detailed patient history is an integral part of surveillance for elimination and should be implemented at the fixed points of care irrespective of onward follow up irrespective from onward follow. Follow-up of a case to ensure compliance with treatment and complete cure is also part of case investigation.

In Tanzania mCBS is currently introduced in very low transmission risk areas, and will be expanded in low transmission risk strata.

In the areas of the Country suitable for MCBS implementation there are six fundamental steps to be followed (see Figure 7)

Figure 7: The six MCBS steps

The six steps are set as a continuum of activities triggered by the passive detection of a malaria case in the health facility. Each step determines the next activity depending on the findings. The passively detected malaria case (also defined as index case) is carefully classified and notified (step 1). The classification (local or imported case) will orient the health staff of an eventual need of follow up in the index case residence place (step 2). Aggregated reported cases in a defined period and location might initiate a **pro-active case detection**



(step 3). An abnormal number of passively and actively detected cases in a defined area and time should be **identified as a focus** of malaria transmission (step 4). The focus need to be further **investigated** by a technical team to verify the determinants of persistent malaria transmission (step 5) and, finally adequate **response** should be organized and implemented to control the transmission (step 6).

Routine DHIS2 and modified eIDSR platforms will be used to inform the service providers at community, health facility and council level, where and when to put in place to individual or focalized response.

These guidelines were adapted to include case detection and case classification (see section 3, pages 32, 33 and 35) to suit the needs of mCBS.

Malaria molecular biological surveillance

Alongside with recent threats to effective malaria diagnosis and treatment (medicine resistance, hrp2/3 deletion) and in view of getting into a malaria elimination phase, the role

of molecular biology is becoming critical. PCR based technique managed by NMCP partner research institutions will provide essential epidemiological and programmatic information about:

- parasite population genetic diversity and dynamics, including parasite migration pattern in Tanzania mainland and Zanzibar
- prevalence and distribution of falciparum parasitaemia undetectable by conventional mRDT and routine microscopy in Tanzania
- prevalence and distribution of non-falciparum malaria species in Tanzania
- prevalence and distribution of resistance markers for antimalarial drugs currently used for treatment and preventive therapies in Tanzania
- map and monitor the trends of pfdhps 540 mutation to assess the use of SP for IPT
- map and monitor the trends of hrp2/hrp3 gene deletion to assess the performance of HRP2 based malaria diagnostic tests (mRDTs)

12.3 Malaria Services and Data Quality Improvement Framework

Malaria Services and Data Quality Improvement (MSDQI) is a comprehensive system for assessment of health facilities readiness to deliver standard malaria care, staff adequate performances and adherence to guidelines, consistency, completeness and timeliness of data management and client's satisfaction. The assessment is followed by the identification of gaps and the development of a quality improvement plan. All service delivery sections (OPD, IPD, Laboratory, Pharmacy, Store and RCH clinic) are assessed and respective plans are agreed upon. MSDQI is aligned with national Quality Improvement requirements and interventions such as National Supportive Supervision guidelines, National DQA, accountability tool and malaria interactive dashboard.

MSDQI tool is comprised of 7 checklists and a dedicated DHIS2 mobile phone application which are used by supervisors at the respective service delivery areas in health facilities. The check list is generating scores that allow the classification of readiness and performances in term of adequate, average, and below average/substandard.

Objectives of MSDQI

- Continuous monitoring and improvement of health service provider's adherence to the national guidelines for delivering malaria services.
- Continuous monitoring of knowledge and skills for improving the quality of services rendered to suspected malaria patients.
- Continuous monitoring and improvement of recorded malaria data in various sections of the HFs.

Routine supervision using MSDQI modules and checklists are conducted from national, regional and district teams. At the council level, all facilities should be visited at least once a year for each MSDQI module. Health facilities showing outliers performances using the malaria interactive dashboard (see section 0, page 127) are prioritized for MSDQI assessment.

Quality improvement plan with clear activity, timeline and responsible person is the primary outcome of the assessment and will be followed up for its implementation.

12.4 Programmatic Monitoring of the Efficacy of ACT and mRDT,

Introduction and Definitions

HRP2/3 gene deletion: Most of the currently available commercial RDT kits work by detecting a specific protein expressed only by *P. falciparum*, called HRP2, in the blood of people infected with falciparum malaria. The antibodies on the test strip recognize the PfHRP2 antigen but may cross-react with protein expressed by another member of the HRP gene family, pfhrp3, because of the strong similarity of the amino acid sequence. In certain situations, HRP2-detecting tests are less sensitive, particularly for parasites that express little or no target antigen, resulting in a false-negative result. The prevalence of parasites with pfhrp2/pfhrp3 gene deletions varies, however, from locality to locality.

Antimalarial resistance is defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a medicine given in doses equal to or higher than those usually recommended but within tolerance of the subject.

Multidrug resistance (MDR) is resistance to more than 2 antimalarial compounds of different chemical classes. This term usually refers to *P. falciparum* resistance to chloroquine, SP, and a third antimalarial compound.

Artemisinin resistance is defined as delayed parasite clearance following treatment with an Artesunate monotherapy or with an ACT. Nevertheless, the majority of patients who have delayed parasite clearance are still able to clear their infections following treatment with an ACT with an effective partner medicine or with an Artesunate treatment lasting seven days

Treatment failure is defined as the inability to clear malarial parasitaemia or prevent recrudescence after administration of an antimalarial medicine, regardless of whether clinical symptoms are resolved. Many factors can contribute to treatment failure, including incorrect dosage regimen, poor patient compliance, poor drug quality, and drug interactions and resistance. Most of these factors are addressed by therapeutic efficacy studies (TESs).

Emergence of ACT resistant malaria: The *Plasmodium falciparum* resistance to ACT could be linked either to the artemisinin derivatives or to the ACT medicine partner. The suspect of resistance to the artemisinin derivatives, is raised when the following criteria are met in therapeutic efficacy studies:

- The proportion of patients with persistent parasitaemia by microscopy at 72 hours (day 3) after treatment with ACT or artemisinin derivative as monotherapy should be $\geq 10\%$ or if it is $< 10\%$ but increasing with time, or
- The percentage of patients carrying K13 resistance-validated mutations of $\geq 5\%$
The suspect of resistance to artemisinin derivatives, must be documented with well conducted therapeutic efficacy studies of 7 days artesunate monotherapy and presence of K13 resistance-validated mutations

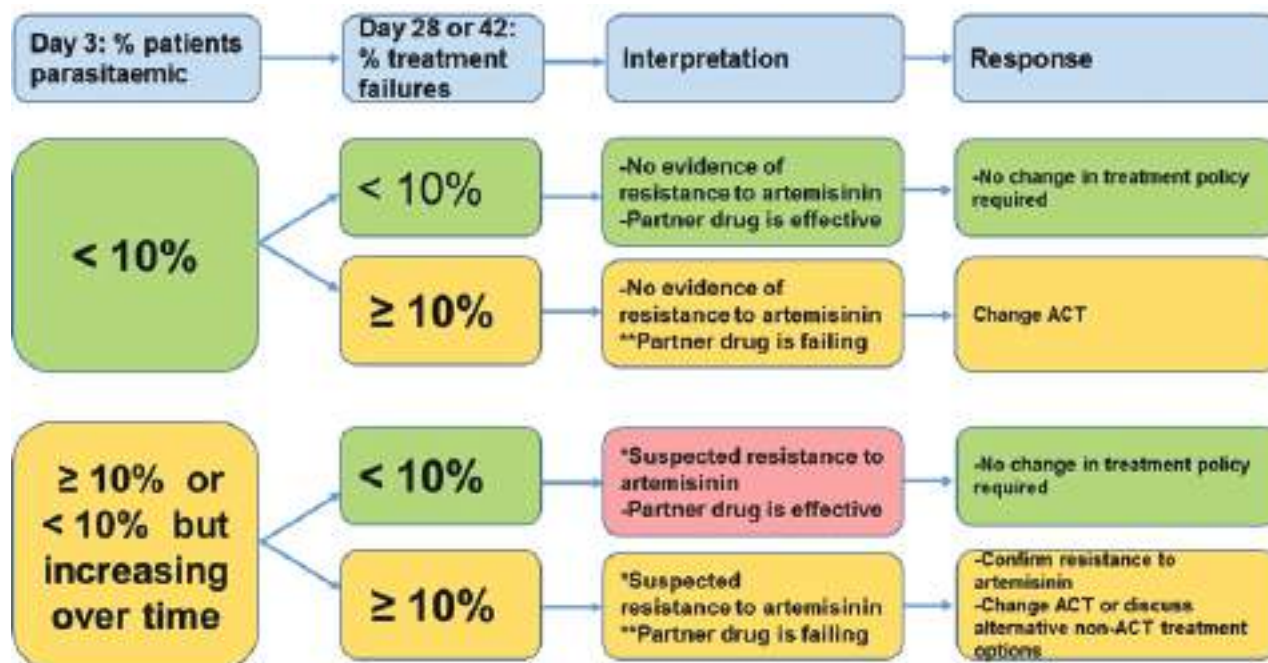
Changing the national treatment policy for *P. falciparum*: A change in the national malaria treatment policy should be initiated if the total treatment failure rate is $\geq 10\%$, as assessed through TESs across the sentinel sites. The antimalarial medicines with a parasitological cure rate greater than 95% should be used for case management. In a scenario where some sentinel site report confirmed failure rate $\geq 10\%$, alternative ACT with superior efficacy should be recommended plus intensification of malaria interventions in the area. The steps for making treatment policy decisions in response to TES results is indicated below (Figure 8).

Figure 8: Criteria for changing the national treatment policy for *P. falciparum* based on therapeutic efficacy studies results (WHO, GMP Status report, 2018)

Monitoring therapeutic efficacy of first-line ACT and recommended alternative treatments

Therapeutic efficacy studies (TES) of artemisinin-combination therapies

The primary objective of monitoring therapeutic efficacy is to evaluate the sensitivity of the



recommended 1st and alternative antimalarial medicines. The country regularly monitors the efficacy of the ACTs in use to ensure that the appropriate ACT is being deployed. Therapeutic efficacy involves measurement and reporting of parasite clearance after treatment with first or alternative ACTs. Delayed parasite clearance beyond day 3 is the first signals of artemisinin resistance. According to the WHO protocol, national malaria control programmes should evaluate the efficacy of first and alternative antimalarial medicines at sentinel sites at least once every 24 months (WHO, 2009). The TES should be implemented for the recommended ACTs in the treatment of *P. falciparum* to provide results of:

- the proportion of patients who are parasitaemic on day 3, which is currently the indicator of choice for routine monitoring to identify suspected artemisinin partial resistance in *P. falciparum*;
- the proportion of treatment failure by day 28 or 42 (days of follow-up is determined according to the half-life of the ACT partner medicines).

Treatment Failures Reporting at the Facilities

Also, close follow-up of routine cases in the health care facilities: regular monitoring of sensitivity of antimalarial medicine is by following-up of confirmed cases of malaria that do not respond to antimalarial treatment. It is recommended that this good clinical practice is done routinely in ensure early detection and management of clinical failures.

For generating early warning signal at the facilities, if the patient returns after Day 4 to 14 of treatment with recommended antimalarial medicines with recurrent infection or treatment failure, blood samples (Whole blood, DBS) may be collected, if possible, and stored for molecular genotyping once the many common cause of treatment failure listed below have been excluded.

Causes of non-response (treatment failures) to antimalarial treatment may include:
Vomiting the medicine
Inadequate dose and dosage regimen
Fever/symptoms from a cause other than malaria
Poor quality of the medicine
Parasite resistance to the medicine
Drug interaction(s)
Individual genetic profile
Malnutrition, pregnancy and other physiological conditions

The clinician should indicate treatment failure if the patient has taken the antimalarial medicine appropriately i.e. according to the correct dosage and duration. The clinician should carry out further investigations to rule out other causes, if malaria is still suspected re-confirm by microscopy and change the antimalarial medication to the second line treatment according to national guidelines. If the clinician observes frequent occurrence of suspected non response to first line antimalarial therapy, he/she should alert relevant authorities. The used patient register must have the needed information when record is reviewed.

Monitoring of histidine-rich protein 2 and 3 (hrp2/3) gene deletions

In most settings, genetic mutations like deletion of pfhrp2/pfhrp3 in parasites are not likely to be the main cause of false-negative results in RDTs, and more studies are required to determine the true prevalence of these mutations. False-negative RDT results are more likely to be due to the **procurement and use of poor-quality RDTs** or use of the wrong comparator for the diagnostic test, such as **poor-quality microscopy for cross-checking** negative RDT results. **Poor transport and storage conditions** for RDTs, with sustained exposure to high temperature, can affect their diagnostic performance. **Operator errors** during performance and/or interpretation of RDT results can result in false-negative results. Many of the potential causes of false-negative results can be prevented or minimized by procuring good-quality RDTs, by improving the quality control of procured RDTs (lot verification) and by good training of users.

The recommended mRDT in Tanzania contain combo HRP2 and pLDH as stipulated in Appendix A. However, there is concern regarding increasing levels of histidine-rich protein 2 and 3 (hrp2/3) gene deletions that threaten the ability mRDT to appropriately diagnose people infected with *P. falciparum* malaria. Although preliminary evidence suggests that the prevalence of hrp2/3 gene deletions in our setting is low, further monitoring is required. It is recommended that, if pfhrp2 gene deletions causing negative HRP2 RDTs are found to be prevalent at 5% or above among symptomatic individuals (lower 95% confidence interval is > 5%), then a change in malaria testing strategy is needed, using RDTs which target Pan-pLDH or Pf-pLDH antigens .

New!

False negative results are the outcomes of poor device quality, poor transport and storage, operator errors.

In a few cases *hrp2/3* gene deletion is responsible of negative results. Monitoring is ongoing in the Country.

Monitoring is recommended to guide on the implication of *hrp2/3* gene deletions for diagnosis and case management. Monitoring is biannual through the selected health facilities across the country and should be nested within the setup of therapeutic efficacy studies (TES) conducted in the eight NMCP sentinel sites across the country. To implement National monitoring, the WHO standardized protocol is set to investigate and report *hrp2/3* gene deletions (including sample size calculations) and SOPs.

Appendix

Appendix A: Choice of Malaria Rapid Diagnostic Tests (mRDTs)

Malaria Rapid Diagnostic Tests (mRDT) detection rate focuses on consistency of performance for registered products. It is not a single measure of mRDT clinical sensitivity, nor positivity rate against the panel of malaria parasites, but rather a combined measure of positivity rate along with inter-test and inter-lot (inter-batch) consistency.

The above described detection rate of mRDTs is a WHO and FIND (Foundation for Innovative New Diagnostics) evaluation program procedure to assess the performance of commercially available malaria RDTs and allow direct product comparisons that would assist agencies and governments in making procurement decisions.

In broad terms the detection rate of mRDT product is the percentage of malaria samples in the panel giving a positive result by two mRDTs per lot at the lower parasite density (200 parasites/ μ L) and a single MRDT per lot at the higher parasite density (2000 or 5000 parasites/ μ L).

For detecting *P. falciparum* in low to moderate transmissions areas, it is highly advisable to select MRDTs with a *P. falciparum* panel detection score well above 75% at 200 parasites/ μ L .

For detecting *P. vivax* in low to moderate transmissions areas; the panel detection score for *P. vivax*, should be equivalent to those for *P. falciparum* – well above 75% at 200 parasites/ μ L.

Plasmodium falciparum mRDT targeting HRP2 antigen demonstrated the highest detection rates ..

The MoHCDGEC technical recommendation in the choice of mRDT:

The MoH recommends the following minimum criteria for selection of mRDT to be used in the public sector:

Malaria RDT device

- Malaria antigen Pf/Pan which detects all four human parasite with heat stable specific Pf (HRP2) antigen as an independent component
- Format of the test: cassette is preferred
- 'Inverted cup' as blood transfer device (designed for reliable uptake and release.i.e. blood volume accuracy of whole blood when in contact with blood drop. Similarly, easily drains the entire volume when put in contact with blood sample whole of mRDT device)
- Registration: it should be registered by Tanzania Medicines and Medical Devices Authority (TMDA)

Performance

- Product for procurement is short listed from the performance assessment results of WHO-FIND malaria RDTs continuing evaluation programme
- False positive rate less than 10% (i.e. sensitivity of 90% and above)
- Invalid rate less than 5% (i.e. without visible control line)
- Detection rate: malaria RDTs with minimum detection rate of 90% for *P. falciparum* and 75% for *P.vivax* at low parasitaemia of 200 parasites/ μ L

- Heat stability at 40°C temperatures show test line; intended for storage, transport and use.

The manufacturer should provide:

- Complete packing; kit comprises all required gargets required for testing
- Individual packed test in moisture-proof container
- Product support such as larger lot, bulk buffer
- Blood-transfer device (pipette, dropper etc)
- Pickers and
- Swab

Appendix B: Reporting of blood smear results

Thick Films

Parasites per microliter of blood:

In this method it is assumed that 1 microliter (μl) of blood contains 8,000 white blood cells (WBC). The number of parasites counted relative to the number of leucocytes counted can thus be converted to the number of parasites per μl of blood by the simple formula given below:

$$\frac{\text{Number of parasites} \times 8000 \text{ WBC}}{\text{Number of leucocytes counted}} = \text{Parasite count per microliter (}\mu\text{l)}$$

In practice, this means that if 200 leucocytes are counted (denominator in the formula), the number of parasites should be multiplied by 40 and if 500 hundred are counted, the number of parasites is multiplied by 16. This is the preferred method of reporting thick blood smear results.

Thin Films

Stop counting when about 20 fields with about 250 red cells (about 5000 red cells) have been counted. Record the actual numbers of parasitized and other red cells counted on an appropriate worksheet. Use these figures to calculate the total parasite count per μL of blood. When counting is completed, calculate the parasite density from an estimated average red cell count of 5 000 000/ μL using the following formula.

Number of parasites per μL of blood:

$$\frac{\text{No. of parasitized red cells} \times 5\,000\,000}{20 \text{ fields} \times 250 \text{ RBCs}} = \text{Parasites} / \mu\text{L}$$

In practice, this means that if 250 RBCs (uninfected cells) are counted at about 20 fields (denominator in the formula), the number of parasitized red cells (infected cells) should be multiplied by 1000. This is the preferred method of counting and reporting in thin film.

Note that the final result in thin film is rounded to the nearest whole number.

Appendix C: Integrated Management of Childhood Illness algorithm for child with fever

Does the child have fever?				
If yes, then ask: for how long?				
Look and Feel	Test	Test Result	Classify	Identify Treatment/Management
Any General danger sign Neck stiffness	Do not Perform a mRDT Test	Not Applicable	SEVERE MALARIA and/or VERY SEVERE FEBRILE DISEASE	<ul style="list-style-type: none"> Give Artesunate injectable IM (first dose) Give first dose of an appropriate antibiotic Treat the child to prevent low blood sugar Give one dose of paracetamol in the clinic for high fever (38.5 °C or above) Refer URGENTLY to the hospital
Fever By history, within 48 hours Feels hot Temperature 37.5 °C or above No danger signs	mRDT available: Perform a mRDT	mRDT Positive	<u>CONFIRMED MALARIA</u>	<ul style="list-style-type: none"> Treat with first line antimalarial (AL) for three days; give first AL dose as DOT in the clinic Give one dose of paracetamol in the clinic for high fever (38.5 °C or above) Investigate for other causes of fever Advise mother/guardian to return immediately if condition worsen Follow up in 2 days if fever persist If fever is present every day for more than 7 days, refer for assessment Advise the mother/guardian on use of ITN (Insecticide Treated Nets)
		mRDT Negative	FEBRILE ILLNESS (NOT MALARIA)	<ul style="list-style-type: none"> Investigate for other causes of fever and manage accordingly Give one dose of paracetamol in the clinic for high fever (38.5 °C or above) Advise mother/guardian to return immediately if condition worsen Follow up in 2 days if fever persist or immediately if condition worsen If fever is present every day for more than 7 days, refer for assessment Advise the mother/guardian on use of ITN
		mRDT Invalid	Not applicable	Repeat mRDT and then continue according to results
	mRDT not available	Not applicable	<u>CLINICAL MALARIA</u> or Other FEBRILE ILLNESS	<ul style="list-style-type: none"> Treat with first line antimalarial (AL) for three days; give first AL dose as DOT in the clinic Give one dose of paracetamol in the clinic for high fever (38.5 °C or above) Investigate for other causes of fever Advise mother/guardian to return immediately if condition worsen Follow up in 2 days if fever persist or immediately if condition worsen If fever is present every day for more than 7 days, refer for assessment Advise the mother/guardian on use of LLIN

Appendix D: Time schedule for 1st, 2nd and 3rd dose of Artemether-Lumefantrine

1st dose	2nd dose	3rd dose	Dozi ya kwanza		Dozi ya 2		Dozi ya 3	
1:00 AM	9:00 AM	8:00 PM	7:00	usiku	3:00	asubuhi	2:00	usiku
2:00 AM	10:00 AM	8:00 PM	8:00	usiku	4:00	asubuhi	2:00	usiku
3:00 AM	11:00 AM	8:00 PM	9:00	usiku	5:00	asubuhi	2:00	usiku
4:00 AM	12:00 PM	8:00 PM	10:00	alfajiri	6:00	mchana	2:00	usiku
5:00 AM	1:00 PM	8:00 AM	11:00	alfajiri	7:00	mchana	2:00	asubuhi
6:00 AM	2:00 PM	8:00 AM	12:00	alfajiri	8:00	mchana	2:00	asubuhi
7:00 AM	3:00 PM	8:00 AM	1:00	asubuhi	9:00	mchana	2:00	asubuhi
8:00 AM	4:00 PM	8:00 AM	2:00	asubuhi	10:00	jioni	2:00	asubuhi
9:00 AM	5:00 PM	8:00 AM	3:00	asubuhi	11:00	jioni	2:00	asubuhi
10:00 AM	6:00 PM	8:00 AM	4:00	asubuhi	12:00	jioni	2:00	asubuhi
11:00 AM	7:00 PM	8:00 AM	5:00	asubuhi	1:00	usiku	2:00	asubuhi
12:00 PM	8:00 PM	8:00 AM	6:00	mchana	2:00	usiku	2:00	asubuhi
1:00 PM	9:00 PM	8:00 AM	7:00	mchana	3:00	usiku	2:00	asubuhi
2:00 PM	10:00 PM	8:00 AM	8:00	mchana	4:00	usiku	2:00	asubuhi
3:00 PM	11:00 PM	8:00 AM	9:00	mchana	5:00	usiku	2:00	asubuhi
4:00 PM	12:00 AM	8:00 AM	10:00	jioni	6:00	usiku	2:00	asubuhi
5:00 PM	1:00 AM	8:00 PM	11:00	jioni	7:00	usiku	2:00	usiku
6:00 PM	2:00 AM	8:00 PM	12:00	jioni	8:00	usiku	2:00	usiku
7:00 PM	3:00 AM	8:00 PM	1:00	usiku	9:00	usiku	2:00	usiku
8:00 PM	4:00 AM	8:00 PM	2:00	usiku	10:00	alfajiri	2:00	usiku
9:00 PM	5:00 AM	8:00 PM	3:00	usiku	11:00	alfajiri	2:00	usiku
10:00 PM	6:00 AM	8:00 PM	4:00	usiku	12:00	alfajiri	2:00	usiku
11:00 PM	7:00 AM	8:00 PM	5:00	usiku	1:00	asubuhi	2:00	usiku
12:00 AM	8:00 AM	8:00 PM	6:00	usiku	2:00	asubuhi	2:00	usiku

Appendix E1: Preparation and administration of Injectable Artesunate

Use the IM route only if the IV route is not feasible					
Step 1 Reconstitute	Inject contents of the sodium bicarbonate ampoule (1ml) into Artesunate vial (60mg) Shake for 2-3 minutes Wait till completely dissolved and solution is clear Artesunate is now reconstituted into a solution of 60mg/ml				
Step 2 Dilute	For intravenous injection (IV)			For intramuscular injection (IM)	
	Dilute with 5%Dextrose/0.9% saline	5ml	Dilute with 5%Dextrose/0.9% saline	2ml	
	Total (with 1ml sodium bicarbonate)	6ml	Total (with 1ml sodium bicarbonate)	3ml	
	Concentration of IV solution is 10mg/ml Artesunate			Concentration of IV solution is 20mg/ml Artesunate	
Step 3 Calculate dose	Dose: 2.4 mg (or 3 mg) per kg of body weight divided by the concentration of IV solution (10mg/ml)			Dose: 2.4mg (or 3 mg) per kg of body weight divided by the concentration of IM solution (20mg/ml)	
	$\frac{\text{Body weight} \times 2.4 \text{ (or 3)}}{10} = \text{dose needed in ml}$			$\frac{\text{Body weight} \times 2.4 \text{ (or 3)}}{20} = \text{dose needed in ml}$	
	10 >Round up to nearest ml			20 >Round up to nearest ml	
Step 4 Inject	Draw the required dose into the syringe Inject intravenously over about 5 minutes Discard any solution not used within 1 hour			Draw the required dose into the syringe Inject slowly Discard any solution not used within 1 hour	
Step 5 Repeat Injection	Dosing schedule 0hrs,12hrs,24hrs,48hrs until patient can take oral medication Administer for a minimum of 24hours (3 doses), even if the patient can take oral medication and follow -up with a full 3-day course of ACT				
Precautions:					
• Inject immediately after reconstitution			• Discard if solution is not clear		
• Discard any solution not used within 1 hour			• Do not use in intravenous drip		

Appendix E2: Artesunate injectable dose chart

Dose: 2.4mg/kg of body weight, 3.0 mg/kg of body weight for children below 20 k

Weight	Dose	ml per dose strength 60mg		Vials of Artesunate 60mg needed**
		i/v	i/m*	
		10 mg/ml	20 mg/ml	
Kg	mg/kg			
<5	3	1.5	1	1
5-8	3	2	1	1
9-12	3	4	2	1
13-16	3	5	3	1
17-20	3	6	3	1
21-25	2.4	6	3	1
26-29	2.4	7	4	2
30-33	2.4	8	4	2
34-37	2.4	9	5	2
38-41	2.4	10	5	2
42-45	2.4	11	6	2
46-50	2.4	12	6	2
51-54	2.4	13	7	3
55-58	2.4	14	7	3
59-62	2.4	15	8	3
63-66	2.4	16	8	3
67-70	2.4	17	9	3
71-75	2.4	18	9	3
76-79	2.4	19	10	4
80-83	2.4	20	10	4
84-87	2.4	21	11	4
88-91	2.4	22	11	4
92-95	2.4	23	12	4
96-100	2.4	24	12	4

*Half the i/v dose rounded up to 1ml

**Full vial(s) might not be required for a given weight band. The left-over solution must be discarded within 1hr of preparation and must not be reused

Appendix F: Coma scales

The Glasgow coma scale

The **Glasgow Coma Scale** is a neurological scale that aims to give a reliable, objective way of recording the conscious state of a person for initial as well as subsequent assessment. A patient is assessed against the criteria of the scale, and the resulting points give a patient score between 3 (indicating deep unconsciousness) and 14.

		Score
Eyes open:	Spontaneously	4
	To speech	3
	To pain	2
	Never	1
Best verbal response:	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Best motor response:	Obeys command	5
	Localises pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
Total		3-14

A state of unrousable coma is reached at a score of <10.

This scale can be used repeatedly to assess improvement or deterioration.

The Blantyre coma scale

The **Blantyre coma scale** is a modification of the Glasgow Coma Scale, designed to assess malarial coma in children, including those who have not learned to speak.

		Score
Best motor response:	Localises painful stimulus ^(a)	2
	Withdraws limb from pain ^(b)	1
	Non-specific or absent response	0
Verbal response:	Appropriate cry	2
	Moan or inappropriate cry	1
	None	0
Eyes movements:	Directed (e.g. Follow mother's face)	1
	Not directed	0
Total		0-5

A state of unrousable coma is reached at a score of <3

This scale can be used repeatedly to assess improvement or deterioration

^a rub knuckles on patient's sternum

^b firm pressure on thumbnail bed with horizontal pencil

AVPU scale

The **AVPU scale** (an acronym from “alert, voice, pain, unresponsive”) is a simplified system to measure and record a patient’s responsiveness, indicating their consciousness. It is the IMCI recommended coma scale.

		Score
A	Alertness (is the patient alert?)	0
V	Response to voice command (does the patient respond to his/her name?)	1
P	Response to pain (does the patient feel pain?)	2
U	Unresponsive (patient does not respond at all)	3

Appendix G: Classification and management of anaemia by severity in children one week up to 5 years of age according to IMCI

Signs	Classification	Action
Severe palmar pallor	SEVERE ANAEMIA	<ul style="list-style-type: none">Refer <u>urgently</u> to health facilities where blood transfusion services are available
Some palmar pallor	ANAEMIA	<ul style="list-style-type: none">Give folic acid and iron for three monthsGive mebendazole to a child aged 1 year and above if has not received it in the previous 6 monthsFollow up in 14 days to check for severity of anaemia; if no deterioration continue with iron and folic acid for three months
No palmar pallor	NO ANAEMIA	<ul style="list-style-type: none">No additional treatment

The level of consciousness worsens as you move down in the scale

Appendix H: Adverse Medicine Reaction Reporting Form



REPORT OF SUSPECTED ADVERSE REACTION TO MEDICINES OR VACCINES

(Made under regulations 33, 36(1)(a), 38(1), and 46(1))

Note: Identities of reporter, patient and institution will remain confidential

Follow up report: Yes/No

I. PARTICULARS OF PATIENT

Patient Initials or Record No.: - _____

Sex: - Male ☐

Female ☐

Date of Birth (dd-mm-yyyy) or age:- _____

Weight in kg:- _____

II. DETAILS OF ADVERSE REACTION

Description of reaction:

Date Reaction Started → ____/____/____

Date Reaction Stopped

(if known) → ____/____/____

Onset latency.....

Duration (min/hours)

Health related information/ Other additional information: Medical history (e.g. hepatic, renal, HIV), allergies, pregnancy, smoking, alcohol use, etc.

Please write any relevant medical and laboratory results including dates (if done)

III. DETAILS OF SUSPECTED MEDICINE/VACCINE USED

Name of suspected medicine(s)/ vaccine(s) (Specify brand name or manufacturer if known) include dosage form and strength	Dosage	Frequency	Route	Therapy Date	Batch. No & Expiry date (If known)	Reason for use
--	--------	-----------	-------	--------------	------------------------------------	----------------

1.							
2.							
3.							

Other medicines used at the same time and or one month before (including herbal medicines)

1.							
2.							
3.							

IV. MANAGEMENT OF ADVERSE REACTION

Reaction subsided after stopping the suspected drug/reducing the dose: ☐ Yes ☐ No ☐ Unknown

Reaction reappeared after reintroducing drug: ☐ Yes ☐ No ☐ Not applicable

Seriousness of the Reaction (**please tick all that apply**): Is the reaction serious? ☐ Yes ☐ No (If Yes, specify)

☐ Required or prolonged hospitalization

☐ Caused a congenital anomaly

☐ Life threatening

☐ Patient Died

☐ Caused persistent disability or incapacity

☐ Others, please give details

Treatment of adverse reaction ☐ No ☐ Yes (if yes please specify):.....

Outcome of the reaction

Not yet recovered
☐

Recovered (Date):__/__/__

☐ Died (Date):__/__/__

Unknown ☐

Cause of death.....

V. THERAPEUTIC FAILURE

PLEASE WRITE IF THE MEDICINE(S)/VACCINE(S) SHOWED LACK OF EFFICACY BELOW : (Continue at the back)

VI. MEDICATION ERRORS AND OVERDOSAGE

PLEASE WRITE DETAILS OF MEDICATION ERRORS AND OVERDOSAGE BELOW:

VII. PARTICULARS OF REPORTER /HEALTH CARE PROVIDER

Name: _____ Profession: _____

Name and Address of the health facility:

Contact phone No: _____ E-mail: _____ / /

Signature: _____ Date of this report: _____

☐ Please tick if you wish to receive information about other local reports associated with the suspected drug(s)

Thank you for your cooperation

Submission of an ADR case report does not discredit the competence of the reporter.

Ref No. (for official use)

First Fold

Guide to filli

How to report?

Dully fill in the form as required
Use a separate form for each patient
Report direct to AUTHORITY through the following addresses:-



Mail: Tanzania medicines and Medical devi
Authority,

P. O. Box 77150, Dar es Salaam



Fax:: 22- 2450793

Phone: 22-2450512 / 2450751/ 0658 445222



An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable patient effect suspected to be associated with drugs.

Report even if:

You're not sure that the product caused the event
You don't have all the details

When to report? As soon as possible

Submission of follow-up reports:

Second Fold

No postage stamp required

If posted in Tanzania

POSTAGE WILL BE
PAID BY LICENCEE

BUSINESS REPLY SERVICE
LICENCE No. BRS 01

TO: THE DIRECTOR GENERAL

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

P. O. BOX 77150

DAR ES SALAAM

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY



ADVERSE REACTION PATIENTS' REPORTING FORM

(For reporting adverse reactions and product problems by non-health care providers)

Note: Identities of patient will remain confidential

I. PERSON REPORTING

Patient ☐ Community health worker ☐ Mother ☐ Sex: - Male ☐ Female ☐
Relative ☐

Other ☐ Specify: _____

Age of the patient _____

Name of the health facility the medicine was obtained from:

II. BRIEF DESCRIPTION OF THE REACTION/EVENT

.....
.....
.....
.....
.....
.....
.....
.....

Date Reaction Started → ____/____

Date Reaction Stopped
(if known) → ____/____

Date reported.....

III. DETAILS OF SUSPECTED MEDICINE USED

Name of suspected medicine(s)	Dosage	Frequency	Route	Therapy Date	
				Start	Stop
1.					
2.					
3.					

IV. DESCRIPTION OF ANY HERBAL MEDICINE THE PATIENT WAS TAKING

V. SERIOUSNESS OF THE ADVERSE REACTION

☐ Discomfort but able to work ☐ Caused persistent disability or incapacity

☐ Discomfort could not work ☐ Caused a congenital anomaly

☐ Required or prolonged hospitalization ☐ Patient Died: _____ Date of death _____

☐ Life threatening ☐ Others, please give details.....

VI. SOURCE OF THE MEDICINE

☐ Hospital Pharmacy

☐ Traditional Healer

☐ Retail Pharmacy

☐ Supermarket/Open Market

☐ Wholesale Pharmacy

☐ Family/Neighbor

☐ ADDO Shop

☐ Others, please specify.....

VII. REPORTER NAME AND CONTACT ADDRESS

Name: (Optional):

Contact Address:

Contact Phone No:

E-mail: (if available)

Date of this report:

Thank you for your cooperation

Ref No. (for official use)

--	--	--	--	--	--	--	--	--	--

First Fold

Guide to filling the form

How to report?

Dully fill in the form as required
Report direct to TFDA through the following addresses:-



Mail : Tanzania Medicines and Medical Devices
Authority,

P. O. Box 77150, Dar es Salaam



Fax:: 22- 2450793



Phone: 22-2450512 / 2450751

An Adverse Drug Reaction (ADR) is defined as a reaction which is noxious and unintended, and which occurs at doses normally used in human for prophylaxis, diagnosis, or therapy of a disease, or for the modification of physiological function.

What to report?

Please report all undesirable effects suspected to be associated with drugs, cosmetics or medical devices use.

Moisten gum and fold. For maximum adhesion, press down for few seconds

Second Fold

POSTAGE
WILL BE PAID
BY LICENCEE

No postage stamp required

If posted in Tanzania

**BUSINESS REPLY
SERVICE LICENCE No.
BRS 01**

TO: THE DIRECTOR GENERAL

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

P. O. BOX 77150

DAR ES SALAAM

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY



MEDICAL DEVICES ADVERSE EVENT/INCIDENT REPORTING FORM FOR CONSUMERS AND HEALTH FACILITIES

TMDA Internal Use Only			
Report Number:		Date received:	
1. Device details			
Brand name:		Catalogue:	
		Model number:	
Manufacturing date:		Serial number:	
Expiry date:		Batch number/lot number:	
Is the Device CE marked?		Instructions for use provided (where possible please attach a copy)	
Yes No		Yes No	
Manufacturer name :		Address:	
Name of supplier		Address:	
		Telephone:	
Current location of the device:			
2. Event/Incident details		Date of incident:	
Type of incident (patient related): Death <input type="checkbox"/> Serious <input type="checkbox"/> Distress <input type="checkbox"/> minor <input type="checkbox"/>			
None other			
Type of incident (device related): Inadequate design inaccurate labeling			
malfunction deterioration other			
Event/Incident description narrative (explain what went wrong with the product)			
Measures taken by the user			
Number of patients involved:			
Operator at the time of the event/incident (please choose): (Please cross where required)		Laboratory personnel	Other Health care personnel
Have you informed the supplier /manufacturer?		Yes No	Date:

3.Reporter details	
Name of Person/facility:	
Postal address:	Street Name:
City:	District/Region:
Telephone/Mobile phone:	Fax:
Name of contact person:	
Email of contact person:	
Date of report:	
Signature:	

Send to:

The Director General,

Tanzania Medicines and Medical Devices Authority (TMDA), ☐ ☐

P. O. Box 1253, Makole Street, PSSSF Building, 7th Floor, Dodoma, or

P.O. Box 77150, Off Mandela Road, Mabibo-External, Dar es Salaam

Tel: +255-22- 2450512/2450751/2452108, +255 68 445222/777 700002/685 701735

Email: info@tmda.go.tz

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY



MEDICAL DEVICES ADVERSE EVENT/INCIDENT REPORTING FORM FOR MANUFACTURERS

Note: identities of reporter, patient and institution will remain confidential.

TMDA Internal Use Only	
Report Number:	Date received:
1. Administrative information	
Date of this report:	Reference number assigned by the manufacturer:
Type of report	<input type="checkbox"/> Initial report <input type="checkbox"/> Follow-up report <input type="checkbox"/> Combined Initial and final report <input type="checkbox"/> Final report
Does the incident represent a serious public health threat? Yes <input type="checkbox"/> No <input type="checkbox"/>	Please explain.....
2. Manufacturer information	
Name:	Postal address
Email	Physical address
Phone	Fax
Contact person's name	Postal address
Email	Physical address
Phone	Fax
3. Local Representative information	
Name:	Postal address
Phone	Physical address
Fax	Email
Contact person's name	
Phone	Email
5. Device details	
Brand name	Catalogue number:
	Model number:
Manufacturing date:	Serial number:
Expiry date:	Lot/batch number:
Is the Device CE marked? Yes <input type="checkbox"/> No <input type="checkbox"/>	Instructions for use provided (where possible please attach copy) Yes <input type="checkbox"/> No <input type="checkbox"/>

6. Event/Incident details	
User facility report reference number, (if applicable)	
Manufacturer's awareness date	Date the incident occurred
Incident description narrative	
Number of patients involved	Number of products involved
Current location of the device	
Usage of the medical device	Initial use Reuse of a single use , Reuse of a reusable, Re-serviced/ refurbished Problem noted prior use other (please specify)
7. Manufacturer's preliminary comments (Initial/Follow-up report)	
Manufacturer's preliminary analysis (Narrative)	
Initial corrective actions/preventive actions implemented by the manufacturer	
Expected date of next report	
8. Results of manufacturers final investigation (Final report)	
The manufacturer's device analysis results	
action/ Field Safety Corrective Action	
Action taken to prevent further risk to the patient (Narrative)	
Time schedule for the implementation of the identified actions	
Final comments from the manufacturer	
Further investigations	
Is the manufacturer aware of similar incidents with this type of medical device with a similar root cause?	
Number of similar incidents.	
If yes, state in which countries and the report reference numbers of the incidents.	
Has a similar event occurred in these regions?	
9. Conclusion	
I affirm that the information given above is correct to the best of my knowledge Name..... Signature.....Date.....	

Send to:

The Director General,

Tanzania Medicines and Medical Devices Authority (TMDA),

P. O. Box 1253, Makole Street, PSSSF Building, 7th Floor, Dodoma, or

P.O. Box 77150, Off Mandela Road, Mabibo-External, Dar es Salaam

Tel: +255-22- 2450512/2450751/2452108, +255 68 445222/777 700002/685 701735

Email: info@tmda.go.tz

References

- ¹https://www.tulane.edu/~wiser/protozoology/notes/pl_sp.html
- ²WHO 2005. Malaria control in complex emergencies, and inter-agency field handbook. WHO/HTM/MAL/2005.1107, Geneva, Switzerland
- ³WHO 2008. Global malaria control: Report of a technical review. 17-18 January, 2008. Geneva, Switzerland
- ⁴NMCP 2018; Supplementary Malaria Strategic Plan 2018-2020
- ⁵WHO 2010. Guidelines for the treatment of Malaria. 2nd Edition. Geneva. Switzerland
- ⁶Abdunoor M et al .2012. Therapeutic efficacy studies of Artemether-Lumefantrine and Amodiaquine –Artesunate in Tanzania. Paper presented at the 51st Annual conference of the American Society for Tropical Medicine and Hygiene
- ⁷Dondrop Am, et al. 2010. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT); an open labeled, randomized trial. Lancet, 2010. 10.1016/S0140-6736 (10) 61924 -1
- ⁸WHO 2015. Guidelines for the treatment of malaria, 3rd Edition, Geneva, Switzerland
- ⁹WHO 1998. WHO expert committee on malaria: twentieth report. Geneva, World Health Organization
- ¹⁰WHO 2012: Disease surveillance for malaria control: an operational manual
- ¹¹With the exception of some low-transmission and elimination countries that may admit uncomplicated malaria cases to ensure full adherence to treatment or radical cure
- ¹²The concept of inpatient malaria cases serving as a proxy for severe malaria cases in Africa is contained in the WHO document, “Information systems for the evaluation of malaria programs. A practical guide. WHO Regional Office for Africa, Brazzaville, 1994. AFRO/CTD/94.3”
- ¹³Valerie D’Acromont, et al. Study to investigate the causes of fever in children living in urban Dar es Salaam and rural Ifakara, Dar es Salaam. City Council, Ifakara Health Institute, United Republic of Tanzania and the Swiss Tropical and Public Health Institute 2011
- ¹⁴2017; Kathleen Maloney; Expanding access to parasite-based malaria diagnosis through retail drug shops in Tanzania: evidence from a randomized trial and implications for treatment MAL.J
- ¹⁵WHO technical consultation on research requirements to support policy recommendations on highly sensitive point-of-care diagnostics for *P. falciparum* malaria
- ¹⁶NMCP: 2020; Malaria case based surveillance reference manual

- ¹⁷WHO, March 2009; Microscopy quality assurance manual, version 1,
- ¹⁸WHO 2015. Guidelines for the treatment of Malaria. 3rd Edition. Geneva. Switzerland
- ¹⁹Administration of the correct dose in young children may be difficult where paediatric formulations are unavailable. It is recommended a flavored dispersible tablet paediatric formulation of artemether plus lumefantrine since it enhances its use in young children
- ²⁰2018; Sarah-Blythe Ballard; Updated CDC Recommendations for Using Artemether-Lumefantrine for the Treatment of Uncomplicated Malaria in Pregnant Women in the United States
- ²¹2017; Julie Gutman; et al.: Safety, tolerability, and efficacy of repeated doses of dihydroartemisinin-piperaquine for prevention and treatment of malaria: a systematic review and meta-analysis; Lancet
- 2017; Quique Bassat, Clara Menéndez Dihydroartemisinin-piperaquine: if it works for control, can we use it for elimination? Lancet
- ²²WHO 2019; The use of artesunate-pyronaridine for the treatment of uncomplicated malaria;
- ²³WHO 2012; Single dose Primaquine as a gametocytocide in Plasmodium falciparum malaria
- ²⁴WHO 2015; Guidelines for the treatment of malaria. Third edition
- ²⁵WHO 2004. A strategic framework for malaria prevention and control during pregnancy in the African Region
- ²⁶WHO 2015; intermittent screening and treatment in pregnancy and the safety of ACTs in the first trimester;
- ²⁷2018; Sarah-Blythe Ballard; et al.: Updated CDC Recommendations for Using Artemether-Lumefantrine for the Treatment of Uncomplicated Malaria in Pregnant Women in the United States
- ²⁸WHO 2015; Guidelines for the treatment of malaria. Third edition
- ²⁹Hochman S, Kim K. The Impact of HIV and Malaria Coinfection: What Is Known and Suggested Venues for Further Study. Interdiscip Perspect Infect Dis. 2009;2009: 617954. doi:10.1155/2009/617954
- ³⁰Flateau C, Le Coup G and Pialoux. 2011. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. Lancet Infect. Dis 11:541-56
- ³¹Newman PM, Wanzira H, Tumwine G, et al. Placental malaria among HIV-infected and uninfected women receiving anti-folates in a high transmission area of Uganda. Malar J. 2009;8:254. Published 2009 Nov 14. doi:10.1186/1475-2875-8-254
- ³²Alemu A, Shiferaw Y, Addis Z, Mathewos B, Birhan W. Effect of malaria on HIV/AIDS

- transmission and progression. *Parasit Vectors*. 2013;6:18. Published 2013 Jan 17. doi:10.1186/1756-3305-6-18
- ³³Snehal N. Shah, Ernest E. Smith, Charles O. Obonyo, Kevin C. Kain, Peter B. Bloland, Laurence Slutsker, Mary J. Hamel, HIV Immunosuppression and Antimalarial Efficacy: Sulfadoxine-Pyrimethamine for the Treatment of Uncomplicated Malaria in HIV-Infected Adults in Siaya, Kenya, *The Journal of Infectious Diseases*, Volume 194, Issue 11, 1 December 2006, Pages 1519–1528, <https://doi.org/10.1086/508892>
- ³⁴Dreyfuss M L, Msamanga G I, Spiegelman D, et al. Determinants of low birth weight among HIV-infected pregnant women in Tanzania. *Am J Clin Nutr*. 74: 814-26
- ³⁵Van Eijk A M, Ayisi J G, Ter Kuile F O, et al. 2002. Malaria and human immunodeficiency virus infection as risk factors for anaemia in infants in Kisumu, western Kenya. *Am. J Trop Med Hyg*. 67: 44-53
- ³⁶Flateau C, Le Coup G and Pialoux. 2011. Consequences of HIV infection on malaria and therapeutic implications: a systematic review. *Lancet Infect. Dis* 11:541-56
- ³⁷WHO 2015. Guidelines for the treatment of malaria. 3rd Edition. Geneva, Switzerland
- ³⁸WHO 2015. Guidelines for the treatment of malaria. 3rd Edition. Geneva, Switzerland
- ³⁹Ministry of Health, Community Development, Gender, Elderly and Children (MoHCDGEC) [Tanzania Mainland], Ministry of Health (MoH) [Zanzibar], National Bureau of Statistics (NBS), Office of the Chief Government Statistician (OCGS), and ICF. Tanzania Malaria Indicator Survey 2017. Dar es Salaam, Tanzania, and Rockville, Maryland, USA: MoHCDGEC, MoH, NBS, OCGS, and ICF
- ⁴⁰2010; Brian Greenwood; Anti-malarial drugs and the prevention of malaria in the population of malaria endemic areas; *Mal.J*
- ⁴¹WHO 2012. Policy Recommendation (October 2012) Intermittent Preventive Treatment of malaria in pregnancy using Sulfadoxine-Pyrimethamine (IPTp-SP)
- ⁴²Ministry of Health and Social Welfare. Prevention of Mother to Child Transmission, National Guidelines, 2011
- ⁴³Julie Makani et al, Malaria in patients with sickle cell anaemia: burden, risk factors, and outcome at the outpatient clinic and during hospitalization, *The American Society of Haematology*, 2010
- ⁴⁴Charlotte F. McAuley et al, High mortality from *Plasmodium falciparum* malaria in children living with sickle cell anaemia on the coast of Kenya, *The American Society of Haematology*, 2010
- ⁴⁵Oniyangi O, Omari AAA. Malaria chemoprophylaxis in sickle cell disease. *Cochrane Database of Systematic Reviews* 2006, Issue 4
- ⁴⁶2019 Esther J. Ndegeulaya, George M. Bwire, et al.: Utilization patterns of malaria

chemoprophylaxis among Tanzanian children attending sickle cell clinic in Dar es Salaam tertiary hospitals; Mal.J

⁴⁷WHO 2020; Policy recommendation on Intermittent Preventive Treatment during infancy with sulphadoxine-pyrimethamine (SP-IPTi) for Plasmodium falciparum malaria control in Africa

⁴⁸2018, Thandile Nkosi-Gondwe et al.; Introducing post-discharge malaria chemoprevention (PMC) for management of severe anemia in Malawian children: a qualitative study of community health workers' perceptions and motivation BMC Public Health

⁴⁹WHO 2013. Seasonal Malaria Chemoprevention with Sulphadoxine-Pyrimethamine plus Amodiaquine in children. Geneva;

⁵⁰East Africa Network for Monitoring Antimalarial Therapy, 2004

⁵¹WHO 2017; Mass drug administration for falciparum malaria. A practical field manual,

⁵²2020, Lauren M Cohee et al.: Preventive malaria treatment among school-aged children in sub-Saharan Africa: a systematic review and meta-analyses DOI: 10.1016/S2214-109X(20)30325-9 The Lancet Global Health · October 2020

⁵³2015; R. Matangila; Efficacy and safety of intermittent preventive treatment for malaria in schoolchildren: a systematic review Junior MAL.J 2015

⁵⁴WHO 2015; The role of mass drug administration, mass screening and treatment, and focal screening and treatment for malaria

⁵⁵2020, NMCP. Introduction of malaria community case management (draft March 2020)

⁵⁶2018, Lucy C Okell, et al. Emerging implications of policies on malaria treatment: genetic changes in the Pfmdr-1 gene affecting susceptibility to artemether–lumefantrine and artesunate–amodiaquine in Africa; BMJ

⁵⁷NMCP, Monitoring and evaluation Plan 2008-2013

⁵⁸(with the exception of some low-transmission and elimination countries that may admit uncomplicated malaria cases to ensure full adherence to treatment or radical cure)

⁵⁹WHO Regional Office for Africa, Brazzaville, 1994. The concept of inpatient malaria cases serving as a proxy for severe malaria cases in Africa is contained in the WHO document, "Information systems for the evaluation of malaria programs. A practical guide. AFRO/CTD/94.3"

⁶⁰WHO 2017; False-negative RDT results and implications of new reports of P. falciparum histidine-rich protein 2/3 gene deletions

⁶¹WHO (2019). False-negative RDT results and P. falciparum histidine-rich protein 2/3 gene deletions <https://apps.who.int/iris/bitstream/handle/10665/258972/WHO-HTM-GMP-2017.18-eng.pdf>;

⁶²WHO (2020). Template protocols to support surveillance and research for pfhrp2/pfhrp3 gene deletions.<https://www.who.int/malaria/publications/atoz/hrp2-deletion-protocol/en/>

⁶³WHO 2009. product testing of malaria RDTs, performance summary results, rounds 1 and 2 (2008-2009)

⁶⁴WHO 2010. Information note on recommended selection criteria for procurement of malaria rapid diagnostic tests (RDTs); 16 September 2010

⁶⁵WHO, FIND, 2009, Malaria rapid diagnostic test performance summary results of WHO product testing of malaria RDTs: rounds 1 and 2 (2008-2009)

⁶⁶WHO-Geneva; Technical Consultation meeting for RDT experts on parasitological confirmation of malaria diagnosis; October 2009

⁶⁷Modified from the IMCI protocol for district health workers



National Malaria
Control Programme

MoHCDGEC-HPS-PRINTING PRESS DSM