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GUIDELINES

Current guidelines for malaria treatment in Somalia: evidence-based recommendations

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ABSTRACT

Case management – rapid diagnosis and prompt administration of artemisinin-based combination therapy (ACT) – is a fundamental pillar of recommended malaria interventions in Somalia. Unfortunately, the emergence and spread of drug resistant falciparum parasites continues to pose a considerable threat to effective case management.

With technical and financial support from WHO, the efficacy of recommended ACTs has been regularly monitored in sentinel sites since 2003. These studies provided evidence that supported the adoption of artesunate-sulfadoxine/pyrimethamine as first-line treatment in 2005 and artemether-lumefantrine as second-line treatment in 2011. Efficacy studies conducted between 2011 and 2015 showed high artesunate-sulfadoxine/pyrimethamine treatment failure rates of 12.3% - 22.2%, above the threshold (10%) for a change of treatment policy as recommended by WHO. This was also associated with high prevalence of quadruple and quintuple mutations in the dihydrofolate reductase (Pfdhfr) and dihydropteroate synthase (Pfdhps) genes, which are associated with sulfadoxine/pyrimethamine resistance.

Based on these findings, national malaria treatment guidelines were updated in 2016, with artesunate-sulfadoxine/pyrimethamine replaced by artemether-lumefantrine as first-line treatment and dihydroartemisinin-piperaquine recommended as second-line treatment. Subsequent efficacy studies in 2016 and 2017 confirmed that both the current first- and second-line treatments remain highly efficacious (cure rate above 97%). Technical and financial support from WHO has been instrumental in generating evidence that informs malaria treatment policy and should therefore continue to ensure that effective treatments are available to malaria patients in the country.

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Background

Malaria remains a major global public health problem with an estimated 229 million cases and 409 000 deaths in 2019 [1]. Most of the malaria cases (94%) and deaths (94%) occurred in the African Region. Case management – prompt diagnosis and effective treatment – is a fundamental pillar of the essential malaria interventions recommended by WHO. Unfortunately, the emergence and spread of drug resistant malaria parasites continues to pose a considerable challenge to controlling malaria. The development of *Plasmodium falciparum* resistance to safe and cost-effective monotherapies like chloroquine and sulfadoxine-pyrimethamine [2] led to an increase in malaria mortality [3, 4].

In order to mitigate the problem WHO recommended the use of artemisinin-based combination therapy for the treatment of uncomplicated malaria in 2001 [5]. Artemisinin and its derivatives have short half-lives (1-3 hrs) and would result in poor cure rates when used as monotherapy [6]. Combining them with a long half-life partner drug ensures sustained anti-malarial pressure after the blood levels of the artemisinin component has fallen below therapeutic levels, leading to increased treatment efficacy and reduced selective pressure for resistance. Artemisinin-based combination therapy (ACT) is founded on the ability of the artemisinin component to rapidly reduce parasite biomass leaving few parasites to be

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cleared by the the partner drug and eventually reducing the pool of parasites from which resistance can emerge [7].

The currently recommended ACTs are artemether-lumefantrine, artesunate-amodiaquine, artesunate-sulfadoxine/pyrimethamine, artesunate-mefloquine, dihydroartemisinin-piperaquine and artesunate-pyronaridine [8]. All *P. falciparum* endemic countries have adopted ACTs as first or second-line treatment for uncomplicated malaria following the WHO recommendations [1]. The recommended treatments for severe malaria are parenteral artesunate (first choice), intramuscular artemether (second choice) or parenteral quinine (third choice) [8]. ACTs have also proven to be effective against *Plasmodium vivax* infection and are recommended in areas with chloroquine resistant *P. vivax* [8].

Malaria in Somalia

Malaria is an important health problem in Somalia with about 51% of the total population (7.6 million) living in areas where the burden of disease is >1 case per 1000 population [1,9,10]. Due to climatic and meteorological factors, malaria transmission varies between different parts of the country, ranging from unstable and epidemic-prone areas in the north and in some of the central regions to moderate-to-high transmission in the southern regions. In areas with stable transmission particularly along the Juba and Shabelle rivers, children below 5 years, pregnant women and non-immune migrants carry most of the disease burden. In the unstable transmission settings including epidemic-prone areas, all age groups are affected. There are two transmission seasons coinciding with the two wet seasons: April to June and October to November.

The dominant malaria species in the country has been *P. falciparum* accounting for more than 95% of the infections [9]. However, an increased proportion of *P. vivax* has recently been reported from the North-east region (Puntland state). Screening of patients (n=697) with a history of fever attending health facilities in Bosaso town from 4 January to 14 February 2016 showed 49.8% (347/697) test positivity rate of which 74.4% (258/347) and 25.6% (89/347) were *P. falciparum* and *P. vivax,* respectively, (unpublished data from the Puntland Malaria Control Program).

There are limited national data on the true burden of malaria in Somalia. The World malaria report 2020 estimated that there were around 759,000 cases and 1,942 deaths in Somalia in 2019 [1]. It is important, though, to note that there are different factors which make it difficult to arrive at a true malaria burden in the country. The protracted civil war that led to the collapse of public institutions, including health services, has affected the availability and accessibility of public health facilities with reliable laboratory diagnostic facilities and treatment options for malaria. The latest Malaria Indicators Survey (2017) showed that febrile patients were more likely to seek treatment at a private clinic (59%) or drugstore/pharmacy (34%) [11]. Routine malaria data in these facilities are not captured for the national Health Information System (HMIS), which is usually the case in public health facilities.

Providing timely treatment with effective ACT is the cornerstone of malaria control strategies in malaria-endemic countries, including Somalia. Currently recommended malaria treatments and chemoprevention are summarized in the box below. The process of evidence generation and the development of current malaria treatment guidelines are described in the following sections.

Recommended antimalarial treatments in Somalia, 2016

Uncomplicated malaria:

- Artemether-lumefantrine as the first-line treatment for all species and for all population except pregnant women in first trimester
- Dihydroartemisinin-piperaquine as second-line treatment for all species and population except pregnant women in first trimester.
- Quinine as first line-treatment for pregnant women during the first trimester. If quinine is not available, or adherence to a 7-day treatment regimen cannot be assured, artemether-lumefantrine can be given.

Anti-gametocyte for P. falciparum:

- Primaquine single dose co-administered with the first-line or second-line treatment for falciparum infected patients except infants <6 months, pregnant women and women breastfeeding infants aged < 6months.

Anti-relapse for P. vivax:

- Primaquine 14-day treatment as anti-relapse for P. vivax infection, except infants <6 months, pregnant women and women breastfeeding infants aged <6 months and individuals with G6PD deficiency.

Severe malaria:

- Artesunate IV or IM (first option) or artemether IM (second option) or quinine IV (third option) for the treatment of severe malaria at the hospital level. Where complete treatment of severe malaria is not possible and injectables are available, single dose im artesunate (first option) or artemether im (second option) or quinine im (third option) as a pre-referral treatment. Where intramuscular injections of these medicines are not available, a single dose of rectal artesunate should be given to children below 6 years.

Intermittent preventive treatment during pregnancy (IPTp):

- Sulfadoxine/pyrimethamine as IPTp in areas with moderate or high transmission.

Generating evidence to inform malaria treatment policy

The efficacy of antimalarial medicines is a critical element in the selection of antimalarial medicines to be included in treatment policy. Therapeutic efficacy studies, using the WHO protocol as the gold standard, are crucial for generating evidence to inform malaria treatment policy [2]. In therapeutic efficacy studies, the clinical and parasitological response of patients to directly observed treatment of uncomplicated *P. falciparum* malaria is evaluated prospectively for 28 days (short half-life drug) or 42 days (long half-life drug) at selected surveillance sites. Drug efficacy outcomes are based on parasite and clinical clearance following treatment. Blood samples from patients with recurrent parasites during the follow up are subjected to polymerase chain reaction (PCR) analysis to differentiate recrudescence (true failure) from re-infection [2]. Therapeutic efficacy studies help to inform about the proportion of patients with treatment failure. It also helps to determine the proportion of patients with malaria parasites in the blood on day 3 which is indicative of partial artemisinin resistance in *P.falciparum*. To complement the therapeutic efficacy studies, molecular markers of antimalarial drug resistance are assessed to confirm parasite resistance [12].

Surveillance sites for monitoring antimalarial drug efficacy were successfully established in Jamame (Lower Jubba region), Janale (Lower Shabelle region) and Jowar (Middle Shabelle) in 2003 and in Bosaso (Bari region) in 2014. Unfortunately, Jamame and Janale could not be accessed from 2013 and 2015, respectively, due to security problems. The sentinel sites for monitoring drug efficacy have been maintained by the WHO through funding provided by both WHO and the Global Fund. The efficacy of the recommended first-line and second-line treatments for uncomplicated *P. falciparum* malaria were routinely monitored in order to generate critical data to inform treatment policy of the country. The findings of therapeutic efficacy studies conducted between 2003 and 2017 are reported in several publications [13, 15, 16, 17] and summarized in Table 1. In addition to efficacy evaluation, mutations in the *P. falciparum* dihydrofolate reductase (*Pfdfhr*) and dihydropteroate synthase (*Pfdhps*) genes associated with SP resistance and the mutations in *P. falciparum* K13 propeller (*Pfk13*), associated with artemisinin resistance, were investigated.

The efficacy of artesunate-sulfadoxine/pyrimethamine, evaluated between 2003 and 2006 in Jamame, Janale and Jowhar sites, showed high cure rate (94.9-99%) with 5.1% treatment failure (Table 1) supporting the treatment policy with artesunate-sulfadoxine/pyrimethamine as first-line drug in 2005 [14]. As part of routine surveillance, therapeutic efficacy of artesunate-sulfadoxine/pyrimethamine was again assessed in Jamame, Janale and Jowhar in 2011 and in Bosaso in 2015. These studies revealed high treatment failure rates, 22.2% in Jamame and 12.3% in Bosaso, while the treatment failure rates for Janale and Jowhar were below 5% (Table 1)

Table 1. Summary results of therapeutic efficacy studies in surveillance sentinel sites in Somalia 2003–2017. (*PCR analysis to differentiate recrudescence from new infection was not done; AS-SP = artesunate-sulfadoxine/pyrimethamine; AL = artemether-lumefantrine, DHA-PPQ = dihydroartemisinin-piperaquine)

Test Drug	Study Year	Study Site	Cases	Treatment Outcome		Source
				Failure rate n (%)	Cure rate n (%)	
AS-SP	2003-2006*	Jamame	98	5 (5.1)	93 (94.9)	[13]
		Janale	96	1 (1.0)	95 (99)	
		Jowhar	99	1(1.0)	98 (99)	
	2011	Jamame	81	18 (22.2)	63 (77.8)	[15]
		Janale	91	4 (4.4)	87 (95.6)	
		Jowhar	97	1 (1.0)	96 (99)	
	2015	Bosaso	81	10 (12.3)	71 (87.7)	[16]
AL	2013	Janale	94	0	100 (100)	
		Jowhar	100	1 (1.0)	99 (99)	
	2015	Bosaso	100	2 (2.4)	82 (97.6)	
	2017	Jowhar	51	0	84 (100)	[17]
		Bosaso	84	0	51 (100)	
DHA-PPQ	2016	Jowhar	51	1 (1.0)	102 (99)	[13]
		Bosaso*	80	2 (2.5)	78 (97.5)	

Table 2 shows the patterns of *Pfdfhr*/*Pfdhps* mutations at the four sites in 2014-2015. High levels of combined *Pfdfhr*/*Pfdhps* mutations (quadruple or quintuple) associated with clinical failure with sulfadoxine/pyrimethamine were observed in Jamame (59.3%) and Jowhar (41.2%) in 2011 [15] and in Bosaso (88.9%) in 2015 [16]. The high treatment failure rates with artesunate-sulfadoxine/pyrimethamine observed in Jamame and Bosaso were associated with quadruple or quintuple mutations. The finding confirmed that artesunate-sulfadoxine/pyrimethamine was failing as first-line therapy due to resistance to sulfadoxine/pyrimethamine, the partner drug. Despite the presence of *Pfdfhr*/*Pfdhps* quadruple and quintuple mutations, the rate of treatment failure with artesunate-sulfadoxine/pyrimethamine in Jowhar was very low. The stronger immunity of the older study population in Jowhar compared to Jamame may have masked the in vivo treatment failure [15]. Studies evaluating the efficacy of artemether-lumefantrine conducted in Janale, Jowhar and Bosaso between 2013 and 2017 [16, 17] showed PCR corrected treatment failure rates below 3% (Table 1). Similarly low rates of PCR corrected treatment failure (below 3%) were observed in patients treated with dihydroartemisinin-piperaquine at the Jowar and Bosaso sites in 2016 (Table 1).

The need for regular updating of evidence-based treatment guidelines

The results of therapeutic efficacy studies are the main reference from which national malaria programmes

Table 2. Combined *Pfdhfr* and *Pfdhps* mutants detected in Jamame, Janale and Jowar sites in 2011 and in Bosaso in 2015. (n refers to number of specimens tested)

Pfdhfr/*Pfdhps* combined mutation	Jamame (n=86)	Janale (n=79)	Jowhar (n=102)	Bosaso (n=90)
Triple 51I/59R/108N+Wild type	-	-	-	10 (11.1%)
Triple mutant N51I/S108N + S436A	-	3 (3.8%)	-	-
Triple mutant C59R/S108N + S436A	-	-	2 (2.0%)	-
Triple mutant C59R/S108N + A437G	2 (2.3%)	-	-	-
Quadruple	30 (34.9%)	2 (2.5%)	26 (25.5%)	-
N51I/S108N & A437G/K540E	19 (22.1%)	2 (2.5%)	23 (22.6%)	12 (13.3%)
C59/ S108N & A437G/K540E	11 (12.8%)	-	3 (2.9%)	-
Quintuple	21 (24.4%)	4 (5.1%)	16 (15.7%)	68 (75.5%)
N51I/ C59R/S108N & A437G/K540E	21 (24.4%)	4 (5.1%)	16 (15.7%)	10 (11.1%)
51I/108N+437G/540E/581G	-	-	-	58 (64.4%)

determine their national treatment policy. To ensure the efficacy of medicines listed in national malaria treatment policies, WHO recommends that National malaria programmes adopt antimalarial medicines with a parasitological cure rate of more than 95%. The efficacy of recommended medicines should be monitored at least every two years at surveillance sentinel sites. A change in the national malaria treatment policy should be initiated if the total treatment failure rate reaches 10% or greater [2].

The first Somali national treatment guidelines were developed in 2005 following a consensus meeting held in Nairobi where artesunate-sulfadoxine/pyrimethamine was recommended as first line treatment [14]. The guidelines were updated in 2011, keeping artesunate-sulfadoxine/pyrimethamine as first-line treatment and recommended artemether-lumefantrine as second line treatment for uncomplicated malaria. Therapeutic efficacy studies conducted in 2011, 2013 and 2015 revealed high treatment failure rates of 12-22% following artesunate-sulfadoxine/pyrimethamine treatment [15,16]. These treatment failure rates were above the 10% threshold level recommended by WHO for changing antimalarial treatment policy [2]. Furthermore, studies evaluating artemether-lumefantrine and dihydroartemisinin-piperaquine treatments showed high cure rates (>97% cure rate) in treating uncomplicated falciparum malaria [16, 17]. On the basis of this evidence, the national malaria treatment guidelines were again updated in February 2016, replacing artesunate-sulfadoxine/pyrimethamine with artemether-lumefantrine as first-line treatment and recommending dihydroartemisinin-piperaquine as second-line treatment [18]. These ACTs are recommended for all malaria species.

The objectives of treatment for uncomplicated malaria are to cure (radical) the infection rapidly, prevent progression to severe disease, reduce transmission of the infection to others and prevent the emergence of anti-malarial drug resistance. The objectives of treatment for severe malaria are to prevent death, neurological deficit and recrudescence. In settings where a diagnostic option (microscopy or rapid diagnostic test) is available, it is recommended that only confirmed cases be treated with artemether-lumefantrine. In settings where diagnostic service is not available, treatment with ACT should be based on clinical diagnosis. The guidelines also provide recommendations for anti-malarial medicines for intermittent preventive treatment during pregnancy in settings with moderate and high transmission of malaria.

The current updated guidelines from 2016 (see box) provide adequate information to health workers on the specific details of malaria treatment for both uncomplicated and severe malaria infection at different levels of the health care system. Health workers at all levels of health care delivery services were trained on the guidelines. Therapeutic efficacy studies conducted in 2017 confirmed that the currently recommended first-line (artemether-lumefantrine) treatment for uncomplicated malaria remains efficacious.

Concluding remarks

The emergence of *P. falciparum* resistant to antimalarials continues to pose a threat to the provision of effective antimalarial treatment, underscoring the need to monitor the efficacy of currently used ACTs at least every two years, as recommended by WHO [2]. With technical and financial support from WHO, the efficacy of recommended ACTs was regularly monitored, providing important evidence for national malaria treatment guidelines. This support was critical at a time when public health services were collapsing due to the protracted civil war. Continued technical and financial support from WHO would serve to ensure that effective treatments are made available also to future malaria patients in the country.

Summary in Somali

CINWAAN

Tilmaamaha habraaca haatan ee daaweynta duumada Soomaaliya: talooyin ku qotoma daliilo cad

SOOKOOBID

Maareynta xaaladaha duumada- bukaanka qaba cudurka duumada ee baaritaanka iyo daaweynta degdegga loo sameeyo iyaddoo la adeegsanayo daawada isku dhafka ah ee ku saleysan artemisinin - waa tiir aasaasi u ah talooyinka wax ka qabashada cudurka duumada ee Soomaaliya. Nasiib darrose, soo

shaac-bixidda iyo faafidda dulinka falciparum oo u adkeysta daawada duumada ayaa weli khatar weyn ku haya, in si wax-ku-ool ah loo maareeyo bukaanka duumada. Taageerada farsamo iyo midda dhaqaale ee laga helay hay'ada Caafimaadka Aduunka (WHO), ayaa suurtagal ka dhigtay in si joogta ah loo kormeero aagga hawlgalka xarumaha caafimaad ee loo xushay ururinta xogta xaaladaha cudurka (sentinel sites) tan iyo 2003dii. Daraasadahaani waxay bixiyeen caddayn taageeraysa ansixinta isticmaalka dawooyinka artesunate-sulfadoxine/pyrimethamine 2005-tii, oo galay safka koowaad ee ku daaweynta cudurka duumada, iyo in artemether-lumefantrine loo xulay sannadkii 2011 safka labaad ee ku daaweynta.

Daraasado la xiriira wax ku oolnimada daawada oo la sameeyey intii u dhaxeysay 2011 iyo 2015 waxay muujiyeen hoos dhac weyn oo kuyimid waxtarka daawada artesunate-sulfadoxine/pyrimethamine oo gaartay 12.3% - 22.2%, oo ka sarreysa heerka 10% oo lagu saleeyey in haddii la gaaro siyaasadda daaweynta la beddelo, sida ay ku talisay WHO. Tani waxay la xiriirtaa baahsanaan gaaraysa afar-jibbaar iyo shan-jibbar ee isbedelka hiddo-wadaha (Gene mutation) oo sameeya enzimyada (enzymes) dihydrofolate reductase (Pfdhfr) iyo dihydro pteroate synthase (Pfdhps), kuwaasoo keena u-adkeysi sulfadoxine/pyrimethamine oo daawo u ah cudurka duumada.

Iyadoo lagu saleynayo natiijooyinkaas, ayaa tilmaamaha daaweynta duumada qaranka la cusbooneysiiyay 2016, iyadoo artesunate-sulfadoxine/pyrimethamine lagu beddelay artemether-lumefantrine oo noqday daaweynta safka koowaad iyo dihydroartemisinin-piperaquine oo lagu taliyay inuu noqdo daaweynta safka labaad. Daraasadahaas wax ku oolka ah ee 2016 iyo 2017 la sameeyey waxay xaqiijiyeen in daaweynta koowaad iyo tan labaadba ay weli yihiin kuwo aad waxtar u leh oo heerka daaweyntoodu ka sarreeyo 97%. Taageerada farsamo iyo dhaqaale ee WHO waxay kaalin weyn ka geysteen soo saarista cadeymo wargelinaya siyaasadda daaweynta duumada, hawlahaasne waa in la sii wadaa si loo hubiyo, in daawo wax-ku-ool ah loo heli-karo bukaanka duumada qaba ee ku sugan dalka.

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Author contributions

MW, AAO, AHH, AA, AM and JHA contributed to the compilation of relevant information. MW conceived the review and led the analysis of the data and the preparation of the manuscript. AMH, MAA, FEY were part of the core team of the therapeutic efficacy studies along with the authors. All authors contributed to the writing and approved the final version of the manuscript.

Disclosure statement

The authors declare that they have no conflict of interests.

Ethics and consent

The data used in this paper is publicly available information in the form of published articles and unpublished reports. The efficacy studies referred to in the manuscript were approved by the relevant authorities and written consent/assent was obtained for each patient as indicated in the respective articles [13, 15, 16, 17].

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Paper context

The emergence of antimalarial drug resistance in *P. falciparum* continues to pose a threat to the provision of effective antimalarial treatment in Somalia and underscores the need to monitor the efficacy of currently used ACTs at least every two years, as recommended by WHO [2]. With technical and financial support from WHO, the efficacy of recommended ACTs has been regularly monitored in Somalia, providing evidence for the adoption and updating of national malaria treatment guidelines. This support from WHO should therefore continue to ensure that effective treatments are available for future malaria patients in the country.

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