



POLICY BRIEF

Review of Antimalarial Medicines Available to Treat *P. falciparum* in the Amazon Region

Background

Malaria is a substantial public health threat in the Americas. In 2010, the Americas had approximately 675,000 cases of malaria, even after experiencing a 43 percent decline over the preceding decade (WHO 2011). In 2002, the Amazon Malaria Initiative (AMI) was formed to address malaria-related issues within the region. Management Sciences for Health, through multiple projects funded by the US Agency for International Development, has assisted countries with medicine supply management by implementing selection, procurement, and use initiatives.

Since the initiation of AMI, many changes have been made to treatment regimens for *Plasmodium falciparum* because of chloroquine and sulfadoxine-pyrimethamine resistance. In the mid-2000s, all the South American countries changed their standard treatment guidelines to include artemisinin-based combination therapies (ACTs), and some countries have since added primaquine to the recommended regimen. Current treatment regimens include artesunate + mefloquine (AS+MQ) and artemether-lumefantrine (AL) with or without primaquine (Carter 2012). Peru uses a combination of artesunate and mefloquine in monotherapy formulations, whereas Bolivia and Brazil use them in a fixed-dose combination. Brazil, Colombia, Ecuador, Guyana, and Suriname use AL in a fixed-dose combination.¹

Malaria cases have declined in almost all the countries in the Americas during the previous decade, with the exception of the Dominican Republic, Haiti, and Venezuela. The number of cases declined more than 90 percent in some AMI countries, while others showed less substantial declines. The reduced incidences resulted in antimalarial stock supply issues in various countries—either overstocking or stock-outs. Redistribution of medicines within the region and consolidated procurements mitigated the stock supply problems, but countries' different treatment regimens limit these initiatives' effectiveness. This brief reviews the two *P. falciparum* antimalarial regimens currently used in South America, so countries can make decisions about future treatment protocols.

Review of Artemisinin-Based Combination Therapies

Countries and regions use several criteria to determine which antimalarial medicines to include as the standard treatment. Current World Health Organization (WHO) guidelines recommend that *P. falciparum* cases be treated with an ACT, except for pregnant women in the first trimester (WHO 2010c). Primaquine can be added to treatment regimens in countries in disease preelimination or elimination phases. The main factor WHO uses to determine its policy is the medicine's therapeutic efficacy (WHO 2010c). Other important

¹ Artemether-lumefantrine (AL) 1.7/12 mg/kg of body weight, two doses/day for three days; artesunate-mefloquine (AS+MQ) 2–10 mg/kg of artesunate for one dose for three days and 25mg/kg split over two or three days for mefloquine.

criteria used to determine which antimalarials are best for a country include their effect on the development of resistance through selection pressure, cost of the medicine, ability to make co-formulated tablets (Nosten and Brasseur 2002), and availability of national and international manufacturers of the medicines.

Pharmacokinetics

ACTs combine a quick-acting artemisinin derivative with a longer-acting partner medicine. South American countries currently use either artemether or artesunate in combination therapy (WHO 2011). The derivatives are synthesized from artemisinin because the molecule is practically insoluble in water or lipids but dissolves in ethyl alcohol. Because absorption into the body is poor, it is not the ideal form to deliver the medicine. Artemether is the methyl ether of artemisinin and is soluble in lipids (Onori and Majori 1989). Artesunate is a sodium succinyl salt of artemisinin and is soluble in water (Onori and Majori 1989). The body metabolizes artesunate and artemether into dihydroartemisinin, which is the main active metabolite that kills the plasmodium parasite (Davis, Karunajeewa, and Ilett 2005). The body absorbs all three metabolites more easily than artemisinin. Artesunate absorbs quickest into the bloodstream after oral administration because it is water soluble and has the quickest elimination half-life. Diet can affect the absorption of artemether because it is fat soluble. The medicine seems to absorb faster when taken with high-fat foods (Davis, Karunajeewa, and Ilett 2005). Table 1 summarizes the time needed to reach peak blood-level concentrations and half-life of the medications AML countries use to treat *P. falciparum*.

Table 1: Time to Peak Plasma Level and Half-Life for Antimalarial Medicines Used for *P. falciparum* Treatment

Medicine	Time to peak (hours) and (C _{max})	Elimination half-life
Artesunate	1 ^a	< 1 hour (converted to dihydroartemisinin) ^{a,d,e}
Artemether	2 ^b	3–7 hours (converted to dihydroartemisinin) ^{a,d,e}
Dihydroartemisinin	2 ^a	45 minutes ^{a,d,e}
Mefloquine	0.36–2.0 ^c	13–24 days ^{a,d,e}
Lumefantrine	> 2 ^d	4–5 days ^{a,b,e}

a. Miller et al. 2009.

b. Djimdé and Lefèvre 2009.

c. Onori and Majori 1989.

d. Aweeka and German 2008.

e. Eastman and Fidock 2009.

The rate of recrudescence is high when taking only an artemisinin because of its short half-life (Onori and Majori 1989). Therefore, to be effective, artemisinins need to be paired with a partner drug that has a longer half-life (Davis, Karunajeewa, and Ilett 2005). Studies in the Americas have shown no difference in effectiveness between AS+MQ and AL (WHO 2010a). Interestingly, however, one study in Asia that compared fixed-dose AS+MQ to the loose drugs indicated that the absorption of MQ was 40 percent higher when patients took the fixed-dose combination (Ashley et al. 2006).

Treatment efficacy

Medication efficacy is related to the resistance or tolerance a parasite develops to it. Resistance happens in two phases: the first phase involves a genetic mutation that produces a resistant mutant parasite. The second phase requires an environment that is conducive to the resistant parasite having a fitness advantage over the nonresistant parasite. As a result, the resistant parasites reproduce faster than nonresistant parasites, creating a parasite population that is no longer susceptible to the antimalarial drug (WHO 2010a). Several

environmental factors allow resistant parasites to gain an advantage over nonresistant parasites, including the number of parasites exposed to a drug, concentration of the drug in the body, pharmacokinetics and pharmacodynamics of a drug, degree of resistance conferred by a mutation, degree of host immunity, and exposure of the parasite to other drugs to which it is not resistant (Nosten and Brasseur 2002).

WHO-approved treatment regimens for malaria have proven to be highly effective in treating all malaria cases in the Americas (WHO 2010a). WHO guidelines indicate that countries should consider changing existing treatment regimens if local resistance studies yield treatment failure greater than 10 percent. Several efficacy studies have been carried out in the Americas in the last 10 years. For example, nine AL efficacy studies completed between 2004 and 2008 in five Amazon Basin countries showed treatment failure ranging between 0.0 and 4.7 percent with no treatment failure observed in five of the studies (WHO 2010a).

As previously stated, AL is best absorbed with a high-fat diet, although studies that evaluated the difference in cure rates between high- and low-fat diets have shown no difference. These studies have taken place in Africa and Asia, where the diets are low in fat (both continents), and resistance to ACTs is high (Asia) (Djimé and Lefèvre 2009). Therefore, diet does not appear to affect the efficacy of AL.

Eleven studies in Amazonian countries were completed between 2002 and 2008 for AS+MQ. Eight of them showed no treatment failures, and the range of treatment failure for all the studies was between 0.0 and 5.8 percent (WHO 2010a). Studies did not show any difference in treatment outcomes between the fixed-dose combination and the separate forms of AS and MQ.

Overall, the efficacy studies carried out in South America have not shown differences in the efficacies of currently used antimalarial treatments in South America.

Cost

The cost of one course of treatment can be seen in Table 2. AL is the cheaper of the two medicine options currently used in South America.

Table 2. Cost of Course of Treatment for *P. falciparum* Malaria for an Adult

Medicine	Strength	Dose	Price offered to PAHO ^a (USD)	International Drug Price Indicator Guide ^b (USD)
Artemether-lumefantrine	20 mg + 120 mg	24 tablets ^c	1.47	1.40
Artesunate + mefloquine	100 mg + 250 mg	6 tablets AS + 6 tablets MF ^c	Not applicable	3.85

USD = US dollars.

a. Results of solicitation for bids by Pan American Health Organization (PAHO), 2012.

b. MSH 2011.

c. WHO 2010b.

Manufacturers

WHO has prequalified four manufacturers of AL. One manufacturer produces co-formulated AS+MQ; it is currently in WHO's and the individual countries' product registration phase, which can take from six months to two years to complete (Medicines for Malaria Venture 2012). The manufacturer of AS+MQ has donated medicines to South American countries, but the countries are not able to purchase the medicine while it awaits WHO approval. Currently AL is easier to purchase because of the greater availability of sources in the market.



Conclusion

AL and AS+MQ are efficacious in treating *P. falciparum*, making them both good treatment alternatives in South America. Because AL is considerably cheaper than AS+MQ, AL is the better cost-saving option. AL should also be easier for South American countries to procure because of the four existing WHO-qualified manufacturers. Therefore, Bolivia, Brazil, and Peru, which still use AS+MQ, should consider shifting to AL as the recommended treatment for uncomplicated *P. falciparum*. As an additional benefit, all South American countries would then share the same treatment regimen, which would facilitate exchanging and donating medications throughout the region. Countries in the region currently using AS+MQ purchase them separately or rely on donations of the medicines. These practices are not sustainable in the long term because artesunate is not readily available as a monotherapy and donations are not predictable.

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