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School-aged children based seasonal malaria chemoprevention using artesunate-amodiaquine in Mali

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ABSTRACT

Introduction: Malaria is still a public health problem in Africa. Seasonal Malaria Chemoprevention (SMC) is an efficient control strategy recommended by WHO that targets children under five year old living in areas of seasonal malaria transmission. SMC uses the combination amodiaquine (AQ) – sulfadoxine-pyrimethamine (SP). However SP selects rapidly drug resistant parasites. And malaria burden may increase in older children where SMC is implemented. We initiated a pilot study to assess an alternative approach to SMC in older children in Mali.

Methods: A randomized open-label clinical trial was conducted to test the efficacy and safety of SMC using artesunate – amodiaquine in school aged children in Mali. Two hundred pupils aged 6–15 years old were enrolled and randomized into two arms of 100 each, to receive either artesunate–amodiaquine (ASAQ) monthly or no intervention. Both arms were followed and clinical malaria were diagnosed and treated with arthemeter-lumefanthrine as recommended by Mali National Malaria Control Program. ASAQ was administered 3 days under study team direct observation and during 4 consecutive months starting in October 2013. Follow up was continued until April 2014.

Results: Overall, 20 cases of uncomplicated clinical malaria were encountered in the Control arm and three cases in the ASAQ arm, showing a protective efficacy of 85% 95% CI [80.1–89.9] against clinical malaria. Protective efficacy against malaria infection was 69.6% 95% CI [58.6–21.4]. No effect on anemia was observed. ASAQ was well tolerated. Most common solicited adverse events were abdominal pain and headaches of mild intensity in respectively 64% and 44% of children that swallowed ASAQ.

Conclusion: ASAQ is effective and well tolerated as SMC targeting older children in a *peri* urban setting in Mali. Its administration at schools is a feasible and accepted strategy to deliver the intervention.

1. Introduction

Despite tremendous reduction in the burden of malaria in the last decade thanks to control efforts, malaria remains a public health

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problem in most malaria endemic countries and accounted for 445,000 deaths in 2016, 91% of which occurred in sub Saharan Africa (WHO, 2017). Seasonal malaria chemoprevention (SMC) is an effective control strategy specifically recommended by WHO in April 2012, for countries where > 60% of the burden of malaria occurred in the three months of the rainy season, that coincides with the malaria transmission season (WHO, 2012). SMC targets children aged under five years and consists of administering a single curative dose of Sulfadoxine-Pyrimethamine (SP) associated with a three-day course of amodiaquine (AQ). The combination treatment is given once a month during 3 months with the aim to prevent malaria during the transmission season (WHO, 2012). Evidence in several African countries has shown that SMC using SP-AQ is highly efficacious, eradicating almost severe malaria and leading to strong reduction in *P. falciparum* prevalence, in the incidence of clinical uncomplicated malaria and malaria anemia (Dicko et al., 2011a; Konaté et al., 2011; Odhiambo et al., 2010; Bojang et al., 2011). However large-scale implementation of SMC has been associated with selection of Pfdhfr-dhps quintuple mutant genotype (Maiga et al., 2016). Furthermore, administration of SP during pregnancy has been associated with selection of parasites carrying genetic quintuple mutations (Pfdhfr 51I, 59R, and 108 N; Pfdhps 437G and 581G) (Conrad et al., 2017). The quintuple mutation is known to be associated with falciparum parasite resistance to SP. Therefore, in places where SMC is implemented using SP, a critical recommendation is to monitor closely the level of circulating parasites sensitivity to SMC drugs. In addition, more studies are encouraged to find alternative treatment regimens to SP-AQ. One alternative regimen constitutes the use of a highly efficacious artemisinine (AS) derivative in association with AQ. Artesunate is a soluble derivative quickly adsorbed orally, the highest concentration in blood is achieved 1 h following an oral intake and the half-life is between 20 and 72 min (Orrell et al., 2008; Saunders et al., 2012; Matar et al., 2014). AS pharmacokinetics parameters are similar when AS is given alone and when AS is combined with AQ (Orrell et al., 2008). Artesunate (AS) is highly efficacious in West Africa. Efficacy studies done *in vivo* have not detected any slowness in parasite clearance time (Maiga et al., 2012). AS has been assessed in combination therapies with AQ (ASAQ) in community-based studies in Ghana under a SMC regimen in children aged 6–60 months (Ahorlu et al., 2011). ASAQ reduced parasite carriage rate by 90.0%, and the prevalence of anemia by 43.1%. In addition the prevalence of fever was reduced by 85.0% (Ahorlu et al., 2011; Kweku et al., 2008). A similar efficacy pattern was reported in a trial done in Kenya where ASAQ was compared to SP-AS in children aged < 5 years (Odhiambo et al., 2010). ASAQ stands therefore as an interesting alternative SMC regimen in case resistance to SP would arise in West Africa.

Areas of seasonal malaria transmission in West Africa constitute the places where SMC is the most cost-effective approach. These are also the places where decrease in malaria burden is being reported (WHO, 2017) associated with a shift in the disease burden to include older children, in particular school-aged children (Nankabirwa et al., 2014a). There is no control intervention that specifically target school-aged children. Moreover, where SMC is scaled-up, the overall reduction in malaria burden is associated with an increase in malaria morbidity in older children (Nankabirwa et al., 2014a). Therefore, specific interventions targeting school-aged children are urgently needed.

In this pilot study we have evaluated the impact of SMC using four doses of ASAQ at one-month intervals in school-aged children at the periphery of Bamako, the capital city of Mali. We aimed to assess the impact of the intervention on malaria morbidity. We also aimed to assess the delivery of SMC strategy using schools as a modality to have access to a large well characterized target population.

2. Materials and methods

This was an open-label, randomized controlled clinical trial designed to assess the efficacy and safety of SMC using ASAQ in school-aged children.

2.1. Study setting

The study was conducted in Sirakoro-Meguetana, a setting of 15,000 inhabitants located at the southeastern suburbs of Bamako, the capital city of Mali. Malaria transmission is low, seasonal from July to December and annual rainfall ranges between 700 and 1300 mm per year. Malaria prevalence is not known in Sirakoro-Meguetana. However, the setting is similar to Sotuba, another *peri* urban area located in the northern suburbs of Bamako. In Sotuba malaria transmission is variable from one year to another, depending on the level of rainfall. With abundant rainfalls, during the rainy season, malaria prevalence in children aged < 15 years, can reach 15.1% (n = 1142) (Sissoko et al., 2015). While in years with lower annual rainfall malaria prevalence is limited to 8% (n = 171) (Dicko et al., 2007). The village hosts a large scholar complex composed of five schools offering primary and secondary education with 4000 pupils recorded in 2013. Close to the school a community based health care center provides curative and preventive care to Sirakoro-Meguetana community members under the leadership of a medical doctor.

2.2. Participants

Participants were children aged 6 to 15 years attending the fundamental school in Sirakoro-Meguetana. After a screening for eligibility, they were included if they agreed to comply with study follow up procedures, had no clinical signs and symptoms of danger, had no known allergic reaction to amodiaquine and artesunate, and if their parents or legal guardians gave a written informed consent. Exclusion criteria were the presence of a low hemoglobin level (< 10 g/dL), a low blood sugar level (< 70 mg/dL) or a positive malaria smear at screening, the presence of any concurrent acute illness, the presence of chronic illnesses such as diabetes or hypertension, the intake of any antimalarial drugs within 15 days preceding the screening.