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Modelling the impact of antimalarial quality on the transmission of sulfadoxine-pyrimethamine resistance in *Plasmodium falciparum*

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ABSTRACT

Background: The use of poor quality antimalarial medicines, including the use of non-recommended medicines for treatment such as sulfadoxine-pyrimethamine (SP) monotherapy, undermines malaria control and elimination efforts. Furthermore, the use of subtherapeutic doses of the active ingredient(s) can theoretically promote the emergence and transmission of drug resistant parasites.

Methods: We developed a deterministic compartmental model to quantify the impact of antimalarial medicine quality on the transmission of SP resistance, and validated it using sensitivity analysis and a comparison with data from Kenya collected in 2006. We modelled human and mosquito population dynamics, incorporating two *Plasmodium falciparum* subtypes (SP-sensitive and SP-resistant) and both poor quality and good quality (artemether-lumefantrine) antimalarial use.

Findings: The model predicted that an increase in human malaria cases, and among these, an increase in the proportion of SP-resistant infections, resulted from an increase in poor quality SP antimalarial use, whether it was full- or half-dose SP monotherapy.

Interpretation: Our findings suggest that an increase in poor quality antimalarial use predicts an increase in the transmission of resistance. This highlights the need for stricter control and regulation on the availability and use of poor quality antimalarial medicines, in order to offer safe and effective treatments, and work towards the eradication of malaria.

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1. Introduction

The spread of antimalarial resistance is hampering malaria control and elimination efforts globally (Ambroise-Thomas, 2012; World Health Organization, 2010a). Poor quality antimalarials can be categorised into three main groups: falsified; substandard; and degraded (WorldWide Antimalarial Resistance Network, 2010). Each of these can be a source of subtherapeutic doses of the active ingredient(s), which promote the emergence and transmission of drug resistant parasites through selection pressures (Barnes, Watkins, & White, 2008; Simpson et al., 2000; White et al., 2009). Falsified antimalarials are those that are fraudulently made and typically contain an incorrect amount of active ingredient, incorrect active ingredient, toxic substances, or no active ingredient. Substandard antimalarials are those made by licenced companies but use poor manufacturing practices. Degraded antimalarials degrade from their initial quality due to inadequate storage conditions, such as excessive heat. In addition, within poor quality antimalarials, we include those that are not recommended in the World Health Organization (WHO) guidelines.

Approximately 30% of antimalarial medicines in Africa and Asia are considered to be falsified or substandard (Ambroise-Thomas, 2012; Newton, Green, & Fernandez, 2009). The outcome for those receiving poor quality antimalarials ranges from prolonged malaria symptoms, unexpected side effects, financial strain due to loss of income or healthcare costs, or even death (Ambroise-Thomas, 2012; Newton, Green, Fernández, Day, & White, 2006; Tabernero, Fernández, Green, Guerin, & Newton, 2014). In Kenya, prior to 2004, sulfadoxine-pyrimethamine (SP) had been recommended as first-line for treatment of malaria. Due to increasing resistance to SP, stemming from mutations in the *P. falciparum* dihydrofolate reductase (DHFR) gene, which affects pyrimethamine, and the dihydropteroate synthase (DHPS) gene, which affects sulfadoxine, Kenya adopted artemether-lumefantrine (AL) as its first-line treatment in 2004. In 2001, WHO recommended the use of artemisinin-based combination therapies (ACTs) as first-line policy (World Health Organization, 2010b). In December 2007, a report was produced surveying the antimalarial medicines available in Kenya and their quality. The researchers identified a wide range of products on the market, the majority of which were not in-line with the new national guidelines, and a high proportion were either unregistered or of low quality (Ministry of Health Republic of Kenya, 2007).

The effect of antimalarial use on the transmission of resistance has been modelled previously (Hastings, 2006; Klein, 2014; Koella & Antia, 2003; Mackinnon & Hastings, 1998; Tchuenche, Chiyaka, Chan, Matthews, & Mayer, 2011). Notably, the models currently available do not take into account the quality or percentage of antimalarial active ingredient and its effect on transmission. As summarised by Koella and Antia (2003), part of the issue preventing these resistance transmission models from being developed and used is a lack of complete, comprehensive datasets for key parameters. Since their model was published, work has been carried out to look at the effect of drug quality on resistance within mice (Huijben et al., 2010a, 2013) and the effect of treatment in humans with SP-resistant infections (Barnes, Little, et al., 2008; Méndez et al., 2007).

Here we develop a new model to explore the impact of antimalarial quality, defined as poor quality SP, as defined above, and good quality AL, on the transmission of SP antimalarial resistance in *Plasmodium falciparum*. To assist in more realistic parameterisation of the model, we applied the model to Kenya in 2006, rather than Kenya being a focus for actual predictions. The model assumes that low to moderate SP-resistance conferred by mutations in the DHFR gene, the target of pyrimethamine, has already been established within both human and mosquito populations.

2. Materials and methods

2.1. Model structure

We developed a deterministic compartmental model to explore the impact of antimalarial quality on the transmission of *P. falciparum* SP resistance (Fig. 1). The model quantifies the transmission dynamics of SP-sensitive (denoted w) and SP-resistant (denoted r) *P. falciparum* between female *Anopheles* mosquitoes and humans. The human-mosquito system is modelled using ordinary differential equations (ODEs) (Eq. (A1), Appendix A1). Humans may be infected by SP-sensitive strains (w), SP-resistant strains (r), or both (wr). Resistance to SP was defined as the presence of DHFR-51 and DHFR-108 pyrimethamine resistance-conferring mutations (Méndez et al., 2007), used as proxy for all low to moderate SP-resistant conferring mutations in *P. falciparum* (Sridaran et al., 2010). At baseline, the percentage of humans and mosquitoes with SP-resistant infections was set to 42% (Kum, Thorburn, Ghilagaber, Gil, & Björkman, 2013; Spalding et al., 2010) and mixed infections was set to 8% (Kum et al., 2013).

Humans free of *P. falciparum* were classified as susceptible and denoted by $S(H)$. When transmission of sporozoites occurs from female *An.* mosquitoes to humans during a blood meal, the human moves into the exposed class ($E(H)_i$) at the rate $\beta_{H,i}$. The script i indicates a SP-sensitive (i is w) or SP-resistant (i is r) *P. falciparum* infection. Due to the difference in the latent periods for asexual *P. falciparum* and gametocytes, it is assumed that antimalarial treatment is sought while in the exposed class to treat malaria symptoms as part of the asexual lifecycle (Poser & Bruyn, 1999). There are four types of treatment available, each used as a proxy for 'good quality' or 'poor quality' treatments. Infected humans receive each treatment type with probability θ_d, where the subscript d is q for a full dose of AL (good quality); m for a full-dose of SP monotherapy (poor quality); p for a half-dose SP monotherapy (poor quality); and n for no treatment, either through no antimalarial compound within the medicine sought or choosing not to seek treatment (poor quality). Following the gametocyte latency period, those in the exposed class move into the infectious class at rate σ_H , which is assumed to be equal for both SP-sensitive and SP-