

## Mefloquine versus Sulfadoxine–Pyrimethamine for Intermittent Preventive Treatment in Pregnancy: A Joint Analysis on Efficacy and Tolerability

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**Abstract.** Since there is no ideal candidate to replace sulfadoxine–pyrimethamine (SP) for intermittent preventive treatment (IPTp), alternatives need to be evaluated on basis of their benefit–risk ratio. We reanalyzed the first Beninese trial on mefloquine (MQ) versus SP for IPTp using a multiple outcome approach, which allowed the joint assessment of efficacy and tolerability. Overall superiority of MQ to SP was defined as superiority on at least one efficacy outcome (low birth weight [LBW], placental malaria, or maternal anemia), non-inferiority on all of them as well as on tolerability defined as cutaneous or neuropsychiatric adverse events (AEs) or low compliance with the treatment. The analysis included 1,601 women. MQ was found to be overall superior to SP ( $P = 0.004$ ). Performing several sensitivity analyses to handle both missing data and stillbirths provided similar results. Using MQ for IPTp as an example, we show that a multiple outcome analysis is a pragmatic way to assess the benefits/disadvantages of one drug compared with another. In the current context of a lack of antimalarials that could be used for IPTp, such a statistical approach could be widely used by institutional policy makers for future recommendations regarding the prevention of malaria in pregnancy (MiP).

### INTRODUCTION

In moderate-to-high transmission areas, malaria in pregnancy (MiP) is responsible for maternal anemia and low birth weight (LBW),<sup>1</sup> which contributes to increased morbidity and mortality in infancy. Since the early 2000s, strategies to prevent MiP have been based on intermittent preventive treatment (IPTp), insecticide-treated nets, and the effective management of malaria cases.<sup>2</sup> IPTp consists of the administration of a single curative dose of sulfadoxine–pyrimethamine (SP) at predefined intervals during pregnancy whether women are infected. Recently, the World Health Organization (WHO) recommended that SP–IPTp should be administered at each scheduled antenatal care visit rather than only twice during pregnancy—as was first recommended—on the basis that three doses of SP are more efficacious than two doses in the prevention of the deleterious consequences of MiP.<sup>3</sup> Although the strategy still remains efficacious for the prevention of MiP in areas of high SP resistance,<sup>4</sup> important concerns have been raised about the useful lifespan of SP for IPTp, so new drugs or strategies are urgently needed. At present, no antimalarial drugs meet all the ideal properties for IPTp so alternatives need to be evaluated on the basis of their benefit–risk ratio.<sup>5</sup> Mefloquine (MQ) is one of the few options for which data are already available. In two recent clinical trials, MQ–IPTp has proven to be equivalent to SP–IPTp in preventing LBW.<sup>6,7</sup> It was also found to be more efficacious than SP–IPTp in preventing maternal anemia, symptomatic malaria, and placental, and peripheral malaria infections at delivery both in human immunodeficiency virus (HIV)–negative and HIV-positive women.<sup>6–9</sup> However, owing to its moderate tolerability, the Malaria Policy Advisory Committee to the WHO, which met

in September 2013, proposed that MQ at the 15 mg/kg dose regimen should not be recommended for IPTp.<sup>10</sup>

In the current debate regarding the relevance of MQ for IPTp, we reanalyzed data from the first Beninese trial with an original statistical approach already used to assess treatments in rheumatology,<sup>6</sup> which made it possible to perform a global comparison of SP and MQ for IPTp taking into account both the preventive and adverse effects of the treatments simultaneously.<sup>11</sup> Indeed, separate analyses of efficacy and tolerability are routine in reporting clinical trial results, sometimes making the results difficult to collate. Separate analyses do not make it possible to account for correlations between end points and may lead to biased results. In this article, we circumvented this difficulty by using a powerful statistical approach to analyze simultaneously LBW, maternal anemia, and placental malaria as well as low compliance of women to the treatment owing to adverse events (AEs) and the occurrence of severe adverse events (SAE) that we considered to be unacceptable for IPTp.

### MATERIALS AND METHODS

**Material and outcomes.** The original trial was designed to establish the equivalence between MQ and SP in terms of efficacy (LBW, equivalence margin 5%).<sup>6</sup> It was approved by the ethics committees in France (Comité Consultatif de Déontologie et d'Éthique, IRD) and Benin (Comité d'Éthique de la Faculté des Sciences de la Santé, Université d'Abomey-Calavi, Cotonou, Avis 002/2004); Clinicaltrials.gov: NCT00274235. It was conducted in 2005–2008 in southern Benin, where malaria is mainly due to *Plasmodium falciparum* and the prevalence of HIV in the general population is approximately 2%. Women of all gravidities between 16 and 28 weeks of gestation, without history of neurological or psychiatric disorder, nor prior use of SP or MQ or report of adverse reactions to sulfa-containing medications, were eligible. Women known to be HIV infected before enrollment or detected HIV positive at the time of recruitment were not eligible. Eligible women were included after providing a signed

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written informed consent. Then, they were randomized to receive either SP (75–1,500 mg) or MQ (15 mg/kg) in a single intake twice during pregnancy (first dose between 16 and 28 weeks of gestation and second dose from 30 weeks of gestation). AEs were recorded during visits at home within 1 week after each IPTp intake and during the following antenatal care visit.

For this analysis, three efficacy and one tolerability binary outcomes were considered. For efficacy, the criteria were LBW (< 2,500 g), maternal anemia (hemoglobin [Hb] < 10 g/dL) at delivery, and placental malaria (presence of asexual-stage parasites in the placental thick blood smear). Placental malaria was considered as an efficacy end point in the same way as LBW and maternal anemia, since it is the key indicator of efficacy for an antimalarial drug and is closely associated with multifactorial poor outcomes—in the mother and the child—such as LBW and anemia. Therefore, it is the most likely to be influenced by a drug’s efficacy. Low tolerability was defined for cases of either severe AEs, reluctance—eventually followed by acceptance—to receive the second IPTp dose because of AEs at the first dose or refusal to receive the second dose whatever the reason.

**Statistical analysis.** A multiple outcome analysis was conducted to assess the overall superiority of MQ to SP. This approach, which generalizes an approach initially proposed for comparing multivariate means of either binary or quantitative variables,<sup>12</sup> has been described elsewhere.<sup>11</sup> It makes it possible to demonstrate the overall superiority of a new treatment to a standard one in the context of multiple outcomes being simultaneously of interest. Indeed, the overall superiority of one treatment to another could be defined in several ways. In our testing procedure, which controls for the global type I error, overall superiority was defined with univariate comparisons as follows: superiority of the new treatment to the standard one according to some outcomes and non-inferiority according to some (possibly other) outcomes. Here, MQ and SP were considered as the new and standard treatments, respectively, and overall superiority was defined as 1) superiority on at least one of the three efficacy outcomes defined above in the Material and Outcomes section and 2) non-inferiority on all three efficacy outcomes and tolerability. For non-inferiority assessment, margins were defined as follows: 5% for LBW and maternal anemia and 3% for placental malaria and tolerability. Overall *P* values were calculated by bootstrap resampling methodology.<sup>11</sup> Here, 10,000 bootstrap samples were used. Statistical significance was achieved for *P* values < 5%. Analyses were performed using SAS 9.3 software (SAS Institute Inc., Cary, NC).

Unlike standard multivariate analysis methods, our approach did not require complete datasets so it did not discard observations as soon as one value was missing. The global testing procedure was based on all available information for each outcome. Nevertheless, we paid particular attention to missing data, exploring their impact with sensitivity analyses.

All women were included according to their randomized treatment. In the main analysis, birth weight of the 65 stillbirths, miscarriages, and multiple pregnancies were not taken into account, as in the previous analysis of the trial,<sup>6</sup> whether they had been recorded in the database (*N* = 53 cases) or not (*N* = 12 cases). Indeed, these special pregnancies are well known to be associated with LBW. Then, several sensitivity analyses were performed by crossing two aspects: the influ-

ence of accounting for birth weights of the special pregnancies and the influence of missing data on the three outcomes tested for superiority, which were handled according to three strategies, denoted as “No imputation,” “Failure,” and “Random.” “No imputation” was the default case where missing data were not imputed. In the “Failure” strategy, missing data were always considered as failures (i.e., occurrence of LBW, anemia, and placental infection). In the “Random” strategy, missing data were imputed as failures or not, with a probability equal to the prevalence of the outcome in the cohort whatever the treatment group (i.e., 10% for LBW, 3% for placental malaria, and 18% for maternal anemia). Since this strategy involved a random drawing phase, imputations were repeated five times and the global *P* values were the mean of these five replications. For the “Random” and “Failure” strategies, missing data were imputed as failures independently of the group of treatment and only for the superiority component of the global test, to be the most conservative. Our imputation strategies should not be considered as a classical imputation procedure as missingness affects only outcome variables. These strategies aimed at assessing the robustness of the main analysis.

RESULTS

In our princeps study, 1,601 (802 and 799, in the MQ and SP groups, respectively) women were randomized and considered for analyses. Stillbirths, miscarriages, or multiple pregnancies were reported in 4.2% of women. Missing data accounted for 5.2% (birth weight), 17.6% (placental parasitemia), 20.9% (maternal anemia), and 0.5% (tolerability). In the modified intention-to-treat analysis (i.e., missing birth weights excluded), the proportions of LBW were 8% (MQ) and 9.8% (SP), and the treatments were shown to be equivalent.<sup>6</sup> Placental parasitemia and maternal anemia at delivery were lower in the MQ group than in the SP one (1.7% versus 4.4%, *P* = 0.005; 16% versus 20%, *P* = 0.09, respectively) (Table 1). The proportion of women who reported AEs after at least one treatment administration was significantly higher in the MQ group than in the SP one (78% versus 32%, *P* < 0.001). There was a single severe neurological AE in the MQ group, and six women had minor rashes (two and four after MQ and SP administration, respectively). Overall, 7.1% of women in the MQ group compared with 3.7% in the SP group had a severe AE (i.e., neurological or

TABLE 1  
Effect of MQ–IPTp vs. SP–IPTp on poor mother and child outcomes, univariate analysis, Benin, 2005–2008\*

Outcome	Missing data (n)	Prevalence in MQ group (%)	Prevalence in SP group (%)	Univariate comparison <i>P</i> value
LBW†	136	8.0	9.8	0.22
LBW‡	83	9.7	11.1	0.36
Placental malaria	282	1.7	4.4	0.004
Anemia	335	16.5	20.2	0.09
Low tolerability§	7	7.1	3.7	0.002

LBW = low birth weight; IPTp = intermittent preventive treatment; MQ = mefloquine; SP = sulfadoxime–pyrimethamine.

\*Missing data were excluded from the analyses; birth weights recorded in the event of stillbirth, spontaneous abortion, or multiple pregnancy were considered as missing data.

†Results when not including birth weight of stillbirths, abortions, or multiple pregnancies.

‡Results when including birth weight of stillbirths, abortions, or multiple pregnancies.

§Low tolerability was defined as severe adverse event (SAE), reluctance—eventually followed by acceptance—to receive the second IPTp dose because of an adverse event (AE) at the first dose, or refusal to receive the second dose whatever the reason.

TABLE 2

Multiple outcome analysis including both efficacy and tolerability outcomes, Benin, 2005–2008\*

Strategy for handling missing data†	Birth weight information in the event of stillbirth, abortion, or multiple pregnancy	
	Not accounting for <i>P</i> value	Accounting for <i>P</i> value
No imputation	0.004	0.005
Random	0.01	0.01
Failure	0.07	0.18

The upper left entry in the table gives the *P* value of the main analysis.

\*Multiple outcome global comparison of mefloquine (MQ) with sulfadoxine-pyrimethamine (SP): 1) superiority of MQ to SP on at least low birth weight (LBW), placental malaria, and maternal anemia at delivery, 2) non-inferiority of MQ to SP on LBW, placental malaria, maternal anemia, and tolerability. *P* values according to various strategies for handling missing data and accounting for birth weight information in the 65 stillbirth, spontaneous abortion, or multiple pregnancy cases or not.

†“No imputation”: missing data were excluded; “Random”: missing data were imputed according to the observed prevalence of the outcome in the cohort, “Failure”: missing data were considered as failures (i.e., LBW, anemia, or placental malaria). Missing data on tolerability were neither imputed nor considered as failures.

cutaneous) or had to be encouraged to receive the second IPTp dose owing to troublesome symptoms following the first intake or refused to receive the second IPTp dose whatever the reason.

**Multiple outcome analysis.** In the main analysis, MQ was significantly superior to SP based on the efficacy and tolerability hypotheses tested (global *P* value = 0.004 with the “No impute” strategy) (Table 2). Concordant results were found when birth weight from stillbirths, miscarriages, or multiple pregnancies were accounted for (global *P* value = 0.005). With the “Random” strategy, MQ was also superior to SP (global *P* values averaged at 0.01), irrespective of whether birth weights from special pregnancies were accounted for. Significance was not achieved using the “Failure” strategy, which corresponds to the pessimistic and unlikely hypothesis where missing data are always failures. In that case, the *P* values were < 0.20.

## DISCUSSION

In this article, we reanalyzed data from the first trial, which assessed MQ–IPTp in HIV-negative women in Benin. MQ was overall superior to SP based on the joint assessment of efficacy and tolerability of the treatments. The superiority of MQ to SP was established on the basis that MQ was more efficacious than SP on at least one efficacy outcome (LBW, placental malaria, or maternal anemia at delivery) and not inferior to SP on the three efficacy outcomes as well as on tolerability. Although the trial was carried out 8 years ago, we think these results are still valid since markers of resistance of parasites to SP in pregnant women were found to be globally unchanged between 2005–2008 and 2011.<sup>13,14</sup> Because MQ is not commonly used in Benin, the level of resistance to the drug is probably as low as demonstrated by Aubouy in 2005.<sup>15</sup> Similar low levels of resistance have been reported in Nigeria for the period 2007–2008.<sup>16</sup>

Assessing the benefit of a drug therapy requires consideration of both therapeutic and adverse effects, which should not be evaluated independently. Indeed, when dependencies between the response variables are not taken into account, results are likely to be biased. For this reason, we used a multiple outcome methodology that allowed us to assess several outcomes simultaneously while taking into account their

non-independence. Since statistical conclusions were based on the bootstrap methodology, no distributional assumption is necessary. Only a *P* value is provided as no regression parameter was estimated, meaning that no confidence interval can be calculated. Moreover, this statistical strategy provided a unique and more pragmatic response regarding the benefit of MQ over SP in such a way that benefit in terms of efficacy could be counterbalanced with tolerability. Since all outcomes are similarly important, they do not need to be ranked, nor is there any need to build a composite criterion from a mathematical combination of the different outcomes.

In terms of efficacy, MQ can be considered globally superior to SP since it was more efficacious on at least one clinical (i.e., LBW or maternal anemia) or parasitological (i.e., placental parasitemia) outcome and not inferior on any of them. Since SP was still efficacious to prevent LBW at the time of the trial and both LBW and maternal anemia are multifactorial outcomes (i.e., not only due to malaria),<sup>17</sup> a better parasitological effect, albeit not associated with better clinical outcomes, was considered to be relevant. A non-inferiority margin of 5% was used for LBW and maternal anemia as in the original analysis,<sup>6</sup> though 3% was used for placental malaria and tolerability to be more stringent regarding these two factors, which were the most likely to influence the analysis.

MQ showed poorer tolerability than SP with a higher frequency of AEs such as vomiting and dizziness.<sup>6</sup> Most of these AEs were mild and abated rapidly and spontaneously. For these reasons and thanks to the benefits of MQ, mild AEs were considered as only potentially interfering with compliance in the analysis. Therefore, we checked whether MQ was not inferior to SP in terms of low compliance with the treatment because of mild AEs and SAEs, which were considered to be the two main reasons for ruling out MQ for IPTp. However, these results were based on a composite variable, and the non-inferiority margin was rather high (3%). Recently, a larger clinical trial conducted in five African countries confirmed that MQ at the dose of 15 mg/kg was not associated with an increased risk of severe neuropsychiatric effects.<sup>7</sup>

Another strength of this study is the way in which missing data were handled. Missing data on LBW, placental malaria, and maternal anemia were likely to be random since most deliveries, which occurred outside the maternity clinics and for which outcomes could not be measured, were associated with traveling from outside the study area or transportation difficulties. Moreover, the proportion of one of the three outcomes (e.g., LBW) was similar in women with or without missing data for the other two (i.e., placental malaria and maternal anemia) (data not shown). Finally, the proportion of missing data, the reasons for which data were missing and the baseline characteristics of women for which data were missing, were similar in both groups of treatment.<sup>6</sup> All the three strategies on missing data—no imputation, always considered as failures, which was the most pessimistic strategy, and imputed using the mean prevalence of the outcome in the population, which was the most realistic—provided consistent results in favor of MQ, without reaching statistical significance for the last one. Additional sensitivity analyses were performed regarding stillbirths and miscarriages, which are likely to be associated with LBW but may also be related to malaria.<sup>18</sup> Concordant findings were found whether the birth weights



from these pregnancies were excluded from the analysis, which strengthens confidence in our results on LBW.

Other properties that are required by an alternative drug for IPTp are a long half-life and ease of administration, as well as being affordable and having an acceptable reprotoxicity profile. In this analysis, reprotoxicity profile was not one of the components of the multiple outcome analysis because we considered that any significant association of the drugs with either stillbirth or congenital malformation would have made this analysis not appropriate. Although concerns have been raised about a possible increase in stillbirths in women treated with curative doses of MQ,<sup>19</sup> this finding was confirmed neither in larger datasets nor in two recent multicenter trials on MQ for IPTp conducted in around 6,000 pregnant women.<sup>6,7,9,20,21</sup>

As guidelines, we would recommend not including overcoming AE criteria such as stillbirths, congenital malformations, or mother-to-child transmission (MTCT) of HIV—when relevant—in the multiple outcome analysis since these outcomes have to be evaluated separately, prior to other criteria. In such cases where the drug “under test” has been associated with a significant increased risk for one of these major outcomes, we consider that the multiple outcome approach is not appropriate because the drug should not be given in this indication. Otherwise, a multiple outcome analysis including only criteria that are considered to be similarly important seems the most adequate approach.

## CONCLUSION

Here, we used MQ as an example for the multiple outcome approach since it is a good illustration of a drug that needs to be evaluated on basis of its benefit–risk ratio. Indeed, though efficacious, it has been at the center of a debate involving clinical and political issues for many years. By considering similarly important efficacy outcomes including LBW as well as placental malaria and maternal anemia, our results were in favor of MQ in HIV-negative women. However, recent publications, which assessed MQ on LBW as primary end point and suggested a positive interaction between MQ–IPTp and MTCT in HIV-infected women, incited WHO working groups not to recommend MQ in this indication.<sup>7,9,10</sup>

Generally, when a trial involves therapies for life-threatening conditions such as antimalarial drugs, which can potentially save newborns’ lives, several outcomes should be systematically taken into account. Judging by a sole, albeit important, criterion may lead to permanently ruling out a potentially important drug, given its high efficacy and the heavy burden of the disease. This statistical approach has yet not been used in the treatment of infectious diseases. In our opinion, such multiple outcome analyses are needed in every field of public health in the future before taking any decision that may involve critical issues.

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