1   Population Pharmacokinetic properties of Sulfadoxine and Pyrimethamine: A pooled analysis to

2   Inform Optimal Dosing in African Children with Uncomplicated Malaria.

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14   Running Head: PK of Sulfadoxine/Pyrimethamine in African Children

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17

18 **Abstract**

19 Sulfadoxine/pyrimethamine with amodiaquine is recommended by the World Health Organization as

20 seasonal malaria chemoprevention for children between 3 to 59 months in the sub-Sahel regions of

21 Africa. Sub-optimal dosing in children may lead to treatment failure and increased resistance. Pooled

22 individual patient data from four previously published trials on the pharmacokinetics of sulfadoxine

23 and pyrimethamine in 415 paediatric and 386 adult patients were analysed using nonlinear mixed

24 effects modelling to evaluate the current dosing regimen and, if needed, propose an optimised

25 dosing regimen in children under five years old. The population pharmacokinetics of sulfadoxine and

26 pyrimethamine were both best described by a one-compartment disposition model, with first-order

27 absorption and elimination. Body weight, age and nutrition status (measured as weight-for-age z-

28 scores) were found to be significant covariates. Allometric scaling with total body weight and

29 maturation of clearance in children using post-gestational age improved the model fit. Underweight-

30 for-age children were found to have 15.3% and 26.7% lower bioavailability of sulfadoxine and

31 pyrimethamine, respectively, for each z-score unit below minus 2. Under current dosing

32 recommendations, simulation predicted that the median day 7 concentration was below the 25th

33 percentile of a typical adult patient (50 kg) for sulfadoxine for patients in 8-9, 19-24, 46-49 and 74-79

34 kg weight bands, and for pyrimethamine for the weight-bands 8-9, 14-24 and 42-49 kg. An evidence-

35 based dosing regimen was constructed that would achieve sulfadoxine and pyrimethamine exposure

36 in young children and underweight-for-age young children that was similar to that currently seen in

37 a typical adult.

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Introduction

41 While substantial progress has been made in the recent years to lower mortality rates, malaria

42 remained the fourth leading cause of death in sub-Saharan children under the age of five in 2015,

43 with a child dying from malaria every two minutes (1). Children are particularly vulnerable as in

44 areas of moderate to high intensity transmission, immunity to severe malaria is generally acquired

45 by the age of five years and immunity to uncomplicated malaria only attained in early adulthood (2).

46 Malaria treatment outcomes depend on several factors including level of parasite resistance to

47 antimalarial drugs, host factors such as acquired immunity, and the pharmacokinetic (PK) properties

48 of the antimalarial treatment. As age and acute malaria may alter the pharmacokinetic properties of

49 most antimalarial drugs, studies in healthy adult volunteers are not sufficient for determining dosing

50 regimens in children (3).

51 Sulfadoxine/pyrimethamine with amodiaquine is recommended by the WHO as seasonal malaria

52 chemoprevention (SMC) in the Sahel sub-region of Africa in areas with highly seasonal malaria

53 transmission, where *P. falciparum* is sensitive to both antimalarial medicines. A full treatment course

54 of sulfadoxine/pyrimethamine with amodiaquine is administered to children between 3 to 59

55 months old at monthly intervals during the malaria season (1).

56 The disposition of sulfadoxine/pyrimethamine in children is poorly understood, even though the

57 drugs have been used widely for over 50 years. Available data suggests sub-optimal dosing in

58 children (3). Dosing of antimalarials, such as sulfadoxine/pyrimethamine, has often been based on

59 age for practical reasons, but this could lead to under- or over-dosing (4).

60 PK studies are gaining recognition as tools to inform antimalarial drug policies and dosing regimens.

61 Traditional PK data analysis requires multiple samples per patient, which can be challenging,

62 particularly in small ill children. Population PK modelling requires less intensive sampling and can

63 estimate PK parameters at the population and study arm level, while accounting for individual

64 differences. This method does well to study the nature of antimalarial drugs in children (5, 6).

65 There is uncertainty regarding the precise PK determinants of treatment outcome in malaria. There

66 is evidence that suggests day 7 concentrations (C_{day7}) are a good determinant of outcome. The

67 period between dosing and day 7 is crucial because it determines whether the parasite population is

68 eliminated or causes recrudescence, assuming that drug concentrations will have been above the

69 day 7 level for 7 days (four 48-hour parasite life-cycles) (7). Toxicity is most likely to be related to the

70 maximum concentration (C_{max}) of the drug, but no threshold for toxicity is reported for

71 sulfadoxine/pyrimethamine.

72 In this work, we present a pooled population pharmacokinetic analysis of data from four African

73 studies (3, 5, 8, 9). The aims of this study were to 1) characterise the pharmacokinetic parameters of

74 sulfadoxine/pyrimethamine comparing young children to adults using nonlinear mixed-effects

75 modelling, 2) explore the effect of predefined covariates including nutrition status and 3) if needed,

76 use simulation to optimise dosing in young children.

77

78 **Materials and Methods**

79 All relevant published pharmacology studies were identified by searching PubMed, Embase, Google

80 Scholar, ClinicalTrials.gov and conference proceedings using the key words 'sulfadoxine or

81 pyrimethamine pharmacokinetics' or 'sulfadoxine or pyrimethamine concentrations' and 'clinical

82 study'. The first and last authors of identified studies were contacted and invited to join this pooled

83 analysis by contributing individual patient data to the World Wide Antimalarial Resistance Network

84 (WWARN) repository as part of a study group if their studies were prospective sulfadoxine and

85 pyrimethamine studies in African non-pregnant patients with uncomplicated *P. falciparum* infection,

86 especially children under the age of five. The WWARN automated data management, curation and

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87   analysis tools converted the submitted data into a set of defined data variables in a standard format,

88   following the WWARN clinical and pharmacology data management and statistical analysis plans (10,

89   11). Study reports were generated from the formatted datasets and sent back to investigators for

90   validation or clarification. All participating authors agreed to the WWARN terms of submission (12)

91   that ensure all data uploaded were anonymized and obtained with informed consent, and in

92   accordance with any laws and ethical approvals applicable in the country of origin.

93

94   The pharmacokinetic data used for modelling was pooled from 4 different previously published

95   clinical studies (3, 5, 8, 9) from the African countries of Mozambique, South Africa, Mali, and Malawi,

96   and was collected in 8 different study sites. The data from studies in Mali and Malawi were only

97   from children while the data from studies in Mozambique and South Africa included both children

98   and adults. Adults received a single dose of 1500 mg sulfadoxine and 75 mg of pyrimethamine and

99   children a minimum of 25 mg/kg sulfadoxine and 1.25 mg/kg pyrimethamine according to weight

100   bands shown in Table 1. Sulfadoxine/pyrimethamine was administered alone (250 children, 304

101   adults) or in combination with chloroquine (34 children), artesunate (85 children, 113 adults), or

102   amodiaquine (29 children). All sulfadoxine/pyrimethamine concentrations were measured in

103   capillary whole blood dried spots on filter paper (n=4214), except in the study conducted by Bell et

104   al., where concentrations were measured in liquid samples, either capillary (n=285) or venous (n=84)

105   whole blood. Six to nine samples per patient were collected in all sites at least pre-dose and day 1, 3,

106   7, 14, 21 and 28.

107   Nonlinear mixed-effects modelling was implemented in the software Monolix Suite 2016R1 (Lixoft,

108   France) to analyse the pharmacokinetic data, and parameters were estimated using the Stochastic

109   Approximation Expectation Maximization (SAEM) algorithm. The pharmacokinetics of sulfadoxine

110   and pyrimethamine were first modelled independently to determine their structural model and

111   covariate effects, and then combined into one model to investigate possible correlations between

112   the pharmacokinetic parameters of the two drugs. One, two, and three compartment disposition

113   models with first-order absorption were evaluated for the structural model. Between-subject

114   variability (BSV) was evaluated on the pharmacokinetic parameters assuming a log-normal

115   distribution. A combined error model with both additive and proportional components was used for

116   the residual unexplained variability (RUV). The -2 x log-likelihood value (-2LL), goodness of fit plots,

117   visual predictive checks (n=1000), residual error plots, and Wald's test guided the model

118   development.

119   All concentration results were available as the original value reported by the analytical laboratory

120   assay, including the readings below the lower limit of quantification (LLOQ), except for the data

121   collected in 2 sites in Mozambique, for which all concentrations lower than 10 ng/mL for

122   pyrimethamine and 10 μg/mL for sulfadoxine were censored and reported as below the LLOQ (BLQ).

123   These censored values were handled using the M3 approach suggested by Beal (13) using the

124   censoring functionality in Monolix. All other BLQ readings were used in the model as the original

125   value reported by the laboratory to make the best use of the data. Drug concentration samples were

126   collected before dosing to determine if any drug was still present in circulation from previous

127   treatment. If detectable values were found in these pre-dose samples, it was assumed that the

128   pharmacokinetic profile was in the terminal elimination phase and all the disposition compartments

129   in the model were initialised to the observed drug concentration. Biologically implausible samples

130   were identified and excluded using a model-based approach where values with extreme NPDE's for

131   both drugs were discarded.

132   The effect of weight, age, nutritional status (measured as weight for age z-score; unfortunately, no

133   data was available on height or mid-upper arm circumference), study site, sex, baseline

134   haemoglobin, total mg/kg dose, concomitant medications, baseline parasitemia, and sample blood

135   matrix were tested as predefined covariates.

136   The effect of body size was taken into account using allometric scaling (14) with total body weight to

137   adjust all volumes with exponent 1 and flow rates (clearance and flow rates to and from peripheral

138   compartments) with exponent 0.75 (15). Unfortunately, no height information was available for the

139   patients, so testing alternative size descriptors such as fat-free mass or adjustments for BMI were

140   not possible. The effect of age on clearance (14) was tested using a sigmoidal maturation function of

141   post-gestational age, as shown below.

$$MAT = \frac{PGA^{\gamma}}{PGA^{\gamma} + PGA_{50}{}^{\gamma}}$$ (1)

142   where PGA is the post gestational age, PGA_{50} is PGA at which the clearance is 50% that of the mature

143   value, and γ is the Hill coefficient determining the steepness of the curve.

144   The nutritional status of children was determined based on weight for age z-scores calculated using

145   the R macro and igrowup.standard function provided on the WHO website (16). The weight-for-age

146   z-score is determined from growth curves developed by the WHO Multicentre Growth Reference

147   Study (MGRS). It was undertaken between 1997 and 2003 to generate new growth curves for

148   assessing the growth and development of infants and young children around the world. The MGRS

149   collected primary growth data and related information from approximately 8500 children from

150   widely different ethnic backgrounds and cultural settings (Brazil, Ghana, India, Norway, Oman and

151   the USA). Children were considered malnourished if they had a z-score less than -2 (17). This effect

152   was added to the model using a "hockey stick" model, according to the formula equation 2.

$$Effect = (change\ in\ bioavailability\ per\ unit\ change\ in\ z-score)\ \times (z-score+2)$$ (2)

153   For other categorical covariates (study site, sex, concomitant medications, and sample blood matrix),

154   one reference sub-category (REF) was defined and relative differences from REF were calculated for

155   each of the other sub-categories. For other continuous covariates (baseline haemoglobin, mg/kg

156   dose and, baseline parasitemia), the linear covariate effects on the log-transformed PK parameters

157   were explored, centred on the median value in the population in order to incorporate the central

158   tendency of the data as shown in equation 3.

$$Log(P_i) = log(P_{pop}) + \beta\ log\ (cov/m) + \eta_i$$

159   where P_i is the individual parameter value, P_{pop} is the population parameter value, β is the covariate

160   effect, *cov* is the continuous covariate, *m* is the median value and η_i is the random effect for

161   parameter P_i. This ensures that positive PK parameters are preserved and the effect can be

162   interpreted approximately as a relative change in parameter value for a unit change in the covariate.

163   In case of several categorical and/or continuous covariate effects on the same PK parameter, all

164   effects were included using a multiplicative relationship.

165   Covariate effects were screened for using the "full approach", where all effects with potential impact

166   on sulfadoxine/pyrimethamine PK are estimated simultaneously, and tested for statistical

167   significance using the Wald test (p-value<0.05). The covariate effects detected as significant with the

168   Wald Test were then included in the model with a step-wise approach. First, they were added one by

169   one and retained if they produced a decrease in the -2LL of more than 3.84 for one degree of

170   freedom (p<0.05). Then, they were confirmed with a backward elimination step, where each

171   covariate-PK parameter relationship was removed one by one, and retained only if an increase

172   greater than 10.83 in -2LL for one degree of freedom (p<0.001) was observed.

173   No widely-accepted PK targets for either efficacy or toxicity are available for

174   sulfadoxine/pyrimethamine, and effective concentrations increase with the accumulation of

175   dihydrofolate reductase and dihydropteroate synthase mutations. The clinical dataset contained

176   data on a large number of patients where adults achieved high efficacy and in both adults and

177   children very little toxicity was reported. It was therefore decided pragmatically to target the

178   concentrations that the model predicted for the patients included in our analysis. Median values of

179   C_{day7} and C_{max} were chosen as reference values with the same tolerance threshold. The use of the

180   25% tolerance margin was dictated by pragmatic considerations, to accommodate for the feasibility

181   of the suggested optimised regimen in a programmatic setting (i.e., to avoid the creation of too

182   many weight-bands and/or the breaking of tablets).

183   Monte Carlo simulations based on the final PK model were used to evaluate dosing regimens. The

184   median C_{day7} for a typical 50 kg patient, after standard recommended dosing, were simulated and

185   efficacy targets were fixed to 75% of these values. The median C_{max} were simulated and toxicity

186   thresholds were fixed to 125% of the highest value amongst the weight -bands with good

187   representation in our clinical data. Dosing regimens were evaluated based on whether they achieved

188   median C_{day7} higher than the efficacy targets and median C_{max} lower than the toxicity thresholds for

189   patients with different bodyweights. We first evaluated the currently recommended WHO dosing

190   regimen (18) and then explored alternative dosing regimens. Historical malaria patient data from

191   several studies (19–26), and unpublished data from routine clinical monitoring of malaria infected

192   children (under five years) patients and the patients used in this study, were used to create a model

193   describing weight for age in malaria patients (appendix 1). This model was used to simulate plausible

194   weight for age values: 20 *in silico* patients were generated for each kilogram of weight between 5 to

195   80 kg. In weight bands that contained children under the age of five, in which age-for-weight z-

196   scores are defined, 40 more patients per kg (20 with z-score < -3 and 20 with -3 ≤ z-score < -2) were

197   simulated (60 patients in total per each bodyweight in kg). None of the simulated patients had z-

198   scores less than -4.27, as no patients in the studies pooled for our PK analysis had a z-score less than

199   -4.27. The resulting database had 1880 *in silico* malaria patients with age between 1 and 50 years.

200   The current WHO dosing guidelines were simulated in 500 hypothetical clinical trials using the 1880

201   *in silico* patients and the final developed population PK model.

202   **Results**

203   **Data**

204   Pharmacokinetic data was collected in 801 patients, 415 of whom were children (Table 1). 259 out of

205   8981 (2.88%) samples were excluded as outliers (i.e. biologically implausible), resulting in a total of

206   4567 blood concentrations for sulfadoxine and 4155 for pyrimethamine available for analysis. There

207   were 152 (18.9%) and 125 (15.6%) patients with detectable but low pre-dose concentrations of

208   sulfadoxine and pyrimethamine, respectively.

209   **Pharmacokinetic Model**

210   A 1-compartment model with first-order absorption and elimination provided the best fit for both

211   sulfadoxine and pyrimethamine. The combined model for both sulfadoxine and pyrimethamine

212   supported between-subject variability in clearance, volume of distribution, absorption rate constant,

213   and bioavailability and a combined error structure. The final model parameter values are shown in

214   Table 2. Prediction-corrected visual predictive checks, to adjust for the site effects, of the observed

215   drug concentrations versus time are shown in Figure 1. Additionally, visual predictive checks

216   (without prediction correction) stratified by study site and age and other goodness of fit plots

217   stratified by age, weight and nutrition score are included in the supplementary material. These plots

218   show that the median of the observed data generally fits well within the confidence interval for the

219   50th percentile of the model prediction in each age category, although some sites and age groups

220   displayed more variability than others and the model would sometimes over- or under-predicted the

221   extreme percentiles. The model simulations used for dose optimisation were therefore performed

222   with the parameter values of the reference site - which contained most patients (55% for

223   sulfadoxine and 53% for pyrimethamine) – and targeting median values, which were more

224   consistently well predicted.

225   Allometric scaling with total body weight improved the model fit substantially (S: Δ-2LL=320 P: Δ-

226   2LL=855) and decreased BSV in volume of distribution for both drugs. Maturation of clearance

227   improved the model fit and decreased the -2LL by 47 points (S: Δ-2LL=15, df=2 p<0.001; P: Δ-2LL=32,

228   df=2 p<0.001). Malnutrition, as characterised by low weight for age z-score, was found to affect

229   bioavailability (S: Δ-2LL=21, df=2, p<0.001; P: Δ-2LL=81, df=2, p<0.001), with children who had a z-

230   score of -3 having 15.3% and 26.7% lower bioavailability of sulfadoxine and pyrimethamine,

231   respectively than children with a z-score greater or equal to -2.

232   Even after adjusting for body size, maturation, and nutrition score, significant site-specific

233   differences between the pharmacokinetic profiles remained. For sulfadoxine, compared to the

234   reference group (Magude, Bancoumana, Bela Vista, Catuane, Chileka), group A (Mpumalanga,

235   Boane, Namaacha) had 39.7% lower observed concentrations (Δ-2LL=263, df=1, p<0.001). For

236   pyrimethamine, compared to the reference group (Magude, Mpumalanga, Boane, Chileka), group B

237   (Catuane, Bancoumana, Bela Vista) had 22% higher observed concentrations (Δ-2LL=1342, df=1,

238   p<0.001) and group C (Namaacha) 20.2% lower observed concentrations (Δ-2LL=183, df=1, p<0.001).

239   The Bell et al. study had a 54.9% lower pyrimethamine clearance (Δ-2LL=3668, df=1, p<0.001)

240   compared to the other sites. No other pre-defined covariates (sex, baseline haemoglobin, mg/kg

241   dose, concomitant medications and baseline parasitemia) were found to be significant and these

242   were therefore excluded from the model.

243   The simulated (n=500) median day 7 concentrations (C_{day7}) for a typical 50 kg patient were 81.7

244   µg/mL for sulfadoxine and 132 ng/mL for pyrimethamine after standard WHO recommended dosing.

245   Efficacy targets were fixed to 75% of these values: 61.3 µg/mL for sulfadoxine and 98.9 ng/mL for

246   pyrimethamine. The simulations also revealed that, median maximum concentrations (C_{max}) for a

247   typical 10 kg patient (highest Cmax amongst the weight-bands with good representation in our

248   clinical data) were 263 µg/mL for sulfadoxine and 785 ng/mL for pyrimethamine and toxicity

249   thresholds 329 µg/mL and 981 ng/mL respectively (125% of median value).

250   Under the current dosing recommendations, patients who weigh 8-9, 19-24, 46-49 and 74-79 kg

251   showed simulated median sulfadoxine C_{day7} lower than the efficacy target for sulfadoxine, while for

252   pyrimethamine this occurred in the weight-bands 8-9, 14-24 and 42-49 kg. Optimised weight-based

253   dosing using a maximum of five weight bands given 0.5, 1, 1.5, 2, 3 and 4 tablets of 500 mg

254   sulfadoxine/25 mg pyrimethamine were simulated. The optimised dose that achieved median C_{day7}

255   higher than the efficacy target and median C_{max} lower than the toxicity threshold is shown alongside

256   the current WHO dosing regimen in Table 3, and in Figure 2 and Figure 3 for sulfadoxine and

257   pyrimethamine, respectively.

258   Under current dosing recommendations, among children with a body weight of 10 kg, moderate

259   malnutrition (z-score between -2 and -3) resulted in 6.68% and 21.9% lower median C_{day7} for

260   sulfadoxine and pyrimethamine, respectively, while severe malnutrition (z-score less than -3)

261   resulted in 20.3 % and 44.3% lower median C_{day7} for sulfadoxine and pyrimethamine, respectively

262   (Figure S2, in supplementary material). Thus, an alternative age-based dosing regimen for children

263   under the age of five was explored. A comparison of the weight-based and age-based optimised

264   dosing regimens, to achieve a median C_{day7} higher than the efficacy target and median C_{max} lower

265   than the toxicity threshold for each weight or age band, is shown in Table 4, with simulated C_{day7} and

266   C_{max} for the optimised weight-based and age-based dosing regimens presented in Figure 4 and Figure

267   5, respectively.

268

269   **Discussion**

270   In this study, a population pharmacokinetic nonlinear mixed-effects model was used to analyse data

271   pooled from four studies in eight study sites. The overall aim was to describe the pharmacokinetic

272   properties of sulfadoxine and pyrimethamine in paediatric and adult malaria patients, characterise

273   the effect of clinical and demographic covariates, and design an optimised dosing regimen. The most

274   significant differences between adults and children were found to be body size (accounted for with

275   allometric scaling) and age, affecting maturation of organ function. Additionally, children who were

276   underweight-for-age had lower bioavailability compared to adequately nourished children.

277   Simulation-based predictions revealed that patients with a body weight of 8-9, 19-24, 46-49 and 74-

278   79 kg for sulfadoxine and 8-9, 14-24 and 42-49 kg for pyrimethamine, did not reach the chosen

279   efficacy target with the current dosing recommendation. Based on the model, a revised dosing

280   regimen was devised and is expected to provide therapeutic exposures in small children similar to

281   adults, which could improve malaria treatment in children under the age of five and provide insight

282   into dosing for chemoprevention in children.

283   To our knowledge, this study is the largest analysis of the pharmacokinetics of

284   sulfadoxine/pyrimethamine to date (3, 5, 8, 9, 27–29), pooling data from four different clinical

285   studies, for a total of 8722 pharmacokinetic samples in 801 patients in Africa, of whom 415 were

286   children. Pooling of these data empowers it to address novel research questions and detect new

287   covariate effects (30) for which the single studies were not adequately powered, such as the effect

288   of malnutrition. Our results can be used to inform treatment regimens in children, one of the most

289   vulnerable groups affected by malaria (1).

290   The final model has estimated parameters with comparable values to those in previous studies

291   (Table 5) with high precision and acceptable model diagnostics. Allometric scaling significantly

292   explained some of the differences between adults and children by accounting for changes in body

293   size. No information on patient height was available, so we could not attempt to adjust for body

294   composition and test fat-free mass for scaling, which could arguably be a better predictor for the

295   size of drug-metabolising organs (31). The absence of height information in children was more of a

296   limitation when trying to determine the nutritional status of the children. We could only calculate

297   weight-for-age z-scores as a measure of nutritional status and no attempt could be made to

298   distinguish between stunting and wasting. Children who were underweight for age were found to

299   have lower bioavailability than adequately nourished children in the study. This could be due to

300   decreased or delayed absorption of the drugs, or possibly to increased total body water, lower

301   albumin levels, or other pathophysiological changes observed in malnourished children (32). As both

302   sulfadoxine and pyrimethamine are highly protein bound (90%), lower levels of albumin may cause

303   higher free drug concentrations resulting in higher clearance and larger volume of distribution,

304   which would have the same effect on the PK profile as a decrease in bioavailability. However,

305   changes in protein binding are not expected to affect unbound drug levels, so no dose adjustment

306   would be necessary.

307   The inclusion of allometric scaling could not fully explain the pharmacokinetics in children younger

308   than 2 years old, due to the significant maturation of drug clearing organs (14, 33). This was

309   described in the model with the inclusion of a maturation function accounting for the fact that

310   young children have a lower clearance than adults, after adjusting for the effect of body size. The

311   model estimated the age (months after conception) at which maturation reaches half of its maximal

312   value (PGA_{50}) at around 8.1 months for sulfadoxine and 11.9 months for pyrimethamine, similarly to

313   previous values reported by Salman et al. (34), 9.03 months for sulfadoxine and 10.6 months for

314   pyrimethamine. As renal function and many hepatic enzymes are expected to reach maturity by age

315   2 (35), a limitation is that our study does not contain data on children under the age of 1. More

316   information is therefore needed to assess fully the effect of maturation on clearance in infants.

317   Even after adjusting for body size, maturation, and nutrition score, significant site-specific

318   pharmacokinetic differences remained. We could include 55% of patients for sulfadoxine and 53% of

319   patients for pyrimethamine in the reference site, but for patients in other sites an adjustment factor

320   was needed. Additionally, the study by Bell et al. was found to have a 54.9% slower clearance than in

321   the other sites. This study was the only one that assayed whole blood liquid samples (capillary dried

322   blood spot samples were assayed in all the other studies) and its samples were assayed in a different

323   lab. Thus, it was not possible to determine whether this difference is explained by matrix, assay

324   method and / or population-specific factors.

325   Young children in areas of high malaria transmission are particularly vulnerable, as immunity is

326   acquired with age and after repeated infections (2). Malaria-induced inflammation can also cause

327   iron deficiency anaemia in children with asymptomatic malaria (36). It is therefore important that

328   children receive adequate doses of sulfadoxine/pyrimethamine as treatment. Appropriate drug

329   dosing in children is particularly challenging (3) and a number of studies have reported sub optimal

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330   exposures for children receiving antimalarial treatment (3, 8, 9). The final model developed in this

331   study demonstrated sufficient predictive performance, deeming it suitable for dose optimisation

332   simulations. It was therefore used to simulate sulfadoxine/pyrimethamine exposures for different

333   body weights with the current dosing guidelines and to develop optimised weight-based and age-

334   based dosing regimens. A proposed optimised dosing regimen based on simulations is provided for

335   the range of weights of 5-79 kg. The weight bands were designed using the currently available tablet

336   size, and allowing only multiple of half tablets. No widely-accepted PK targets for either efficacy or

337   toxicity are available for sulfadoxine or pyrimethamine, therefore efficacy was prioritised, since

338   adverse reactions are infrequent and severe cutaneous toxicity is rare and idiosyncratic (and not

339   dose-related) (37). Furthermore, pyrimethamine has also been used safely in children at doses as

340   high as 2 mg/kg for the treatment of toxoplasmosis (38). However, more precise definitions of

341   efficacy and safety thresholds would further improve, and potentially simplify, dosage

342   recommendations.

343   Alternate optimised dosing in age bands rather than weight bands (Table 4) for children under five

344   years, was proposed to address the concerning finding of significantly lower sulfadoxine and

345   pyrimethamine exposure in underweight-for-age young children, and resulted in more satisfactory

346   exposures. Age-based dosing shows a lot of promise for malnourished children, but further data

347   would be needed for drawing definitive conclusions on optimal dosing in this doubly vulnerable

348   population.

349   Although very young patients (1 – 12 months) were included in the weight-for-age data set, we did

350   not have any patient data below the age of 12 months in the pharmacokinetic dataset used to build

351   the model. Simulated optimised dosing for children less than 12 months (125 mg / 6.25 mg

352   sulfadoxine / pyrimethamine for less than 5 kg) was made possible by inclusion of a maturation

353   function in the model. However, further pharmacokinetic data is needed for investigation into the

354   maturation of clearance of sulfadoxine and pyrimethamine in children under 12 months to inform

355 optimal dosing in this age group. This is reflected by the relative standard error (56% for Sulfadoxine

356 and 13% for Sulfadoxine) in the parameter for post gestational age at which CL is 50% that of the

357 mature value (PGA50).

358

359 **Conclusions**

360 This study reports the largest pharmacokinetic analysis of sulfadoxine/pyrimethamine to date and

361 proposes a model accounting for the effect of body size, maturation, and nutritional status. The

362 analysis revealed suboptimal sulfadoxine/pyrimethamine exposures in some weight bands when

363 given the current WHO recommended dose regimens. Children who were underweight-for-age had

364 decreased bioavailability, with a greater effect on pyrimethamine. Accounting for all these effects,

365 the model was used to propose an optimised sulfadoxine/pyrimethamine dosing regimen, essential

366 to ensure that children, and particularly malnourished children, achieve similar exposures to adults

367 and so have an equivalent likelihood of treatment success. Improved treatment success would

368 reduce the selective pressure for the development of resistance and prolong the useful therapeutic

369 life-span of sulfadoxine/pyrimethamine.

370

371 **Acknowledgments**

378

379   **Conflict of Interest**

380   KIB is a member of the WHO Technical Expert Group (TEG) on Malaria Chemotherapy and of the

381   WHO TEG on Drug Resistance and Containment. The remaining authors declare that no competing

382   interests exist.

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496

Table 1: Population characteristics of pharmacokinetic studies included stratified by study and site.

Parameter	Study									Total
	Barnes *et al.* (4)			Bell *et al.* (9)	Tekete *et al.* (12)	Allen *et al.* (13)				
	Site									
	Bela Vista	Mpumalanga	Namaacha	Chileka	Bancoumana	Boane	Cutuane	Magude	Namaacha	
N	65	122	91	102	114	78	33	124	72	801
Sampling times										
Blood samples collected	Before dosing and day 1, 2, 3, 7, 14, 21, 28, 42 post dosing.	Before dosing and day 1, 2, 3, 7, 14, 21, 28, 42 post dosing.	Before dosing and day 1, 2, 3, 7, 14, 21, 28, 42 post dosing.	Before dosing and day 2, 3, 7, 14, 28 post dosing.	Before dosing and day 1, 3, 7, 14, 21, 28 post dosing.	Before dosing and day 1, 2, 3, 7, 14, 21, 28, 42 post dosing.	Before dosing and day 1, 2, 3, 7, 14, 21, 28, 42 post dosing.	Before dosing and day 1, 2, 3, 7, 14, 21, 28, 42 post dosing.	Before dosing and day 1, 2, 3, 7, 14, 21, 28, 42 post dosing.	
Dose: Number of tablets (500mg/25mg SP)										
< 10 kg	1	1	1	1/2	1/2	N/A	N/A	N/A	N/A	
10 – 14 kg	1	1	1	3/4	3/4	1	1	1	1	
15 kg	1	1	1	1	3/4	1	1	1	1	
16 - 20 kg	1	1	1	1	1	1	1	1	1	
21 – 22 kg	2	2	2	1 1/4	1 1/4	2	2	2	2	
23 – 35 kg	2	2	2	N/A	N/A	2	2	2	2	
36 - 40 kg	2	2	2	N/A	N/A	3	3	3	3	
>40	3	3	3	N/A	N/A	3	3	3	3	
Sex										
Male	30 (46%)	72 (59%)	48 (53%)	57 (56%)	63 (55%)	31 (40%)	18 (54%)	45 (36%)	34 (47%)	398 (50%)
Age										
< 2	0 (0%)	0 (0%)	19 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	13 (18%)	32 (4%)
>2 – 5	38 (58%)	2 (1.6%)	25 (22%)	102 (100%)	114 (100%)	14 (18%)	11 (33%)	48 (39%)	29 (35%)	383(47%)
>5 – 20	17 (26%)	66 (54%)	20 (19%)	0 (0%)	0 (0%)	23 (29%)	17 (52%)	44 (35%)	10 (13%)	197 (25%)

20+	10 (15%)	54 (44%)	27 (30%)	0 (0%)	0 (0%)	41 (52%)	5 (15%)	32 (26%)	20 (28%)	189 (24%)
Treatment arm										
SP	65 (100%)	122 (100%)	91 (100%)	28 (27%)	41 (36%)	28 (36%)	17 (52%)	63 (51%)	35 (49%)	490 (61%)
SP + AQ	0 (0%)	0 (0%)	0 (0%)	20 (20%)	40 (35%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	60 (7%)
SP + CQ	0 (0%)	0 (0%)	0 (0%)	26 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (3%)
SP + AR	0 (0%)	0 (0%)	0 (0%)	28 (27%)	33 (29%)	50 (64%)	16 (48%)	61 (49%)	37 (51%)	225 (28%)
Nutrition score in children under 5 years										
Normal	36 (95%)	2 (100%)	43 (98%)	86 (85%)	102 (89%)	7 (50%)	11 (100%)	29 (60%)	29 (100%)	326 (85%)
-3 <= z-score < -2	2 (5%)	0 (0%)	0 (0%)	15 (14%)	7 (6%)	4 (28%)	0 (0%)	13 (27%)	0 (0%)	41 (11%)
z-score < -3	0 (0%)	0 (0%)	1 (2%)	1 (1%)	5 (5%)	3 (22%)	0 (0%)	6 (13%)	0 (0%)	16 (4%)
Weight										
Median weight [IQR] in kg	15 [12 - 37]	50 [32 - 58]	26 [13 - 55]	11 [9 - 12]	14 [11 - 16]	55 [32 - 63]	32 [15 - 45]	25 [14 - 50]	15 [12 - 54]	18 [12 - 50]
Baseline Haemoglobin										
Median baseline haemoglobin [IQR] in g/dL	11 [10 - 12]	12 [11 - 13]	11 [10 - 12]	9 [8 - 10]	11 [9 - 12]	11 [10 - 14]	12 [11 - 13]	11 [10 - 12]	11 [9 - 13]	11 [10 - 12]
Baseline Parasitaemia										
Geometric mean baseline parasitaemia [95% range] in count/µL	16028 [2140 - 96995]	22522 [1870 - 169992]	19874 [2065 - 211999]	52717 [2364 - 212647]	41694 [7282 - 138275]	5719 [62 - 99646]	768 [41 - 64200]	1853 [15 - 143277]	12561 [82 - 290493]	21700 [4532 - 63083]

Table 2: Parameter estimates for final combined sulfadoxine/pyrimethamine population

pharmacokinetic model.

Parameter	Sulfadoxine		Pyrimethamine	
	Estimate	RSE (%)[a]	Estimate	RSE (%)[a]
F	*1 fixed*	-	*1 fixed*	-
CL/F [L/h] [b]	0.0264	3	0.829	3
V/F [L] [b]	5.29	2	91.4	3
ka [/h]	0.521	16	1.40	80
Change in F for each point in z-score below -2 [%]	-15.3	31	-26.7	13
PGA$_{50}$ [months after conception]	8.12	56	11.9	13
γ -Hill coefficient	3.20	21	3.01	46
Difference in clearance in Bell et al. [%]	-	-	-54.9	4
Scaling on observations in Bancoumana, Bela Vista, Catuane [%] [#]	-	-	20.2	19
Scaling on observations in Namaacha [%] [#]	-	-	-22.0	23
Scaling on observations in Mpumalanga, Boane, Namaacha [%] *	-39.7	5	-	-
BSV in F [%] [c]	38.4	12	36.1	4
BSV in ka [%] [c]	126	21	171	25
BSV in V [%] [c]	11.2	23	15.5	14
BSV in Cl [%] [c]	33.9	5	29.0	5
Correlation in CL of the two drugs [%]	60.0	6	60.0	6
Additive error [ug/mL for sulfadoxine; ng/mL for pyrimethamine]	3.79	5	6.58	5
Proportional error [%]	17.1	3	23.2	2

RSE, relative standard error; F, relative bioavailability; CL/F, elimination clearance for a fully matured child; V/F, apparent volume of distribution; ka, first-order absorption rate constant; PGA$_{50}$ is the PGA at which CL is 50% that of the mature value; BSV, between subject variability.
[a] RSE (%) is calculated from the Fisher information determined by stochastic approximation.
[b] Clearance and volume were allometrically scaled with total body weight centred on the median body weight (18 kg).
[c] BSV were assumed as log-normally distributed and are reported here as approximate CV%
* Reference group for scaling on observation for sulfadoxine: Magude, Bancoumana, Bela Vista, Catuane, Chileka.
[#] Reference group for scaling on observation for pyrimethamine: Magude, Mpumalanga, Boane, Chileka.

Table 3: Dose-optimisation simulations.

Number of tablets (500 mg/25 mg SP)	Dose	Current WHO dosing recommendations (ref 17)	Optimised dosing recommendations (for patients older than 1 year)
		Weight	Weight
0.5	250mg / 12.5mg SP	5 – 9 kg	< 8kg
1	500mg / 25mg SP	10 – 24 kg	8 – 13 kg
1.5	750mg / 37.5mg SP	-	14 – 24 kg
2	1000mg / 50mg SP	25 – 49 kg	25 – 38 kg
2.5	1250mg / 62.5mg SP	-	39 – 49 kg
3	1500mg / 75mg SP	≥ 50 kg	50 – 68 kg
4	2000mg / 100mg SP	-	≥ 69 kg

Table 4: Optimised dosing proposal for patients under 60 months of age: Weight-based (left) and

age-based dosing (right).

Weight-based optimised dosing			Age-based optimised dosing		
Weight (kg)	Number of tablets (500 mg/25 mg SP)	Dose	Age (months)	Number of tablets (500 mg/25 mg SP)	Dose
< 8	0.5	250 mg / 12.5 mg SP	< 16	0.5	250 mg / 12.5 mg SP
8 – 13	1	500 mg / 25 mg SP	16 – 41	1	500 mg / 25 mg SP
14 – 25	1.5	750 mg / 37.5 mg SP	42 – 60	1.5	750 mg / 37.5 mg SP

Table 5: Other published studies of sulfadoxine/pyrimethamine pharmacokinetic data in patients with uncomplicated malaria

Author ,year (reference)	Sarikabhuti et al, 1988 (31)	Hellgren et al, 1990 (32)	Winstanley et al, 1992 (33)	Bustos et al, 2002 (34)	Dzinjalamala et al, 2005 (28)	Obua et al, 2008 (35)[a]
Assay	Bratton-Marshall	HPLC	HPLC	HPLC	HPLC	HPLC
Patient group	Adults with malaria	Children (8-14 years) with malaria	Children with malaria	Adults with malaria	Children (1-12 years) with malaria	Children (2-5 Years) with malaria
Number of participants	Responders, 5 Non-responders, 7	10	8	Sulfadoxine,19 Pyrimethamine,13	ACPR, 49 LTF, 66	55
Sample Type	Plasma	Capillary whole blood	Plasma	Serum	Capillary whole blood spots on filter paper	Capillary whole blood spots on filter paper
Statistic	Median (range)	Median (range)	Mean	Median (range)	Mean	Mean (range)
Sulfadoxine						
Dose	500 mg	29.4 (25.0 - 35.7) mg/kg	25 mg/kg	1500 mg	ACPR: 34.7 mg/kg LTF: 32.3 mg/kg	500 mg
C_{max} (µg/mL)	Responders: 160 (151 - 176) Non-responders: 192 (143 - 243)	94 (78 - 103)	79	169 (124 - 279)	ACPR: 79 LTF: 69	171 (85 - 249)
AUC (µg/mL/h)	Responders: 45,792 (34,656 - 61,560) Non-responders: 43,392 (32,256 - 55,344)	23,064 (13,176 - 28,992)	20,016	66,192 (42,480 - 93,552)	ACPR: 22,368 LTF: 21,312	16,900 (2,840 - 27,500)
$T_{1/2}$ (h)	Responders: 228 (165.6 - 273.6) Non-responders: 184 (172.8 - 252)	214 (125 - 242)	115.2	261.6 (158.4 - 321.6)	ACPR: 172 LTF: 154	98 (18 -177)
Pyrimethamine						
Dose			1.25 mg/kg	75 mg		
C_{max} (ng/mL)			533	591 (173 - 815)		
AUC (ng/mL/h)			62,568	72,696 (28,584 - 161,904)		
$T_{1/2}$ (h)			81.6	69.6 (38.4 - 302.4)		

ACPR, adequate clinical and parasitological response; LTF, late treatment failures; C_{max}, maximum concentration; AUC, Area under the curve; $T_{1/2}$, elimination half-life; a AUC from 0 to 336h
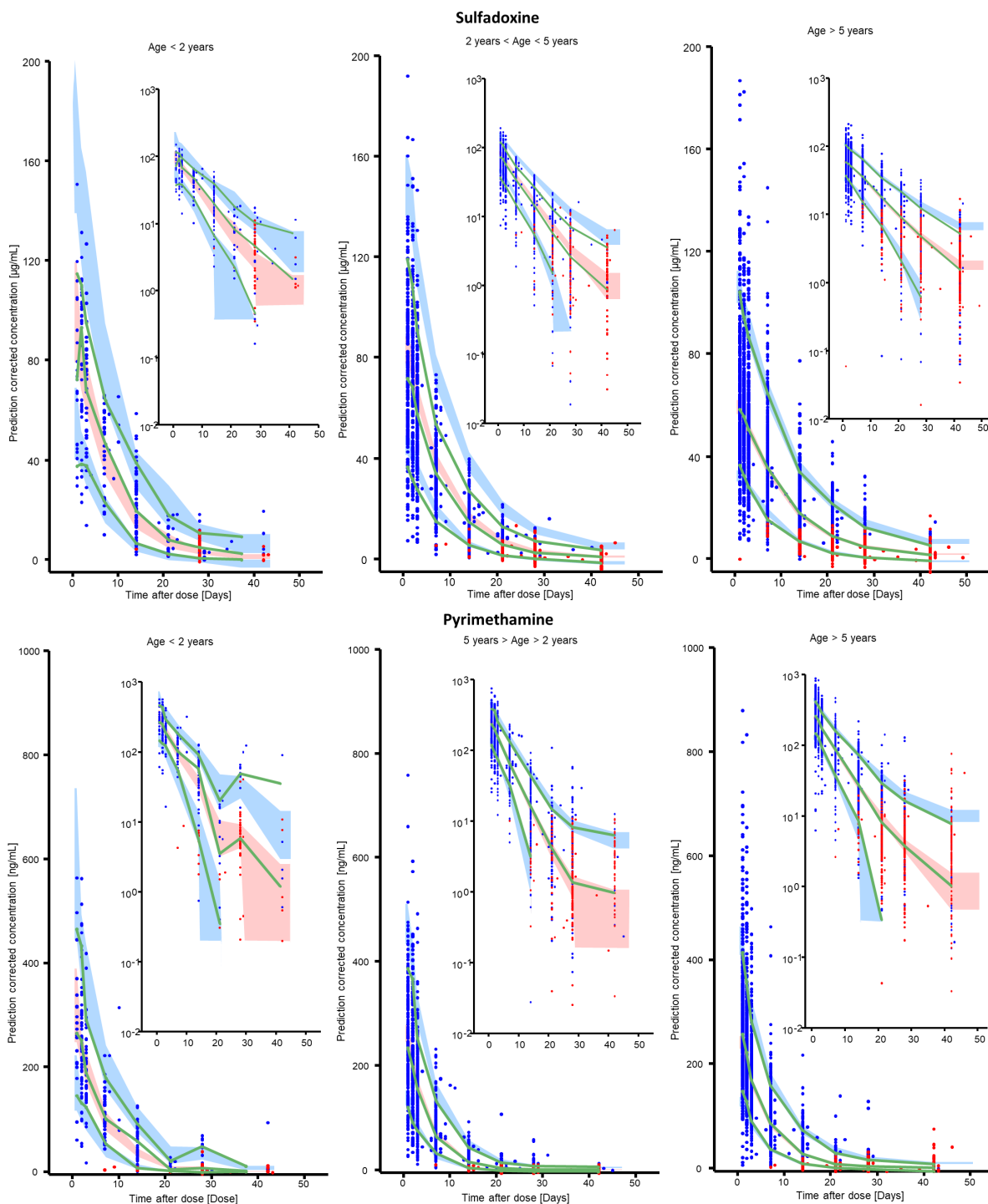
Figure 1: Prediction corrected Visual Predictive Checks for the combined final model, stratified by drug, and age category. The prediction corrected concentrations are plotted as blue dots while the green lines represent the 5th, 50th, and 95th percentiles of the prediction corrected concentrations. The red dots denote censored values (values below, Chileka: 5 μg/mL for sulfadoxine and 50 ng/mL for pyrimethamine, all other sites: 10 μg/mL for sulfadoxine and 10 ng/mL for pyrimethamine) in the dataset, values in the plot are simulated by the model. The shaded areas represent the 90% confidence intervals for the same percentiles, as predicted by the model.
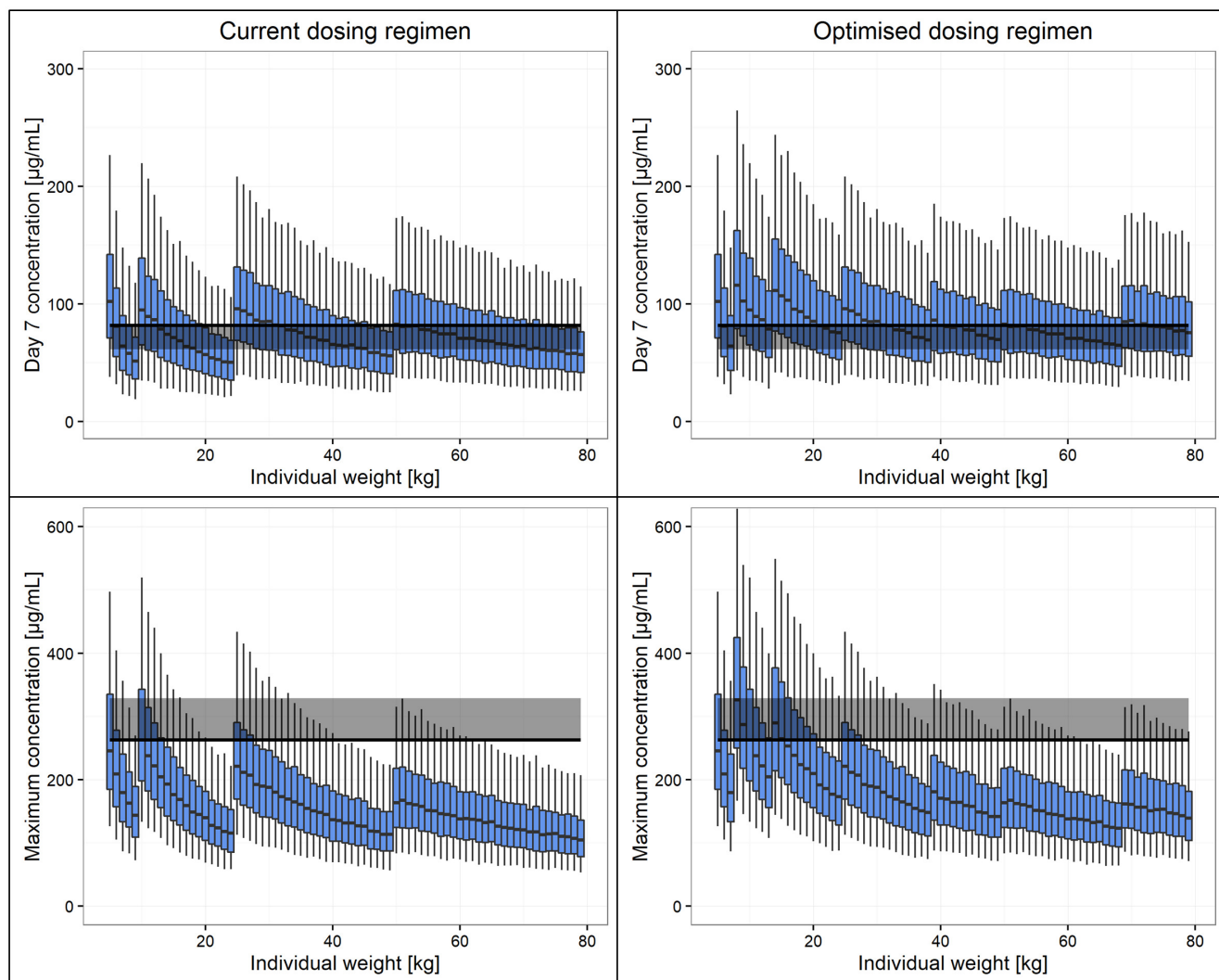
Figure 2 : Sulfadoxine exposure: Current WHO dosing recommendations (left) are compared to optimised dosing recommendations (right). Total exposure is represented by drug concentration at day 7 (C_{day7}) for patients with different body-weights in the top panels. The solid black line and grey band represent the median and 75% of the median of C_{day7}, respectively, for the adult dosed with the highest mg/kg. Maximum concentrations (C_{max}) for patients with different body-weights are shown in the bottom panels. The solid black line and grey band represents the highest median C_{max} and 125% of the highest median C_{max} among the well observed population (7-79 kg) respectively.
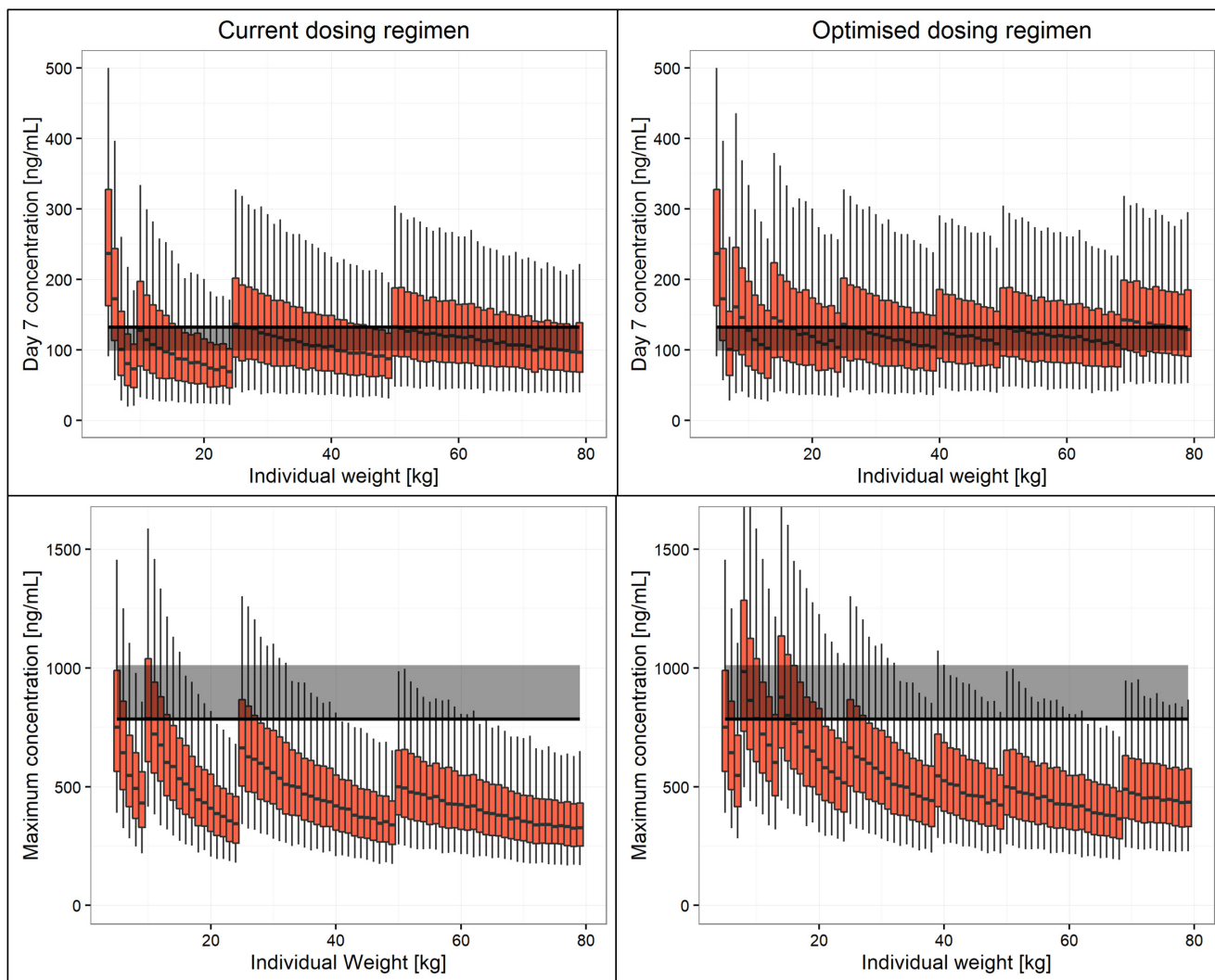
Figure 3 : Pyrimethamine exposure: Current WHO dosing recommendations (left) are compared to optimised dosing recommendations (right). Total exposure is represented by drug concentration at day 7 (C_{day7}) for patients with different body-weights in the top panels. The solid black line and grey band represent the median and 75% of the median of C_{day7}, respectively, for the adult dosed with the highest mg/kg. Maximum concentrations (C_{max}) for patients with different body-weights are shown in the bottom panels. The solid black line and grey band represents the highest median C_{max} and 125% of the highest median C_{max} among the well observed population (7-79 kg) respectively.
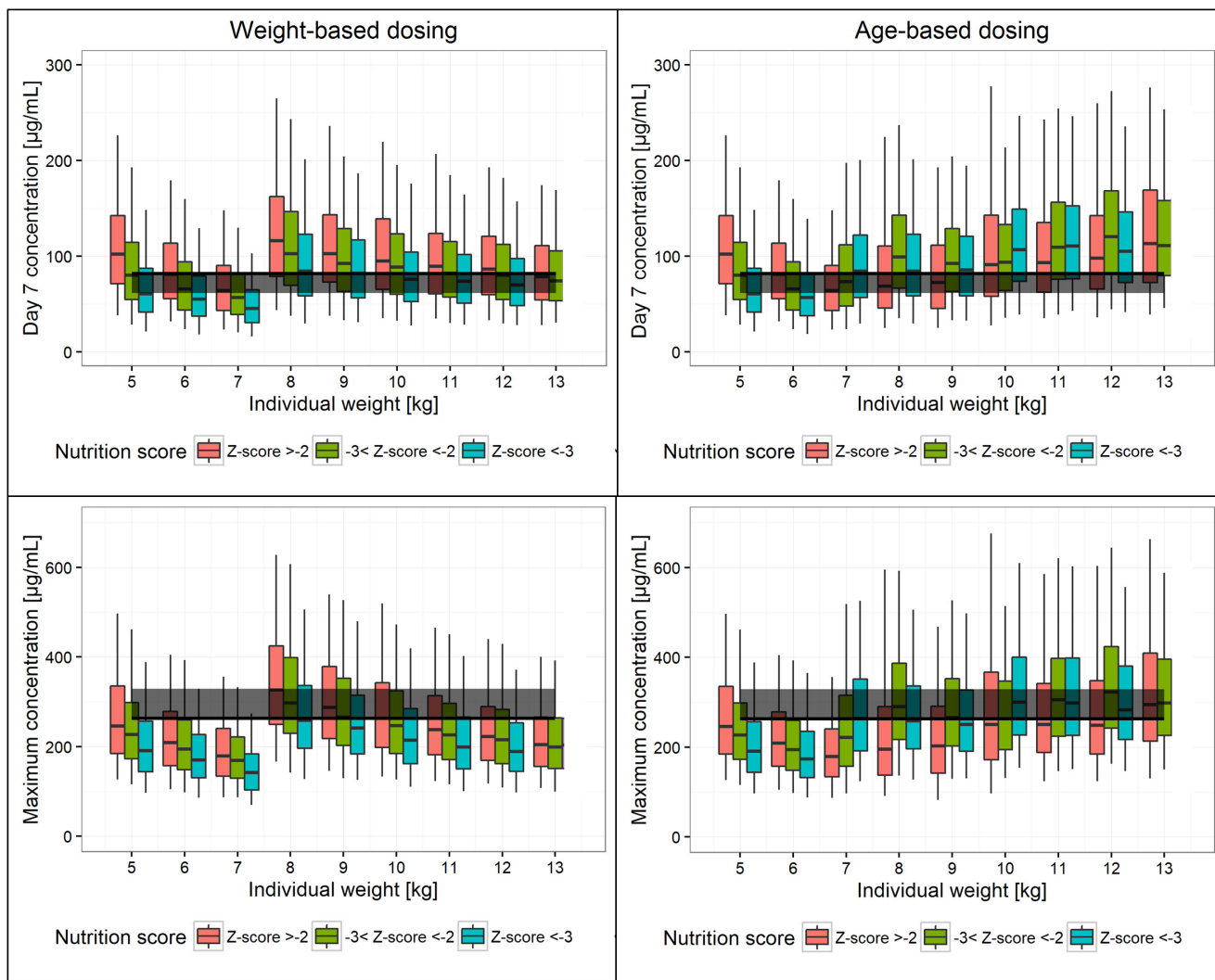
Figure 4 : Sulfadoxine exposure: Weight-based optimised dosing recommendations (left) are compared to age-based optimised dosing recommendations (right) for young children (weight <13kg), stratified by nutrition score. Total exposure is represented by drug concentration at day 7 (C_{day7}) for patients with different body-weights in the top panels. The solid black line and grey band represent the median and 75% of the median of C_{day7}, respectively, for the adult dosed with the highest mg/kg. Maximum concentrations (C_{max}) for patients with different body-weights are shown in the bottom panels. The solid black line and grey band represents the highest median C_{max} and 125% of the highest median C_{max} among the well observed population (7-79 kg) respectively.
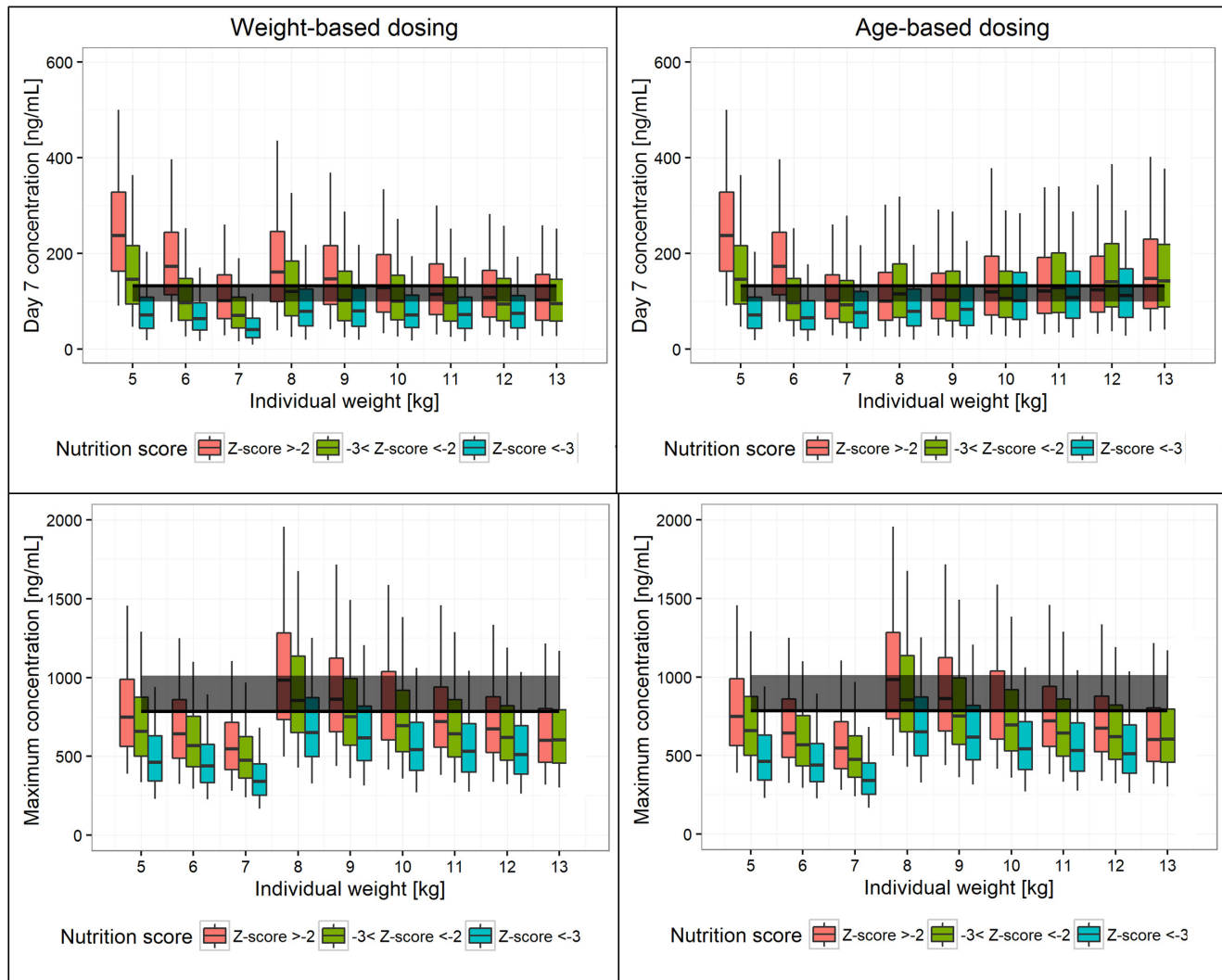
Figure 5 : Pyrimethamine exposure: Weight-based optimised dosing recommendations (left) are compared to age-based optimised dosing recommendations (right) for young children (weight <13kg), stratified by nutrition score. Total exposure is represented by drug concentration at day 7 (C_{day7}) for patients with different body-weights in the top panels. The solid black line and grey band represent the median and 75% of the median of C_{day7}, respectively, for the adult dosed with the highest mg/kg. Maximum concentrations (C_{max}) for patients with different body-weights are shown in the bottom panels. The solid black line and grey band represents the highest median C_{max} and 125% of the highest median C_{max} among the well observed population (7-79 kg) respectively.