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Amodiaquine Dosage and Tolerability for Intermittent Preventive Treatment To Prevent Malaria in Children▽†

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Sulfadoxine-pyrimethamine with amodiaquine (SP-AQ) is a highly efficacious regimen for intermittent preventive treatment to prevent malaria in children (IPTc), but the amodiaquine component is not always well tolerated. We determined the association between amodiaquine dosage by body weight and mild adverse events (AEs) and investigated whether alternative age-based regimens could improve dosing accuracy and tolerability, using data from two trials of IPTc in Senegal, one in which AQ dose was determined by age and the other in which it was determined by weight category. Both dosage strategies resulted in some children receiving AQ doses above the recommended therapeutic range. The odds of vomiting increased with increasing amodiaquine dosage. In one study, incidence of fever also increased with increasing dosage. Anthropometric data from 1,956 children were used to predict the dosing accuracy of existing and optimal alternative regimens. Logistic regression models describing the probability of AEs by dosage were used to predict the potential reductions in mild AEs for each regimen. Simple amendments to current AQ dosing schedules based on the child's age could substantially increase dosing accuracy and thus improve the tolerability of IPTc using SP-amodiaquine in situations where weighing the child is impractical.

Relatively minor adverse reactions to antimalarials that may be acceptable when malaria illness is being treated may not be acceptable when drugs are used on a large scale for intermittent preventive treatment in children (IPTc), when the majority of recipients will be healthy. The response of children and their parents to adverse reactions, even those relatively minor in nature, could limit the uptake of IPTc as a strategy. It is, therefore, important to minimize the side effects associated with this intervention.

Sulfadoxine-pyrimethamine combined with amodiaquine (SP-AQ) has been identified as a highly efficacious regimen for treatment of malaria (4, 8, 11, 23–26) and for IPT (5, 14). However, when used for IPT in children, SP-AQ has been associated with an increased incidence of mild adverse events, particularly vomiting and fever, in the days following the IPT course (5, 14). One answer to this problem would be to use other antimalarials as the partner drug to SP, which has been shown extensively to be safe and well tolerated when used for intermittent preventive treatment (1, 6). Long-acting antimalarials are preferable to artemisinins for IPT because they provide a longer period of posttreatment prophylaxis, which is central to the protection given by IPT (4a, 19). Piperaquine has been identified as a promising partner drug (5) (K. Bojang et al., unpublished data). However, SP-piperaquine is currently not licensed as a combination for use in IPT and there may be some delay in obtaining sufficient safety and pharmacokinetic data to allow deployment of this combination. Any measures that can improve the tolerability of SP-AQ for use in the meantime could therefore be beneficial.

One way in which the tolerability of SP-AQ might be improved is by ensuring that children receive as accurate a dose as possible. The recommended dose for a course of amodiaquine is 30 mg amodiaquine base/kg body weight over 3 days, i.e., 10 mg/kg/day (22). Dosing by weight is therefore the ideal approach, but limitations in resources and training may make this impractical in resource-poor areas (2, 9). Weighing children may be particularly problematic with a large-scale preventive intervention such as IPTc, in which many children will be treated in a short space of time and mobility of health workers may be important for successful delivery (Bojang et al., unpublished data). Development of an accurate dose-for-age schedule would thus be advantageous. Dose-for-age has already been developed for amodiaquine as part of a fixed dose combination with artesunate used for treatment of malaria cases (13, 16), but the priorities may be different for IPT because most children will not be unwell when they are treated. Regimens could be developed specifically for use in IPT.

The regimen used in previous and ongoing trials of IPTc in Senegal consists of one 200-mg AQ tablet for children aged 2 years or over and half a 200-mg tablet for younger children (5; www.clinicaltrials.gov, identifier NCT00712374). Since health workers are used to dichotomizing the dose given to children at 2 years of age, replacing the 200-mg tablet with one with lower AQ content might be a simple way to improve dosing accuracy. One option would be to use a 153-mg AQ tablet that is currently available for treatment. An alternative age-based regimen for amodiaquine was developed using a large anthropo-

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metric data set by Taylor et al. (16) and was recently shown to be well tolerated (13). The AQ doses for this regimen are 67.5 mg for infants as a single tablet and 135 mg for children over 12 months (as two 67.5-mg tablets). The chief problem with this regimen is that children aged between 12 and 23 months are more likely to be overdosed (16). Amending this AQ regimen to include a separate dose for 12- to 23-month-old children might be feasible within an IPT program. Because SP and AQ can both be manufactured to contain any specified amount of the active component, a more flexible option would be to manufacture tablets specifically for seasonal IPT with the optimal concentration of AQ for dosing by age.

This study investigated the accuracy of the amodiaquine dosing strategy used in two recent trials of IPTc using SP-AQ, the relationship between dosage and adverse events, and the potential for alternative amodiaquine regimens to reduce overdosing and adverse events.

MATERIALS AND METHODS

Data from two studies of seasonal IPT in children in Senegal were used for this analysis. The trials were undertaken in Keur Soce, Ndoffane District, Senegal, in 2007 (5) and in Niakhar, central Senegal, in 2004 (14). Brief descriptions are given below.

In Keur Soce, children received sulfalene-pyrimethamine with amodiaquine (SP-AQ) on three occasions during the malaria transmission season of 2007, with dosing based on age group. Sulfalene (sulfamethoxypyrazine) is chemically very similar to sulfadoxine. In September, children under 2 years of age received 250 mg sulfalene/12.5 mg pyrimethamine on the first day they were treated and 100 mg AQ per day for three days; children over 2 years of age received 500 mg sulfalene/25 mg pyrimethamine and 200 mg AQ per day. For the October and November IPT doses, the higher dose of SP was given to all children aged 1 year and over.

While SP-AQ was very effective at preventing malaria, it was also associated with an increased risk of adverse events (AEs) compared to the other treatment regimens. Vomiting, fever, and headache were the most commonly reported symptoms. Differences in incidence of vomiting and fever appeared to be greater in children aged 2 years or older than in younger children. Because children over 2 years of age received a different dose of amodiaquine than children under 2 years of age (a whole tablet [200 mg] of amodiaquine per day rather than a half tablet [100 mg/day]), it seemed plausible that some of the association with adverse events was related to overdosing. Weight data were collected for a sample of study children in September, the month when all children were assessed for AEs, permitting calculation of dosage by body weight. Weight was measured once by trained staff. Children up to 2 years old were weighed naked to the nearest 100 g on electronic plate scales (Nova, India) in their mother's (or caretaker's) arms, using the mother's weight as a tare, and those older than 2 years were weighed alone.

In Niakhar, SP-amodiaquine was given on three occasions during the malaria transmission season of 2004. Dosage was based on body weight. Children weighing <12 kg received 250 mg sulfadoxine/12.5 mg pyrimethamine on the first day and 150 mg amodiaquine once per day for three days. Children ≥ 12 kg in weight received 500 mg sulfadoxine/25 mg pyrimethamine and 250 mg amodiaquine. According to published reference standards, the mean weight at 12 months of age is 8.9 kg for girls and 9.6 kg for boys. At 24 months of age, the mean weight is 11.5 kg for girls and 12.2 kg for boys (20).

SP-AQ was the most effective regimen at preventing malaria but was most poorly tolerated. Weight data were collected for all children enrolled in this study at the time of the September IPT. Weight was measured once by trained staff. Children were weighed naked to the nearest 10 g on mechanical 2- to 16-kg-capacity baby scales (Seca, France) up to 2 years of age and to the nearest 100 g on electronic plate scales (Seca, France) beyond 2 years. All children were visited at home after each IPT round to ask the mother about any adverse events.

Objectives. The accuracy of the amodiaquine dosing strategy used and the association between dosage and incidence of adverse events was determined for both studies. The larger Niakhar anthropometric data set was used to explore the dosing accuracy of potential alternative age-based regimens. Using regression models fitted to the Niakhar adverse event data, the predicted incidence of key AEs with the alternative regimens was calculated in order to determine the possible improvements in the tolerability of SP-AQ.

Dosing accuracy. Weight data were used to estimate the dosage of amodiaquine by body weight that children had received in the SP-AQ treatment group in the two studies. Amodiaquine was also given alongside artesunate in the Niakhar study, but this was apparently better tolerated than AQ with SP (14). Amodiaquine was the focus of this analysis because the recommended range for SP (between 25 mg/kg and 70 mg/kg [18]) is substantially wider than it is for amodiaquine, making it easier to dose accurately, and because in both studies SP combined with a different partner drug was well tolerated (5, 14). An amodiaquine dosage of 10 mg AQ base/kg/day over 3 days is the present target when dosing by weight (21). For dosing by age, the target range for therapeutic AQ doses has been defined as 7.5 to 15 mg/kg/day (i.e., 22.5 to 45 mg/kg in total over 3 days), based on the target dose by weight, published and unpublished data, and clinical expert opinion (16). The dosage of amodiaquine actually received in the two studies was examined in relation to this range.

Association of adverse events with dosage. The incidence of adverse events was tabulated according to dosage. The most commonly reported adverse events in both studies were vomiting and fever. Skin reactions (e.g., rash, pruritus) following SP-AQ were also carefully documented in these studies given the potential for rare severe adverse events, including Stevens-Johnson syndrome (17). No severe skin complaints were seen in the study children, but the relationship of mild skin reactions to dose was investigated.

Logistic regression was used to examine the association between dose received and the probability of fever and vomiting. Linear, curvilinear, and fractional polynomial models were fitted, with the likelihood ratio test used for comparisons. Curvilinear and fractional polynomial approaches were used to explore potential nonlinear relationships between dose and AEs (12). Since age could be associated with the incidence of adverse events, the effect of adjusting for age as a covariate was explored. Despite interest in the tolerability of IPTc in very young infants, there were relatively few children in either data set aged under 6 months. Frequencies of adverse events are tabulated separately for children of <6 months where possible, but in the regression models, all children under 12 months were grouped together.

Dosing accuracy with alternative age-based regimens. To calculate the possible improvements in dosing accuracy that could be achieved with different regimens, the larger anthropometric data set, including all children enrolled in the Niakhar study, was used to predict amodiaquine dosage for various alternatives. For all the alternative regimens considered, the emphasis was on pragmatism. While there may be an "optimal" age-based regimen involving a large number of changes in dose, or cutoffs at specific ages, this probably would not be feasible to implement in the settings in which IPT is likely to be deployed. For this reason, the alternative options considered were based on either currently available tablets or novel regimens using tablets created specifically for IPTc, with practical constraints. These were that changes in dose should occur at whole-year age groups and that it would be possible to deliver an absolute maximum of four different tablet sizes to children under 5 years of age.

The options based on existing AQ regimens were as follows: (i) 150 mg for children under 12 kg and 250 mg for children of ≥ 12 kg (as used in Niakhar); (ii) 200-mg tablets halved for children under 2 years of age (as used in Keur Soce); (iii) 153-mg tablets halved for children under 2 years of age; (iv) 67.5 mg for children under 1 year of age and 135 mg for older children; (v) conditions as for option iv but with a separate dose of 100 mg for 12- to 23-month-old children.

The optimal regimen with one, two, three, and four different tablet sizes was also investigated. Optimal regimens were determined by calculation of the dosing accuracy for different regimens applied to the entire anthropometric data set, with tablet concentrations ranging from 50 to 200 mg in 0.5-mg increments. Following the report of Taylor et al. (16), where several regimens gave identical or very similar results, the option that minimized underdosing was preferred.

Predicted incidence of mild adverse events with alternative regimens. Using the logistic regression model fitted to the Niakhar data set, the predicted probability of vomiting or fever was calculated for each individual based on the dosage of AQ that she or he would have received under the alternative regimens. This analysis was also repeated with adjustment for age, i.e., with dose and age as the predictor variables. The expected proportion of children with vomiting and fever for each alternative regimen was calculated as the mean of the predicted probabilities. By comparison of the predictions, it was possible to examine the potential changes in incidence of adverse events that a change in regimen would produce.

Because the lowest AQ dose received in Niakhar was relatively high (around 12.5 mg/kg/day), it was not possible to fit the regression model to doses of AQ in the lower part of the recommended range. Two approaches were taken to deal with this. The first, and more conservative, was to consider that children given a

TABLE 1. Association of adverse events with overdosing in Keur Soce

Adverse event	% (no.) of results at AQ dose:		Crude odds ratio (95% CI)	*P* value	Age-adjusted odds ratio (95% CI)	*P* value
	≤15 mg/kg/day (n = 208)	>15 mg/kg/day (n = 104)				
Vomiting	26.4 (55)	41.3 (43)	1.96 (1.19, 3.22)	0.01	2.23 (1.14, 4.35)	0.02
Fever	26.4 (55)	29.8 (31)	1.18 (0.7, 1.99)	0.53	0.89 (0.45, 1.75)	0.73
Rash	1.9 (4)	1.9 (2)	1.00 (0.18, 5.55)	1.00	0.75 (0.07, 8.22)	0.82
Itching	1.9 (4)	3.8 (4)	2.04 (0.5, 8.33)	0.32	1.58 (0.16, 15.3)	0.70
Headache	9.6 (20)	5.8 (6)	0.58 (0.22, 1.48)	0.25	0.40 (0.15, 1.36)	0.14

dose lower than 12.5 mg/kg/day would have the same probability of an AE as children with that dose. However, it is probably the case that risk continues decreasing as dose decreases, because trials of IPT with SP+AQ dosed by weight with a target dose of AQ of 10 mg/kg/day have found a low incidence of AEs (3) (Bojang et al., unpublished data). The effect of assuming that the logistic regression model accurately predicted the probability of vomiting below the range for which there are data was thus also explored.

Bootstrapping was used to estimate the uncertainty in these estimates and provide a 95% confidence interval. The children in the SP-AQ arm of the Niakhar trial were sampled with replacement, and the logistic regression model was fitted to this bootstrap data set. The fitted model was then used to predict the expected incidence of adverse events for each of the alternative regimens considered in the analysis of dosing accuracy described above. The bootstrap process was repeated 1,999 times to generate a distribution of the predicted proportion of children with vomiting and fever under the different regimens.

RESULTS

Keur Soce. (i) Dosing accuracy. The amodiaquine regimen used in the Keur Soce trial was 100 mg (half of one 200-mg tablet) AQ per day for 3 days for children under 2 years of age and 200 mg (a whole tablet) for children aged 2 years and over. This avoided underdosing in all but 5 of 312 children (1.6%) (Table 1). However, 104 children (33%) were overdosed. Overdosing was most common in 2-year-old children: 59 of 71 children (83%) received a dose above the recommended upper limit of 15 mg/kg/day AQ, and 10 individuals (14%) received a dose in excess of 20 mg/kg/day. Overdosing was also common among infants <6 months of age (6 of 20 [30%] overdosed) and 3-year-old children (23 of 52 [44%] overdosed). Histograms of dosage by age group are shown in Fig. 1.

(ii) Association of adverse events with age and dose. In the main Keur Soce trial, adverse events such as vomiting, fever, and headache were more common among children over the age of 2 given amodiaquine than in children under 2 years of age (5); this pattern was also seen in the subgroup of children for whom weight data were available. Two-year-old children (the age group at which the AQ dose first increased from 100 mg to 200 mg) appeared to experience an above-average incidence of all adverse events. Children 1, 2, and 3 years old had significantly higher odds of vomiting than children under 12 months of age, with odds ratios (ORs) of 3.41 (95% confidence interval [CI], 1.43, 8.16), 3.39 (95% CI, 1.48, 7.75), and 2.75 (95% CI, 1.14, 6.68), respectively. The association of age group with vomiting became nonsignificant when adjusted for overdosing (see below), except for children aged 12 to 23 months, who retained higher odds of vomiting than infants (OR, 4.06 [95% CI, 1.66, 9.94]). None of the other adverse events (fever, rash, itching, or headache) were significantly associated with age in this data set.

Children who were overdosed were significantly more likely to vomit than children who received a dose lower than 15 mg/kg (crude OR, 1.96 [95% CI, 1.19, 3.22], $P = 0.01$; age-adjusted OR, 2.23 [95% CI, 1.14, 4.35], $P = 0.02$). There was no evidence of an association between odds of any other type of adverse event and dosing over the recommended level. Increased amodiaquine dosage was associated with increased odds of vomiting: for each 1-mg increase in dose, the OR for vomiting was 1.08 (95% CI, 1.00, 1.17; $P = 0.04$); the age-adjusted OR was 1.13 (95% CI, 1.01, 1.26; $P = 0.04$). Other outcomes were not associated with increasing doses of AQ.

Niakhar. (i) Dosing accuracy. The amodiaquine dose in Niakhar was 150 mg for children with body weight <12 kg and 250 mg for children 12 kg and over. The mean weight for different age groups was as follows: 6 to 11 months, 8.0 kg; 12 to 17 months, 9.1 kg; 18 to 23 months, 10.1 kg; 24 to 35 months, 11.7 kg; 36 to 47 months, 13.9 kg; 48 to 59 months, 15.5 kg.

No children were underdosed with amodiaquine, but there was substantial overdosing, with 73.5% of children (352 of 479) receiving a dose of AQ over 15 mg/kg/day. The median dose was 16.7 mg/kg/day (range, 12.5 to 24.9). SP administration by weight avoided overdosing (sulfadoxine > 70 mg/kg) with 19.8% of children (95 of 479) given an underdose (sulfadoxine < 25 mg/kg). The median sulfadoxine dose was 31.3 mg/kg (range, 20.9 to 41.7). Histograms of dose by treatment group are shown in Fig. 2.

(ii) Association of adverse events with age and dose. Age was not associated with the odds of vomiting in this data set. Age was associated with fever in September (chi-square $P = 0.04$); no children under the age of two reported this outcome after the first treatment. Age was also associated with odds of fever over the course of the study (OR for 1-year increase in age: 1.26 [95% CI, 1.01, 1.58; $P = 0.04$]). When adjusted for dose, infants remained at lower odds of reports of fever over the course of the study (OR, 0.06 [95% CI, 0.01, 0.50; $P = 0.01$]), but no association was seen for the other age groups.

In the SP-AQ group, higher doses of amodiaquine appeared to be associated with increased risk of vomiting and fever, both in individual months and over the course of three rounds of IPT (using the September weight as a proxy for weight in later months when children were not weighed) (Table 2).

There was insufficient incidence of skin rash to allow regression models of the effect of dose to be fitted. Regression models were therefore fitted for four outcomes: vomiting and fever in September and vomiting and fever at any of the three IPT doses. Seven outliers with very high amodiaquine doses (>21 mg/kg/day) were removed before the models were fitted. The weight in September was used as a proxy for the weight in later months.

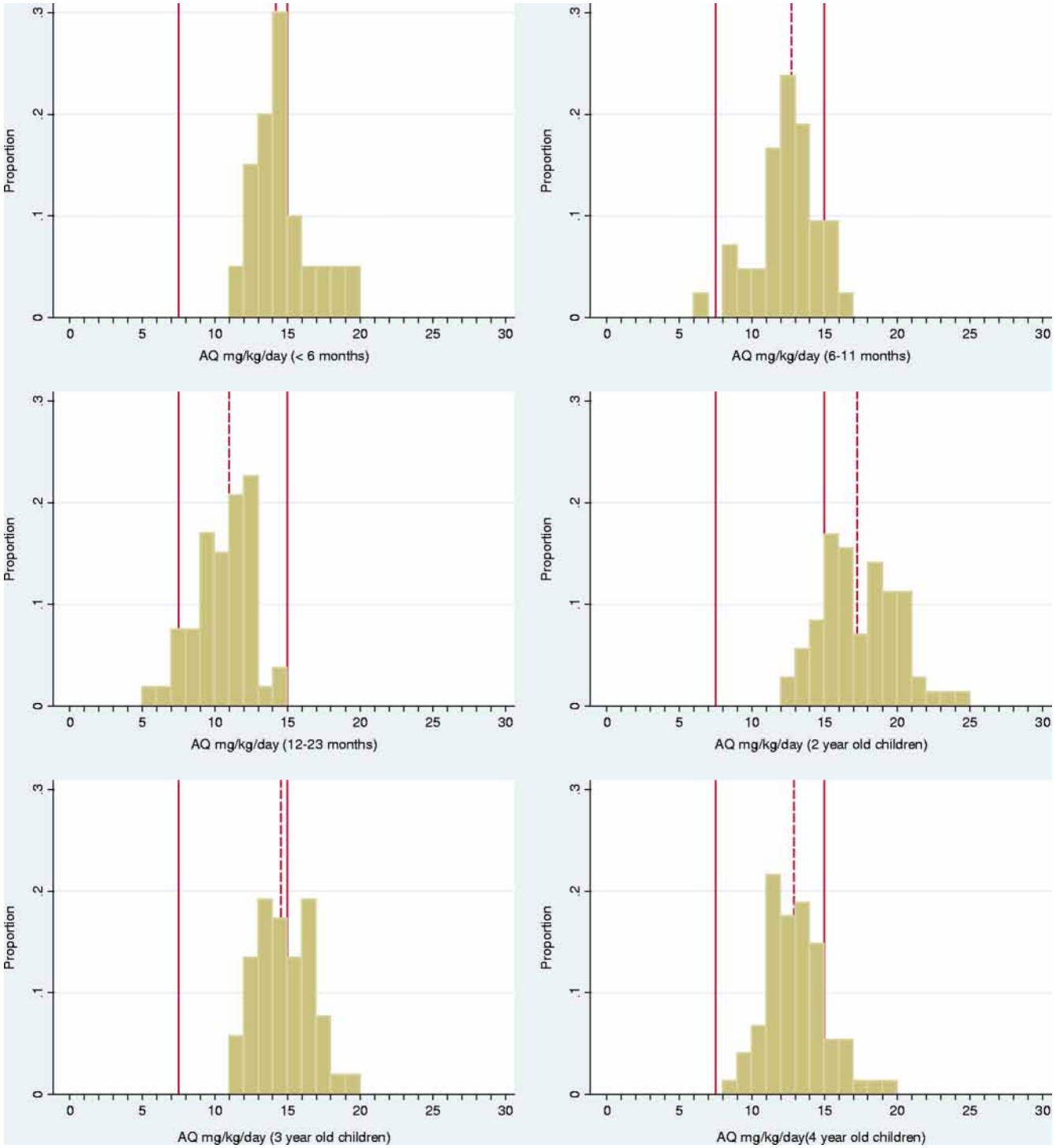

FIG. 1. Amodiaquine dosage in Keur Soce by age group. Dose is shown in mg/kg/day. Solid lines indicate the target dosing range for AQ (7.5 to 15 mg/kg/day for 3 days). The dashed line indicates the median daily dose.

For all outcomes, there was no improvement in model fit by the use of curvilinear or fractional polynomial logistic models. Each 1-mg increase in amodiaquine dose was significantly associated with increased odds of vomiting in September (age-adjusted OR, 1.34 [95% CI, 1.02, 1.77; $P = 0.04$]). The association for fever was similar in magnitude but was not statistically significant (age-adjusted OR, 1.30 [95% CI, 0.96, 1.76; $P = 0.09$]). Vomiting and fever at one of the three IPT courses were both associated with increasing amodiaquine dose (adjusted ORs, 1.18 [95% CI, 1.03, 1.35; $P = 0.02$] and 1.29 [95% CI, 1.13, 1.49; $P < 0.001$], respectively). The predicted probabilities of vomiting and of fever over the course of three IPT doses according to AQ dose is shown in

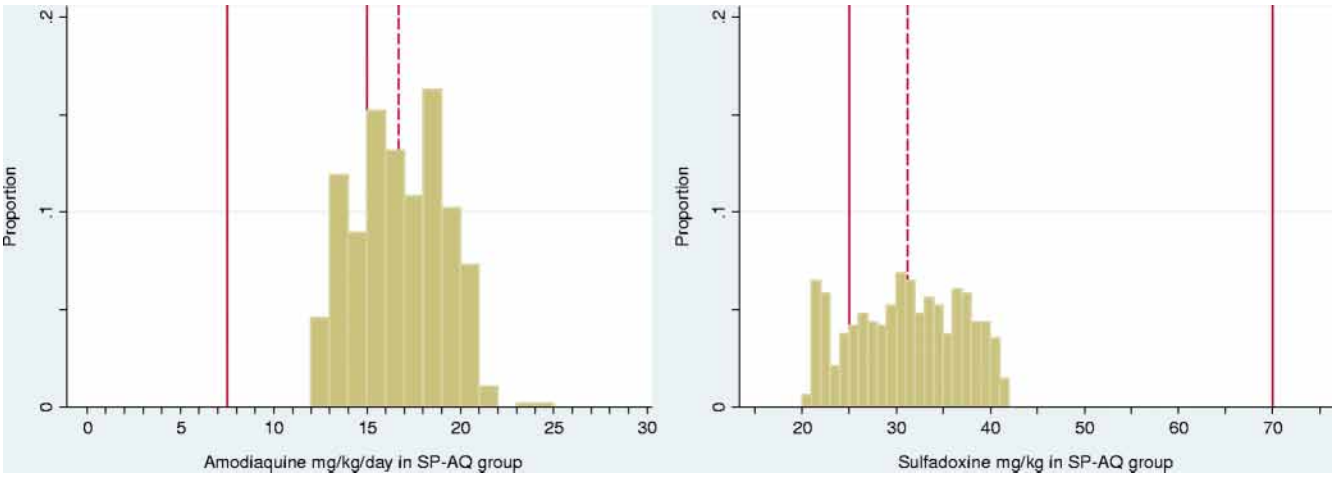

FIG. 2. Amodiaquine and sulfadoxine dosage in the SP-AQ group in Niakhar. Dose is shown in mg/kg/day. Solid lines indicate the recommended dosing range (7.5 to 15 mg/kg/day AQ and 25 to 70 mg/kg SP). The dashed line indicates the median dose.

Fig. 3. A similar pattern was seen for the dose at the September IPT round.

Predicted dosing accuracy for amodiaquine with alternative regimens. The accuracy of different dosing regimens when applied to the anthropometric data set from the 2004 trial is shown in Fig. 4. As occurred in practice, it is predicted that the regimens used in Niakhar (150 mg to children <12 kg and 250 mg to children ≥12 kg) and Keur Soce (100 mg to children <2 years and 200 mg to children ≥2 years) would result in a high risk of overdosing. Alternative approaches would be more accurate.

A switch to the currently available 153-mg tablets, broken in half for children under 2 years of age, would increase the proportion receiving a correct dose to 89.9% but would lead to underdosing in 7.3% of children. Switching to the regimen advocated by Taylor et al. for treatment (67.5 mg for infants and 135 mg for children ≥1 year) would also be an improvement on the regimens used in the previous IPTc trials (89.0% would be correctly dosed and 7.5% overdosed). It is possible to increase the dosing accuracy of this regimen by inclusion of an intermediate dose of 100 mg for 1-year-old children: this results in 95.8% of children receiving the correct dose, with 3.6% underdosed and 0.6% overdosed.

The best concentration for a single tablet that is halved for children under 2 years of age would be 162 mg. With this tablet size, 90.2% of children would receive the correct dose. This is only a modest improvement on that which would be achieved with the existing 153-mg tablet. However, only 4.1% would be underdosed. If two separate tablet sizes can be given to children under five, the best tablet concentration would be 95.5 mg for children <2 years and 144 mg for children ≥2 years. With this regimen, 97.7% could be dosed correctly, with only 0.6% underdosed and 1.7% overdosed. With three separate tablet sizes, a further improvement can be made by creation of a separate dose for infants and 1-year-old children (86 mg for infants, 100 mg for 12 to 23 months, 144 mg for ≥2 years). Addition to the three-tablet regimen of a fourth tablet for 4-year-old children (161 mg) would reduce the amount of underdosing to a very low level. The overall improvements of using three or four tablets over using a two-tablet regimen are quite small.

Predicted effect of alternative regimens on the incidence of adverse events. The predicted proportion with AEs using the alternative regimens are shown in Table 3. Predictions shown are from regression models with the effect of dose adjusted for age. All regimens would be a substantial improvement on the regimen used in the Niakhar study. For a number of the alternative regimens, the probability of vomiting and experiencing fever at the

TABLE 2. Association of adverse events with amodiaquine dosage in Niakhar

Time and parameter or AE	% (no.) of results					OR per 2-mg/kg/day increase (95% CI)		Adjusted *P* value
	At amodiaquine dose, mg/kg/day, of:				For all children	Without age adjustment	Age adjusted	
	<15	15–17	17–19	>19				
September								
n	127	131	130	91	479			
Vomiting	0.8 (1)	2.3% (3)	3.8 (5)	5.5 (5)	2.9 (14)	1.78 (1.04, 3.04)	2.07 (1.13, 3.79)	0.019
Fever	0.8 (1)	3.1 (4)	2.3 (3)	4.4 (4)	2.5 (12)	1.5 (0.86, 2.61)	1.8 (0.98, 3.3)	0.058
Rash	0 (0)	0 (0)	0.8 (1)	0 (0)	0.2 (1)			
At any IPT								
n	128	131	131	92	482			
Ever vomited	7 (9)	9.2 (12)	15.3 (20)	16.3 (15)	11.6 (56)	1.41 (1.08, 1.83)	1.53 (1.14, 2.06)	0.005
Ever febrile	6.3 (8)	10.7 (14)	9.9 (13)	21.7 (20)	11.4 (55)	1.54 (1.17, 2.02)	1.73 (1.3, 2.31)	<0.001
Ever had rash	0.8 (1)	0 (0)	0.8 (1)	2.2 (2)	0.8 (4)			

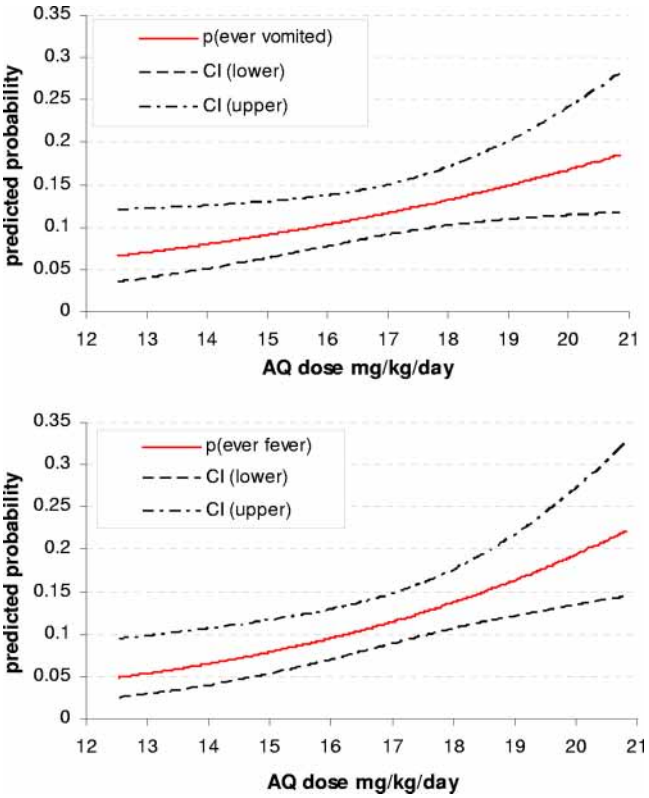

FIG. 3. Predicted probability of vomiting or fever by AQ dose. The predicted probability (plus 95% CI) is shown for vomiting (ever vomited) or having fever (ever fever) at any of the three IPT doses according to the AQ dose received. For clarity, the predicted line for the effect of dose unadjusted for age is shown.

time of a single IPT dose was approximately half that predicted for the regimen used in Keur Soce. The predicted probability of vomiting or fever over the course of three IPT doses on the alternative regimens was approximately one-third lower.

The estimates for reductions in Table 3 may be conservative because it is assumed that all children with a dose of AQ lower than the bottom end of the fitted range (12.5 mg/kg/day) have the same probability of AEs as a child given that dose. It is probably the case that risk continues decreasing as dose decreases. Assuming that the regression line predicts accurately below the range (which seems plausible given that the line appears to fit best at the lower part of the range for which there is data), the predicted incidence would be lower. The alternative regimens could reduce incidence of AEs by up to two-thirds at a single IPT dose and approximately half over the course of three doses in 1 year (data not shown). In all cases the 95% CI for the reduction excludes zero, indicating a demonstrable benefit of switching regimens.

DISCUSSION

Findings. The age-based amodiaquine dosing regimen used in the Keur Soce trial resulted in a third of children receiving a dose above the recommended range. AQ dosage over 15 mg/kg/day was significantly associated with increased odds of vomiting in the 3 days following IPT. For each 1-mg/kg/day increase in AQ dose, the age-adjusted OR for vomiting was 1.13 (95% CI, 1.01, 1.26; $P = 0.04$). In Niakhar, dichotomizing dose based on body weight <12 kg or ≥ 12 kg resulted in 73.5% of children being given over the recommended AQ dose. For each 1-mg/kg/day increase, the age-adjusted OR for vomiting in September increased by 1.34 (95% CI, 1.02, 1.77; $P = 0.04$) and the odds ratio for experiencing vomiting or fever over the course of a whole season of IPT increased by 1.18 (95% CI, 1.03, 1.35; $P = 0.02$) and 1.29 (95% CI, 1.13, 1.49; $P < 0.001$), respectively. Results from the two studies are therefore consistent with the idea that with more accurate dosing by age it would be possible to improve the tolerability of SP-AQ.

Currently available AQ tablets do not have the optimum AQ content for dosing by age in children. If the present approach of using a single tablet that is broken in half for children under two is to be continued, then the existing 153-mg AQ tablets would be preferable to 200-mg tablets. Theoretically, 162-mg tablets would be a better choice for IPT in children under 5 years of age, since this minimizes underdosing. A better approach would be to manufacture two separate tablets: 95.5 mg for children under 2 years of age and 144 mg for older children. This regimen does not seem inherently more complicated to deliver than the existing approach, and it would remove the need to break tablets. With this approach, almost 98% of children would receive a dose within the correct range and very few children (0.6%) would be underdosed. The additional complexity of three or four different tablets does not seem worthwhile because the improvements over the two-tablet regimen are very small.

A number of the alternative regimens considered would reduce the incidence of adverse events to a similarly low level. At a single round of IPT, a conservative prediction is that incidence of vomiting and fever would be approximately half that predicted for the age-based regimen used in Keur Soce and that over the course of three rounds of IPT, incidence of these AEs would be reduced by approximately a third. The alternative regimens might actually reduce incidence of AEs by as much as two-thirds at a single IPT dose and by approximately half over a yearly course of three doses. However, some of the alternative regimens result in underdosing becoming a problem. Depending on what is feasible to implement, the option that minimizes underdosing as much as possible while keeping AEs low should therefore be chosen.

Limitations. The concentration of amodiaquine used in the regression models is based on the dose that children were given by the health worker. Although this is the best estimate possible with these data, it would have been of interest to also examine the association between blood concentrations and adverse events. The approach used here may still be of value because depending on whether vomiting occurs relatively soon after treatment (resulting in loss of drug) or once AQ has been absorbed, blood concentrations might depend on vomiting as well as vice versa. It may be possible to examine this further in future IPTc studies.

The incidences of adverse events were quite different in Keur Soce and Niakhar, Senegal. In Keur Soce, more AEs were reported than in the Niakhar study, despite the prevalence and extent of overdosing being lower. Given the relatively high incidence of AEs in children given piperaquine regimens in Keur Soce (5) and findings from other

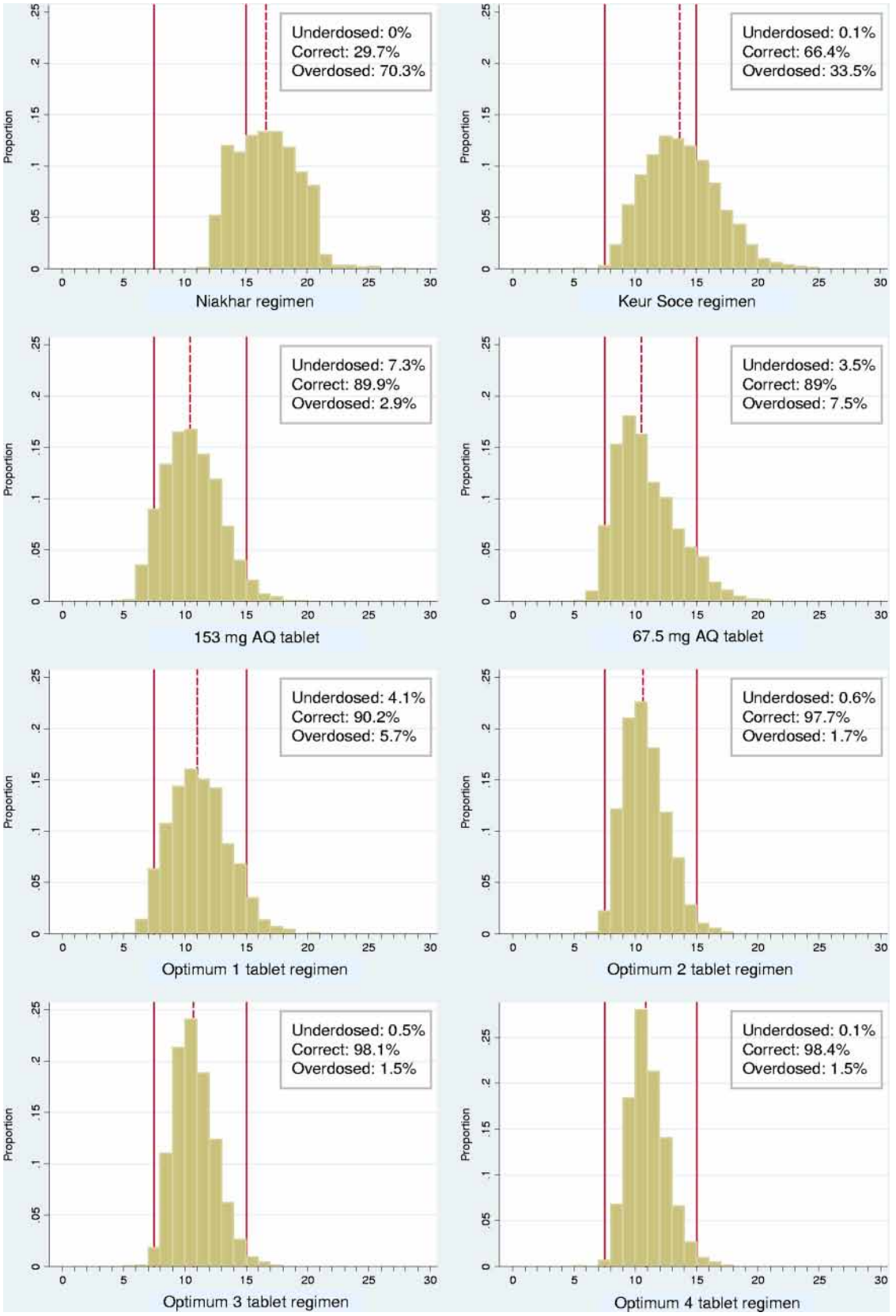

FIG. 4. Dosing accuracy with existing and optimal alternative regimens. Histograms of the predicted dosing accuracy with regimens used in the two IPTc trials, existing alternative regimens, and optimum regimens are shown. Tablet strengths and age cutoffs for the regimens are given in the text. Dose is shown in mg/kg/day. Solid lines indicate the target dosing range for AQ. The dashed lines indicate the median daily dose.

TABLE 3. Predicted percentage of children with vomiting and fever with alternative regimens

Regimen and condition[a]	% predicted incidence (95% CI)[b]			
	Vomiting at one round of IPT	Vomiting during one season of IPT	Fever at one round of IPT	Fever during one season of IPT
Currently available regimens				
Niakhar	2.82 (1.48, 4.38)	11.3 (8.53, 14.1)	2.35 (1.16, 3.83)	11.4 (8.76, 14.0)
Keur Soce	1.47 (0.49, 2.93)	8.15 (5.45, 11.4)	1.27 (0.47, 2.44)	7.66 (5.3, 10.1)
153-mg tablet	0.8 (0.09, 2.63)	6.05 (3.02, 10.24)	0.76 (0.12, 2.14)	4.42 (2.14, 7.44)
Taylor et al. (67.5-mg tablets)	0.82 (0.09, 2.62)	6.18 (3.15, 10.29)	0.76 (0.12, 2.14)	4.62 (2.42, 7.6)
Theoretical regimens				
Optimal (1 tablet)	0.85 (0.11, 2.64)	6.24 (3.25, 10.33)	0.8 (0.15, 2.14)	4.76 (2.45, 7.71)
Optimal (2 tablets)	0.77 (0.08, 2.62)	5.96 (2.91, 10.18)	0.75 (0.11, 2.12)	4.22 (1.97, 7.32)
Optimal (3 tablets)	0.77 (0.08, 2.62)	5.94 (2.9, 10.17)	0.74 (0.11, 2.12)	4.23 (1.97, 7.32)
Optimal (4 tablets)	0.77 (0.08, 2.62)	5.95 (2.91, 0)	0.75 (0.11, 2.13)	4.24 (1.98, 7.32)
Absolute reduction vs Keur Soce regimen (%)				
Currently available				
153-mg tablet	0.63 (0.06, 1.09)	2.04 (0.58, 3.19)	0.47 (0.06, 0.87)	3.12 (1.72, 4.57)
Taylor et al. (67.5-mg tablets)	0.61 (0.06, 1.06)	1.93 (0.54, 3.01)	0.47 (0.06, 0.87)	2.93 (1.59, 4.46)
Theoretical regimens				
Optimal (1 tablet)	0.58 (0.06, 1.01)	1.84 (0.52, 2.89)	0.43 (0.05, 0.81)	2.81 (1.54, 4.10)
Optimal (2 tablets)	0.65 (0.07, 1.14)	2.14 (0.61, 3.32)	0.48 (0.06, 0.90)	3.32 (1.84, 4.86)
Optimal (3 tablets)	0.65 (0.07, 1.14)	2.15 (0.62, 3.34)	0.48 (0.06, 0.90)	3.32 (1.84, 4.86)
Optimal (4 tablets)	0.65 (0.07, 1.13)	2.14 (0.61, 3.33)	0.48 (0.06, 0.90)	3.31 (1.83, 4.85)

[a] AQ dose in mg/kg/day for the regimens with currently available tablets are as follows: Niakhar, <12 kg, 150 mg; ≥12 kg, 200 mg; Keur Soce, <2 years, 100 mg; ≥2 years, 200 mg; 153-mg tablet, <2 years, 76.5 mg; ≥2 years, 153 mg; Taylor et al. (135-mg tablet), <1 year, 67.5 mg; ≥1 year, 135 mg. For the optimal regimens, the dose schedules in mg/kg/day are as follows: 1 tablet, <2 years, 81 mg; ≥2 years, 162 mg; 2 tablets, <2 years, 95.5 mg; ≥2 years, 144 mg; 3 tablets, <1 year, 86 mg; ≥1 year and <2 years, 100 mg; ≥2 years, 144 mg; 4 tablets, <1 year, 86 mg; ≥1 year and <2 years, 100 mg; ≥2 years and < 4 years, 144 mg; ≥4 years 161 mg.

[b] Probabilities are shown for vomiting and fever at individual rounds and during the course of one season (three doses of IPT). Note that predictions for doses outside the range of the Niakhar data (<12.5 mg/kg/day and >21 mg/kg/day) are assumed to be equal to the doses at the extent of the range.

studies using AQ (e.g., references 3 and 13), it appears likely that AEs were overreported in Keur Soce rather than underreported in Niakhar. Direct questioning following treatment with AQ in Burkina Faso led to a very high number of reported AEs (around 75% reported at least one symptom), but none of these were probably or definitely related to the treatment given (13). AEs that were classified as being possibly related to treatment were around 6%, similar to the result in Niakhar. These discrepancies suggest that a standardized protocol for assessment of adverse events might be a useful way to improve the comparability between trials in different settings. Despite the differences in the incidence of adverse events between the two studies, increased incidence with increasing dosage of AQ was a consistent finding. These findings are also consistent with results from other studies of amodiaquine in young children (3; Bojang et al., unpublished data).

It does not seem plausible that the partner drug, SP, is to blame rather than AQ, because SP was accurately dosed within published guidelines and SP with artesunate was very well tolerated (14). SP has also been shown to be safe and well tolerated as a monotherapy when used for intermittent preventive treatment in infants (1).

In Niakhar, where the incidence of adverse events seems more plausible, the lowest AQ dose was 12.5 mg/kg/day. Since this was a retrospective analysis, it was not possible to test the tolerability of the alternative schedules in practice. It is therefore not certain whether lower doses would be progressively better tolerated, although this seems plausible because a recent trial of IPTc using SP-AQ dosed by weight (target AQ dose, 10 mg/kg/day) reported that the intervention was well tolerated with little vomiting after treatment (Bojang et al., unpublished data). Consequently, the analysis that assumed that doses below 12.5 mg/kg/day would have the same probability of an AE is probably conservative. When this condition was relaxed, the advantage of alternative regimens increased.

The calculation of the optimum tablet strength may be influenced by the particular characteristics of the weight-for-age data set. This wider applicability of this analysis will depend on how representative this sample is of children in countries where malaria is endemic. Encouragingly, these data predicted exactly the same optimum amodiaquine tablet strength as the much larger data set used by Taylor et al. (16) when the same constraints were used (data not shown). Even if the tablet strengths calculated in this study are not optimal everywhere, they may still offer an improvement on the AQ tablet concentrations that are widely available (67.5 mg, 153 mg, and 200 mg). Furthermore, optimal tablet concentration may be just one of several differences between sites that will deploy IPTc. The approach used here to determine the optimal concentration is simple and could easily be used to suggest optimal tablet concentration in areas where constraints are different (e.g., where health workers are accustomed to distinguishing between infants and older children rather than children around 2 years of age), as long as accurate and representative weight-for-age data are available.

Interpretation. The risks of both vomiting and fever increase steadily with increasing amodiaquine dose. Although vomiting

is a more commonly reported AE in treatment studies (8), AQ-related fevers may be more obvious when amodiaquine is used for prevention rather than for treatment of malaria, when fever would usually be attributed to disease rather than the drug itself. Consequently, the aim should be to avoid doses higher than that which is necessary to provide adequate protection. By adopting this approach, the tolerability of existing age-based SP-AQ regimens for IPTc could be improved with minimal changes to existing health worker practice. If it is possible to use two tablets rather than using a single tablet which is halved for young children, this would provide a substantial further improvement.

Although SP-AQ can be much more accurately dosed, some problems with tolerability are likely to persist. This analysis did not indicate a safe dose below which there would be no risk of adverse events (Fig. 3), and even the best-tolerated alternative regimens would retain a low level of vomiting and fever associated with treatment. For example, the predicted incidence of vomiting over three IPT doses would be at least 4%, which is between two and three times as much as for SP with artesunate (14). A further obstacle is the bitter taste of the AQ tablets, which is particularly problematic because AQ requires a 3-day course, with two doses usually unsupervised; full adherence to this regimen can be low (15). It is therefore important to consider these measures as a means to improve the success of IPTc with SP-AQ while better-tolerated regimens are developed.

The present study addresses only the incidence of relatively common mild adverse reactions to amodiaquine. Severe adverse reactions such as neutropenia, agranulocytosis, and liver damage have previously been reported (7, 10). Pharmacovigilance systems will therefore need to be in place to monitor the safety of AQ when used for treatment and IPT.

Conclusion. The accuracy of age-based amodiaquine dosing for IPTc could be substantially improved over that used in previous studies. The best option would be to give 95.5 mg AQ/day to children under 23 months of age and 144 mg AQ/day to children 2 years of age and over, which would result in very few children being underdosed. Importantly, this change in regimen would also keep overdosing to a very low level, reduce the severity of what overdosing remains, and bring the dose that most children receive very close to the recommended level of 10 mg/kg/day. This would be expected to reduce the incidence of vomiting and fever after treatment and improve the tolerability of IPT using SP-amodiaquine.

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