Age-based dosing, duration of protection, and predicted cost effectiveness, of IPTc (SMC). 22pp.

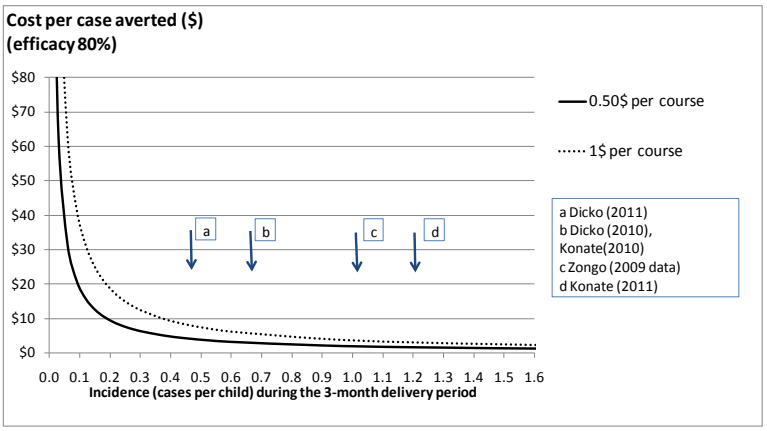
Predicted cost effectiveness of IPTc in relation to malaria transmission intensity
Duration of protection
Time to breakthrough with episodes of severe malaria
Age-based dosing of amodiaquine and sulfadoxine-pyrimethamine for IPTc

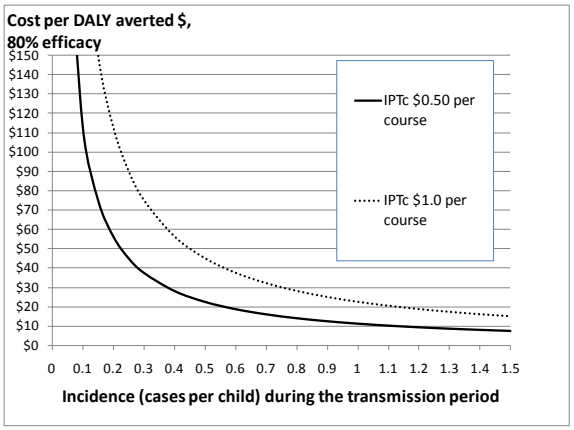
An edited version of these analyses, without the tables, was included in a report compiled by the IPTc working group (Matthew Cairns, Lesong Conteh, Diadier Diallo, Tini Garske, Azra Ghani, Brian Greenwood, Paul Milligan, Arantxa-Roca Feltrer, Anne Wilson) in 2011 for the Technical Expert Group on Chemoprevention.

Predicted cost effectiveness of IPTc in relation to malaria transmission intensity:

To understand how the cost effectiveness of IPTc may be expected to change depending on the level of transmission, the cost per case averted, and cost per DALY averted, can be predicted for a given malaria incidence rate, efficacy, and unit cost per course of IPT treatment using a simple calculation. If the incidence during the three months of the peak transmission period, without IPTc, is 400 cases per 1000 children (a rate of 0.4 per child), and if IPTc has an efficacy of 80%, 320 cases would be averted, and on the basis of a cost of 0.5$ per course, the cost would be 1000x3x0.5$=1500$ for three monthly courses of treatment, so the predicted cost per case averted is 1500/320=$4.69. (Note that it does not matter here what proportion of children received 1, 2 or 3 courses of treatment because the cost is expressed per course administered). The predicted cost per DALY averted (see endnote for details)[i] is $28.

The graphs show the predicted cost per case averted and cost per DALY by IPTc, if the cost per course is 0.5$ or 1$, (corresponding to a cost per child per year of 1.5$ and 3$ respectively), assuming 80% efficacy of IPTc (defined as the percentage reduction in the number of malaria episodes during the three months of IPTc administration, due to IPTc). To put the incidence rates on the x-axis into perspective, the incidence of malaria during the transmission period in children in the control group in recent IPTc trials in Mali (Dicko *et al.* 2010, 2011) and Burkina Faso (Konate *et al.* 2010, 2011; Zongo, unpublished), is shown by vertical arrows[ii].





1$ per course (3$ per child per year) represents a conservative upper limit (it is unlikely costs would exceed this in practice). The cost of delivery in the large scale Senegalese study was 0.5$ per course (1.5$ per child per year), this is an estimate of the financial cost to the provider (the direct cost of delivery in financial terms), obtained from exhaustive documentation of all expenditures from a detailed study in 54 health facilities, it does not include full economic costs which should also include the opportunity cost of staff time and other resource use, (these are currently being evaluated), these should be allowed for when comparing with published costs for ITNs which are based on full economic costs. In The Gambia (Bojang *et al.* 2010), the economic cost of IPTc delivery by community health workers was $1.66 per child per year, adjusted for non-compliance. Conteh *et al.* (2010) estimated economic costs per child of $1.86 to $4.33 (2008 US$) per child per year from a study in Ghana, however these estimates were model-based using data derived from a clinical trial and the upper limit corresponds to children who were given up to 6 monthly treatments with an ACT. Goodman *et al.* (2000) estimated the economic cost of seasonal fortnightly chemoprophylaxis delivery as 1.79$ (adjusted to 2010 US dollars) per child per year adjusted for non compliance, with a 90% range from 1.40$ to 2.20$, assuming that an existing system of village health workers could be used.

To compare these figures with the economic cost per case averted by ITNs, the studies by Mueller *et al.* (2008) (national distribution of LLITNs) and Bhatia *et al.* (2004) (ITNs, low incidence setting) have been used, with costs adjusted to 2010 US $, both studies present gross intervention costs from the provider perspective only (savings due to prevented cases have not been subtracted) and therefore can be directly compared with the IPTc estimates. Mueller *et al.* estimated the costs of country-wide delivery of long-lasting insecticide-treated bednets to children nine months to five years of age, as part of the 2004 measles vaccination campaign in Togo, and calculated cost per case averted on the basis of incidence rates (without the intervention) of 0.24, 1.2 and 1.7 episodes per child per year, and cost per DALY averted for an incidence rate of 1.2 per year. It was assumed nets last for 3 years. Bhatia *et al.* estimated cost per case averted from a cluster randomized trial in a low incidence setting in India (61.5 episodes per 1000 persons per year), comparing ITNs or IRS with a control group that received only case management. It was assumed nets last 4 years and have to be treated each year.

If incidence is over 1 per child during the main transmission period, the predicted cost per DALY averted for IPTc is less than 11$, based on a cost per course of treatment administered of 0.5$, and less than 22$ if the cost per round is as high as $1. Similar results were obtained when the efficacy of IPTc was assumed to be 90% and 70%, and when DALYs were calculated without age weighting. Mueller *et al.* estimated the cost per case averted for LLITNs in Togo was 5$ (adjusted to 2010 $), for an incidence of 1.2 per child per year, 3.5$ for an incidence of 1.7 per child per year, and 25$ when the incidence was 0.24 per child per year. Cost per DALY averted, for an incidence of 1.2 per child per year, was 25$ (this was not age-weighted, but the age-weighted figure was very similar). When incidence was 0.06 per child per year, Bhatia et al. estimated a cost per case averted of ITNs was 71$ (adjusted to 2010). The review by Goodman *et al.* (2000) presented cost per DALY averted for a number of malaria control interventions. They considered situations where the incidence of clinical malaria was assumed to be in the range from 1 to 2.9 episodes per child per year, for children 1-4yrs of age, and they assumed net coverage would be low, and assumed nets would need to be treated. They obtained estimated cost per DALY averted of ITNs of from $19 to $85 (24$ to 108$ in 2010$). Because of the high efficacy of IPTc, the cost per case and per DALY averted is comparable with ITNs even though the intervention effect is only for three months.

Based on recommendation of the Ad Hoc Committee on Health Research Relating to Future Intervention Options (WHO, 1996), interventions costing less than $150 per DALY averted should be considered "attractive" and those costing less than $25 per DALY averted should be considered as "highly attractive". Inflated to 2010 $, these correspond to about 215$ and 36$ respectively. The Word Bank has suggested that in a particular country, a health intervention may be considered cost-effective if it secures a year of healthy life at a cost less than the national average per capita Gross Domestic Product; WHO guidelines state that 1 GDP per capita is considered very cost-effective; 1–3 × GDP per capita is considered cost-effective; >3 × GDP per capita is considered not cost effective (WHO-CHOICE 2011). The GDP per capita for Sahel countries in 2009 ranged from $600 (Niger, Sierra Leone and Guinea Bissau) to 2100$ (Mauritania, Nigeria) and 2300$ Cameroun) (World Bank Development Indicators, 2011).

For incidence rates above 0.1 per child, costs per DALY averted are substantially below the GDP per capita. If incidence is over 0.1 per child during the transmission period, the discounted cost per DALY averted is less than 215$ if the cost per course administered is less than 0.95$ per course administered, if incidence is 0.2 per child, the cost per DALY averted is about 56$ if the cost per course is 0.5$, and $112 if the cost per course is as high as $1. If incidence is above 0.3, the cost per DALY averted is less than $36 if the cost per course is 0.5$. From the graph, as incidence falls below about 0.2 episodes per child the cost per DALY averted rises steeply. Where incidence during the transmission period is 0.2 episodes per child or more, IPTc is expected to be highly cost effective. Where incidence is between 0.1 and 0.2, IPTc (and other malaria interventions), is less cost effective, but IPTc may be considered worthwhile in some situations, and where incidence is lower than 0.1 it is less likely that IPTc would be considered cost effective.

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[i] Cases and DALYs averted were calculated as follows:
The DALY is an aggregate measure of the burden of disease in a population, equal to the number years of life lost plus the number of years spent with disability, due to the disease. The number of DALYs averted by an intervention, and the cost per DALY averted, are convenient measures for comparing impact and cost effectiveness of interventions. The crude number of years of life lost due to a death at age a is considered to be L-a, where L is the life expectancy at birth without the intervention. For a death at age 2.5 years in a population with life expectancy at birth of 55 years, the crude number of years of life lost is 52.5. Each year of the life that is lost, or saved by preventing the death, is not considered to have equal value, most studies apply age weighting to give less weight to very young and old ages and more weight to young adulthood. In addition, a further weighting (time discounting) is used to give more weight to time periods near the present than far in the future. The age weights used in the Global Burden of Disease publications (Mathers *et al.*, 2006) give maximum weight at 25 years of age, and a 3% discount rate is used, so each successive year from the present has 3% less weight. With these weightings, each death at 2.5 years of age, in a population with life expectancy at birth of 55 years, has a DALY value of 32.8 years. To the total DALYs due to deaths, must be added the total time spent unwell, for malaria it is standard to assume the illness lasts 2 weeks, and a disability weight of 0.211 is attached to malaria illness, so 100 malaria episodes would contribute 100x0.211x2/52=0.81 years to the total number of DALYs (age weighting and time discounting become irrelevant for such a short duration). The effect on deaths therefore dominates the DALY estimate.

The total DALYs for a population of children over one year, in which there are D malaria deaths and N malaria cases, is estimated as (Murray and Acharya 1997):

$$DxC.e^{ra}(e^{(r-\beta)a}(1+(r+\beta)a)-e^{(r+\beta)(L+a)}[1+(r+\beta)(L+a)])/[(r+\beta)^2] + (N\text{-}D)x0.0081$$

Values of $\beta=1/25$ per year; $C=0.1665$; $r=0.03$, those used by GDB publications, have been used. 2009 estimates of the expectation of life at birth (L) range from 48 for Chad, to 62 (Senegal). An average value of the expectation of life at birth (mean weighted by population living in areas suitable for IPTc) of 55 has been used (without using separate values for males and females). Malaria cases

and deaths are assumed to occur at an average age of 2.5 years. No allowance has been made for indirect effects of malaria on mortality, so the DALYs may be underestimated. Effects of sequelae and malaria-related anaemia have been ignored. The approach does not take account of rebound effects, nor of cumulative benefits of several years of protection. The number of deaths per 1000 without IPTc is $1000\lambda p/f$, where λ is the incidence rate of malaria during the transmission season, f is the proportion of cases that occur in three months of the year, p is the proportion of cases that result in death, assumed to be 0.005. With IPTc, the number of deaths per 1000 is $1000\ \lambda p[1-E+(1-f)/f]$, where E is the efficacy. The number of cases that survive is $1000\ \lambda(1-p)/f$ without IPTc and $1000\ \lambda(1-p)[1-E+(1-f)/f]$ with IPTc. The number of cases averted per 1000 is $1000\lambda E$ and the number of deaths averted $1000\lambda pE$, the proportion of cases, deaths and DALYs averted is Ef. Note the cost effectiveness of IPTc does not depend on the degree of seasonality (only on the incidence rate without IPTc during the three month period of administration) - cost effectiveness measures do not capture the extent to which interventions reduce the total malaria burden. Efficacy of IPTc is similar in children using ITNs and those not using ITNs, and high efficacy was obtained in trials where children were all given LLITNs, so the cost effectiveness predictions can be considered to reflect cost effectiveness without or in addition to ITNs.

[ii] The incidence rates in children in recent studies in Mali and Burkina Faso are as follows. In Kati district, Mali, in 2008 (Dicko *et al.* 2010), 1508 children in the control group of an IPTc trial were followed up, there were 672 episodes of malaria with parasitaemia of at least 5000/μL) detected in 3.5 months of the main transmission period, a rate per child of about 0.45. In the second year (Dicko *et al.* 2011), 1406 of the children were followed, and there were 914 episodes during the transmission period, a rate of 0.65 per child. In Kourweogo province, Burkina Faso, in the control group of the trial by Konate *et al.* (2010), in the first year (2008), 1505 children were followed, there were 982 malaria episodes during the transmission period, a rate per child of 0.65. In the same group of children in a second year, 1399 children were followed and there were 1659 malaria episodes during the transmission period, a rate per child of 1.2. (The actual rates are slightly higher than this because some children were lost to follow-up). In western Burkina Faso in 2009, 250 children were followed for two months of the transmission period, there were 254 malaria cases with high parasitaemia, a rate of about 1 per child (I Zongo, unpublished data). The predicted cost per case averted by IPTc for these situations, assuming a cost per course of either 0.5$ or 1$, would be as follows:

Predicted cost per case averted, $

Cases per child during the transmission period:	$ per course	Efficacy: 50%	60%	70%	80%	90%
0.45	0.5	$6.67	$5.56	$4.76	$4.17	$3.70
(Kati district, Mali, 2009)	1.0	$13.33	$11.11	$9.52	$8.33	$7.41
0.65	0.5	$4.62	$3.85	$3.30	$2.88	$2.56
(Kourweogo province, Burkina Faso, 2008; Kati district, Mali, 2009)	1.0	$9.23	$7.69	$6.59	$5.77	$5.13
1.0	0.5	$3.00	$2.50	$2.14	$1.88	$1.67
(Western Burkina Faso, 2009)	1.0	$6.00	$5.00	$4.29	$3.75	$3.33
1.2	0.5	$2.50	$2.08	$1.79	$1.56	$1.39
(Kourweogo province, Burkina Faso, 2009)	1.0	$5.00	$4.17	$3.57	$3.13	$2.78

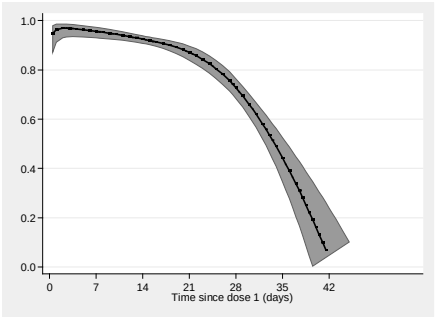
Duration of protection:

To minimise selection for resistance and maximise protection, it is desirable to choose dosing intervals such that protection is sustained throughout the transmission period. It is also desirable that protection persists into the period just after transmission has stopped to minimise the scope for parasites to be exposed to sub-therapeutic levels of IPT drugs as concentrations of the drugs decays after the last treatment course. It is therefore important to estimate the duration of protection when SPAQ is used for IPTc in order to confirm the optimal interval between successive treatments. Protection in infants when SP is used for IPTi persists at a high level for about 5 weeks, and then decays rapidly (Cairns et al 2008). Resistance to SP is likely to shorten the duration of protection, the combination of SP with AQ may therefore be expected to prolong protection, but duration of protection may also be influenced by pharmacokinetic factors which may differ between infants and older children. Cumulative efficacy over three months was greater when SP+AQ was used for IPTc than SP combined with artesunate (Sokhna et al 2008), this may reflect a longer protective effect of SP+AQ. Scope for estimating duration of protection when SPAQ is used for IPTc is limited because doses are given on month apart and the last dose is timed to give protection until the end of the transmission period, in the large trials in Burkina Faso and Mali (Konate *et al.* 2011 and Dicko *et al.* 2011) the level of protection up to about 5 to 6 weeks could be estimated because the interval between rounds varied, ranging from about 25 to 35 days, and surveillance continued for 6 weeks after round 3 during which time there continued to be some malaria cases. The data for the three months was combined, each month was considered a stratum, and in each stratum analysis was limited to those children who received at least the first day's doses that month (SP and at least the first of the daily doses of AQ). Malaria was defined as fever or history of fever with any parasitaemia, detected by passive case detection or when the child was seen for the next IPT round. Observations were censored after the first episode or the date of the first day of the next IPT round (for months 1 and 2) or on the last day of follow-up (for month 3). To obtain an estimate of the protective efficacy as a function of time since the first dose, a Cox model was fitted, with a cubic spline function for the intervention effect. This is a flexible function which gives a smoothed estimate of the proportionate reduction in risk at each time point, to show graphically how the protective effect changes over time. Piecewise constant models were also fitted, to estimate the cumulative efficacy over periods of 2, 3, 4 and 5 weeks after treatment, this provides an estimate of the proportionate reduction in the number of malaria episodes in those time periods, (among those who receive at least the first day's doses that month).

A high level of protection was maintained for 4 weeks, thereafter protection decayed rapidly. The cumulative efficacy over 21 days was 91% and over 28 days 86%. This supports the choice of monthly intervals for IPTc administration with SP+AQ. Children who miss the next monthly round will have some limited protection in the fifth and six weeks. Where each IPTc round of administration takes more than one or two days it is desirable to visit villages in approximately the same sequence each month in order maintain intervals of approximately one month between treatment courses for most children. When different age groups were considered, cumulative efficacy over 28 days was higher in infants and somewhat lower in older children, which may reflect a longer duration of protective effect in the younger age groups. This is consistent with observations by Adjei et al. (2010) who found that clearance of desethylamodiaquine in children was related to bodyweight, with higher total exposure to desethylamodiaquine in children with low bodyweight. These findings indicate there is scope to select age-based dosing that results in somewhat lower doses of amodiaquine in infants relative to older children, in order to limit incidence of vomiting which is most common in infants.

Duration of protection: A - smoothed estimates of the efficacy (percentage reduction in risk) at each time point after dose 1, the band shows pointwise 95% confidence limits. The protective effect decays rapidly after about 3-4 weeks. B – protective efficacy, plotted separately for each age group. C - cumulative efficacy (proportionate reduction in number of malaria episodes) over 2-5 week periods post treatment (with 95% confidence interval) 0-2 weeks, 0-3 weeks, 0-4 weeks and 0-5 weeks, cumulative efficacy (all age groups combined). D – cumulative efficacy over the same periods, by age group.

A)



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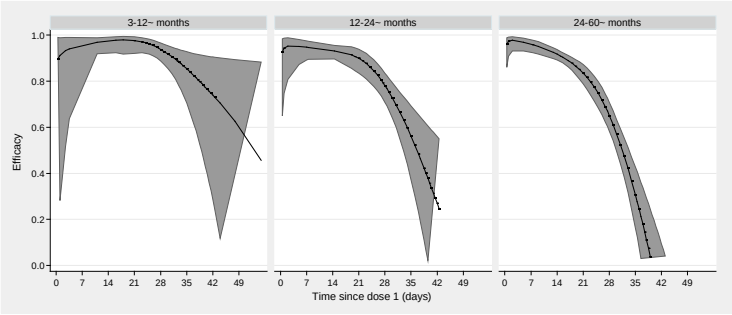
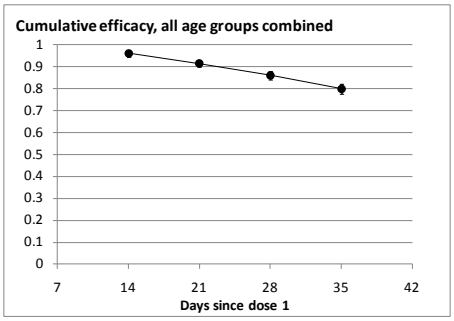
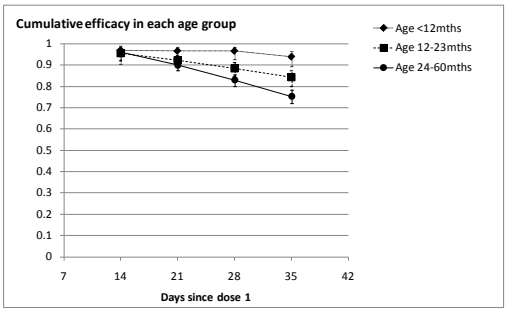


C)



D)



Time to breakthrough with episodes of severe malaria

During the course of the large IPTc trials conducted in Burkina Faso and Mali in the 2009 malaria transmission season, 26 children had an illness which met the WHO definition for severe malaria, 17 in Burkina Faso and 9 in Mali. Twenty -two of the 26 children were in the placebo group. The most frequent manifestation of severe malaria was cerebral malaria which was seen in 12 children (11 in the placebo and 1 in the IPTc group) and severe anaemia (Hb < 5 g/dl) which was recorded in 5 children (4 in the placebo and 1 in the IPTc group). Four children had respiratory distress, all in the placebo group, and one child, also in the placebo group, was jaundiced.

In Mali, there were no cases of severe malaria in the IPTc group. In Burkian Faso, three of the four children with severe malaria in the IPTc group did not receive any doses of IPTc. The fourth child had not received any IPTc before he developed cerebral malaria and received only one course of IPTc after recovery from his illness. All four children had malaria on or shortly before the date of the first round of IPTc and were treated with either coartem or ASAQ, one developed severe malaria before the next round, three were treated again for malaria shortly before the second round, and therefore did not receive IPTc, and developed severe malaria before the date of IPTc round 3.

The pooled estimated of protective efficacy against severe malaria in these trials was 82% (95%CI: 48–94%), this estimate is consistent with the high protective efficacy of IPTc with SPAQ against uncomplicated malaria, but the confidence interval is wide, it is therefore reassuring that no episodes of severe disease were seen among children who had received IPTc treatment courses.

Sign and symptoms of episodes of severe malaria during the intervention period August 2008 - November 2008

	Burkina Faso		**Mali**		**Overall**	
	Placebo N=13	IPTc N=4	Placebo N=9	IPTc N=0	Placebo N=22	IPTc N=4
	n	n	n	n	n (%)	n (%)
Severe anaemia (Hb<5)	3	1	1	0	4	1 (25.0)
Altered consciousness	7	1	4	0	11 (50.0)	1 (25.0)
Convulsion	3	1	4	0	7 (31.8)	1 (25.0)
Respiratory distress	2	0	2	0	4 (18.2)	0 (0.0)
Prostration	2	1	7	0	9 (40.9)	1 (25.0)
Circulatory collapse	1	0	0	0	1 (0.5)	0 (0.0)
Oedema	0	0	1	0	1 (0.5)	0 (0.0)
Hemoglobinuria	0	0	0	0	0 (0.0)	0 (0.0)
Jaundice	1	0	0	0	1 (0.5)	0 (0.0)

Severe malaria was defined based on an algorithm using the WHO standard definition (WHO, 2000)

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Age-based dosing of amodiaquine and sulfadoxine-pyrimethamine for IPTc:

Summary:
In most situations IPTc will be delivered by health workers in the community without access to weighing scales, a simple dosing scheme based on age group is therefore needed. To guide the choice of age-based dosing scheme for IPTc we have investigated the relationship between dose and efficacy and between dose and the risk of mild adverse events, using data from the large clinical trials in Mali and Burkina conducted in 2009 (Konate *et al.*, 2011 and Dicko *et al.*, 2011) and from Senegal (Sokhna et al. 2008 and unpublished data), and estimated the distribution of doses of amodiaquine and sulfadoxine-pyrimethamine for different age-based dosing schemes using age-weight data from these studies. Using these data, the optimum age-based dosing scheme for sulfadoxine-pyrimethamine is half a tablet for children under 12 months, and one tablet for children 12-59 months, this ensures the vast majority of children receive the recommended minimum dose of 25/1.25mg/kg sulfadoxine-pyrimethamine.

For simplicity of administration it is preferable to have the same age cutoff for amodiaquine and SP, the dosing scheme also needs to ensure as many children as possible receive an effective dose while keeping overdosing to a minimum. IPTc efficacy was related to the total dose of amodiaquine per kg bodyweight, this association was stronger among younger children. This highlights the importance of completing the course of treatment each month and of selecting a dose scheme that ensures children are not under-dosed. The most common adverse event after IPTc was vomitting, this was more common in infants and children 1-2 yrs, and in the first treatment round than in subsequent rounds. The incidence of vomiting varied greatly from study to study, with no association across studies between the proportion of children who vomited and the median dose of amodiaquine or the proportion of children receiving doses above 15mg/kg/day. Within studies, the risk of vomiting increased steadily with increasing dose, with an odds ratio of 1.3 (95%CI 1.2,1.4) associated with a 1mg/kg/day increase in dose. There was no evidence that there is a threshold dose associated with a marked increase in risk. Using a statistical model fitted to the data from the Burkina trial to predict the incidence of vomiting with different age-based dosing schemes, when age-based dosing with a switch from ½ tablet to 1 tablet at 24 months was compared to a scheme with a switch at 12 months, the estimated relative increase in risk of vomiting was 47%, regardless of the tablet strength used. Using age-weight data for 7928 children surveyed in Senegal, Mali and Burkina Faso before their first round of IPT treatment, it was estimated that a dosing scheme with ½ tablet for children under 12 months and 1 tablet for children 12-59 months, for both SP (500/25 mg tablets) and for amodiaquine (153mg tablets), would result in 99% of SP doses above the target minimum dose of 25/1.25mg/kg, and 80% of amodiaquine doses above the target dose of 10mg/kg/day, with 98% of total amodiaquine doses (over three days) in the range 23-66.5mg/kg. With this scheme, 22% of amodiaquine doses exceed 15mg/kg/day; the proportion of doses over 15mg could be reduced to 10%, while maintaining the proportion who receive less than the 7.5mg/kg/day less than 4%, if a tablet of 135mg (that would need to be manufactured specifically for IPTc) were used.

On the basis of these analyses the age-based dosing proposed for IPTc is consistent with age-based dosing guidelines for these drugs when used for malaria treatment (WHO 2006). There would be some advantage to manufacturing tablets specifically for IPTc, these could be packaged for infants and for children 12-59 months, avoiding the need to break tablets, with information for community health workers and mothers about the importance of completing the course each month, potential side effects, and the need to seek prompt treatment from health staff in the event of fever.

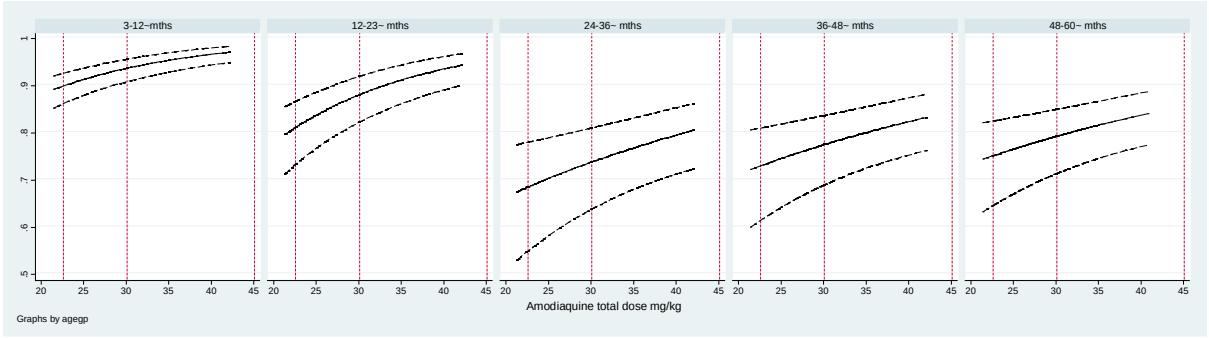
Current dosing recommendations:
Amodiaquine: The recommended dose of AQ is 10mg/kg/day for three days with a suggested therapeutic range of 7.5 to 15 mg/kg/day (i.e. 22.5-45 mg over three days, Taylor et al., 2006). No safe upper dose limit has been proposed but the upper limit of 15mg/kg was proposed on the basis of unpublished data that indicated increased incidence of vomiting in children given AQ at a mean dose of 15mg/kg. For age-based dosing of amodiaquine-artesunate, ½ of a 153mg amodiaquine tablet for infants and 1 tablet for children 1-5 years is recommended (WHO 2006). A fixed dose combination of AQ and artesunate with tablets containing 67.5mg AQ (for infants), 135mg AQ (for children 1-5 years) and 270mg AQ (6-13 years) has been developed by Sanofi, designed to be used in age-based dosing, Taylor et al. found this dosing scheme gave optimum dosing accuracy for amodiaquine and artesunate when doses were predicted using reference data on weights for children under 5 years of age obtained for 21 African countries from DHS datasets.

Sulfadoxine-pyrimethamine: The recommended minimum effective dose of SP is 25/1.25 mg/kg in a single dose, with a suggested upper safe limit of 3.5mg/kg pyrimethamine (70mg/kg sulfadoxine) (Terlouw et al., 2003). A wide range of different age-based dosing schemes have previously been used for SP in treatment guidelines (Terlouw et al.), half a tablet of SP under 12months and 1 tablet 12-59 months is recommended in the most recent WHO guidelines, to minimise the probability of receiving a dose less than the recommended minimum dose of 25mg sulfadoxine/1.25mg pyrimethamine per kg, while avoiding doses over 70/3.5mg/kg, on the basis of predicted dose using the DHS data (ter Kuile personal communication).

Age-based dosing for IPTc:
To estimate the distribution of doses that would be received under different age-based dosing schemes, we have used data from a nutritional survey of 2000 children 6-59 months of age in Niakhar, Senegal in September 2004 (K Simondon, unpublished data), and age and weight data for 3000 children aged 3-59 months in the Mali trial and 3000 in the Burkina trial, both measured in August 2008. We have considered age-based dosing schemes with half or whole tablets, with two age bands, with the cut-off at either 12 or 24 months. The use of more than two age bands, or cutoffs at ages other than integer years, or quarter tablets, was avoided because dosing schemes may then be too complex or time-consuming for large scale delivery in the community. A further consideration was that it is desirable if possible to have the same age-based scheme for SP and amodiaquine. Amodiaquine (AQ) is most commonly available as tablets of 200mg or 153mg amodiaquine hydrochloride, and SP only as standard tablets of 500mg sulfadoxine 25mg pyrimethamine. Tablets could be manufactured specifically for IPTc so we have done calculations for a range of tablet strengths in addition to those currently available.

Relationship between dose and efficacy of IPTc:
To estimate the duration of the protective effect of a course of treatment with SPAQ, data from the Konate *et al.* and Dicko *et al.* (2011) studies were used, these studies were most suitable because all daily doses were supervised, precise dosage was recorded each day, children were weighed shortly before the first treatment round, and malaria incidence was high allowing better precision for estimating protective effects. Most children in the trials received three doses of amodiaquine, for this reason it is difficult to separate the effects of SP and AQ A small number of children did not receive the full course of three amodiaquine doses, this gives some variation in the amodiaquine dose independent of the SP dose, giving some scope to separate the effects of amodiaquine from those of SP, although this analysis has the limitation that it relies on information from a small subgroup. This analysis gave evidence of an association between amodiaquine dose and reduced malaria incidence in the children who received IPTc with SPAQ, the effect depended on age group with the stronger association in children under 2 yrs of age (Fig 1). There was no evidence of an association with the dose of SP. This indicates that it is important to complete the course of amodiaquine tablets each month and to select a dosing scheme that ensures children, especially those under 2yrs, receive as near as possible the target dose. Dosing schemes with half a tablet for infants a whole tablet for children over 12 months of age ensures a higher dose for the 12-23-month age group than when a cut-off age of 24 months is used, and would be expected to improve the efficacy in this age group.

Figure 1: Efficacy of IPTc in relation to total dose of amodiaquine in the Burkina Faso and Mali trials. The dashed lines show the 95% confidence intervals, vertical lines indicate the target dose of 30mg/kg (10mg/kg/day), and the lower and upper limits corresponding to daily doses of 7.5 and 15 mg/kg/day.



The data for the three months of IPTc administration was combined, each month was considered a stratum, and in each stratum analysis was limited to those children who received at least the first day's doses that month (SP and at least the first of the daily doses of AQ). The dose of SP and of AQ was calculated as the total dose received divided by the child's weight in kg measured shortly before the first round of treatment. Malaria was defined as fever or history of fever with any parasitaemia, detected by passive case detection or when the child

was seen for the next IPT round. A cox regression model was fitted to estimate the effects of age group, intervention group, and amodiaquine dose, and interaction of dose with age group, on incidence of malaria, with robust standard errors to allow for repeated observations on the same child.

Relationship between amodiaquine dose and tolerability:

In clinical trials where mothers have been asked about adverse events after IPTc treatments, the incidence of reported vomitting was associated with the dose of amodiaquine in mg/kg, with an estimated odds ratio of 1.1 to 1.3 per mg/kg/day increase in dose (from studies in Senegal, Cairns et al. 2010), the odds of vomiting seem to increase steadily with increasing dosage with no evidence of a threshold dose associated with a marked increase in risk. However, across studies, there is no association between median dose or proportion of children with doses above 15mg/kg, and the incidence of vomitting (Table 1). In Burkina Faso, no child received a dose above 15mg/kg/day, but the incidence of reported vomiting (after any of the three rounds) was 28%; in Niakhar (Sokhna et al. 2008), 10mg/kg/day was considered the desired minimum dose rather than a median dose, 71% of children received doses above 15mg/kg/day, in this study every child was visited 4 days after each treatment round to ask about adverse events and the incidence of any vomiting was 11%.

Table 1: Estimated amodiaquine dosage, and reporting of vomiting after IPTc treatment courses, in 6 studies.

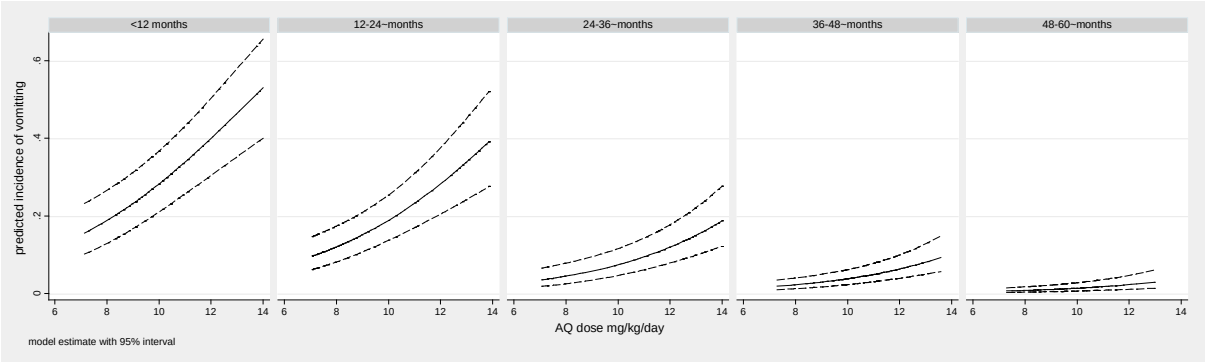
Proportion of children who received above 15mg/kg/day and above 20 mg/kg/day			Total amodiaquine dose, mg/kg			% vomiting
	%>15 mg/kg/day	%>20 mg/kg/day	1%ile	Median dose mg/kg	99%ile	%
Sokhna, 2008	70.6%	9.7%	37.8	50.0	68.9	11%a
Cisse, 2009	33.8%	2.4%	25.4	41.0	65.9	31%b
Bojang, 2010	13.9%	0.1%	25.4	35.7	50.0	5.7%a
Senegal, 2009	33.8%	2.4%	25.4	41.0	65.9	0.1%c
Mali, 2009	0.0%	0.0%	21.4	29.8	42.0	4.0%a
Burkina, 2009	0.0%	0.0%	21.2	30.4	42.0	28%a

a-% that reported vomited after treatment course 1,2 or 3, active follow-up; b – % that reported vomited after the first course of treatment, active follow-up; c – passive detection, % reporting vomiting within 10 days of course 1,2 or 3 at health facilities.

In the large scale effectiveness study in Senegal, surveillance for adverse events was maintained at 60 health facilities serving the study area, staff in each facility were contacted before each round of IPTc administration to remind them about potential adverse events, and again after each round to collect information about any clinic attendance that might be drug-related. Dosing was by age, using in 2008 and 2009, 200mg tablets amodiaquine and 500/25mg SP, with half a tablet of each for children <2yrs, and 1 tablet of each for children 2-4 yrs old, and in 2010, 153mg amodiaquine tablets with the same age cutoff. In 2009, more than half the children aged 24-36 months received doses above 15mg/kg/day, the largest total doses were about 75mg/kg. There were no serious adverse events attributed to IPTc drugs, the incidence of mild adverse events was about 2/1000 treatment courses, or 5.9/1000 per child per year, of these vomiting was the most frequent reason for clinic attendance. IPTc treatments were well tolerated with no evidence that poor tolerability limited adherence to unsupervised doses each month or influenced compliance with subsequent monthly rounds.

Three studies were used to investigate the effect of amodiaquine dose on the risk of vomitting, Konate et al. (2011) in Burkina Faso, and two studies in Senegal (Cairns et al 2010). In the Senegalese studies, Cairns et al estimated that for each 1-mg/kg increase in dose, the odds ratio for vomiting in the first round of administration, adjusted for age, was 1.1 (95% CI, 1.0, 1.3) (Cisse 2009) and 1.3 [95% CI, 1.0, 1.8] (Sokhna et al 2008). In the Burkina Faso trial, analysis of 1295 who received all 3 rounds of IPT and had completed the course each month and had non-missing data on mild adverse events, the odds ratio for vomiting for a 1 mg/kg/day increase in AQ dose was 1.30 (95%CI 1.2-1.4) in the SPAQ group (Fig 2). This model was then used to predict the percentage incidence of vomitting with different age-based dosing schemes, this showed that when an age-cutoff of 12 months is compared to an age cutoff of 24 months, for any given tablet strength, the estimated relative risk of vomiting is 1.47 i.e. 47% higher with the lower age cut-off.

Figure 2. Model estimate of the relationship between AQ dose and the incidence of vomiting, in round 1, with the dosages actually used, by age group, in the Konate *et al.* (2011) study.



Doses were administered in the clinic on days 0,1,2 each month and the mother/carer asked about adverse events in the previous 24 hours on days 1,2,3. The dose in mg/kg/day each month was calculated from the weight measured before round 1, vomitting was defined as any report of vomitting on day 1,2 or 3. A logistic model relating the log odds of vomitting to the dose of AQ in mg/kg/day was fitted to the data for all 3 rounds, with round number and age group as covariates, with a random effect for child to allow for repeated observations in the same child. Placebo and SPAQ groups were included and the coefficient for dose estimated separately in each group and a likelihood ratio test of interaction used to compare the effects in placebo and SPAQ groups. Quadratic and cubic functions of dose were explored but the best fitting model had a linear effect of dose on the log odds of vomitting. This model was then used to predict the percentage incidence of vomitting with different age-based dosing schemes (assuming a zero value for the random effect).

Age-based dosing for IPTc:

Using age-weight data from surveys in Mali, Burkina Faso and Senegal at the start of the period of IPT administration, for SP, a cut-off at 24 months resulted in 30% to 40% of boys and 18%-28% of girls in the 12-23-month age group receiving doses below the target of 25mg/kg (Supplementary tables, Table S1). With a cut-off of 12 months, 1% overall receive a dose below 25mg/kg, and 98% of doses lie within the range 25-72.5mg/kg (Table 1).

Table 1. Dosing accuracy for sulfadoxine-pyrimethamine.

	Dosing accuracy sulfadoxine			Dose of sulfadoxine mg/kg		
median weight	%<25mg/kg	%within 25-70mg/kg	%>70mg/kg	1%ile	median dose	99%ile
½ tablet <12 months, 1 tablet 12-59 months:						
11.5	1.0%	97.5%	1.6%	25.0	39.4	72.5
½ tablet <24 months, 1 tablet 24-59 months:						
11.5	7.7%	92.2%	0.1%	20.5	35.0	57.5

Pooled data from the Niakhar (N=1970), Mali (N=3001) and Burkina Faso (N=2957) studies, total sample size 7928.

For amodiaquine, using a 12 month cut-off, the tablet strength that maximizes the proportion of doses that fall in the range 10-15 mg/kg/day is between 150 and 160mg per tablet (Fig 3), a 153mg tablet results in about 80% of doses above 10mg/kg/day, with 98% of total doses (over three days) in the range 23-66.5mg/kg; 22% of doses exceed 15mg/kg/day. If a 24-month cutoff is used, with a 153mg tablet about 63% receive doses above 10mg/kg/day, with only 6% of doses above 15mg/kg/day (Table 2). 6.6% doses fall below 7.5mg/kg/day, in the 12-23-month age group, 14%-24% of girls and 26%-38% of boys receive less than the target dose of 10mg/kg/day (additional tables for age/gender groups in each site not shown).

The tablet strength that maximizes the proportion of doses in the range 7.5-15mg/kg day, using an age cutoff of 12 months, is between 120 and 140mg (Fig 3). A 135mg tablet results in 86% of doses in the range 7.5 to 15 mg/kg/day, with 60% above 10mg/kg/day and 10% of doses over 15mg/kg/day. Overall, only 3.7% of doses are less than 7.5mg/kg/day, but 40% of doses are less than the target 10mg/kg/day.

Figure 3. Proportion of amodiaquine doses within the range 10-15mg/kg, and within the range 7.5-15mg/kg, in relation to tablet strength, assuming a 12-month cutoff, using age-weight data from Burkina Faso.

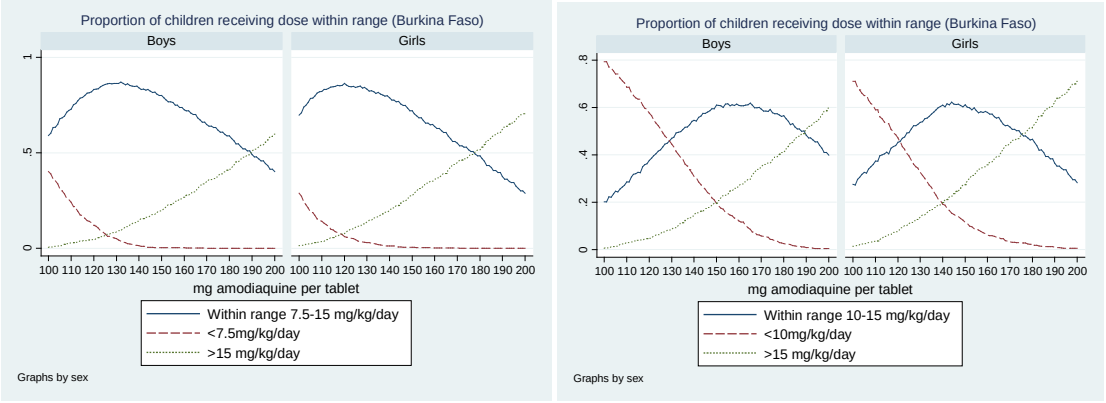


Table 2. Dosing accuracy for amodiaquine with 12- and 24-month cutoffs.

	Dosing accuracy				Total dose AQ mg/kg		
Median Weight	%<7.5 mg/kg/day	%within 7.5-15 mg/kg/day	%>10 mg/kg/day	%>15 mg/kg/day	1%ile	Median dose	99%ile
153mg tablet, ½ tablet <12 months, 1 tablet 12-59 months							
11.5	0.8%	77.1%	81.2%	22.1%	23.0	36.2	66.5
135mg tablet, ½ tablet <12 months, 1 tablet 12-59 months							
11.5	3.7%	85.8%	60.2%	10.5%	20.3	31.9	58.7
153mg tablet, ½ tablet <24 months, 1 tablet 24-59 months							
11.5	6.6%	87.5%	61.8%	5.9%	18.8	32.1	52.8

Conclusions

The choice of amodiaquine dosing depends on whether the aim is to maximise the proportion of doses above 10mg/kg/day, while limiting the proportion over 15mg/kg, or to consider 10mg/kg a target median dose. With simple age-based dosing with half or whole tablets and a switch at 12 months, 153mg tablet is close to the optimum in the first case and a 135mg tablet in the second. There may be an advantage to using the higher dose tablet since efficacy of IPTc is associated with dose. The 12-23 month old children receive the highest doses in relation to bodyweight, the benefit in terms of improved protective efficacy has to be set against an expected increase in the incidence of dose-related adverse events. However, in clinical trials, these doses have been well tolerated.

The proposed age-base dosing is consistent with WHO recommendations for SP and amodiaquine when used as part of treatment for malaria (WHO 2006). Those recommendations were derived using weight-age data from 21 countries, weight of children may be expected to vary geographically and seasonally, we have confirmed their suitability using data from three Sahelian countries, measured at the time children would receive their first dose of IPTc. With the 153mg tablet, when boys and girls in individual age groups in each country are considered, the median total amodiaquine dose ranged from 28mg/kg to 53mg/kg, the lowest, 28mg/kg was in boys 3-12 months in Senegal, in this group the dose range was from 21 to 46mg/kg (98% of doses were within this range), the highest median dose, 53mg/kg, was in girls aged 12-23months in Burkina Faso, here the range was 36 to 76mg/kg.

The association between efficacy and dose of amodiaquine has not been reported previously for IPTc but is consistent with malaria treatment studies (Adjei et al 2010). Hietala et al. (2007) found in patients treated for malaria, recrudescent parasitaemia was more common in patients who had lower concentrations of desethylamodiaquine on day 7, and Sirima et al. (2009) found that when occurrence of relapse parasitaemia was related to the dose of artesunate and of amodiaquine the patient received per kg bodyweight, the median dose of both drugs was higher in those who did not have relapse infection.

The variation between studies in the incidence of vomiting may reflect under- or over-reporting, it is possible that in studies with a high incidence of vomiting, spitting-out of the medicine at the time of administration is being reported as vomiting. Such over-reporting would be expected to dilute any association of vomiting with dose; in the Cisse 2009 study there was a higher incidence of vomitting and the odds ratio for the association with dose was closer to 1. Vomitting is most common in the first round of treatment and is reported less often in each successive round, this is not explained by selective drop-out of children, there is no evidence that those who vomit refuse IPT at the subsequent rounds, it may reflect acquired tolerance, or mothers may be less likely to report mild adverse events once they become reassured that the side effects are not serious.

We have considered simple dosing schemes that could be used with available tablets. If tablets are manufactured specifically for IPTc, the smaller dose need not be exactly half, and could be optimised for infants. Paediatric formulations may be better tolerated. AQ syrup is available in 60ml bottles, containing 50 mg amodiaquine hydrochloride per 5ml, this could potentially be used for the supervised dose but would be a more costly option, there would be substantial wastage if the bottle was left with the mother for the unsupervised doses.

There would be advantages to packaging drugs specifically for IPTc, separate tablets could be made for infants and children 12-59 months, blister packed, with information for the community health worker on the section with the SP and AQ tablet for the supervised dose and information for the mother on the section with the AQ tablets to be left with her, explaining dosing, potential side effects, and the need to seek malaria treatment if the child has a fever.

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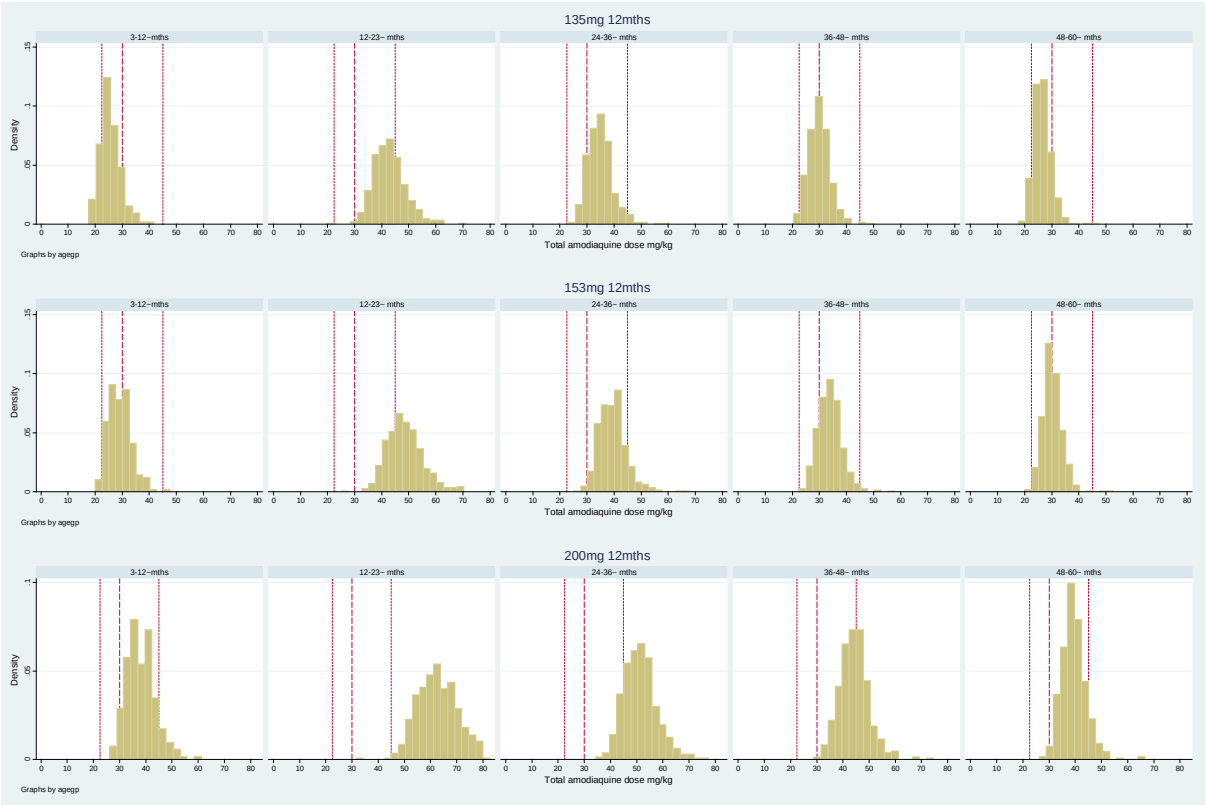
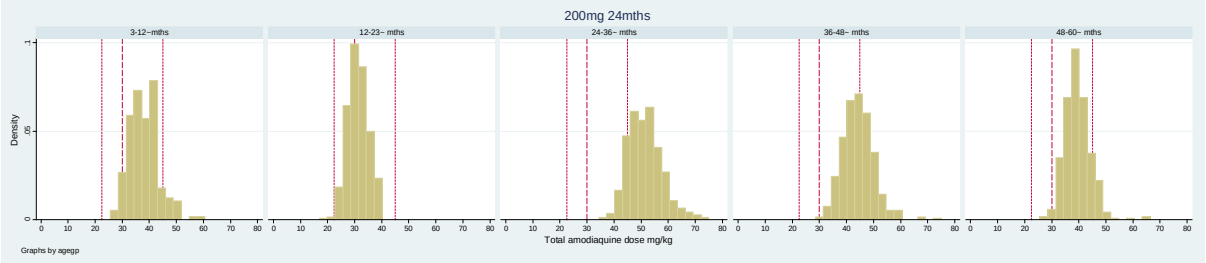
Distribution of dose by age group with a 12-months cut-off (half tablet <12mths, 1 tablet 12-59mths), for amodiaquine (135, 153 or 200mg tablet) and for SP.

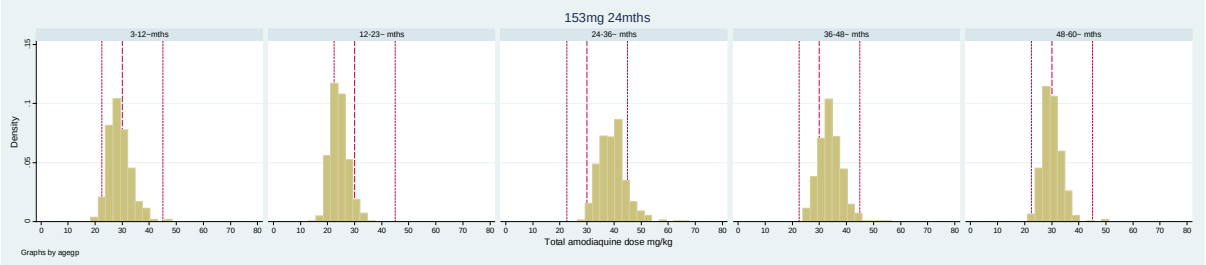


Estimated dose of amodiaquine received in IPTc trials, by age group

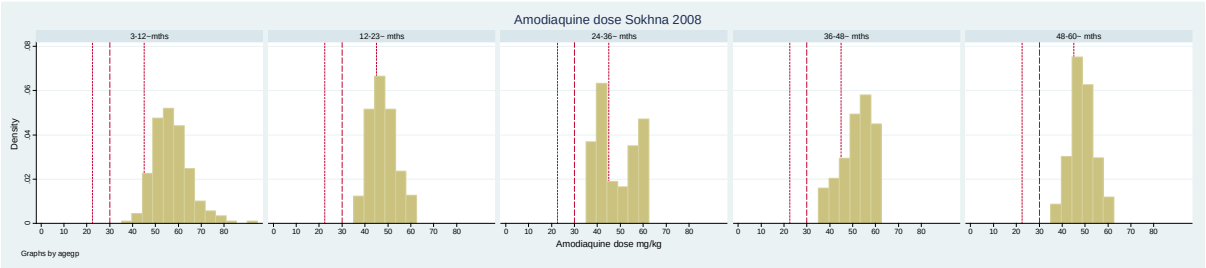
Senegal (2008,2009)



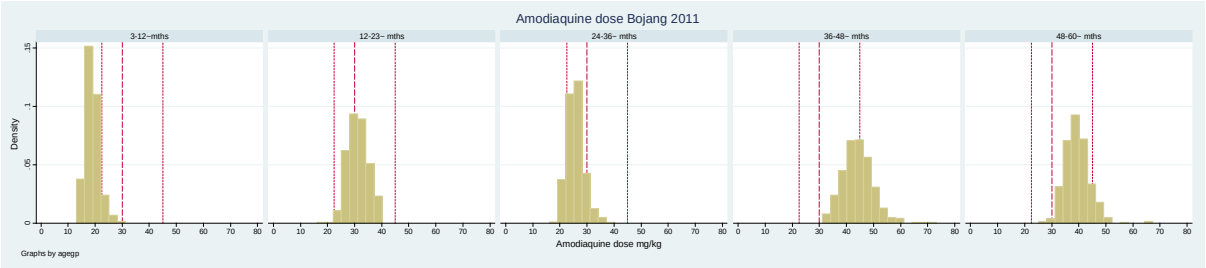
Senegal (2010)



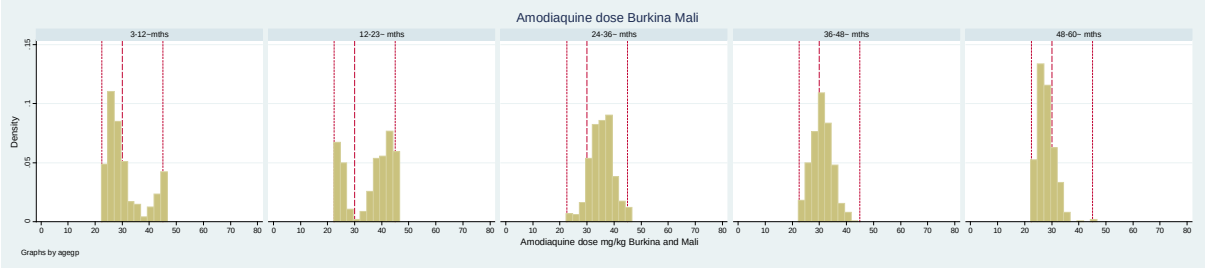
Sokhna et al (2008)



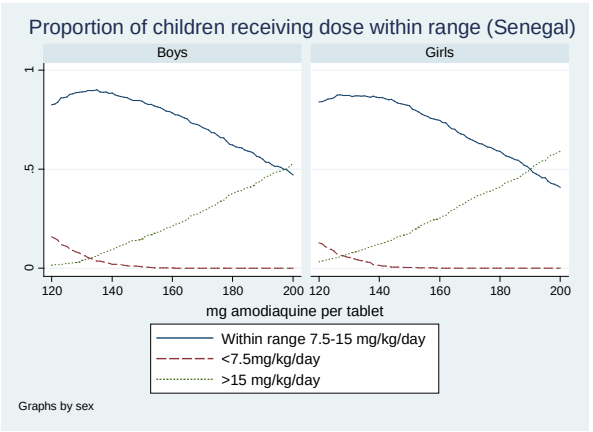
Bojang et al (2011)

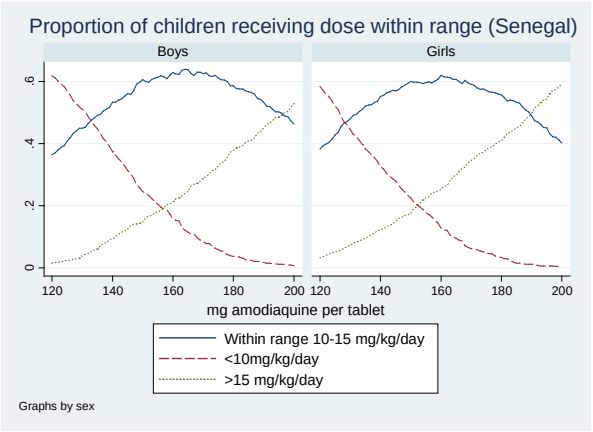


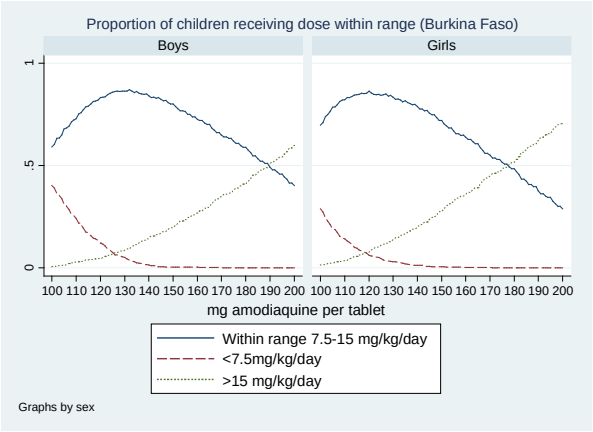
Dicko et al (2011) and Konate et al (2011)

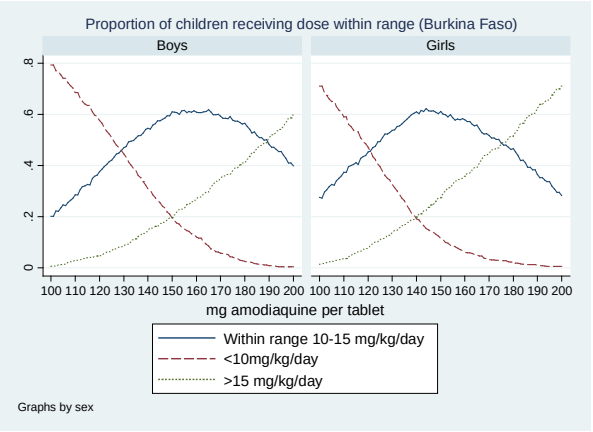


Proportion of amodiaquine doses within the range 10-15mg/kg, and within the range 7.5-15mg/kg, in relation to tablet strength, assuming a 12-month cutoff (half tablet <12mmths, 1 tablet 12-59mths), using age-weight data from Senegal and Burkina Faso.



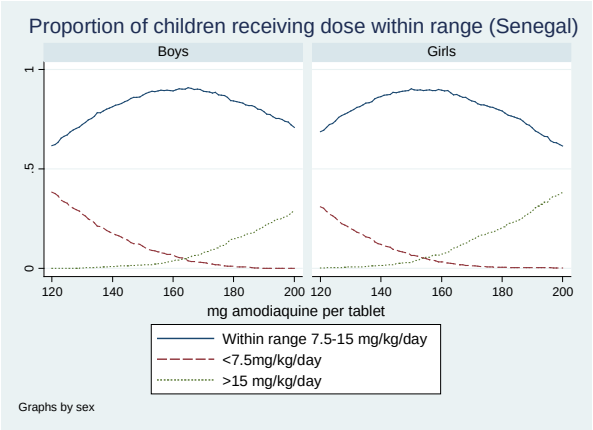


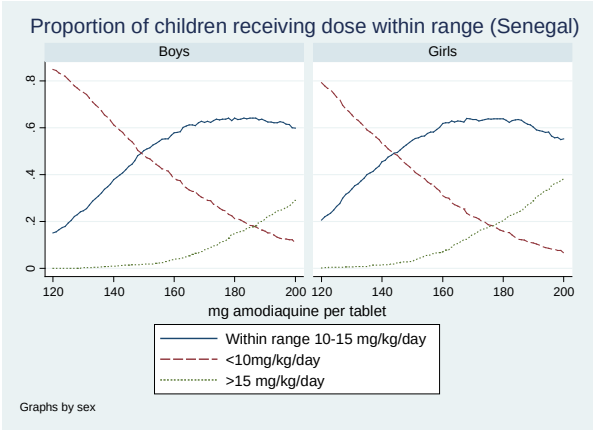


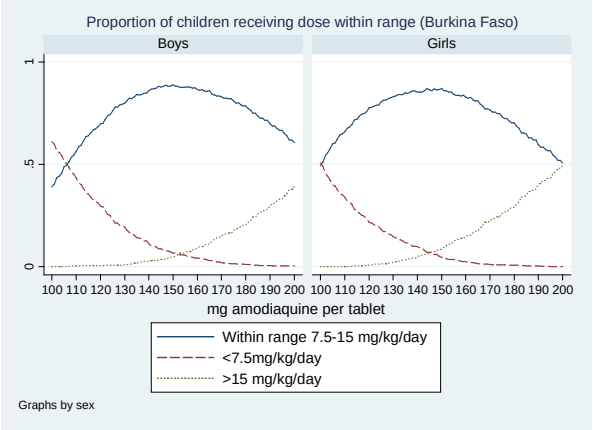


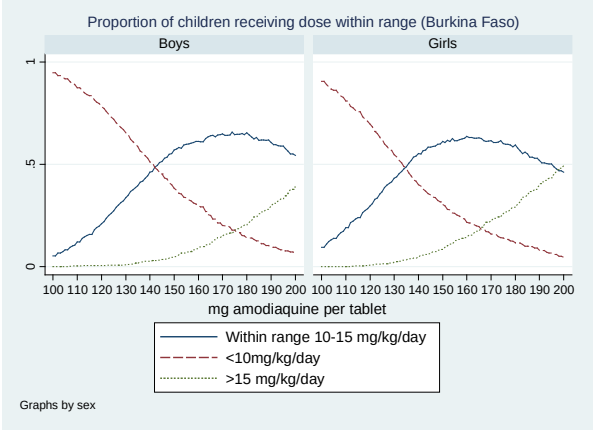
If the aim is to minimise doses outside the range 7.5-15, a tablet size of 135mg is close to optimal for both sexes in both populations. If the aim is to maximise the number that receive at least 10mg/kg, while keeping to a minimum doses over 15mg/kg, a tablet size 140-160mg is optimum.

Proportion of amodiaquine doses within the range 10-15mg/kg, and within the range 7.5-15mg/kg, in relation to tablet strength, assuming a 24-month cutoff (half tablet <24mths, 1 tablet 24-59mths), using age-weight data from Senegal and Burkina Faso.









Additional tables, giving dosing accuracy for boys and girls by age group in Mali, Burkina Faso and Senegal:

Table 1: Dosing accuracy of SP with 0.5 tablet <12 months and 1 tablet 12-59 months

				% dosing accuracy			Dose in mg/kg		
Gender	Source	Age group	Median weight	%<25 mg/kg	% within 25-70mg/kg	%>70 mg/kg	1%ile	median dose	99%ile
Boys	Burkina 2009	3-12~mths	7.4	2.6%	97.4%	0.0%	22.1	33.8	48.2
Boys	Burkina 2009	12-23~ mths	9.3	0.0%	92.1%	7.9%	36.2	53.8	80.8
Boys	Burkina 2009	24-36~ mths	11.3	0.0%	99.0%	1.0%	32.9	44.2	69.5
Boys	Burkina 2009	36-48~ mths	13.2	0.0%	99.7%	0.3%	27.9	37.9	54.9
Boys	Burkina 2009	48-60~ mths	14.8	0.0%	100.0%	0.0%	26.6	33.8	50.6
Girls	Burkina 2009	3-12~mths	6.8	3.4%	96.6%	0.0%	21.9	36.8	50.0
Girls	Burkina 2009	12-23~ mths	8.7	0.0%	89.0%	11.0%	39.4	57.5	83.3
Girls	Burkina 2009	24-36~ mths	10.6	0.0%	99.7%	0.3%	34.5	47.2	65.0
Girls	Burkina 2009	36-48~ mths	12.5	0.0%	100.0%	0.0%	29.1	40.0	55.6
Girls	Burkina 2009	48-60~ mths	14.0	0.0%	100.0%	0.0%	26.3	35.7	48.5
Boys	Mali 2009	3-12~mths	7.7	6.2%	93.8%	0.0%	19.5	32.5	48.1
Boys	Mali 2009	12-23~ mths	9.8	0.0%	96.5%	3.5%	34.2	51.0	78.1
Boys	Mali 2009	24-36~ mths	11.9	0.0%	99.7%	0.3%	29.2	42.0	64.9
Boys	Mali 2009	36-48~ mths	13.8	0.7%	99.3%	0.0%	25.3	36.2	56.2
Boys	Mali 2009	48-60~ mths	15.1	2.8%	97.2%	0.0%	23.5	33.1	51.5
Girls	Mali 2009	3-12~mths	7.3	5.0%	95.0%	0.0%	19.4	34.2	50.0
Girls	Mali 2009	12-23~ mths	9.0	0.0%	91.6%	8.4%	33.3	55.6	82.0
Girls	Mali 2009	24-36~ mths	11.6	0.0%	99.7%	0.3%	29.2	43.1	65.8
Girls	Mali 2009	36-48~ mths	13.3	0.0%	100.0%	0.0%	25.6	37.6	58.1
Girls	Mali 2009	48-60~ mths	15.2	3.3%	96.7%	0.0%	23.6	33.0	49.5
Boys	Niakhar 2004	3-12~mths	8.3	4.6%	95.4%	0.0%	23.0	30.1	50.0
Boys	Niakhar 2004	12-23~ mths	9.7	0.0%	99.1%	0.9%	40.0	51.4	69.5
Boys	Niakhar 2004	24-36~ mths	12.1	0.0%	100.0%	0.0%	32.3	41.3	57.9
Boys	Niakhar 2004	36-48~ mths	13.9	0.0%	100.0%	0.0%	27.9	35.9	47.2
Boys	Niakhar 2004	48-60~ mths	15.4	1.5%	98.5%	0.0%	23.4	32.4	43.1
Girls	Niakhar 2004	3-12~mths	7.8	4.7%	95.3%	0.0%	23.6	31.9	42.7
Girls	Niakhar 2004	12-23~ mths	9.3	0.0%	95.0%	5.0%	37.6	53.7	76.7
Girls	Niakhar 2004	24-36~ mths	11.3	0.0%	99.2%	0.8%	35.7	44.1	62.0
Girls	Niakhar 2004	36-48~ mths	13.3	0.0%	100.0%	0.0%	26.7	37.6	50.0
Girls	Niakhar 2004	48-60~ mths	15.3	0.0%	100.0%	0.0%	26.6	32.6	48.1

Table 2: Dosing accuracy of SP with 0.5 tablet <24 months and 1 tablet 24-59 months

				% dosing accuracy			Dose in mg/kg		
Gender	Source	Age group	median weight	%<25 mg/kg	% within 25-70mg/kg	%>70 mg/kg	1%ile	median dose	99%ile
Boys	Burkina 2009	3-12~mths	7.4	2.6%	97.4%	0.0%	22.1	33.8	48.2
Boys	Burkina 2009	12-23~ mths	9.3	29.7%	70.3%	0.0%	18.1	26.9	40.4
Boys	Burkina 2009	24-36~ mths	11.3	0.0%	99.0%	1.0%	32.9	44.2	69.5
Boys	Burkina 2009	36-48~ mths	13.2	0.0%	99.7%	0.3%	27.9	37.9	54.9
Boys	Burkina 2009	48-60~ mths	14.8	0.0%	100.0%	0.0%	26.6	33.8	50.6
Girls	Burkina 2009	3-12~mths	6.8	3.4%	96.6%	0.0%	21.9	36.8	50.0
Girls	Burkina 2009	12-23~ mths	8.7	17.8%	82.2%	0.0%	19.7	28.8	41.7
Girls	Burkina 2009	24-36~ mths	10.6	0.0%	99.7%	0.3%	34.5	47.2	65.0
Girls	Burkina 2009	36-48~ mths	12.5	0.0%	100.0%	0.0%	29.1	40.0	55.6
Girls	Burkina 2009	48-60~ mths	14.0	0.0%	100.0%	0.0%	26.3	35.7	48.5
Boys	Mali 2009	3-12~mths	7.7	6.2%	93.8%	0.0%	19.5	32.5	48.1
Boys	Mali 2009	12-23~ mths	9.8	40.2%	59.8%	0.0%	17.1	25.5	39.1
Boys	Mali 2009	24-36~ mths	11.9	0.0%	99.7%	0.3%	29.2	42.0	64.9
Boys	Mali 2009	36-48~ mths	13.8	0.7%	99.3%	0.0%	25.3	36.2	56.2
Boys	Mali 2009	48-60~ mths	15.1	2.8%	97.2%	0.0%	23.5	33.1	51.5
Girls	Mali 2009	3-12~mths	7.3	5.0%	95.0%	0.0%	19.4	34.2	50.0
Girls	Mali 2009	12-23~ mths	9.0	25.3%	74.7%	0.0%	16.7	27.8	41.0
Girls	Mali 2009	24-36~ mths	11.6	0.0%	99.7%	0.3%	29.2	43.1	65.8
Girls	Mali 2009	36-48~ mths	13.3	0.0%	100.0%	0.0%	25.6	37.6	58.1
Girls	Mali 2009	48-60~ mths	15.2	3.3%	96.7%	0.0%	23.6	33.0	49.5
Boys	Niakhar 2004	3-12~mths	8.3	4.6%	95.4%	0.0%	23.0	30.1	50.0
Boys	Niakhar 2004	12-23~ mths	9.7	43.2%	56.8%	0.0%	20.0	25.7	34.8
Boys	Niakhar 2004	24-36~ mths	12.1	0.0%	100.0%	0.0%	32.3	41.3	57.9
Boys	Niakhar 2004	36-48~ mths	13.9	0.0%	100.0%	0.0%	27.9	35.9	47.2
Boys	Niakhar 2004	48-60~ mths	15.4	1.5%	98.5%	0.0%	23.4	32.4	43.1
Girls	Niakhar 2004	3-12~mths	7.8	4.7%	95.3%	0.0%	23.6	31.9	42.7
Girls	Niakhar 2004	12-23~ mths	9.3	28.3%	71.7%	0.0%	18.8	26.9	38.3
Girls	Niakhar 2004	24-36~ mths	11.3	0.0%	99.2%	0.8%	35.7	44.1	62.0
Girls	Niakhar 2004	36-48~ mths	13.3	0.0%	100.0%	0.0%	26.7	37.6	50.0
Girls	Niakhar 2004	48-60~ mths	15.3	0.0%	100.0%	0.0%	26.6	32.6	48.1

Table 3: Dosing accuracy of AQ, 153mg tablets, with 0.5 tablet <12 months and 1 tablet 12-59 months

				Dosing accuracy				Total dose mg/kg		
Gender	Source	Age group	median weight	%<7.5 mg /kg/day	%within 7.5-15	%>10 mg /kg/day	%>15 mg/kg/d	1%ile	median dose	99%ile
Boys	Burkina	3-12~m	7.4	2.2%	97.0%	57.4%	0.7%	20.3	31.0	44.2
Boys	Burkina	12-23~ m	9.3	0.0%	26.4%	100.0%	73.6%	33.3	49.4	74.2
Boys	Burkina	24-36~ m	11.3	0.0%	75.1%	99.0%	24.9%	30.2	40.6	63.8
Boys	Burkina	36-48~ m	13.2	0.0%	96.6%	84.9%	3.4%	25.7	34.8	50.4
Boys	Burkina	48-60~ m	14.8	0.0%	98.6%	62.8%	1.4%	24.4	31.0	46.4
Girls	Burkina	3-12~m	6.8	2.6%	94.5%	78.7%	3.0%	20.1	33.8	45.9
Girls	Burkina	12-23~ m	8.7	0.0%	13.9%	100.0%	86.1%	36.2	52.8	76.5
Girls	Burkina	24-36~ m	10.6	0.0%	59.1%	99.3%	40.9%	31.7	43.3	59.7
Girls	Burkina	36-48~ m	12.5	0.0%	94.0%	91.4%	6.0%	26.7	36.7	51.0
Girls	Burkina	48-60~ m	14.0	0.0%	99.2%	74.3%	0.8%	24.2	32.8	44.6
Boys	Mali	3-12~m	7.7	6.2%	93.4%	49.6%	0.4%	17.9	29.8	44.1
Boys	Mali	12-23~ m	9.8	0.0%	38.6%	99.4%	61.4%	31.4	46.8	71.7
Boys	Mali	24-36~ m	11.9	0.0%	82.7%	94.9%	17.3%	26.8	38.6	59.6
Boys	Mali	36-48~ m	13.8	0.0%	98.6%	81.6%	1.4%	23.2	33.3	51.6
Boys	Mali	48-60~ m	15.1	2.4%	96.6%	52.8%	1.0%	21.5	30.4	47.3
Girls	Mali	3-12~m	7.3	4.0%	95.0%	60.1%	1.1%	17.8	31.4	45.9
Girls	Mali	12-23~ m	9.0	0.0%	24.1%	99.1%	75.9%	30.6	51.0	75.2
Girls	Mali	24-36~ m	11.6	0.0%	77.0%	95.8%	23.0%	26.8	39.6	60.4
Girls	Mali	36-48~ m	13.3	0.0%	95.3%	86.2%	4.7%	23.5	34.5	53.4
Girls	Mali	48-60~ m	15.2	2.2%	96.7%	51.1%	1.1%	21.7	30.3	45.4
Boys	Niakhar	3-12~m	8.3	2.3%	96.6%	32.2%	1.1%	21.1	27.7	45.9
Boys	Niakhar	12-23~ m	9.7	0.0%	37.1%	100.0%	62.9%	36.7	47.2	63.8
Boys	Niakhar	24-36~ m	12.1	0.0%	93.5%	98.3%	6.5%	29.6	37.9	53.2
Boys	Niakhar	36-48~ m	13.9	0.0%	99.5%	76.1%	0.5%	25.6	32.9	43.3
Boys	Niakhar	48-60~ m	15.4	1.0%	99.0%	45.9%	0.0%	21.4	29.7	39.6
Girls	Niakhar	3-12~m	7.8	2.8%	97.2%	46.2%	0.0%	21.7	29.3	39.2
Girls	Niakhar	12-23~ m	9.3	0.0%	25.1%	99.5%	74.9%	34.5	49.3	70.4
Girls	Niakhar	24-36~ m	11.3	0.0%	84.4%	99.2%	15.6%	32.8	40.5	56.9
Girls	Niakhar	36-48~ m	13.3	0.0%	97.5%	84.9%	2.5%	24.5	34.5	45.9
Girls	Niakhar	48-60~ m	15.3	0.0%	99.0%	49.0%	1.0%	24.4	30.0	44.1

Table 4: Dosing accuracy of AQ, 135mg tablets, with 0.5 tablet <12 months and 1 tablet 12-59 months

				Dosing accuracy				Total dose mg/kg		
Gender	Source	Age group	Median weight	%<7.5 mg/kg/d	%within 7.5-15 mg/kg/d	%>10 mg/kg/d	%>15 mg/kg/d	1%ile	Median dose	99%ile
Boys	Burkina	3-12~m	7.4	8.9%	91.1%	28.1%	0.0%	17.9	27.4	39.0
Boys	Burkina	12-23~ m	9.3	0.0%	57.9%	98.5%	42.1%	29.3	43.5	65.4
Boys	Burkina	24-36~ m	11.3	0.0%	93.2%	88.0%	6.8%	26.7	35.8	56.3
Boys	Burkina	36-48~ m	13.2	0.9%	98.5%	56.2%	0.6%	22.6	30.7	44.5
Boys	Burkina	48-60~ m	14.8	4.9%	95.1%	21.1%	0.0%	21.6	27.4	41.0
Girls	Burkina	3-12~m	6.8	7.2%	92.8%	49.8%	0.0%	17.8	29.8	40.5
Girls	Burkina	12-23~ m	8.7	0.0%	45.4%	99.7%	54.6%	31.9	46.6	67.5
Girls	Burkina	24-36~ m	10.6	0.3%	86.4%	95.3%	13.3%	27.9	38.2	52.7
Girls	Burkina	36-48~ m	12.5	0.3%	98.7%	68.4%	1.0%	23.5	32.4	45.0
Girls	Burkina	48-60~ m	14.0	3.4%	96.6%	34.7%	0.0%	21.3	28.9	39.3
Boys	Mali	3-12~m	7.7	17.9%	82.1%	20.1%	0.0%	15.8	26.3	38.9
Boys	Mali	12-23~ m	9.8	0.0%	71.8%	97.5%	28.2%	27.7	41.3	63.3
Boys	Mali	24-36~ m	11.9	0.6%	94.9%	81.1%	4.5%	23.7	34.0	52.6
Boys	Mali	36-48~ m	13.8	2.5%	96.4%	43.0%	1.1%	20.5	29.3	45.5
Boys	Mali	48-60~ m	15.1	11.0%	89.0%	16.2%	0.0%	19.0	26.8	41.8
Girls	Mali	3-12~m	7.3	11.9%	88.1%	30.9%	0.0%	15.7	27.7	40.5
Girls	Mali	12-23~ m	9.0	0.0%	52.4%	96.4%	47.6%	27.0	45.0	66.4
Girls	Mali	24-36~ m	11.6	0.6%	93.6%	84.8%	5.8%	23.7	34.9	53.3
Girls	Mali	36-48~ m	13.3	2.2%	96.2%	52.5%	1.6%	20.8	30.5	47.1
Girls	Mali	48-60~ m	15.2	9.5%	90.1%	16.8%	0.4%	19.1	26.7	40.1
Boys	Niakhar	3-12~m	8.3	25.3%	74.7%	8.0%	0.0%	18.6	24.4	40.5
Boys	Niakhar	12-23~ m	9.7	0.0%	76.9%	100.0%	23.1%	32.4	41.6	56.3
Boys	Niakhar	24-36~ m	12.1	0.0%	98.3%	80.4%	1.7%	26.1	33.4	46.9
Boys	Niakhar	36-48~ m	13.9	0.0%	99.5%	37.6%	0.5%	22.6	29.1	38.2
Boys	Niakhar	48-60~ m	15.4	6.7%	93.3%	10.3%	0.0%	18.9	26.2	34.9
Girls	Niakhar	3-12~m	7.8	15.1%	84.9%	11.3%	0.0%	19.1	25.9	34.6
Girls	Niakhar	12-23~ m	9.3	0.0%	59.4%	99.1%	40.6%	30.5	43.5	62.1
Girls	Niakhar	24-36~ m	11.3	0.0%	97.1%	93.0%	2.9%	28.9	35.7	50.2
Girls	Niakhar	36-48~ m	13.3	1.7%	97.9%	55.9%	0.4%	21.7	30.5	40.5
Girls	Niakhar	48-60~ m	15.3	6.7%	93.3%	14.3%	0.0%	21.5	26.4	38.9

Table 5: Dosing accuracy of AQ, 153mg tablets, with 0.5 tablet <24 months and 1 tablet 24-59 months

				Dosing accuracy				Total dose mg/kg		
Gender	Source	Age group	Median weight	%<7.5 mg/kd/d	%within 7.5-15 mg/kg/d	%>10 mg/kg/d	%>15 mg/kg/d	1%ile	Median dose	99%ile
Boys	Burkina	3-12~m	7.4	2.2%	97.0%	57.4%	0.7%	20.3	31.0	44.2
Boys	Burkina	12-23~ m	9.3	26.4%	73.6%	14.2%	0.0%	16.6	24.7	37.1
Boys	Burkina	24-36~ m	11.3	0.0%	75.1%	99.0%	24.9%	30.2	40.6	63.8
Boys	Burkina	36-48~ m	13.2	0.0%	96.6%	84.9%	3.4%	25.7	34.8	50.4
Boys	Burkina	48-60~ m	14.8	0.0%	98.6%	62.8%	1.4%	24.4	31.0	46.4
Girls	Burkina	3-12~m	6.8	2.6%	94.5%	78.7%	3.0%	20.1	33.8	45.9
Girls	Burkina	12-23~ m	8.7	13.9%	86.1%	21.1%	0.0%	18.1	26.4	38.3
Girls	Burkina	24-36~ m	10.6	0.0%	59.1%	99.3%	40.9%	31.7	43.3	59.7
Girls	Burkina	36-48~ m	12.5	0.0%	94.0%	91.4%	6.0%	26.7	36.7	51.0
Girls	Burkina	48-60~ m	14.0	0.0%	99.2%	74.3%	0.8%	24.2	32.8	44.6
Boys	Mali	3-12~m	7.7	6.2%	93.4%	49.6%	0.4%	17.9	29.8	44.1
Boys	Mali	12-23~ m	9.8	37.7%	62.3%	8.2%	0.0%	15.7	23.4	35.9
Boys	Mali	24-36~ m	11.9	0.0%	82.7%	94.9%	17.3%	26.8	38.6	59.6
Boys	Mali	36-48~ m	13.8	0.0%	98.6%	81.6%	1.4%	23.2	33.3	51.6
Boys	Mali	48-60~ m	15.1	2.4%	96.6%	52.8%	1.0%	21.5	30.4	47.3
Girls	Mali	3-12~m	7.3	4.0%	95.0%	60.1%	1.1%	17.8	31.4	45.9
Girls	Mali	12-23~ m	9.0	21.7%	78.3%	15.7%	0.0%	15.3	25.5	37.6
Girls	Mali	24-36~ m	11.6	0.0%	77.0%	95.8%	23.0%	26.8	39.6	60.4
Girls	Mali	36-48~ m	13.3	0.0%	95.3%	86.2%	4.7%	23.5	34.5	53.4
Girls	Mali	48-60~ m	15.2	2.2%	96.7%	51.1%	1.1%	21.7	30.3	45.4
Boys	Niakhar	3-12~m	8.3	2.3%	96.6%	32.2%	1.1%	21.1	27.7	45.9
Boys	Niakhar	12-23~ m	9.7	35.8%	63.8%	3.5%	0.4%	18.4	23.6	31.9
Boys	Niakhar	24-36~ m	12.1	0.0%	93.5%	98.3%	6.5%	29.6	37.9	53.2
Boys	Niakhar	36-48~ m	13.9	0.0%	99.5%	76.1%	0.5%	25.6	32.9	43.3
Boys	Niakhar	48-60~ m	15.4	1.0%	99.0%	45.9%	0.0%	21.4	29.7	39.6
Girls	Niakhar	3-12~m	7.8	2.8%	97.2%	46.2%	0.0%	21.7	29.3	39.2
Girls	Niakhar	12-23~ m	9.3	24.2%	75.3%	8.7%	0.5%	17.3	24.7	35.2
Girls	Niakhar	24-36~ m	11.3	0.0%	84.4%	99.2%	15.6%	32.8	40.5	56.9
Girls	Niakhar	36-48~ m	13.3	0.0%	97.5%	84.9%	2.5%	24.5	34.5	45.9
Girls	Niakhar	48-60~ m	15.3	0.0%	99.0%	49.0%	1.0%	24.4	30.0	44.1

Table 6. Summary of Dosing accuracy for sulfadoxine-pyrimethamine.

	Dosing accuracy sulfadoxine				Dose of sulfadoxine mg/kg		
	median weight	%<25 mg/kg	%within 25-70mg/kg	%>70 mg/kg	1%ile	median dose	99%ile
½ tablet <12 months, 1 tablet 12-59 months:							
Girls	11.1	0.9%	97.1%	2.0%	25.0	40.3	74.1
Boys	11.8	1.0%	97.8%	1.1%	24.9	38.5	70.5
Total	11.5	1.0%	97.5%	1.6%	25.0	39.4	72.5
½ tablet <24 months, 1 tablet 24-59 months:							
Girls	11.1	6.1%	93.8%	0.1%	20.8	35.7	58.8
Boys	11.8	9.3%	90.6%	0.1%	20.2	34.2	56.2
Total	11.5	7.7%	92.2%	0.1%	20.5	35.0	57.5

Pooled data from the Niakhar (N=1970), Mali (N=3001) and Burkina Faso (N=2957) studies, total sample size 7928.

Table 7. Summary of dosing accuracy for amodiaquine

	Dosing accuracy					Total dose AQ mg/kg		
Gender	Median Weight	%<7.5 mg/kg/day	%within 7.5-15 mg/kg/day	%>10 mg/kg/day	%>15 mg/kg/day	1%ile	Median dose	99%ile
153mg tablet, ½ tablet <12 months, 1 tablet 12-59 months								
Girls	11.1	0.7%	74.3%	83.6%	25.1%	23.0	37.0	68.0
Boys	11.8	0.9%	80.0%	78.8%	19.1%	22.8	35.3	64.7
Total	11.5	0.8%	77.1%	81.2%	22.1%	23.0	36.2	66.5
135mg tablet, ½ tablet <12 months, 1 tablet 12-59 months								
Girls	11.1	3.3%	84.0%	64.1%	12.7%	20.3	32.7	60.0
Boys	11.8	4.2%	87.5%	56.3%	8.3%	20.1	31.2	57.1
Total	11.5	3.7%	85.8%	60.2%	10.5%	20.3	31.9	58.7
153mg tablet, ½ tablet <24 months, 1 tablet 24-59 months								
Girls	11.1	5.0%	87.7%	65.0%	7.4%	19.1	32.8	54.0
Boys	11.8	8.2%	87.4%	58.7%	4.4%	18.5	31.4	51.6
Total	11.5	6.6%	87.5%	61.8%	5.9%	18.8	32.1	52.8