

1 Reduced efficacy of intermittent preventive treatment of malaria in malnourished children

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1 **Abstract**

2 Intermittent preventive treatment in infants with sulfadoxine-pyrimethamine (IPTi-SP)
3 reduces malaria episodes by 20-59% across Africa. This protective efficacy, however, may be
4 affected by the high frequency of malnutrition in African infants.

5 We analyzed the impact of malnutrition as defined by anthropometry on the incidence
6 of malaria and on the protective efficacy of IPTi in a cohort of 1200 children in hyperendemic
7 northern Ghana. These children received IPTi-SP or placebo at 3, 9, and 15 months of age and
8 were followed-up until 24 months of age.

9 Malnutrition was present in 32%, 40%, and 50% of children at ages 3, 9, and 15
10 months, respectively. It was associated with increased risks of severe anemia and death but
11 not of malaria. Although malaria slightly contributed to chronic malnutrition, IPTi did not
12 substantially improve child growth. Importantly, the protective efficacies of IPTi in
13 malnourished children were roughly half or even less of those observed in non-malnourished
14 children. In the first year of life, IPTi reduced the incidence of malaria to a significantly lesser
15 extent in infants who received both doses in a malnourished condition (25%; 95%CI, -7–48%)
16 as compared to non-malnourished children (46%; 95%CI, 30–58%; $P = 0.049$). Moreover, in
17 contrast to nutritionally advantaged children, the rate of severe malaria appeared to be
18 increased in malnourished children who took IPTi.

19 IPTi might exhibit reduced efficacy in regions of abundant malnutrition. There,
20 concomitant nutrition programs may be needed to achieve the desired impact.

21

22

23 **Keywords:** malaria, malnutrition, IPTi, prevention, sulfadoxine-pyrimethamine

1 **Introduction**

2 Intermittent preventive treatment in infants (IPTi) with sulfadoxine-pyrimethamine appears to
3 be a promising tool of malaria control in young children. The initial IPTi trial in Tanzania
4 reported a protective efficacy (PE) against uncomplicated malaria in infancy of 59% and some
5 degree of protection persisting into the second year of life (30,31). In subsequent studies at
6 sites of differing endemicity in sub-Saharan Africa, protection in infancy was confirmed,
7 however, with lower PEs of 20-33% (5,14,17,19,25). We have previously reported that in
8 Tamale, northern Ghana, IPTi reduced the incidences of asymptomatic parasitemia,
9 uncomplicated malaria and severe anemia from 3-24 months of age by 29%, 17% and 15%,
10 respectively. These effects were greatest in the first year of life and less pronounced in the
11 second (25).

12 As in many regions of Africa, malnutrition is abundant in northern Ghana reaching
13 prevalences as high as 50% in preschool children, depending on seasonality and food
14 availability (34,43). Malnutrition causes relative immunosuppression, and, *vice versa*,
15 repeated or chronic infections may contribute to poor nutritional status (29). However, the
16 effect of malnutrition on malaria is less clear-cut than would be expected: protein-energy
17 malnutrition has been associated with greater malaria morbidity and mortality in some areas
18 but not in others (4,6,8,23,26,32). Moreover, the risk of antimalarial treatment failure appears
19 to be increased in malnourished children (15,16,24,44). Taken together, this suggests that
20 malnutrition is one factor contributing to malaria-associated morbidity and that malaria-
21 control strategies without concomitant nutrition programs may not have the desired impact on
22 childhood morbidity on a large scale (8). We hypothesized that malnutrition may affect both,
23 malaria morbidity and IPTi efficacy. Alternatively, IPTi might improve children's growth and
24 nutritional status. We re-analyzed data of a cohort from northern Ghana (25) regarding the
25 effect of malnutrition on the protective efficacy of IPTi and here report the results of this
26 secondary analysis.

1 **Methods**

2 *Study site and IPTi trial*

3 The IPTi trial was conducted between March 2003 and July 2005 at Bulpeila Health Centre,
4 located in a semi-urban outskirts of Tamale, northern Ghana. Despite a population of 350,000,
5 the town is of rural character and spread over a vast area. Subsistence farming and small-scale
6 trade are the main income sources. Climate and vegetation are savanna type with rains from
7 May to October. Malaria in the region is hyperendemic with modest seasonal variation;
8 underweight and stunting each affect approximately one out of four children (8). At the time
9 the study was carried out, bed net usage was low (3%), and malaria control consisted basically
10 of chloroquine treatment which achieved cure rates of <50% (24).

11 The study was a randomized, double-blind, placebo-controlled trial on the efficacy of
12 sulfadoxine-pyrimethamine (SP) given alongside the Expanded Program on Immunization
13 (EPI) (trial registration URL: <http://clinicaltrials.gov>, NCT00168948). Informed written
14 consent was obtained from the participants' parent(s). The study protocol was approved by the
15 Ethics Committee, University for Development Studies, Tamale. Details have been described
16 elsewhere (25). In brief, a total of 1200 children received half a tablet of SP (125/6.25 mg;
17 Fansidar; Roche, Basle, Switzerland) or placebo at 3, 9 and 15 months of age and were
18 followed-up at 6, 12, 18, 21, and 24 months of age. For passive case detection, parents were
19 instructed to bring their children to the health center in case of any health problem. A civil
20 conflict involving changing curfews (until August 2004) occasionally impeded children from
21 attending the health center or hospital in the late afternoon. At scheduled visits, children were
22 clinically examined, a medical history was obtained, and a venous blood sample was
23 collected. Blood samples were also collected at unscheduled visits in case of fever (axillary
24 temperature, $\geq 37.5^{\circ}\text{C}$), a history of fever or when requested by the clinician. Asexual malaria
25 parasites were counted against 500 white blood cells on Giemsa-stained thick blood films, and
26 hemoglobin (Hb) was measured (HemoCue, Ångelholm, Sweden). Malaria was defined as

1 parasitemia of any density *plus* fever or a voluntarily reported history of fever within the
2 preceding 48 h, severe anemia as Hb <7 g/dL (33), and severe malaria according to WHO
3 criteria (40). Malaria was treated under observation with artesunate (Plasmodium; Mepha,
4 Switzerland) at a dose of 4 mg/kg (double dose on first day) for five days. Other diseases were
5 treated according to Ghana Health Service guidelines (12).

6

7 ***Measures of malnutrition***

8 At each regular visit, weight and length/height were measured and related to age and sex.
9 Malnutrition was defined by these anthropometric parameters according to the WHO 2006
10 standard reference data (41,42). A weight-for-age z-score (waz) of <-2 standard deviations
11 (SD) characterized underweight, indicating general malnutrition. Likewise, weight-for-height
12 (whz) and height-for-age z-scores (haz) <-2 SD denoted wasting (acute malnutrition) and
13 stunting (chronic malnutrition), respectively. In this paper, the term “overall malnutrition”
14 refers to children in at least one of these conditions. For the present analysis, the nutritional
15 status was categorized using a static and a dynamic approach. Statically, the nutritional state
16 was determined at baseline, at one year of age, and at each IPTi administration. Alternatively,
17 and to account for the dynamic nature of the nutritional status, a non-parametric mixture
18 model for longitudinal data (1) clustered the individual follow-up curves of anthropometrical
19 z-scores from 3-24 months of age. Children whose scores belonged to a cluster <-2SD were
20 categorized as underweight, wasted or stunted.

21

22 ***Data management and statistical analysis***

23 In a first step, the effect of the nutritional status *per se* (static definition) on the main
24 outcomes (asymptomatic parasitemia, uncomplicated malaria, severe malaria, severe anemia,
25 death) was analysed by comparing incidence densities (ID, i.e. events per person-years-at-risk
26 (PYAR)) between malnourished and non-malnourished children using negative binomial

1 regression. Following an event, a child was considered not to be at the respective risk for
2 three weeks and the person time was reduced accordingly. Incidence rate ratios (IRRs, $ID_{\text{non-}}$
3 $\text{malnourished}/ID_{\text{malnourished}}$) were adjusted for intervention group. *Vice versa*, the impact of disease
4 on the development of anthropometrical z-scores from 3-24 months of age was assessed by
5 general estimating equation (GEE) accounting for repeated, correlated observations. The
6 results are given as means of differences in z-scores (Δ z-score) between children with at least
7 one event and those with none, adjusted for the intervention. To further evaluate the effect of
8 IPTi on anthropometrical development, time-dependent changes in weight, length, mid-upper
9 arm circumference (MUAC), and z-scores were calculated, compared by Mann-Whitney-U-
10 test, and expressed as difference per month.

11 As the main analysis, we estimated the protective efficacies of IPTi in strata of
12 nutritional status. For that, incidence densities of asymptomatic parasitemia, uncomplicated
13 malaria, severe malaria, severe anemia and death were calculated. As before, the person time
14 was reduced for three weeks following an event. To account for repeated, dependent
15 measures, the efficacies of IPTi ($1-ID_{\text{Sp}}/ID_{\text{placebo}}$), 95% confidence intervals (CI) and *P*-values
16 were calculated by negative binomial regression and adjusted for rainy season (10) and food
17 availability (2,9). PEs of IPTi in malnourished and non-malnourished children were estimated
18 for various strata and observation periods. For the static classification of nutritional status
19 these were: i) from 3 to 24 months of age grouping children into non-malnourished ($n = 809$)
20 and malnourished ($n = 388$) based on recruitment anthropometry; ii) from 3 to 12 months of
21 age for which children were grouped according to whether they received both IPTi doses in a
22 non-malnourished ($n = 527$) or malnourished condition ($n = 210$); iii) from >12 to 24 months
23 of age with the status at IPTi dose 3 defining the nutritional situation (non-malnourished, $n =$
24 538; malnourished, $n = 540$); and iv) each six months following an IPTi dose. The
25 significance of differences in the PEs between nutritional strata was assessed by Wald-test.
26 Calculations of PEs were repeated for v) the period of 3 to 24 months applying nutritional

1 strata derived from the non-parametric mixture model for longitudinal data (non-
2 malnourished, $n = 200$; malnourished, $n = 999$).

3 The software packages SPSS[®] 14.0 (SPSS Inc., Chicago, IL) and STATA[®] 9.0
4 (StataCorp LP, Chicago, IL) were used.

1 **Results**

2 *Study population*

3 Between March and September 2003, 1200 infants were randomly assigned to receive SP or
4 placebo. Baseline characteristics, drop-out rate and mortality were similar in both study arms
5 (25). Eighty-nine percent of the children received all three doses of IPTi and 87% completed
6 the follow-up until 24 months of age. The prevalences of overall malnutrition at 3, 9 and 15
7 months of age were 32%, 40% and 50%, respectively (Tab. 1). Baseline characteristics of
8 malnourished and non-malnourished children were similar (data not shown).

9

10 *The interaction between nutritional status and malaria*

11 First, we assessed the incidences of asymptomatic parasitemia, uncomplicated malaria, severe
12 anemia, and death during the complete follow-up period. These were compared between
13 children with and without malnutrition (incl. stunting, wasting, underweight) at recruitment.
14 The nutritional status had no influence on asymptomatic parasitemia or on uncomplicated
15 malaria; e.g. the latter occurred at a rate of 1.17/year and 1.11/year in malnourished and non-
16 malnourished children, respectively ($P = 0.38$). Two significant associations were observed:
17 malnutrition increased the risk of dying by 89% (IRR, 1.89; 95%CI, 1.03-3.47; $P = 0.04$), and
18 stunting that of severe anemia by 49% (IRR, 1.49; 95%CI, 1.07-2.07; $P = 0.02$).

19 *Vice versa*, the impact of the disease status on the development of nutritional indices
20 was examined by GEE. Parasitemia and malaria were associated with measures indicating
21 stunting: height-for-age z-scores aggravated in children who experienced at least one episode
22 as compared to unaffected children (parasitemia, Δ haz, -0.17; $P = 0.02$; malaria, Δ haz, -
23 0.18, $P = 0.01$). Regarding severe anemia, this influence was more pronounced (Δ haz, -0.30,
24 $P < 0.0001$) and also discernible in terms of underweight (Δ waz, -0.21, $P = 0.001$).

25

1 ***The influence of IPTi on child growth***

2 The changes in weight, height, MUAC and z-scores with increasing age are displayed in
3 Table 2. IPTi improved weight gain exclusively in the first year of life and only to a small
4 extent (14 g/month; $P = 0.02$). Moreover, this effect was restricted to children who were not
5 malnourished when receiving IPTi doses 1 and 2 (19 g/month; $P = 0.08$ vs. malnourished, 0.3
6 g/month; $P = 0.73$). No beneficial impact of IPTi on nutritional indices was observed in the
7 second year of life, or for the complete follow up period (Tab. 2).

9 ***The efficacy of IPTi in malnourished children***

10 Table 3 shows the PEs of IPTi against the main outcome parameters according to nutritional
11 status and adjusted for rainy season and food availability. Overall, the protective efficacies of
12 IPTi in malnourished children were roughly half or even less of those observed in non-
13 malnourished children. Also, in this analysis, significant risk reductions due to IPTi were only
14 observed among non-malnourished children. For instance, IPTi reduced the number of
15 episodes of uncomplicated malaria by only 9.5% ($P = 0.32$) in malnourished children but by
16 18.4% ($P = 0.006$) among their non-malnourished counterparts (Tab. 3). Generally, these
17 differences in the impact of IPTi according to nutritional status did not yield statistical
18 significance. Nonetheless, during infancy IPTi reduced malaria incidence to a significantly
19 greater extent in nutritionally advantaged participants (46%) as compared to malnourished
20 children (25%, $P = 0.049$). This was particularly pronounced following IPTi dose 1 (34% vs.
21 -14%; $P = 0.02$; Tab. 4). A similar difference was observed with respect to severe anemia
22 following IPTi dose 2 ($P = 0.002$; Table 4) and in the second year of life ($P = 0.047$; Tab. 3).
23 The comparatively diminished efficacies of IPTi in malnourished children were largely
24 confirmed not only for periods of six months following each treatment dose (Tab. 4) but also
25 by a non-parametric mixture model (1) which categorizes nutritional status during the
26 complete follow-up period (Fig. 1). However, in children who experienced malaria episodes

1 during six months after IPTi administrations, time periods until the respective first or only
2 event were only slightly reduced in malnourished as compared to non-malnourished children
3 and only following dose 2 (11.3 ± 8.5 vs. 12.1 ± 8.6 weeks) and dose 3 (10.7 ± 6.8 vs. $11.1 \pm$
4 6.8 weeks) but not so following dose 1 (14.1 ± 5.0 vs. 13.3 ± 6.2 weeks; all comparisons, $P >$
5 0.5 ; Mann Whitney U test).

6 A specific constellation was observed regarding IPTi, nutritional status and severe
7 malaria. Severe malaria occurred at similar rates in malnourished and non-malnourished
8 children (both, 0.03/year). In the latter, IPTi provided a non-significant degree of protection
9 (PE, 14%; $P = 0.67$). Remarkably, however, the mere opposite was seen in children
10 malnourished at recruitment: 14 episodes of severe malaria (0.046/year) occurred in children
11 receiving SP as compared to 5 episodes (0.016/year) in the placebo group (PE, -169%;
12 95%CI, -670% - 6.3%; $P = 0.07$). This reversed impact of IPTi in malnourished children was
13 significantly different from the protective effect in their non-malnourished counterparts ($P =$
14 0.04). Repeating this analysis by applying the non-parametric mixture model (1) as before, the
15 increased risk of severe malaria in malnourished children receiving SP appeared less
16 pronounced but was still discernible (PE, -35%; 95%CI, -152% - 28%; $P = 0.35$; Wald test, P
17 $= 0.16$).

1 Discussion

2 IPTi is a simple means of malaria control in young children particularly when administered
3 alongside the well established EPI schedule. This approach has the potential to overcome one
4 of the predominant problems in disease control in sub-Saharan Africa, i.e. limited access to
5 health structures providing accurate treatment or prevention. Due to the advantages of low
6 cost, single-dose treatment, and favorable safety profile, most IPTi trials so far have used SP
7 (5,14,17,19,25,30), although the use of other drugs is also conceivable. The mode of action of
8 IPTi with SP is not fully understood but comprises properties of both treatment and
9 chemoprophylaxis, the latter appearing to predominate (25). The protective effect may also
10 result from an attenuation or containment of parasites exposed to SP consequently preventing
11 clinical disease but providing an enhanced opportunity to develop protective immunity
12 (13,31). If that is true, some degree of SP resistance might be tolerable but its exact level is
13 unknown. In fact, SP resistant *P. falciparum* parasites have spread throughout Africa in recent
14 years, a development which is also discernible in Ghana (20,22).

15 Malnutrition among infants is shamefully frequent in many parts of Africa and has
16 been shown to affect antimalarial treatment response, drug absorption, and immune responses,
17 among others (15,16,24,29,35,38,44). It is thus proximate to hypothesize that the nutritional
18 status influences the effect of IPTi. In fact, in the present study, the protective efficacies of
19 IPTi were roughly halved in malnourished children, and - as regards malaria - significantly so
20 in the first year of life when this intervention usually achieves its highest impact (17,25). Not
21 astonishingly therefore, IPTi did not improve the growth of children with malnutrition.

22 A general problem in prospectively relating the nutritional status to morbidity or IPTi
23 efficacy is the dynamic nature of the former. Not only did the prevalence of malnutrition
24 increase during follow-up. Also did anthropometric measures exhibit various longitudinal
25 patterns, e.g. poor or good initial values subsequently declining, persisting or increasing. Our
26 *post hoc* analysis is thus simplified in that these dynamic changes are largely not accounted

1 for. We nevertheless consider our results valid because stratified analyses of shorter time
2 periods following various starting points basically produced the same results (Tab. 4). We
3 consider the static classification of nutrition comprehensible and tangible, and, in terms of
4 potential nutritional intervention, the status of a child beginning with IPTi appears to be
5 practically relevant. Reassuringly, the non-parametric mixture model (1) which categorized
6 nutritional status during the complete follow-up period essentially confirmed the findings
7 produced by the static approach. Nevertheless, this limitation should be kept in mind when
8 construing our data.

9 How could malnutrition abate the protective efficacy of IPTi? An increased incidence
10 of malaria in malnourished infants could lead to the impression that IPTi is less effective in
11 these children. However, such increased morbidity was not observed in the present study,
12 contrasting previous findings (4,6,32) but corresponding with others (26). Malnutrition did
13 increase all-cause mortality. Due to the civil conflict during study conduct many deaths
14 occurred at home, and a reliable diagnosis was not available for all children. Most deaths,
15 however, presumably resulted from gastroenteritis, respiratory infections and malaria. In
16 accordance with current concepts (29,32) this indicates that malnutrition compromised anti-
17 pathogen immunity. Considering the hypothesis that (possibly enhanced) immune responses
18 to parasites attenuated or contained by SP treatment might be part of the mode of action of
19 IPTi (13,31), immune suppression caused by poor nutritional status may thus translate into a
20 reduced protective efficacy. Such could be reflected by efficacy differences between
21 malnourished and non-malnourished children increasing with age. Yet, in the present study,
22 this was not observed. Also, malnutrition may influence the efficacy of SP by reducing the
23 contribution of immunity to parasite clearance (11). In fact, in malnourished children the risk
24 of failure to antimalarial treatment (16,24) including SP (15,44) appears to be increased,
25 although not uniformly (18,21). Altered pharmacokinetics of SP in malnourished children
26 could also play a role, e.g. increased clearance, reduced drug concentrations, and reduced

1 half-life as has been shown for quinine (35). Likewise, oral chloroquine treatment has been
2 reported to be associated with reduced peak and overall drug concentrations in children with
3 kwashiorkor suggesting decreased bioavailability (38). If pharmacokinetic properties of SP
4 were altered in malnourished children (and related to the reduced efficacy of IPTi), such
5 influence would be expected to be pronounced. This is because under-nourished infants in the
6 present study received a fixed and thus a comparatively higher dose of SP than well-nourished
7 children. Regrettably, no pharmacokinetic data of SP in malnourished children let alone in
8 IPTi *per se* are available. This gap needs to be urgently closed and the selection of alternative
9 or future drugs for IPTi should also allow for pharmacokinetic properties.

10 What is the relevance of a reduced efficacy of IPTi in malnourished children?
11 Affirmatively, the potential of IPTi appears to be higher than thought (25) considering the
12 46% of protective efficacy against malaria in well-nourished children during the first year of
13 life. Contrarily, the abundance of malnutrition in African infants may impair the value of one
14 of the few available malaria control measures. The worsening international food crisis
15 primarily affects the poor and vulnerable, and malnutrition in African children can
16 consequently be expected to even increase. Already, the average Ghanaian family spends
17 some 70% of its budget on food (37). At present, it is unknown whether malnourished
18 children would benefit from refeeding in terms of IPTi, and after which time period.
19 Moreover, individual nutritional assessment preceding IPTi would question the concept of a
20 simple and affordable tool piggybacked onto the EPI system. Such operational difficulties are
21 key issues in implementing IPTi and, overall, in reducing morbidity and mortality among
22 African children. However, as stated previously (8) and confirmed here, malaria control
23 programs will have limited effects without targeting the underlying causes including
24 malnutrition. On a large scale, training to detect poor nutritional status, nutritional counselling
25 and education of caretakers and feeding programs are needed. Specifically, operational trials
26 assessing the potential impact of refeeding on the efficacy of IPTi are warranted.

1 In malnourished children, the protective effect of IPTi against severe malaria appeared
2 to be reversed, i.e. malnourished children receiving SP experienced an excess of episodes.
3 Because of small numbers and borderline statistical significance, this finding needs to be
4 interpreted with caution. As reported previously (25), most of these cases emerged during 16-
5 24 months of age and were due to severe malarial anemia (Hb <5 g/dL). Folate deficiency
6 complicating overall malnutrition could partially explain our findings: in the 1970s, folate
7 deficiency was seen in 70% of young Ghanaian children (27) and no major improvement was
8 recently observed in neighbouring Togo (3). Deficient children will experience a decrease in
9 plasma tetrahydrofolate concentrations after 3-4 months of insufficient folate intake which
10 will result in increasing megaloblastic anemia (39). SP inhibits the *P. falciparum*
11 dihydropteroate synthase and dihydrofolate reductase causing a disturbed folate metabolism
12 in the parasite (28). In wistar rats, SP induced folate deficiency (36), probably by the
13 parasite's ability to assimilate external folate reservoirs as observed in Malawian children (7).
14 The administration of SP in malnourished and concomitantly folate deficient children may
15 eventually contribute to the development of severe anemia. Unfortunately, concentrations
16 could not be assessed in the present study. Further investigations are thus needed to rule the
17 above hypothesis out.

18 In conclusion, in northern Ghana, IPTi in malnourished children achieved only
19 roughly half of the protective efficacy attainable under normal nutritional conditions.
20 Moreover, malnourished children did not benefit from IPTi in terms of weight gain or growth
21 and, possibly, bear the risk of rare but severe adverse events. This latter aspect should
22 carefully be looked at in ongoing IPTi trials and during potential implementation. Further
23 investigations on the interaction between malnutrition and IPTi and on the potential impact of
24 nutritional programs in this regard are warranted. In regions where malnutrition is frequent
25 IPTi might not achieve its maximum effect.

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14 *falciparum* in vivo to chloroquine and pyrimethamine-sulfadoxine in Rwandan patients in
15 a refugee camp in Zaire. *Trans. R. Soc. Trop. Med. Hyg.* **89:**654-656.

1 Table 1. Prevalences of malnutrition at application of intermittent preventive treatment at 3, 9
2 and 15 months of age

3

Nutritional status (%)	dose 1 (n = 1199)	dose 2 (n = 1127)	dose 3 (n = 1086)
Non-malnourished	809 (67.5)	672 (59.6)	538 (49.5)
Malnourished	388 (32.4)	451 (40.0)	540 (49.7)
Underweight	84 (7.0)	268 (23.8)	367 (33.8)
Wasting	292 (24.4)	290 (25.7)	218 (20.1)
Stunting	102 (8.5)	182 (16.1)	411 (37.8)

4

5 Two children at dose 1, four children at dose 2 and eight children at dose 3 could not be
6 categorized as malnourished or non-malnourished due to at least one missing
7 anthropometrical measure. The calculated mean dosages of sulfadoxine/pyrimethamine at
8 IPTi doses 1, 2, and 3 in malnourished children were $52.1 \pm 12.9 / 2.6 \pm 0.7$, $39.1 \pm 5.0 / 2.0 \pm$
9 0.3 , and $33.4 \pm 3.7 / 1.7 \pm 0.2$ mg/kg, respectively. The respective figures in non-
10 malnourished children were $43.5 \pm 5.5 / 2.2 \pm 0.3$, $32.5 \pm 3.1 / 1.6 \pm 0.2$, and $28.5 \pm 2.5 / 1.4 \pm$
11 0.1 mg/kg, respectively (all comparisons, $P < 0.0001$; Mann Whitney U test).

12

13

Table 2. Child growth according to age and use of intermittent preventive treatment

Child growth	First year of life			Second year of life			3-24 months of age		
	Placebo	SP	Δ (SP-Placebo) ^a	Placebo	SP	Δ (SP-Placebo) ^a	Placebo	SP	Δ (SP-Placebo) ^a
mean weight gain (g/month)	235.6	249.7	14.1 ^c	190.1	191.0	0.9	210.3	215.3	5.0
mean height gain (mm/month)	133.6	133.3	-0.3	73.2	75.4	2.1	9.8	9.9	0.1
mean MUAC ^b gain (mm/month)	-0.9	0.0	0.9	4.4	4.8	0.4	0.2	0.3	0.1
mean change in z-scores/month									
weight-for-age	-0.2	-0.2	0.0	<0.1	<0.1	0.0	-0.1	-0.1	0.0
weigh-for-height	-0.1	-0.1	0.0	0.1	0.1	0.0	<0.1	<0.1	0.0
height-for-age	-0.2	-0.2	0.0	-0.1	-0.1	0.0	-0.1	-0.1	0.0

^a, mean growth in SP group – mean growth in placebo group; ^b, mid-upper arm circumference; ^c, $P < 0.05$ by Mann-Whitney-U-Test

Table 3. Protective efficacies of intermittent preventive treatment separated by nutritional status

Outcome	First year of life	Second year of life	3-24 months
Asymptomatic parasitemia			
Non-malnourished	52.8 (32.1-67.2) ^a	26.6 (5.0-43.3) ^c	24.7 (12.5-35.3) ^a
Malnourished	16.0 (-35.4-47.9)	14.6 (-10.3-33.9)	10.9 (-9.5-27.5)
Uncomplicated malaria			
Non-malnourished	46.0 (30.0-58.4) ^{a,d}	18.6 (1.8-32.5) ^c	18.4 (5.7-29.4) ^b
Malnourished	25.2 (-7.3-47.9)	-4.5 (-26.1-13.4)	9.5 (-10.3-25.7)
Severe anemia			
Non-malnourished	48.2 (16.3-68.0) ^b	21.3 (-8.3-42.8) ^d	22.7 (3.0-38.5) ^c
Malnourished	-31.8 (-168.9-35.4)	10.2 (-17.3-31.2)	16.8 (-15.6-40.1)

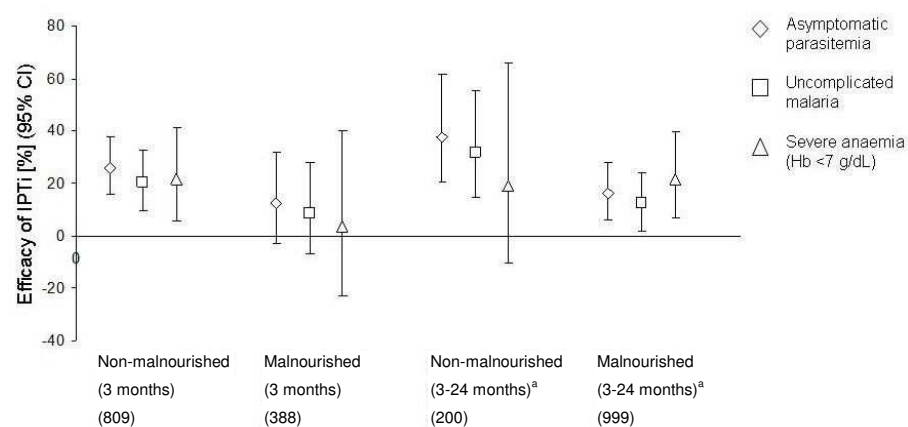
Data are protective efficacies $(1 - (\text{Events}_{\text{non-malnourished}} / \text{PYAR}_{\text{non-malnourished}}) / (\text{Events}_{\text{malnourished}} / \text{PYAR}_{\text{malnourished}}))$ and 95% confidence intervals calculated by negative binomial regression adjusted for rainfall and food availability at the respective IPTi dose administration(s). For the definition of nutritional strata see Methods section. In the first year of life, 420 children received either IPTi dose 1 or 2 in a malnourished condition. In these children, protective efficacies were: asymptomatic parasitemia, 37.1 (11.7-55.2); malaria, 14.4 (-15.2-36.4), and severe anaemia, 17.5 (-56.1-56.4). ^a, $P < 0.0001$; ^b, $P < 0.01$; ^c, $P < 0.05$; ^d, protective efficacy differs significantly between malnourished and non-malnourished children, $P < 0.05$ (Wald test)

Table 4. Protective efficacies of intermittent preventive treatment during six months following each dose stratified for nutritional status at time of dose administration

Outcome	6 months post dose 1	6 months post dose 2	6 months post dose 3
Asymptomatic parasitemia			
Non-malnourished	52.0 (32.3-65.9) ^a	43.1 (14.3-62.3) ^b	15.1 (-15.7-37.8)
Malnourished	36.1 (-2.4-60.1)	25.8 (-14.2-51.8)	2.5 (-32.0-28.0)
Uncomplicated malaria			
Non-malnourished	33.8 (14.6-48.7) ^{b,d}	36.5 (16.8-51.6) ^b	22.9 (3.9-38.1) ^c
Malnourished	-13.6 (-63.2-20.9)	35.3 (10.3-53.0) ^b	-1.2 (-26.0-18.8)
Severe anemia			
Non-malnourished	38.9 (-18.4-68.5)	54.6 (26.7-71.9) ^{b,d}	11.6 (-30.8-40.2)
Malnourished	-13.7 (-174.5-52.9)	-39.1 (-138.3-18.9)	19.1 (-10.9-41.0)

Data are protective efficacies $(1 - (\text{Events}_{\text{non-malnourished}} / \text{PYAR}_{\text{non-malnourished}}) / (\text{Events}_{\text{malnourished}} / \text{PYAR}_{\text{malnourished}}))$ and 95% confidence intervals calculated by negative binomial regression adjusted for rainfall and food availability at the respective IPTi dose administration(s). ^a, $P < 0.0001$; ^b, $P < 0.01$; ^c, $P < 0.05$; ^d, protective efficacy differs significantly between malnourished and non-malnourished children, $P < 0.05$ (Wald test)

Figure 1 Protective efficacies and 95% confidence intervals of intermittent preventive treatment from 3-24 months of age by nutritional status



Efficacies of IPTi were obtained by negative binomial regression and were adjusted for rainfall and food availability. Adjustment for possible socioeconomic confounders and differences in clinical parameters at baseline did not lead to meaningful differences. ^a, A non-parametric mixture model for longitudinal data modified according to Aitkin (1) classified the individual follow-up curves of anthropometrical z-scores from 3-24 months of age.