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Impact of Intermittent Preventive Anti-Malarial Treatment on the Growth and Nutritional Status of Preschool Children in Rural Senegal (West Africa)

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Abstract. Negative consequences of malaria might account for seasonality in nutritional status in children in the Sahel. We report the impact of a randomized, double-blind, placebo-controlled trial of seasonal intermittent preventive anti-malarial treatment on growth and nutritional status in 1,063 Senegalese preschool children. A combination of artesunate and sulfadoxine-pyrimethamine was given monthly from September to November. In the intervention arm, mean weight gain was significantly greater (122.9 ± 340 versus 42.9 ± 344 [SD] g/mo, $P < 0.0001$) and losses in triceps and subscapular skinfold measurements were less (–0.39 ± 1.01 versus –0.66 ± 1.01 mm/mo, and –0.15 ± 0.64 versus –0.36 ± 0.62 mm/mo, respectively, $P < 0.0001$ for both). There was no difference in height increments. The prevalence of wasting increased significantly in the control arm (4.6% before versus 9.5% after, $P < 0.0001$), but remained constant in intervention children: 5.6% versus 7.0% ($P = 0.62$). The prevention of malaria would improve child nutritional status in areas with seasonal transmission.

INTRODUCTION

In sub-Saharan Africa, malnutrition and malaria are major causes of morbidity and mortality in preschool children.[1,2] Malaria is responsible for ~800,000 deaths each year among children < 5 years of age in Africa.[3] It also induces neurologic disorders, including epilepsy, and cognitive defects may persist in survivors.[4] Stunting, which is the main type of malnutrition in young children, is also associated with impaired cognitive development, reduced academic achievement, and decreased physical work capacity in adulthood, with negative consequences on economic development of societies.[5] Stunting and wasting (acute malnutrition) are strongly associated with risk of death,[6,7] and malnutrition is an underlying factor in ~50% of all deaths in preschool children in less developed countries. Thus, malaria and child malnutrition remain major public health concerns in most sub-Saharan countries.

Food supplementation often has only a limited impact on child growth and nutritional status in less developed countries. Infections, by stimulating the production of proinflammatory cytokines, cause decreased appetite and abnormal metabolism of nutrients, making food resources of limited benefit. Previous studies have provided some evidence for a positive effect of malaria prevention on the nutritional status of young children including that achieved through chemoprophylaxis.[1] In this paper, we report the impact of seasonal intermittent preventive treatment (IPT) on nutritional indices in young Senegalese children.

A randomized, double-blind, placebo-controlled intervention study of intermittent preventive treatment of malaria was conducted in a cohort of 2- to 59-month-old children living in a rural area of Senegal where transmission of malaria is highly seasonal. Treatment consisted of monthly doses of artesunate and sulfadoxine-pyrimethamine given during the months of September, October, and November, the peak malaria transmission season. The intervention was highly efficacious, reducing the risk of a clinical malaria attack by 86% as described previously.[8] This study describes the nutritional benefits of malaria prevention in this cohort.

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MATERIALS AND METHODS

Study area and population. The study was conducted in an area close to the village of Niakhar, a rural area of Senegal 150 km from the capital city Dakar. The study area contains 30 villages within an area of 230 km^2.[9] In January 2003, there were 32,837 inhabitants, almost exclusively of the Sereer ethnic group. Rainfall occurs only from late June to early July to October (yearly average, 1982–2004: 443 mm), and malaria is transmitted from August to October. The predominant parasite is *Plasmodium falciparum* and the main vector is *Anopheles gambiae ss*. The mean entomologic inoculation rate is 10 infective bites per person per year.[10] Since 1983, a demographic surveillance system has been operating in the area, and dates of birth and death are known with precision for all inhabitants. Infant (< 1 year), < 5 (0–4 years), and child (1–4 years) mortality rates were 80, 213, and 144 per 1,000 livebirths, respectively, from 1994 to 1999; malaria is estimated to be responsible for ~25% of all deaths in 1- to 4-year-old children.[11,12]

The nutritional status of infants and preschool children varies strongly by season. Body weight is greatest in the dry season (April–May) and lowest at the end of the rainy season (October–November).[13,14]

Outcomes. This report describes changes in nutritional status and in the prevalence of malnutrition, which were secondary outcomes of the trial. Results related to the incidence of clinical attacks of malaria have been published previously.[8]

Subjects. Criteria for inclusion of individual children in the study were as follows: an age between 6 weeks and 59 months, no enrollment in any other malaria study, parental intention to remain in the area for the duration of the intervention (3 months), and informed consent from the parents. Oral, witnessed, informed consent of parents was sought at a specific home visit by study staff 2–3 weeks before the start of the trial. Exclusion criteria were the presence of a severe illness or severe anemia (hemoglobin [Hb] < 8 g/dL) at the time of an initial screening visit.

Another (observational) malaria study was being conducted in two of the villages in the Niakhar study zone at the time of this trial.[15] Eleven of the remaining 28 villages were selected for participation in the IPT trial on the grounds of

size, accessibility, and interest in the study. On the basis of a census conducted in July 2002, 1,203 children 2–59 months of age were selected from among those in the eligible age range, and 1,088 were included in the trial. Fifteen children had no anthropometric measurements taken during the first assessment in September 2002, and 10 were excluded from the analysis because of unlikely measurements (height-for-age or weight-for-age < −6 z-scores or > +2 z-scores, height increment from September–November < −2 cm or > +6 cm). Thus, 1,063 children (515 boys and 548 girls) were included in this analysis, 529 and 534 from the intervention and control groups, respectively. Among them, 486 (92%) and 495 (93%), respectively, had complete data at both time points in Year 1 and were included in analyses on growth rates during the intervention period. In Year 2, 954 and 934 children, respectively, were included in the anthropometric surveys conducted in July and December.

Intervention. Details of the study intervention and how it was administered have been given previously.[8] In brief, artesunate (4 mg/kg body weight) and sulfadoxine-pyrimethamine (sulfadoxine: 25 mg/kg; pyrimethamine: 1.25 mg/kg) or matching placebo were given monthly on three occasions at the height of the rainy season during the first year of the study (from mid-September to mid-November). No chemoprevention was given during the second year of observation. Compliance with the protocol was high: in both groups, 99% of subjects received the first dose and 93% received all three doses of either preventive treatment or placebo.

Case management. During the study, children with clinical malaria benefited from rapid treatment, following the national malaria public health program in Senegal: chloroquine as first-line treatment, quinine or sulfadoxine-pyrimethamine as second-line treatment, and injectable quinine for cases with persistent vomiting or severe malaria. Children who presented with pale mucosae or an illness suggestive of anemia were provided with iron supplementation. Clinically malnourished children were offered free treatment at an ad hoc nutrition rehabilitation center.

Data collection. Anthropometric data were collected at health centers by two trained measurers during drug administration in September and November 2002 (Year 1) and during home visits in July and December 2003 (Year 2), in accordance with internationally recommended procedures.[16] Weight measurements were taken using baby scales (SECA, Hamburg, Germany), precise to the nearest 10 g, for children weighing < 16 kg, and an electronic scale (Téfal, Paris, France), precise to the nearest 100 g, for older children. Recumbent length measurements were taken for children < 2 years of age, whereas standing height was measured in children beyond that age. Measurements were precise to the nearest millimeter. Left upper-arm circumference (MUAC) measurements were taken using a non-extensible tape to the nearest millimeter, and triceps and subscapular skinfold thickness were measured using a Holtain adipometer (Siber-Hegner, Miribel, France), precise to the nearest 0.2 mm. All measurements except for weight were taken twice, and the average was used for analysis. Because of error, MUAC measurements were omitted in September 2002.

Socio-demographic data (child age, sex, and village of residency, maternal age, religion, education, and professional activity) were taken from the Niakhar study area database.

Ethics. All children benefited from participation in the trial, because both intervention and control children received rapid treatment if they had malaria. Case detection was active and passive, because mothers do not necessarily seek health care for their ill children. The study protocol was approved by the ethical review committees of the Senegalese Ministry of Health and the London School of Hygiene and Tropical Medicine.

Statistical analysis. The nutritional indicators height-for-age (HAZ), weight-for-height (WHZ), and weight-for-age (WAZ) were computed in z-scores of the WHO/NCHS reference,[17] using Epi Info software V.6. Stunting, wasting, and underweight were defined as being < −2 z-scores for HAZ, WHZ, and WAZ, respectively. Arm muscle circumference

TABLE 1

Characteristics of intervention and control children at inclusion in the Senegalese trial of seasonal intermittent preventive malaria treatment in children

	Intervention (N = 529)	Placebo (N = 534)
Child age (mo)*		
1.5–11.9	90 (17.0)†	98 (18.4)
12–23.9	120 (22.7)	106 (19.9)
24–35.9	116 (21.9)	102 (19.1)
36–47.9	102 (19.3)	111 (20.8)
48–59.9	101 (19.1)	117 (21.9)
Sex		
Female	280 (52.9)	264 (49.3)
Male	249 (47.1)	271 (50.7)
Village		
1	12 (2.3)	20 (3.8)
2	48 (9.1)	48 (9.0)
3	32 (6.1)	28 (5.2)
4	28 (5.3)	27 (5.1)
5	45 (8.5)	47 (8.8)
6	80 (15.1)	66 (12.4)
7	41 (7.8)	54 (10.1)
8	76 (14.4)	93 (17.4)
9	71 (13.4)	57 (10.7)
10	27 (5.1)	31 (5.8)
11	69 (13.0)	63 (11.8)
Maternal age (years)‡		
15–24	119 (23.7)	120 (23.4)
25–29	126 (25.1)	132 (25.8)
30–34	111 (22.1)	94 (18.4)
35–49	147 (29.2)	166 (32.4)
Maternal religion§		
Moslem	351 (70.3)	350 (68.4)
Christian	137 (27.5)	149 (29.1)
Animist	11 (2.2)	13 (2.5)
Maternal education¶		
Any level	59 (11.8)	59 (11.5)
Bednet use (by child)		
Yes	92 (18.1)	100 (19.7)
Prevalence of malnutrition*		
Stunting	130 (24.6)	122 (22.9)
Underweight	111 (21.0)	103 (19.3)
Wasting	33 (6.2)	26 (4.9)
Mean nutritional status*		
BMI (kg/m^2)	15.6 ± 1.4	15.6 ± 1.5
Height-for-age (z-score)	−1.21 ± 1.13	−1.24 ± 1.16
Weight-for-age (z-score)	−1.18 ± 1.07	−1.16 ± 1.07
Weight-for-height (z-score)	−0.53 ± 0.96	−0.49 ± 1.01
Triceps skinfold (mm)	9.7 ± 2.4	9.7 ± 2.3
Subscapular skinfold (mm)	6.6 ± 1.7	6.6 ± 1.7

* At inclusion in September 2002.
† Percents in parentheses.
‡ Data missing for 48 women.
§ Data missing for 52 women.
¶ Data missing for 50 women.

TABLE 2

Mean growth during the placebo-controlled seasonal intermittent preventive treatment trial in Senegalese preschool children from September to November in year 1 by intervention group and the occurrence of clinical malaria

	Clinical malaria*†	Intervention‡§	Control	Difference¶ (intervention – control)	*P* value
Weight (g/mo)	No	+130 ± 344 (437)	+53 ± 327 (277)		< 0.01
	Yes	+109 ± 301 (49)	+38 ± 365 (218)		0.22
	Both	+123 ± 340 (486)	+43 ± 344 (497)	+80 (+35, +125)	< 0.001
Triceps skinfold (mm/mo)	No	–0.37 ± 1.00	–0.59 ± 0.99		< 0.01
	Yes	–0.11 ± 1.04	–0.55 ± 1.03		< 0.01
	Both	–0.39 ± 1.01	–0.66 ± 1.01	+0.27 (+0.14, +0.39)	< 0.0001
Subscapular skinfold (mm/mo)	No	–0.16 ± 0.64	–0.35 ± 0.64		< 0.001
	Yes	–0.13 ± 0.61	–0.41 ± 0.57		< 0.01
	Both	–0.15 ± 0.64	–0.36 ± 0.62	+0.21 (+0.13, +0.28)	< 0.0001
Height (mm/mo)	No	+7.6 ± 7.4	+8.1 ± 7.1		0.35
	Yes	+7.1 ± 8.0	+6.6 ± 7.2		0.41
	Both	+7.2 ± 7.5	+7.6 ± 7.2	–0.4 (–1.3, +0.6)	0.43

* Clinical malaria was defined as a body temperature > 37.5°C or a history of fever or vomiting within the previous 24 hours; no other obvious reason for the fever or vomiting; and a blood film positive for *P. falciparum.*

† When broken down by malaria status (the Yes and No row for each of the four growth variables), the means were adjusted for child age and village of residency within GLM, because of differences in these variables between those with and without malaria.

‡ Values are means ± SD (*N*).

§ When broken down by arm of the trial (the Both row for each of the four growth variables), unadjusted means were compared using *t* tests, because the randomization ensured that the arms had similar characteristics.

¶ 95% confidence interval in parentheses.

(AMC) was computed using MUAC and triceps skinfold (TSF) as AMC = MUAC – ($\pi \times$ TSF). Increments in weight, height, skinfold thicknesses, and arm circumference during the transmission seasons of Year 1 and Year 2 were computed as the difference between measures at extremities of the intervals, divided by the precise duration (in months).

All analyses were done using intention-to-treat; children who had only received one or two preventive treatments (of three possible) were kept in the analysis. Five age groups at the first anthropometric assessment (September 2002) were created (0–11.9, 12–23.9, 24–35.9, 36–47.9, and 48–59.9 months) and maternal school education was made binary (any versus none). Mean nutritional status in September and November of Year 1 and July and December of Year 2 and growth between September and November of Year 1 were compared between intervention and control children using *t* tests, whereas the prevalence of stunting, wasting, and underweight were compared using χ^2 test, without any adjustment for confounders as children had been randomly allocated to intervention and control groups.

In sub-analyses, growth rates between groups were compared separately for those who had suffered clinical malaria from September to November in Year 1 (49 intervention and 218 control children) and those who had not (437 intervention and 277 control children), using general linear models (GLMs) to adjust for potential confounders (5 groups of child age and 11 villages of residency) because the risk of clinical malaria and rate of growth differed for each of these variables. Clinical malaria was defined, using active case detection data, as an illness with a body temperature of 37.5°C or greater, or a history of fever or vomiting within the previous 24 hours, or both; no other obvious cause for the fever or vomiting; and the presence of *P. falciparum* asexual stage parasitemia at any density.

GLM was also used for testing the change in HAZ, WHZ, and WHZ over time. The change in the prevalence of malnutrition over time was tested using the Mantel-Haenszel procedure for repeated measures, i.e., by means of a stratified analysis where each subject constituted a stratum.[18] SAS (version 8.2) was used for all analyses.

RESULTS

At inclusion into the trial, the mean age of the study children was 31 months. There were no significant differences between intervention groups in socio-demographic status, village of residency, use of a bed net, or nutritional status (Table 1).

TABLE 3

Mean change in weight and skinfold thickness during the seasonal intermittent preventive treatment trial in Senegalese preschool children by age category and intervention group

Age group (months)	Weight gain (g/mo)		Triceps skinfold change (mm/mo)		Subscapular skinfold change (mm/mo)	
	Intervention (*N* = 487)	Placebo (*N* = 496)	Intervention	Placebo	Intervention	Placebo
2–11 (*N* = 172)	169 ± 326	113 ± 350 ns	–0.53 ± 0.96	–0.86 ± 1.09*	–0.41 ± 0.58	–0.57 ± 0.70 ns
12–23 (*N* = 201)	132 ± 345	49 ± 341 ns	–0.35 ± 0.80	–0.52 ± 1.05 ns	–0.17 ± 0.67	–0.33 ± 0.60 ns
24–35 (*N* = 199)	113 ± 303	50 ± 310 ns	–0.17 ± 1.11	–0.65 ± 1.14†	–0.01 ± 0.63	–0.22 ± 0.56†
36–47 (*N* = 199)	85 ± 311	46 ± 358 ns	–0.47 ± 1.18	–0.60 ± 0.90 ns	–0.10 ± 0.69	–0.32 ± 0.57*
48–59 (*N* = 212)	116 ± 408	–30 ± 347†	–0.47 ± 0.91	–0.66 ± 0.86 ns	–0.12 ± 0.55	–0.34 ± 0.57†
P for interaction		0.59		0.63		0.99

Differences between intervention and placebo groups within age categories: **P* < 0.05, †*P* < 0.01.

NS, not significant.

TABLE 4

Change in prevalence of malnutrition during seasonal IPT in rural Senegalese preschool children, by intervention group

Type of malnutrition	Intervention group	September Year 1	November Year 1	*P* value*
Stunting	IPT	24.1	24.7	0.62
	Control	23.3	24.4	0.38
Wasting	IPT	5.6	7.0	0.29
	Control	4.6	9.5	< 0.0001
Underweight	IPT	20.2	25.1	< 0.01
	Control	19.3	26.4	< 0.0001

* Change in prevalence over time was tested using the Mantel-Haenszel procedure for repeated measurements within SAS.[18]

The prevalences of stunting, wasting, and underweight were 23.7% (95% CI: 21.4, 26.5), 5.6% (95% CI, 4.2, 6.9), and 20.1% (95% CI, 17.7, 22.5), respectively, whereas mean nutritional indices were −1.23 ± 1.15, −0.51 ± 0.98, and −1.17 ± 1.07 (SD) for HAZ, WHZ, and WAZ, respectively. Initial nutritional status varied strongly by age ($P < 0.001$ for all indicators) but not by sex.

Growth during the malaria transmission season in Year 1. There was a significant difference in weight gain between children in intervention and control groups between September and November in Year 1; children in the intervention group gained almost three times more weight than those in the control group ($P < 0.0001$; Table 2). Triceps and subscapular skinfold thickness fell in both groups, but this loss was significantly greater in the control group than in the intervention group ($P < 0.0001$ for both). These differences were also significant when the analysis was restricted to children who had not experienced any clinical malaria episode during the period of follow-up (Table 2). Sex and maternal age did not modify significantly the effect of the intervention on growth in weight or skinfolds and neither did age of the child (Table 3). There was no difference in height gain between the two groups (Table 2).

Change in the prevalence of malnutrition during the transmission season in Year 1. Although the prevalence of wasting increased slightly during the course of the transmission season of Year 1 in the intervention group, this change was not significant. In contrast, it increased significantly in the control group ($P < 0.001$; Table 4).

There was a significant increase in the prevalence of underweight over time in both the intervention and control groups ($P < 0.01$ and $P < 0.0001$, respectively; Table 4), whereas the prevalence of stunting did not vary over time in either of the two groups.

Nutritional status at the end of the Year 1 transmission season. Mean MUAC and triceps and subscapular skinfold thicknesses were significantly greater in the intervention group ($P < 0.05$, < 0.01, and < 0.001, respectively) at the end of the Year 1 malaria transmission season, but the differences between groups were modest (Table 5). There was no significant difference between groups in terms of the mean HAZ, WAZ, WHZ, and arm muscle circumference (Table 5).

Growth after the Year 1 transmission season. There was no difference between groups in terms of changes in weight, height, MUAC, or skinfold thickness from November of Year 1 to July of Year 2. Similarly, growth did not differ between groups during the subsequent malaria transmission season (from July to December 2003). In July and December of Year 2, the only difference in nutritional status that persisted between groups was a slightly greater mean subscapular skinfold thickness in the intervention group (6.0 versus 5.8 mm, $P < 0.05$ and 6.5 versus 6.2 mm, $P < 0.05$ for the two periods, respectively).

Change in nutritional status over time. The prevalence of stunting and underweight decreased significantly between November of Year 1 and December of Year 2 in both groups of children. Stunting decreased mainly between July and December of Year 2 (from 21.0% [95% CI: 18.4, 23.6] to 12.2% [95% CI: 10.1, 14.3], $P < 0.0001$), whereas underweight became less prevalent between November of Year 1 (26.2%; 95% CI, 23.4, 29.0) and July of Year 2 (14.3%; 95% CI, 12.1, 16.5) and remained constant thereafter (13.4%; 95% CI, 11.2, 15.6 in December of Year 1). There was no significant change in the prevalence of wasting.

Because the prevalence of stunting may change with age, and our cohort aged by 15 months during the course of the study, additional analyses were conducted to compare the change in mean HAZ over time within age categories. There was a significant linear trend of increase over time for all age groups (results not shown) and for almost all age- and intervention-specific groups (Table 6).

DISCUSSION

IPT during the few months of intense malaria transmission had a strong positive effect on gain in weight and on subcutaneous fat reserves in rural Senegalese preschool children. These positive effects remained when only children without

TABLE 5

Nutritional status in November in Year 1 of the placebo-controlled seasonal intermittent preventive treatment trial in Senegalese preschool children, by intervention group

	Intervention group ($N = 496$)	Control group ($N = 506$)	Difference (Intervention vs. control)	*P*
HAZ	−1.25 ± 1.14*	−1.28 ± 1.10	0.03 (−0.11, 0.17)†	0.65
WHZ	−0.63 ± 0.93	−0.71 ± 1.03	0.08 (−0.04, 0.20)	0.20
WAZ	−1.28 ± 1.03	−1.37 ± 1.06	0.08 (−0.05, 0.21)	0.22
Triceps skinfold (mm)	9.0 ± 2.3	8.6 ± 2.2	0.42 (0.14, 0.70)	< 0.01
Subscapular skinfold (mm)	6.3 ± 1.7	6.0 ± 1.6	0.34 (0.14, 0.54)	< 0.001
MUAC (cm)	14.7 ± 1.3	14.5 ± 1.3	0.20 (0.04, 0.36)	< 0.05
AMC (cm)	11.9 ± 1.1	11.8 ± 1.1	0.07 (−0.07, 0.20)	0.37

* Values are means ± SD.
† 95% confidence intervals in parentheses.
HAZ, height-for-age z-score; WAX, weight-for-age z-score; WHZ, weight-for-height z-score, all relative to the NCHS growth reference 17; MUAC, mid-upper arm circumference; AMC, mid-upper arm muscle circumference.

TABLE 6
Mean HAZ by child age, group of intervention, and period

Child age (months)	Group	September Year 1	November Year 1	July Year 2	December Year 2	Change in mean	*P*	*P* for trend*
12–23	Control	–1.43	–1.38	–1.10	–1.19	+0.24	NS	0.035
	IPT	–1.42	–1.52	–1.05	–1.07	+0.35	< 0.01	< 0.01
24–35	Control	–1.46	–1.49	–1.30	–0.91	+0.55	< 0.001	< 0.001
	IPT	–1.40	–1.39	–1.26	–0.90	+0.50	< 0.001	< 0.001
36–47	Control	–1.36	–1.43	–1.48	–1.13	+0.23	NS	0.22
	IPT	–1.38	–1.40	–1.32	–0.96	+0.42	< 0.01	< 0.01
48–59	Control	–1.28	–1.21	–1.10	–0.93	+0.35	0.09	0.012
	IPT	–1.06	–1.04	–1.15	–0.87	+0.19	NS	0.36

* Test for trend: period is dealt with as a continuous variable (from 1 to 4) within GLM.
NS, not significant.

any clinical malaria during the transmission season were included (Table 2).

Season is a strong determinant of many aspects of life in rural areas of West Africa, particularly in the Sahelian and Sudanese-Sahelian climatic zones, which are defined by average yearly rainfalls of 250–500 and 500–900 mm, respectively, and include Burkina Faso, The Gambia, Mali, Mauritania, Niger, Senegal, Sudan, and Tchad (in total or partly). Body weight varies strongly with season in newborns,[19] 9-month-old infants,[13] preschool children, and adults.[20–22] In preschool children, reduced food intake because of lack of resources and an increased work load in women during the rainy season are considered important risk factors for malnutrition, in addition to increased morbidity from diarrhea and malaria, but evidence of the relative importance of each of the factors in constraining growth is scarce.

This study had several strengths. First, randomization of study children to the intervention and placebo groups and the double-blind design prevented a number of potential problems in interpretation of the findings. Second, anthropometric measurements were taken by well-trained, experienced field workers providing powerful comparisons even for skinfold measurements.

The observed differences in growth and nutritional status between intervention and placebo groups probably underestimated the true negative impact of malaria in unprotected populations, because control children benefited from frequent home visits and early treatment of a clinical malaria episode with an effective anti-malarial drug, conditions that do not always occur outside a trial situation. Also, the impact of the intervention on growth and nutritional status was assessed in early November at the time of administration of the last dose of intermittent preventive treatment, and the study could therefore not capture the likely nutritional benefit of this third dose.[8]

Conversely, intermittent treatment with artesunate could have had an impact on the prevalence of *Schistoma haematobium* infection,[23] and this may, in turn, have had an impact on nutrition that was unrelated to malaria prevention.

It seems that the intervention had an effect mainly on fat mass, because differences in skinfold thickness were highly significant, whereas those in arm muscle circumference were not. Also, the difference in change in triceps skinfold between intervention and control groups was significantly greater in villages with more intense exposure to malaria, suggesting a stronger beneficial effect of the intervention in these villages (data not shown). The same tendency existed for weight gain, but it was not significant.

There was no interaction between child age and the effect of the intervention on growth in weight and skinfold thickness. However, the difference in weight gain between groups was greatest among the 4-year-old children, considerably greater than among their 1-year-old counterparts (146 versus 83 g/mo).

Malaria prevention has been shown to have a positive effect on child weight and arm circumference in a number of studies. A community-randomized impregnated bed net trial among preschool children in The Gambia resulted in significant increases in WAZ and WHZ ($P < 0.01$ for both) but not in HAZ.[24] Eighteen months after the implementation of an impregnated bed net intervention among preschool children with perennial exposure to malaria, the mean arm circumference was greater in the intervention group (–1.05 versus –1.25 z-scores, $P = 0.008$), and there was a non-significant tendency towards a greater mean HAZ (–1.06 versus –1.21, $P = 0.14$).[25,26] In Tanzania, combined chemoprophylaxis and use of impregnated bed nets improved weight gain during the rainy season in preschool children, particularly in those 6–17 months of age,[27] whereas a randomized IPT trial providing sulfadoxine-pyrimethamine to infants at 2, 3, 4, and 9 months of age did not have any impact on body weight at 18 months.[28]

There was no positive effect of the IPT on linear growth in these Senegalese preschool children. The time period chosen for assessment of impact on growth (September–November) might have been too short to detect any effect on linear growth. Also, many authors consider that linear growth is sensitive to environmental stress (food intake and infections) mainly up to 2 years of age.[29] Bradley-Moore and others[30] reported on a significantly greater mean HAZ in children receiving malaria chemoprophylaxis compared with controls, within the age range of 12–23 months (93.2% versus 91.7% of the NCHS mean, $P < 0.05$). However, we found no impact of the intervention even among children < 2 years of age (results not shown).

Unexpectedly, we found an impressive 50% decrease in the prevalence of stunting in both groups (from 23.7% in September of Year 1 to 12.2% in December of Year 2). This occurred especially during the rainy season in Year 2, although no specific malaria prevention program was provided at that time. This change was apparent already in April of Year 2 during a nutritional survey conducted on a subgroup of 543 study children 6–42 months of age: compared with September of Year 1, HAZ and the prevalence of stunting had decreased from –1.48 to –1.02 z-scores and from 31.8% to 17.4%, respectively ($P < 0.0001$ for both).[31] As would be expected, the prevalence of underweight also decreased

sharply (because weight is closely correlated with height), contrasting with a constant prevalence of wasting.

This positive trend in height-for-age over time contrasts with results of prior studies in preschool children in this area. In one large-scale study (~6,000 children), mean height-for-age decreased from birth up to 18–24 months of age and remained constant from 2 to 5 years.[7] No seasonal variations occurred for this indicator. In a cohort study of 443 children, the prevalence of stunting was 35.9%, 30.7%, 31.1%, and 30.5%, respectively, and mean HAZ was –1.7, –1.5, –1.5, and –1.4, respectively, at four 6-month rounds conducted at mean ages of 18.0, 23.4, 28.7, and 34.2 months.[14]

Few controlled nutrition or health interventions have achieved similar effect sizes on height status. However, the difficulty in interpreting the results of this study is that both intervention and control groups had improved height-for-age and study children benefited from several medical services, independently of malaria prevention and treatment. Management of acute, clinical malnutrition in an ad hoc nutritional rehabilitation center during the study is not likely to have had any notable impact on linear growth, because few children were enrolled and stayed for an average of 7 days only (A. Diallo, unpublished observations). However, weekly contacts between health workers and study children for active malaria case detection may have had a non-specific positive effect on child health and growth, the so-called "health worker effect."[32,33]

If malaria-specific interventions are responsible for this accelerated linear growth rate, the most likely explanation is that early treatment of clinical malaria prevented prolonged carriage of *P. falciparum* and its associated growth-depressing immune response. Snow and others[1] suggested that clinical malaria, if adequately managed, has limited or no effects on linear growth in young children. In contrast, long-term carriage, resulting from either sub-clinical infections or non-treated clinical malaria with spontaneous recovery, may have a strong negative effect through the production of growth-depressing cytokines. Tumor necrosis factor-α (TNF) is produced in response to malaria[34] and is known to inhibit the production of insulin-like growth factor (IGF), which mediates the effect of growth hormone. However, although biologically plausible, little evidence is available to support this hypothesis at the present time. In African adolescents, malaria-induced TNF production was associated with significantly lower BMI, but linear growth was not considered.[34]

Thus, other studies are necessary to test our hypothesis of a long-term negative effect of parasite carriage on linear growth in preschool children through the production of pro-inflammatory cytokines,[34] but the design is challenging because it is ethically impossible to monitor growth in children without treating cases of clinical malaria.

In conclusion, nearly complete prevention of clinical malaria by seasonal intermittent preventive treatment improved growth in weight and skinfolds of preschool children over a 2-month period, but did not affect linear growth compared with controls benefiting from active malaria case detection and prompt treatment.

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