Active Malaria Morbidity Management Has Limited Impact on Height Status of Preschool Senegalese Children

Florie Fillol, Amandine Cournil, Cécile Cames, Cheikh Sokhna, and Kirsten Bork Simondon

Abstract

Although infections contribute to growth faltering in preschool children, malaria prevention seems to have limited impact on height status. In 2002–2003, a malaria intermittent preventive treatment (IPT) trial was conducted in Senegal, including randomly selected preschool children from 11 villages. A rapid decrease in stunting prevalence (from 28.3 to 16.3%; P < 0.0001) was reported in both intervention and placebo groups. During this 15-mo period, both groups of children benefited from active detection and prompt treatment of malaria attacks. In this study, we investigated whether management of malaria morbidity could explain the improvement of height status. An anthropometric survey, conducted in September 2004 in the area, included 929 2- to 5-y-old children. Some 539 children, previously included in the 2002–2003 IPT trial, benefited from active malaria morbidity management and formed the malaria trial group. The remaining 390 children constituted the control group. Mean height-for-age and stunting prevalence in September 2004 were compared between groups adjusting for age and mother’s activity. Mean height-for-age Z-scores did not differ between trial (~1.17 ± 0.93) and control children (~1.24 ± 1.00; P = 0.25). Only 36- to 47-mo-old malaria trial children had a lower prevalence of stunting than controls of similar age (19.4 vs. 28.7%; P = 0.044). Compared with the usually slow progression of height status related to better living conditions, it seems very likely that the rapid improvement observed among IPT study children resulted from the trial. These findings suggest that improved health services provided by the trial may also have benefited children not included living in study villages.

Introduction

Stunting remains highly prevalent in developing countries and affects 38% of children under 5 y of age in sub-Saharan Africa (1). Growth faltering is known to be a major cause of impaired cognitive development, decreased school performance, and, later, reduced physical work capacity and reproductive outcome (2). Among multiple risk factors associated with stunting, infections strongly participate in growth faltering. Indeed, acute and chronic infections may affect linear growth by decreasing food intake and nutrient absorption and increasing metabolic requirements (3). Numerous studies have investigated the impact of malaria prevention on childhood nutritional status. It has been widely demonstrated that malaria prevention improves the weight gain of children living in malaria endemic areas (4–7); however, few trials have shown a significant effect on linear growth (8,9).

In 2002, a randomized, double-blind, placebo-controlled intervention study of seasonal intermittent preventive treatment (IPT) of malaria was conducted in a cohort of 2- to 59-mo-old children living in a rural area of Senegal where transmission is mainly seasonal. The intervention was highly successful; the risk of a clinical attack was reduced by 86% (10). The prevalence of wasting increased significantly in the control group during the transmission season but remained constant in intervention children (11). In addition, an unexpected 42% decrease in stunting was observed in both groups during follow-up: from 28.3% (95% CI: 25.6–31.0) at inclusion to 16.3% (95% CI: 13.9–18.7) 15 mo later at the end of the intervention (P < 0.0001). The main hypothesis to explain this result was that this dramatic decrease did not result from the intervention per se (in that case, it would have benefited the intervention group only) but rather from malaria morbidity management provided to all children during the study. Indeed, all children included in this trial benefited from active weekly malaria case detection and prompt treatment during 2 consecutive transmission seasons.

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5 Abbreviations used: DHS, Demographic and Health Survey; HAZ, height-for-age Z-scores; IPT, intermittent preventive treatment; SP, sulfadoxine-pyrimethamine; WAZ, weight-for-age Z-scores; WHZ, weight-for-height Z-scores.
To test this hypothesis, a cross-sectional anthropometric survey conducted in September 2004 allowed for the comparison of height-for-age of children who had taken part in the 2002–03 IPT study to that of a control group of children who had not participated in any interventions. These 2 groups were comparable due to random selection of IPT study children within the 11 study villages. We hypothesized that children who had benefited from malaria morbidity management would display a better height status (higher mean height-for-age and lower prevalence of stunting) compared with children who had not received such health care.

Materials and Methods

Study area and population. The study was conducted in an area close to Niakhar, a rural district of Senegal located 150 km from the capital city Dakar. The area contains 30 villages within 230 km². Since 1983, a demographic surveillance system has been operating in the area and dates of birth and death are known with accuracy for all inhabitants. The mortality rate for children aged 1–4 y was 144 per 1000 live births from 1994 to 1999 (12) and malaria accounted for one-fourth of all deaths in this age group (13). *Plasmodium falciparum* malaria transmission occurs from August to October and preschool death rates increase sharply at that time of the year (12,14).

The nutritional status of infants and preschool children also varies widely by season. Body weight is highest in the dry season (April–May) and lowest at the end of the rainy season (October–November) (12).

2002–2003 IPT trial. A randomized, double-blind, placebo-controlled, intermittent preventive antimalarial treatment trial was conducted in 2002 and 2003 in this area. Details on this intervention have been provided previously (10). In brief, in 2002, an IPT trial included 1088 children aged 2–59 mo in September 2002 randomly selected within 11 villages in the area (10). Then, each child was randomly assigned to the treated group or placebo group. Artesunate and sulfadoxine-pyrimethamine (SP) or matching placebo were given monthly 3 times at the height of the rainy season during the first year of the trial (from mid-September to mid-November). During the 2003 transmission season, an observational follow-up study evaluated the potential rebound effect of the intervention, i.e. the risk of a higher clinical attack rate in former intervention children. Thus, no chemoprevention was provided during the follow-up, but all children included in this trial benefited from weekly active malaria case detection from July to December (through home visits by medical staff). Children ill with malaria received prompt treatment: in 2002, chloroquine as first-line treatment and SP or quinine as second-line treatment, and in 2003 SP as first-line treatment and quinine as second-line treatment. At all times, injectable quinine was administered in case of persistent vomiting or severe malaria. In 2002, children received an antimalaria treatment immediately after a malaria attack was confirmed biologically (parasitaemia > 3000 parasites/μL), whereas in 2003, all children with symptoms evocative of malaria attack were treated prior to parasitological confirmation. Furthermore, passive surveillance was operating at 2 dispensaries in the area; in addition to the nurse in-charge, a physician was appointed by the research project for the investigation of all children who presented with symptoms evocative of malaria. Treatment was identical to that of cases identified through active surveillance. There was no evidence of any rebound effect in 2003; indeed, former intervention children did not have higher rates of clinical attacks compared with placebo children (incidence ratio: 0.98 (0.82; 1.17)) (10).

During the study, 4 anthropometric surveys were conducted (September and November 2002, July and December 2003) (11).

2004 IPT trial. An additional trial was conducted from September 2004 to December 2004 in 14 villages, including the 11 villages involved in the 2002–03 IPT trial (15). This trial included a total of 2020 children aged from 6 to 59 mo who were randomly allocated to 4 different IPT regimes. A baseline survey was conducted at inclusion in September 2004 for the collection of anthropometric data.

Study design. The present study was set up as a comparison of height-for-age and stunting in September 2004 between children exposed and those not exposed to health interventions (active malaria attack detection and prompt treatment) within the 2002–03 malaria prevention trial.

Participants. Criteria for inclusion in the present analysis were age between 26 and 59 mo in September 2004 and residence in 1 of the 11 villages included in the 2002–03 IPT trial. Exclusion criteria consisted of refusal to participate and the presence of a detectable handicap that might alter linear growth.

Among the 2020 children aged 6–59 mo enrolled in the intervention in September 2004, 1452 lived in the 11 IPT villages. Among them, 539 children (aged 26–59 mo) had previously been included in the 2002–2003 IPT trial and were included in the malaria trial group. Among the 913 remaining children, 390 were aged 26–59 mo in September 2004 (i.e. aged from 2 to 36 mo in September 2002) and were included in the control group. The parents of 38 children, randomly selected from the database to take part in the 2002–3003 trial, refused participation. However, for this analysis, they were kept in the malaria trial group to maintain comparability of groups (intent-to-include analysis).

Oral, witnessed, informed consent of parents was sought at home visits prior to anthropometric assessment.

Data collection. In September 2004, anthropometric data were collected in 2 health centers by well-trained and experienced measurers in accordance with internationally recommended procedures (16). Weight was measured using an electronic scale to the nearest 10 g (SECA). Standing height of children was measured using locally made wooden boards precise to the nearest millimeter. Height measurements were taken twice and the mean used for the analysis. Anthropometric data from IPT 2002/2003 and 2004 were collected in the same manner by the same 2 anthropometrists. Sociodemographic data (the child’s date of birth, village of residence, and maternal occupation and education) were taken from the Niakhar study area database.

Statistical analysis. The nutritional indicators height-for-age, weight-for-age, and weight-for-age were computed in Z-scores of the WHO 2006 child growth standards (17) using SAS software version 8.2. Stunting, wasting, and underweight were defined for values < −2 for height-for-age Z-scores (HAZ), weight-for-height Z-scores (WHZ), and weight-for-age Z-scores (WAZ), respectively.

Sociodemographic and anthropometric characteristics were compared between the malaria trial and control groups using t tests for quantitative variables and chi-square tests for qualitative variables. Mean HAZ was compared between malaria trial and control groups using a general linear model. Comparison of stunting prevalence between the 2 groups was performed using a multiple logistic regression and corresponding odds ratio was estimated. Analyses were conducted with adjustment for variables that tend to be associated with study group (P < 0.20).

To test whether height status varied with age within each study group, ANOVA and logistic regressions were used for HAZ and stunting, respectively. Interaction between study group and age group was tested for both models to test whether child age was an effect modifier in the relationship between study group and height status. Finally, analyses stratified on age were performed using Mantel-Haenszel test and t tests for the mean (PROC MULTTEST, SAS V8.2) for stunting prevalence and mean HAZ, respectively.

Values in the text related to the nutritional indicators are means ± SD and those related to stunting, wasting, underweight, and sociodemographic characteristics are percent. All differences were considered significant at P < 0.05.

Ethics. The study protocol was approved by the ethical review committees of the Senegalese Ministry of Health and the Institut de Recherche pour le Développement.
Results

Children included in the malaria trial group and those included in the control group did not differ in terms of village of residence (data not shown), sex, or maternal characteristics (Table 1). However, the 2 groups differed significantly by age group. Indeed, children included in the malaria trial group were slightly older than those included in the control group (Table 1).

When adjusting for age and mother’s activity in a multivariate analysis, mean HAZ did not differ between malaria trial and control children ($\beta = -0.07; P = 0.25$; Table 1). Similar results were found for prevalence of stunting [odds ratio (malaria trial vs. control) = 1.28; 95% CI (0.92; 1.79); $P = 0.14$].

Neither mean WHZ nor mean WAZ differed significantly between groups and prevalence of malnutrition was similar as well (Table 1).

Addition of an interaction term between age and study groups (malaria trial vs. control) in the multivariate models allowed for testing whether the impact of malaria morbidity management differed according to age. Interaction terms between intervention group and age were not significant for either mean HAZ ($P = 0.18$) or the prevalence of stunting ($P = 0.25$).

Mean HAZ and stunting prevalence differed with age within the control group ($P = 0.01$): the highest mean HAZ values and lowest stunting prevalence were found in the oldest age group (48–59.9 mo) (Table 2). No differences with age were noted in the malaria trial group.

In age-specific subanalyses, mean HAZ tended to be higher in the malaria trial group compared with the control group among 36- to 47.9-mo-old children only ($P = 0.08$; Table 2), whereas the prevalence of stunting was lower in this age group for malaria trial children compared with control children ($P = 0.044$; Table 2).

| TABLE 1 | Sociodemographic and anthropometric characteristics of the 2002–2003 malaria trial and control groups 9 mo after the trial’s end (September 2004) |
| --- | --- | --- |
| Characteristics | Malaria trial | Control |
| --- | --- | --- | --- | --- | --- |
| Total | 539 | 390 |
| Child age, mo | | | | | |
| 24–35.9 | 156 | 28.9 | 144 | 36.9 |
| 36–47.9 | 196 | 36.4 | 135 | 34.6 | 0.03 |
| 48–59.9 | 187 | 34.7 | 111 | 28.5 |
| Sex | | | | | |
| Female | 276 | 51.2 | 206 | 52.8 |
| Male | 263 | 48.8 | 184 | 47.2 |
| Maternal characteristics | | | | | |
| Mother’s instruction$^3$ | 99 | 18.4 | 73 | 18.7 | 0.89 |
| Mother’s activity$^4$ | 66 | 12.2 | 64 | 16.4 | 0.07 |
| Nutritional status | | | | | |
| HAZ | 539 | $-1.17 \pm 0.93$ | 390 | $-1.24 \pm 1.00$ | 0.25$^5$ |
| WHZ | 539 | $-0.34 \pm 1.04$ | 390 | $-0.32 \pm 0.97$ | 0.75$^5$ |
| WAZ | 539 | $-0.91 \pm 0.92$ | 390 | $-0.93 \pm 0.90$ | 0.68$^5$ |
| Prevalence of malnutrition | | | | | |
| Stunting | 96 | 17.8 | 84 | 21.5 | 0.14$^5$ |
| Wasting | 31 | 5.8 | 19 | 4.9 | 0.58$^5$ |
| Underweight | 58 | 11.0 | 43 | 10.8 | 0.78$^5$ |

$^1$ Values are means $\pm$ SD or %.
$^2$ $P$-value for between-group comparisons.
$^3$ Percent of mothers who ever attended primary school.
$^4$ Percent of mothers with a professional activity.
$^5$ Comparison between groups was done using a logistic model adjusted for age groups and mother’s activity.

Discussion

In this study, we sought to determine whether malaria morbidity management might be an explanation for the impressive 42% decrease in prevalence of stunting (from 28.3 to 16.3%) observed in both placebo and malaria-preventively treated children at the end of the 2002–2003 IPT study (11). Indeed, all children included in this study benefited from weekly active malaria case detection by home visits and prompt treatment. Children who have benefited from active malaria management morbidity during the IPT intervention were compared with control children living in the same villages who did not receive such health care.

We found no significant difference in height status (mean HAZ or stunting prevalence) between children who had benefited from active malaria morbidity management during the IPT intervention (the malaria trial group) and control children, according to our preplanned global analysis. Thus, our hypothesis of a role of active malaria morbidity management for explaining the improvement in height status of IPT children was not confirmed by this analysis. However, in post-hoc, age-specific subanalyses, malaria trial children aged 36–47.9 mo had a lower prevalence of stunting than controls of same age (19.4 vs. 28.9%; $P = 0.044$).

The major limitation of our study is the lack of information concerning baseline nutritional status of control children. The 2002–2003 IPT study was based entirely on a comparison between children benefitting from malaria prevention treatment and placebo children. Therefore, the present study relies on the assumption that the 2 groups had similar nutritional status at baseline; i.e. at the beginning of the 2002-IPT study. This seems...
plausible, because the 2002-IPT intervention was conducted among a randomly selected group of children within the 11 study villages (10). To respect randomization, 38 children whose parents had refused participation in the malaria trial and who had thus not benefitted from active malaria surveillance and treatment were maintained in the intervention group for this analysis. However, excluding them from the study or including them in the control group did not change the results (data not shown).

Thus, our findings showed very limited differences in the prevalence of stunting between malaria trial and control groups in September 2004. Therefore, we hypothesize that the control group has experienced an important decrease in stunting from 2002 to 2004 almost similar to that of to the malaria trial group.

The significantly lower stunting prevalence in malaria trial children aged 12–23.9 mo at the initiation of malaria surveillance and treatment in 2002 and linear growth is most sensitive to environmental insults in younger children (18,19). However, the apparent lack of impact of participation in the IPT trial on linear growth of children aged below 12 mo had thus not benefitted from active malaria surveillance and treatment of same age might be a chance finding. On the other hand, these children were aged 12–23.9 mo at the initiation of malaria surveillance and treatment in 2002 and linear growth is most sensitive to environmental insults in younger children (18,19). However, the apparent lack of impact of participation in the IPT trial on linear growth of children aged below 12 mo in 2002 is surprising given the malaria incidence rate was not lower among infants (10).

We have compared our results to data of mean HAZ in central Senegal and Fatick (the region in which the Niakhar study area is located) provided by the Senegalese Demographic and Health Surveys (DHS) and the Multiple Indicators Cluster Surveys. These data indicate that the mean HAZ of preschool children increased from $-1.49 \pm 1.2$ to $-1.15 \pm 1.00$ from 1984 to 1993 (DHS-II 1992/1993) to $-1.35 \pm 1.79$ in 2000 (Multiple Indicators Cluster Surveys-II-2000), and $-1.01 \pm 1.30$ in 2005 (DHS-IV, 2005). These increases were highly significant ($P = 0.008$ and $P = 0.004$ for the 2 periods, respectively).

Thus, a marked increase in height status of preschool children occurred in the region between 2000 and 2005 and also in the country globally (data not shown). This improvement of height status was probably related to better socioeconomic conditions. Indeed, data from the World Bank showed an increase in gross national income per capita from 510 U.S. dollars in 2000 to 750 U.S. dollars in 2006 (20,21). Thus, an improvement in living conditions in the Niakhar area might partly explain the decrease in stunting observed among preschool children during the IPT intervention.

Among recent economic changes in the study area, one might cite improved techniques of cattle raising (i.e. cross-breeding between the traditional hampered ox and cattle imported from Europe; Amady Ndiaye-Sarr, personal communication).

Specific nutrition programs for 6- to 35-mo-old children and pregnant women have been carried out in Senegal, first in urban and thereafter also in rural areas, and might theoretically have contributed to this reduction of malnutrition. However, they do not seem to have had any impact on stunting prevalence compared with control areas (22). Furthermore, these programs have never been operating in the Niakhar area (Abdoulaye Ka, personal communication).

For 2003, we have data for 12- to 59-mo-old children only. With regards to change in mean HAZ or stunting prevalence from 1984 [based on the original data of a study by Garenne et al. (23)] to 2009 among 12- to 59-mo-old children living in the 11 study villages (Table 3), the impressive increase in mean HAZ during the IPT trial occurred very rapidly over a 15-mo period. Moreover, the comparison of mean HAZ of 12- to 59-mo-old children between 2004 and 2009 suggested that children's height status worsened during this 5-y period ($P = 0.03$) and that the improvement in height status from 2002 to 2003 was a temporary phenomenon.

Improvement of height status associated with better socioeconomic conditions has been described as a slow and regular process spanning several years (24–26). Therefore, the secular trend or the overall improvement of living conditions in the area suggested by data of the DHS may have contributed to the decrease in stunting prevalence observed between September 2002 and December 2003 in IPT children. However, it is unlikely to entirely explain this dramatic decrease. Other mechanisms must be involved. The implementation of the IPT intervention seems to be the most likely cause. Our hypothesis is that although they did not benefit from active malaria detection, children benefited from several medical services implemented in the villages during the trial, notably through treatment free of charge by well-qualified physicians present at dispensaries 7 dwk for malaria attacks and other diseases as well. In addition, long-term presence of health workers and medical doctors in the villages during rounds for active malaria surveillance may have promoted better health care for the population as a whole and in particular for children. This phenomenon has been described previously (27).

Because the IPT trial provided general health and medical services not focusing on malaria morbidity only, the intervention could also result in mothers’ awareness of their children’s health. Consequently, changes in mothers’ behavior associated with better health facilities free of charge might have improved the general morbidity management in study villages and contributed to this important decrease in the prevalence of stunting.

Although the IPT trial appeared to be the most likely explanation for the improvement of height status of the children living in study villages, it might theoretically also result from a chance finding.

In conclusion, the results of this study did not confirm our study hypothesis of a specific role of active malaria morbidity

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**TABLE 3** Change in HAZ and stunting prevalence of 12- to 59-mo-old children living in the 11 study villages using the WHO 2006 international growth standard 1

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<tbody>
<tr>
<td>$n$</td>
<td>1274</td>
<td>864</td>
<td>688</td>
<td>1299</td>
<td>1237</td>
</tr>
<tr>
<td><strong>HAZ</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>$-1.49 \pm 1.2$</td>
<td>$-1.54 \pm 1.1$</td>
<td>$-1.15 \pm 1.00$</td>
<td>$-1.22 \pm 1.05$</td>
<td>$-1.31 \pm 1.07$</td>
</tr>
<tr>
<td>$P^3$</td>
<td>0.32</td>
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<td>&lt; 0.0001</td>
<td>0.14</td>
<td>0.03</td>
</tr>
<tr>
<td>Stunting (HAZ $&lt;-2$)</td>
<td>31.2</td>
<td>31.4</td>
<td>18.8</td>
<td>20.1</td>
<td>24.7</td>
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<tr>
<td>$P^4$</td>
<td>0.96</td>
<td></td>
<td>&lt; 0.0001</td>
<td>0.51</td>
<td>0.006</td>
</tr>
</tbody>
</table>

1 Values are means $\pm$ SD or %.
2 Computed from the original data of the study conducted by Garenne et al. (23).
3 Mean HAZ comparison between two consecutive studies using t tests.
4 Stunting prevalence comparison between two consecutive studies using chi-square tests.
management for the improvement of height status in IPT-included children. However, medical services, improved health facilities, and the long-term presence of health workers and medical doctors in the villages during the IPT trial seem the most likely causes of the rapid decrease in stunting prevalence observed during the 15-mo period of the IPT trial. These findings suggest that health services associated with the implementation of the IPT study have benefited both included and nonincluded children in study villages.

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