Comparative effects of vivax malaria, fever and diarrhoea on child growth

Gwenyth Lee,1 Pablo Yori,1,2 Maribel Paredes Olortegui,2 William Pan,3,4 Laura Caulfield,1 Robert H Gilman,1 John W Sanders,5 Hermann Silva Delgado,6,7 and Margaret Kosek1,2*

1Department of International Health, Johns Hopkins School of Public Health, Baltimore, MD, USA, 2Biomedical Research Unit, AB PRISMA, Ramirez Hurtado 622, Iquitos, Peru, 3Duke Global Health Institute, Duke University, Durham, NC, USA, 4Nicholas School of the Environment, Duke University, Durham, NC, USA, 5Naval Medical Research Center Detachment, Lima, Peru, 6Cuidados Intensivos Neonatales, Servicio de Neonatología Hospital Apoyo Iquitos and 7Facultad de Medicina, Universidad Nacional de la Amazonia Peruana

*Corresponding author. Department of International Health, Johns Hopkins School of Public Health and Hygiene, 615 N. Wolfe St w5515, Baltimore, MD 21205, USA. E-mail: mkosek@jhsph.edu

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Background The adverse impact of Plasmodium vivax on child health beyond acute febrile illness is poorly studied. The effect of vivax malaria on child growth was evaluated and compared with diarrhoeal disease and non-specific fever.

Methods Using data from a 43-month longitudinal cohort of children 0–72 months of age (n=442) in the Peruvian Amazon, ponderal and linear growth velocities over 2-, 4- and 6-month periods were examined using longitudinal models and related to the incidence of disease during the same period.

Results An episode of vivax malaria led to 138.6 g (95% confidence interval (CI) 81.9–195.4), 108.6 g (62.8–153.2) and 61 g (20.9–101.1) less weight gain over 2-, 4- and 6-month intervals, respectively. These deficits were larger than both diarrhoea (21.9, 17.2 and 13.8 g less weight gain, respectively) and fever (39.0, 30.3 and 25.6 g less weight gain, respectively). An incident episode of vivax also led to 0.070 cm (0.004–0.137) and 0.083 cm (0.015–0.151) less linear growth over 4 and 6 months, respectively, which were also larger than deficits from diarrhoea (0.029 and 0.028 cm, respectively) and fever (not associated with linear growth deficits).

Despite the larger effect of P. vivax incident episodes on growth of a particular child, diarrhoeal disease had a larger cumulative impact on growth deficits as diarrhoeal incidence rates in this community are >10-fold higher than vivax malaria.

Conclusions Disease control measures for vivax malaria and diarrhoeal disease have the potential to improve the growth of children in endemic areas.

Keywords Vivax malaria, diarrhoea, fever, human growth, paediatric
Introduction

Undernutrition is a major underlying cause of mortality in the low- and middle-income countries, responsible for ~21% of deaths in children aged under 5 years principally through the modulation of the outcomes of major infectious diseases. It has been consistently shown that undernutrition is associated with poorer cognitive development, decreased adult stature and work capacity and poorer maternal outcomes, leading to a lifelong, multi-generational health burden. Height not gained during critical first years of life is not completely recovered and therefore linear deficits in early childhood can be seen as markers of human potential lost. The interactions of infection and undernutrition are complex and bidirectional. However, the implementation of disease control strategies for infectious diseases linked with early growth deficits merits prioritization.

Diarrhoea is associated with decreases in ponderal velocity (lowered weight gain) and linear velocity (lowered length/height gain) and attained weight and height in children. Other principal illnesses of childhood such as respiratory infections have been studied to a more limited extent. A few studies have examined the impact of fever on growth, with inconsistent findings.

Considering the global burden of malaria, the number of well-designed studies quantifying its effects on growth is limited. Several cross-sectional studies have reported a relationship between undernutrition and falciparum malaria, and between current nutritional status and recent prior incidence of Plasmodium falciparum or Plasmodium vivax. Early longitudinal studies in the Gambia and Uganda and a vitamin A intervention trial have found that falciparum malaria among infants was associated with poorer weight gain. A variety of malaria prevention programmes, utilizing insecticide-treated bednets, prophylactic treatment or indoor spraying, have also been found to have a positive effect on growth.

Loreto and the area surrounding Iquitos in the Peruvian Amazon have high rates of childhood diarrhoea and febrile disease and are hypoendemic for malaria. In cross-sectional thick smear surveys of asymptomatic individuals, the rates of parasitaemia (for either P. vivax or P. falciparum) are only 2.5% and asymptomatic parasitaemia is even less common in children. This relative paucity of asymptomatic parasitaemia makes the region an ideal site for the determination of the effect of vivax malaria on early childhood growth, as well as the cumulative impact of multiple childhood infections on growth.

Methods

Site and surveillance

Data were collected from a prospective, community-based study of 442 children 0–72 months of age in the community of Santa Clara, located 15 km southeast of Iquitos, in the Loreto province of Peru, between October 2002 through April 2006. The study was established to explore the association between common aetiologies of diarrhoea and early childhood growth. The cohort was chosen after a community census. Siblings were not eligible to participate in the cohort simultaneously. Details of this cohort have previously been reported.

Participating families were visited three times weekly by a trained health promoter to document the number and consistency of stools passed by the child over the previous 24-hour period, as well as other symptoms. This generated a continuous history of illness over the surveillance period for each participating child. Families also reported medications prescribed uniquely for vivax malaria and distributed by the local health post. The initiation of treatment required a positive thick smear for malaria. As per national guidelines, the treatment for P. vivax infection is chloroquine, with or without primaquine (not given to children under 6 months of age). These medications are used exclusively for the treatment of vivax malaria allowing for the retrospective diagnosis from medication history. Drugs distributed through the Peruvian health system have been found to be of high quality and malarial medications are not available in the private sector; self-medication for suspected malaria is not possible. No supply shortages of anti-malarial medications occurred during the study period.

Ascaris and Trichuris infections were determined by parasitology in diarrhoeal and quarterly asymptomatic stools. Instances of helminth treatment were defined by reported albendazol and/or mebendazol use, separated by at least 3 treatment-free days.

Length/height and weight were measured monthly, with each child measured on the day of their birth. Children were weighed on Salter scales (Salter Housewares Ltd, Tonbridge, UK). Length (children 0–23 months) or height (children 24–72 months) was measured using a marked platform with a sliding footboard. Socio-economic and demographic information was collected during two community censuses before and during the study period. Informed consent was obtained and the study protocol was approved by the institutional review boards of Johns Hopkins Bloomberg School of Public Health (Baltimore, MD), US Navy Medical Research Center (Silver Springs, MD), Asociacion Benefica PRISMA (Lima, Peru), and the Regional Health Department of Loreto Peru.

Clinical definitions

Diarrhoea was defined by three or more semi-liquid stools reported over a 24-hour period. Episodes of diarrhoea or fever were defined by symptoms separated by at least 3 symptom-free days. The incidence of vivax malaria was determined by at least 1 day
of reported primaquine or chloroquine treatment. If anti-malarial therapy was repeated within 28 days, it was interpreted as a single episode. Diarrhoea and vivax malaria were considered ‘associated with fever’ whenever fever was reported within 2 days of the illness episode. Stunting and underweight in this population were defined according to the 2006 WHO standards.26

**Statistical analysis**

The primary outcomes of interest were ponderal and linear velocities for each child (see Supplementary Table S1), computed over 2, 4 and 6 months to account for both short- and longer-term trends within the confines of the data available. Incidence rates (IRs) and 95% CIs were computed for each age category using Poisson regression. Unadjusted smoothed plots of growth velocity among children with and without vivax malaria, and with >75th percentile diarrhoea, and <25th percentile diarrhoeal incidence for their age, were generated.

Longitudinal linear models with random effects were used to examine the effects of diarrhoea, fever and vivax malaria on ponderal and linear velocity. The covariance structure of the models was determined based on a visual inspection of the autocorrelation function as well as model fit. Linear velocity models explicitly accounted for the correlated nature of the data by specifying an appropriate autoregressive covariance structure for each 2-, 4- and 6-month model; ponderal velocity retained an unstructured covariance. Age terms were included as fractional polynomials, which is a method to adjust for curvilinear relationships.27

Based on prior literature documenting the importance of the detected presence of helminth infection,28 seasonality,29 socio-economic status,30 parental height,31 and prior nutritional status on childhood growth, variables considered for model inclusion included Ascaris and Trichurus infections, sex, mother’s height, per-capita income, seasonality (as a categorical variable, with each category representing a calendar month), underweight and stunting, birth weight, maternal age, maternal education, crowding, the presence of a household latrine, household water connection type, and breast-feeding status; variables were selected into the final model based on model fit. In linear but not ponderal velocity models, incident episodes that occurred in the 2 weeks before anthropometry were discounted (subtracted from the total incidence in the period).

The final ponderal and linear velocity models are shown in Equation 1. The models tested the impact of diarrhoea, *P. vivax* and fever controlling for age, sex, per-capita income, seasonality and the presence of underweight and stunting.

\[
(Y_{ij} - Y_{i-1,j}) = b_j + b_0 + b_1 \text{diarrhoea} + b_2 \text{vivax} + b_3 \text{fever} + b_4 \text{gender} + \cdots + b_21 \text{Age Term 1} + b_{22} \text{Age Term 2} + \epsilon_{ij}
\]

In Equation 1, \(j\) represents the child, \(i\) represents the age in months, \((Y_{ij} - Y_{i-1,j})\) the change in total length or weight in the previous \(n\) months \((n = 2, 4\) or 6 representing the 2-, 4- or 6-month model), diarrhoea, fever and vivax refer to the number of incident episodes over the \((i-n)\) period.

All analysis was performed using Stata 11 (Statacorp, College Station, TX, USA).

**Results**

Of the 442 children enrolled, eight were excluded because of limited anthropometric data. The 434 remaining children yielded 838.78 total child-years of surveillance and 11,248 monthly anthropometry visits. Breastfeeding was nearly universal, and the timing of the introduction of complementary foods and weaning fairly homogeneous, with 85.7% of 3-months-olds exclusively breastfed, 76.6% 9-month-olds partially breastfed and 88.8% fully weaned by 2 years. The community was also fairly homogeneous socio-economically, with 52.5% of mothers having completed primary education and 46% having completed secondary education. Sixty-eight percent of families had a household water connection and 69% had a private latrine (Supplementary Table S2). An average of 0.60 Ascaris or Trichurus infections per child per year were identified through study stools, and 1.25 albendazole or mebendazole treatments per child per year were reported.

**Disease incidence**

A total of 3987 diarrhoeal and 5613 fever episodes were identified. Of the fever episodes, 4117 (73.3%) were not temporally associated with diarrhoea or malaria; fever associated with 33 falciparum malaria episodes was also discounted. The mean duration of diarrhoeal episodes was 2.6 days and the median 1 day (inter-quartile range 3 days). The mean duration of non-diarrhoeal, non-malaria fever was 1.7 days (median 1 day, inter-quartile range 2 days). Diarrhoeal incidence was highest (9.6 episodes/year) in the 12–17 month age group, and declined in older children; fever was highest in the youngest children (6.5 episodes/year) and declined more gradually (Table 1). Two hundred and three vivax malaria episodes were identified. Two hundred and ninety-seven children never experienced vivax malaria during the study period (68.4%), 95 experienced 1 episode (21.2%) and 42 experienced >1 (16.9%). Infection was most
frequent in May (27 episodes) and least frequent in December (7 episodes).

Participants with vivax malaria during the study period were similar to participants without in mother’s education ($P = 0.286$), per-capita income ($P = 0.146$), birth weight ($P = 0.91$), birth length ($P = 0.68$) and mean height-for-age and weight-for-age (by two-sided t-tests at 12, 24, 36, 48, 60, 72 months of age, data not shown). The incidence of vivax malaria was lower among children <24 months of age, and roughly stable among children 24–72 months (see Table 1).

Effects of diarrhoea, fever and malaria on growth

Smoothed plots of the unadjusted data (Supplementary Figure S1) suggested that children with relatively higher diarrhoeal burdens experienced, on average, decreased ponderal and linear velocities compared with children with less disease. Similarly, the data suggested that vivax malaria was associated with decreased 6-month ponderal and linear velocities (Supplementary Figure S2).

In the adjusted models, these relationships persisted. Diarrhoeal incidence predicted decreases in ponderal velocity of 21.9, 17.2 and 13.8 g/episode for 2-, 4- and 6-month intervals, respectively, and decreases in linear velocity over 4- and 6-month intervals of 0.029 and 0.028 cm/episode, respectively (Tables 2, 3 and Figure 1).

Non-diarrhoea, non-malaria associated fever predicted decreased ponderal velocities over all intervals of 39.0, 30.3 and 25.6 g/episode less for 2-, 4- and 6-month intervals), but was consistently non-predictive of linear velocity (Table 2, 3 and Figure 1).

Vivax malaria led to decreases in ponderal velocity of 138.6 (95% CI:81.9, 195.4), 108.0 (62.8, 153.2) and 61.0 (20.9, 101.1) g/episode over 2, 4 and 6 months, respectively (Table 2). Vivax malaria also predicted a 0.070 cm/episode decrease in 4-month linear velocity and a 0.083 cm/episode decrease over 6 months (Table 3).

Cumulative impact of infections

Figures 2 and 3 represent the cumulative impact of diarrhoea, fever and vivax malaria on mean velocities at the population level. Overall, the combined burden of these three illnesses on the cohort was estimated to be 12.2% (95% CI 15.3–9.0%), 13.9% (17.4–10.4%), 11.5% (14.3–8.7%) and 9.5% (7.2–11.5%) less weight gain at 12, 24, 36 and 48 months of age, respectively. Diarrhoea and vivax malaria were estimated to decrease length gain by 1.5% (95% CI 0.7–2.2%), 2.4% (1.3–3.5%), 1.9% (1.1–2.8%) and 1.5% (0.8–2.1%) at 12, 24, 36 and 48 months of age, respectively.

The effect of diarrhoea was greater than that of vivax until 35 months of age. After 42 months, fever became the largest cause of decreases in ponderal velocity. The three illnesses combined had the largest absolute effect at 13 months (66.7 g less weight gain), but resulted in the greatest percent effect at 20 months (14.2% less weight gain). Similarly, diarrhoea and vivax malaria led to 0.11 cm less linear gain at 17 months, but had the greatest percent decrease (2.4%) at 24 months of age. Although a single episode of vivax malaria was associated with the greatest decline in linear velocity compared with diarrhoea and fever, its low incidence in this community meant that its contribution to growth faltering at the population level was lower than that of diarrhoea.

Discussion

This prospective cohort study evaluated the effect of vivax malaria, diarrhoea and fever on the growth of children 0–72 months of age in an area of unstable malaria transmission. An episode of vivax malaria had effects on ponderal and linear velocity that were 4–6 and 2–3 times greater than for diarrhoea, respectively. However, the high incidence of diarrhoeal illness makes it a more important determinant of linear growth deficits in this community. The cumulative effect of these three syndromes resulted in deficits
### Table 2 Ponderal velocity models

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>2 months weight gain (grams)</th>
<th>4 months weight gain (grams)</th>
<th>6 months weight gain (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea incidence</td>
<td>-21.9†† (−33.3, −10.5)</td>
<td>-17.2†† (−26.3, −8.2)</td>
<td>-13.8†† (−22.0, −5.7)</td>
</tr>
<tr>
<td>Vivax incidence</td>
<td>-138.6†† (−195.4, −81.9)</td>
<td>-108.0†† (−153.2, −62.8)</td>
<td>-61†† (−101.1, −20.9)</td>
</tr>
<tr>
<td>Fever incidence</td>
<td>-39.0†† (−51.2, −26.8)</td>
<td>-30.3†† (−40.2, −20.5)</td>
<td>-25.6†† (−34.5, −16.6)</td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex: female</td>
<td>-11.7 (−33.5, 10.1)</td>
<td>0.3 (−38.9, 39.4)</td>
<td>-0.3 (−58.6, 57.9)</td>
</tr>
<tr>
<td>Per-capita income*</td>
<td>15.4†† (4.7, 26.2)</td>
<td>34.8†† (15.3, 54.3)</td>
<td>60.8†† (31.5, 90.1)</td>
</tr>
<tr>
<td><strong>Seasonal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthropometric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunted at onset</td>
<td>-48.4††† (−71.1, −25.7)</td>
<td>-41.2††† (−75.7, −6.6)</td>
<td>9.8 (−33.6, 53.3)</td>
</tr>
<tr>
<td>Underweight at onset</td>
<td>197.7††† (149.2, 246.2)</td>
<td>383.9††† (317.9, 450.0)</td>
<td>509.2††† (431.8, 586.6)</td>
</tr>
<tr>
<td>FP Age Term 1</td>
<td>-56.7††† (−92.9, −20.6)</td>
<td>74.6††† (67.0, 82.1)</td>
<td>-46.7††† (−76.4, −17.0)</td>
</tr>
<tr>
<td>FP Age Term 2</td>
<td>-82.9††† (−98.9, −66.9)</td>
<td>-117.2††† (−162.1, −72.2)</td>
<td>-115.4††† (−135.2, −95.6)</td>
</tr>
<tr>
<td>Constant</td>
<td>351.8††† (312.3, 391.3)</td>
<td>624.2††† (570.0, 678.7)</td>
<td>883.1††† (817.7, 948.6)</td>
</tr>
</tbody>
</table>

†P ≤ 0.10 level.
††P ≤ 0.05 level.
†††P ≤ 0.01 level.
*(variable – mean)/SD.
**Included in each model as a categorical variable (by month), results not shown.
Per-capita income is expressed in terms of standard deviations from the population mean. FP age terms are fractional polynomial age terms (age in days divided by 1000): 2-month velocity model, Age Term 1 = Age\(^{-1}\) and Age Term 2 = Age\(^{-2}\)×ln(Age); 4-month velocity model, Age Term 1 = Age\(^{-2}\) and Age Term 2 = Age\(^{-1}\); 6-month model velocity model, Age Term 1 = Age\(^{-2}\); and Age Term 2 = Age\(^{-3}\)×ln(Age).

### Table 3 Linear velocity models

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>2 months linear gain (cm)</th>
<th>4 months linear gain (cm)</th>
<th>6 months linear gain (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea incidence</td>
<td>-0.007 (−0.022, 0.008)</td>
<td>-0.029††† (−0.043, −0.014)</td>
<td>-0.028††† (−0.043, −0.013)</td>
</tr>
<tr>
<td>Vivax incidence</td>
<td>-0.016 (−0.086, 0.054)</td>
<td>-0.070†† (−0.137, −0.004)</td>
<td>-0.083†† (−0.151, −0.015)</td>
</tr>
<tr>
<td>Fever incidence</td>
<td>0.007 (−0.008, 0.023)</td>
<td>-0.002 (−0.017, 0.013)</td>
<td>-0.004 (−0.019, 0.011)</td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex: female</td>
<td>0.005 (−0.031, 0.042)</td>
<td>0.059 (−0.018, 0.136)</td>
<td>0.076 (−0.035, 0.186)</td>
</tr>
<tr>
<td>Per-capita income*</td>
<td>0.037††† (0.018, 0.055)</td>
<td>0.088††† (0.049, 0.127)</td>
<td>0.125††† (0.074, 0.185)</td>
</tr>
<tr>
<td><strong>Seasonal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthropometric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stunted at onset</td>
<td>0.149††† (0.116, 0.182)</td>
<td>0.413††† (0.361, 0.465)</td>
<td>0.567††† (0.506, 0.628)</td>
</tr>
<tr>
<td>Underweight at onset</td>
<td>-0.126††† (−0.186, 0.067)</td>
<td>-0.130†† (−0.205, −0.056)</td>
<td>-0.108†† (−0.189, 0.027)</td>
</tr>
<tr>
<td>FP Age Term 1</td>
<td>0.186††† (0.17, 0.193)</td>
<td>0.489††† (0.369, 0.610)</td>
<td>0.309††† (0.279, 0.340)</td>
</tr>
<tr>
<td>FP Age Term 2</td>
<td>0.060††† (0.058, 0.063)</td>
<td>-0.392††† (−0.454, −0.330)</td>
<td>0.807††† (0.661, 0.953)</td>
</tr>
<tr>
<td>Constant</td>
<td>1.213††† (1.162, 1.264)</td>
<td>2.165††† (2.082, 2.249)</td>
<td>3.323††† (3.222, 3.424)</td>
</tr>
</tbody>
</table>

†P ≤ 0.10 level.
††P ≤ 0.05 level.
†††P ≤ 0.01 level.
*(variable – mean)/SD.
**Included in each model as a categorical variable (by month), results not shown.
Per-capita income is expressed in terms of standard deviations from the population mean. FP age terms are fractional polynomial age terms (age in days divided by 1000): 2-month velocity model, Age Term 1 = Age\(^{-2}\) and Age Term 2 = Age\(^{-2}\)×ln(Age) and 4-month velocity model, Age Term 1 = Age\(^{-1}\) and Age Term 2 = Age\(^{-1}\)×ln(Age) and 6-month model velocity model: Age Term 1 = Age\(^{-2}\) and Age Term 2 = Age\(^{-1}\).
in the mean ponderal velocity of 7–14% and deficits in mean linear growth of 1–2.4%.

Our study corroborates prior findings that diarrhoeal disease is associated with poorer ponderal and linear growth\(^5,6\) and that fever is associated with decreased ponderal but not linear velocity.\(^8\) This finding is undermined by our inability to ascertain the source of fevers, in particular lower respiratory tract infections. In the context where this surveillance occurred, diagnostic testing is limited, which is typical in underdeveloped areas. Dengue\(^32\) and other viral infections are endemic alongside more common aetiologies such as respiratory or urinary tract infections, and it is quite possible that specific aetiologies of febrile illness within this subset have significantly different effects on child growth compared with the composite category of non-malarial, non-diarrhoeal febrile illness described in this analysis.

This study site offers several advantages in looking at the effects of \(P. \text{ vivax}\) on childhood growth. First, other studies have found that the majority of \(P. \text{ vivax}\) in this community is symptomatic, especially in young children,\(^23,24\) although more asymptomatic vivax is found clustered around cases.\(^33\) Our methods did not allow for the estimation of the effect of asymptomatic infections on growth. Additionally, the public clinic in this area is the heavily utilized, unique distributor of malaria medications, which are prescribed only following a positive thick smear. Therefore, symptomatic malaria in this cohort tended to be identified rapidly and treated correctly. Nevertheless, because untreated episodes could not be counted, our methods may underestimate the incidence of vivax children.

\[\text{Figure 1} \quad \text{This figure shows the mean and estimated 95\% CI for predicted ponderal and linear velocity deficits due to one incident episode of diarrhoea, fever or vivax malaria, using the adjusted models presented in Tables 2 and 3. Declines which were associated with a } P = 0.05 \text{ or less are denoted with an “asterisk”}\]

\[\text{Figure 2} \quad \text{This figure shows the percent difference in model-predicted weight gain between healthy children and children experiencing an average disease burden. For example, 36-month-olds have predicted 2-month ponderal velocity declines of 1.3, 3.5 and 6.7\% due to vivax malaria, diarrhoea and fever, respectively, yielding a cumulative decrement of 11.5\%}\]

\[\text{Figure 3} \quad \text{This figure shows the impact of disease burden on 6-month linear velocity at the population level. For example, 36-month-olds with an average disease burden have a predicted 6-month linear velocity decline of 0.26\% (0.009 cm) and 1.67\% (0.059 cm) due to vivax malaria and diarrhoea, respectively: a cumulative decline of 1.94\%}\]
malaria in this population. Untreated disease or disease for which treatment was delayed could also potentially lead to more severe growth impacts than we observed. Therefore the measured deficits likely underestimate the severity of growth deficits caused by *P. vivax* in settings where treatment is less readily available.

Because in most intervals only a single vivax malaria episode was detected, the decreasing size of the vivax coefficient moving from 2- to 6-month ponderal velocity models provides some suggestion of how long a child might require to overcome the weight-related impact of an infection: the impact of vivax malaria over a 4-month interval was roughly 78% of what it was over 2 months, and over 6 months, roughly 44%. However, the impact of vivax was still large at 6 months, implying that child growth had still not recovered from the episode (Figure 1).

In linear velocity models, episodes that began in the 2 weeks prior to anthropometry were discounted. This choice was based on findings by Checkley et al. that the effect of diarrhoea on height appears to be delayed by at least this long. We verified this relationship in our data by comparing the model fit.

A variety of methods have been used to model attained weight/height by age including fractional polynomial models and cubic spline methods. We chose the automated selection of fractional polynomial to model non-linear age/velocity trends. This allowed us to adjust for the effect of age in our analysis with relatively few terms, and the models generated fit the data well over the age range of our study participants.

Malnutrition is known to prolong the incidence and duration of diarrhoeal episodes. Evidence also suggests that undernutrition augments severity in *P. falciparum* infection, at least in cases of severe undernutrition. In this population under longitudinal surveillance there was no evidence that children who experienced vivax malaria were of poorer nutritional status before the episode than their counterparts based on anthropometric measures. In this epidemiological context of low transmission, children are non-immune or pauci-immune, and it is possible that this association may differ in an area of higher transmission intensity if the immunomodulatory effects of undernutrition are primarily related to the efficacy of the acquired, rather than the innate response. There is evidence to support this. Whether malnutrition predisposes to more severe vivax malaria, however, is a separate issue that cannot be addressed by our data, since no children presented with severe disease.

Plots of observed velocities by recent vivax malaria status (Supplementary Figure S2) suggested a more severe effect on growth in younger children. Therefore, models that included interaction terms between disease incidence and age were considered. Results indicated a greater effect in younger children (<24 months of age); however, they failed to reach statistical significance. The small number of vivax malaria episodes in our study population and limited child-years of data among younger children limit our ability to draw conclusions. Further investigation is needed to clarify whether vivax malaria results in greater decelerations in growth velocity among younger children.

There is strong evidence that helminth infections have a negative impact on growth. In this study, stool collection protocols included the collection of diarrhoeal and quarterly asymptomatic stools and an average of 7.8 stools were analysed per child per year; helminth infections detected were generally treated promptly within 3 days of stool collection. Additionally, treatment was frequently reported when the helminth infection had not been detected, likely as a result of public clinic and parental initiative. Binary variables indicating the presence of Ascaris and Trichuris were not predictive in simple and multi-variate ponderal and linear velocity models. That these infections did not result in growth deficits in this population although they were quite common supports arguments for intensive control programmes.

There are a number of reports documenting the presence of severe clinical disease resulting from *P. vivax* infection. The children in this study had uncomplicated clinical disease and were all treated on an ambulatory basis, did not present signs of severe anaemia, respiratory distress or impaired consciousness and would not meet case definitions of severe disease. Despite this, our findings are evidence that typical clinical cases of *P. vivax* are not benign, especially in young children. Poorer linear growth and weight gain increase a child’s risk of becoming stunted or underweight, conditions that in turn increase a child’s risk of more severe illnesses and of mortality. Furthermore, growth deficits in early life are associated with lifelong deficits in work capacity and cognitive function, an enduring consequence of these common childhood infections.

In developing countries, growth faltering is frequently followed by catch-up growth. However, in settings where infectious diseases are persistent and diets marginal, children who become malnourished often do not catch up.

Our study again reinforces the need for measures to control diarrhoeal disease. Improved water-storage practices and maternal education that extends beyond primary school have previously been identified as low-cost achievable interventions with high potential impact on diarrhoeal burden in this community. Additionally, we found that vivax malaria has an important and previously undescribed impact on childhood growth, extending at least 6 months in duration. Further studies will be required to determine if these deficits are lasting or can be modulated by specific disease control interventions.
Supplementary Data

Supplementary Data are available at IJE online.

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Conflict of interest:
None declared.

KEY MESSAGES

- Vivax malaria in early childhood adversely affects ponderal and linear growth. The effect seen was greater per disease episode than that of diarrhoea for both ponderal and linear growth and that of fever for ponderal growth. This deficit suggests a durable adverse effect of vivax malaria on child health that has not been recognized previously.
- The increased incidence of diarrhoea relative to vivax malaria resulted in greater cumulative deficits in growth due to diarrhoea.
- Successful interventions for both diarrhoea and vivax malaria would be expected to improve child growth in endemic settings.

References

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