Original papers

Plasmodium vivax: a cause of malnutrition in young children


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Summary
We studied the aetiology of malnutrition in a cohort of 1511 children <10 years old in Espiritu Santo, Vanuatu. Malnutrition was categorized using standard anthropometric criteria as: underweight [weight-for-age (WA) Z score <-2], wasting [weight-for-height (WH) Z <-2], or stunting [height-for-age (HA) Z <-2]. On multiple logistic regression analysis, the only factors significantly associated with wasting were age <5 years [OR (95% Cl) 1.8 (1.2-2.9), p = 0.01] and having suffered one or more episodes of clinical P. vivax malaria in the 6 months preceding nutritional assessment [OR 2.4 (1.3-4.4), p = 0.006]. The incidence of P. vivax infection was significantly higher during the 6 months preceding assessment in underweight vs. non-underweight children [incidence rate ratio (IRR) 2.6 (1.5-4.4), p <= 0.0001]. These groups had similar incidences of clinical P. falciparum infection during the same period [IRR 1.1 (0.57-2.1) p = 0.8] and of either species during the 6 months following assessment [IRR P. vivax 1.3 (0.9-2.0) p = 0.2; IRR P. falciparum 1.3 (0.9-1.9) p = 0.2]. In these children, P. vivax malaria was a major predictor of acute malnutrition; P. falciparum was not. Wasting neither predisposed to nor protected against malaria of either species. Although P. vivax malaria is generally regarded as benign, it may produce considerable global mortality through malnutrition.

Introduction
Malnutrition plays a major role in child mortality in tropical communities1-2 and is associated with lasting effects on growth and cognitive development. For the purposes of population studies, it is usually described on the basis of weight-for-age (WA) Z-scores (standard deviation scores from a reference median) and is classified as mild-moderate (WA Z -2 to -3) or severe (WA Z <=-3). It has been estimated that in developing countries, 56% of child deaths are attributable to the potentiating effects of malnutrition, and that 83% of these deaths are attributable to mild-moderate as opposed to severe malnutrition.2 Although in most tropical countries the aetiology is multifactorial, poor nutritional intake and infection appear to play important and synergistic roles.3

The relationship between malnutrition and malaria is complex. On one hand, the potentially malignant
parasite, *P. falciparum*, is almost certainly an aetiologi-
atical agent.4-7 On the other, there is some evidence
that malnutrition may protect against *P. falciparum*
malaria,6,8 although this conclusion is not supported
by prospective data from The Gambia.10 There are,
however, very few data on the relationship between
malnutrition and the benign parasite *P. vivax*.

This study examines the aetiology of malnutrition
on the island of Espiritu Santo in the SW Pacific,
where malaria of both species is endemic.

**Methods**

**Study site**

Espiritu Santo is one of the northern islands of
Vanuatu in Melanesia. The demographic character-
istics of the island are typical of a developing
nation.11 Mortality rates in infants and children < 5
years are 45/1000 and 58/1000, respectively.
Although the island is extremely fertile, and plentiful
supplies of nutritious food are available throughout
the year, it has been estimated that >23% of
children < 5 years old are malnourished.12 Diarrhoea,
a common cause of malnutrition in many areas, is
uncommon in Santo, being associated with < 5% of
illness episodes (TW and KM, unpublished data).

Malaria is endemic throughout the island, and is
one of the leading causes of admission to hospital
in childhood. Transmission persists throughout
the year, although 80% of new *P. falciparum* infections
occur in the wet season (November-May).11 Two
distinct areas can be described on the basis of
malaria prevalence: on the eastern plateau (design-
nated East) malaria is mesoendemic (spleen index
in children 2–9 years 11–50%) whereas in the south
of the island (designated South) the disease is hyper-
endemic (spleen index > 50%). In the South, chil-
dren < 10 years old experience an average of two
clinical malaria episodes each year and malaria is
responsible for 20–25% of childhood fevers.11
Overall, *P. falciparum* is responsible for 60% of
malaria infections in childhood; however, *P. vivax*
is the cause of 60% of infections in the first 2 years
of life, and is the predominant parasite in the dry
season (June–October).11 The α+ thalassaemia gene
frequency in this population is 0.26.13 Full accounts
of the population distribution, clinical effects and
underlying molecular pathology of this condition
have been reported previously.13-16

**Study population**

The study was conducted between January 1992 and
November 1993. All children < 10 years old from
13 villages (three villages in the East, 10 villages in
the South) were recruited. Trained field workers
visited all children once a week, completed a
standard morbidity questionnaire and recorded each
child’s axillary temperature using an electronic digital
thermometer (Toshiba model MT-600–1, Jencons
Scientific). Blood smears for malaria microscopy
were prepared from finger-prick blood on children
with a history of fever during the preceding 24 h or
an axillary temperature > 37.4°C.

**Anthropometry**

Anthropometric assessments were made during a
series of cross-sectional surveys conducted through-
out the study period. For the purposes of this study,
only the first recorded assessment was used for any
child assessed more than once. All children were
weighed in light clothing and without footwear. Those
who were able to stand without support were
weighed on electronic standing scales (Soehnle
model 7300, CMS Instruments). Those unable to
stand were weighed using hanging scales (Salter
MP–25, CMS Instruments). All weights were recorded
to the nearest 100 g. Supine length was measured
on all children < 2 years old using a length board
(AHRTAG design) as modified by Nicoll &
Ulijaszek.17 Standing height was measured on those
≥ 2 years old using a wall-mounted device
(Microtoise, CMS Instruments). Both length and
height were recorded to the nearest 0.1 cm. Birth
dates were ascertained from health records.

**Laboratory methods**

Thick and thin blood films were stained with Giemsa
stain and examined by a trained laboratory techni-
cian using an Olympus binocular microscope model
CH2 (Olympus Instruments). Twenty percent were
checked by a second observer. Films were declared
negative only after 100 thick film fields had been
examined. Parasites were speciated on thin films and
densities calculated from thick films using standard
methods.11 Blood was collected on all children,
DNA extracted and α+ thalassaemia status deter-
mained by the Southern blot procedure.18

**Statistical methods**

All data were stored in a computer database (Paradox
v4.0, Borland). WA, WH and HA Z scores were
 calculated for each individual using Epi Info v6.0
(CDC, Atlanta) which compares data to the National
Centre for Health Statistics (NCHS) reference values.
Underweight and wasting (indices of acute malnutri-
tion) were defined as WA Z ≤ −2 (which approxi-
mates to 80% of the median weight-for-age) and
WH Z \leq -2, respectively, stunting (an index of chronic malnutrition) as a HA Z \leq -2 (approximately 90% of the median height-for-age) and low birth weight as \leq 2.5 kg. Mean WA and HA Z scores between areas of different malaria transmission were compared by ANOVA. Case definitions for clinical malaria have been determined previously by multiple logistic regression; clinical *P. falciparum* malaria was defined as fever in the presence of \geq 1000 asexual forms of *P. falciparum*/µl of whole blood and clinical *P. vivax* as fever with \geq 500 asexual forms of *P. vivax*/µl. The incidence of clinical malaria was determined from active surveillance data for the 6 months before and the 6 months after anthropometric assessment as previously described using the formula: (total clinical malaria episodes/total observations) and are reported as episodes/1000 child-weeks of follow-up (CWFU).

It was predicted that a number of factors might be associated with underweight, wasting and stunting (Table 1). For children living in the South, where malaria was hyper-endemic, such associations were explored using \(\chi^2\) tests for binary variables and \(\chi^2\) for linear trend for factors with >2 categories. Variables significantly associated on univariate analysis (p \leq 0.05) (see Table 1) were included in a multivariate logistic regression analysis including only children with full data for all these variables (n = 703). Variables were dropped sequentially until only those with a significance value \leq 0.05 remained in the model.

To explore the question of reverse causality, that is whether clinical malaria was a risk factor for malnutrition or whether malnutrition altered the risk of subsequent malaria, the incidence of *P. falciparum* and *P. vivax* were compared between underweight and non-underweight, and wasted and non-wasted children and expressed as incidence rate ratios (IRR).
Table 1  The prevalence and associations of underweight and stunting in children living in the area hyper-endemic for malaria

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>WA Z score ≤ -2</th>
<th>HA Z score ≤ -2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>c²</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>236</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>281</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>381</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>464</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>434</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Genotype*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-α/α</td>
<td>74</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>-α/αα</td>
<td>285</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>αα/αα</td>
<td>539</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>6.2</td>
<td>0.01</td>
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<tr>
<td>Birth weight</td>
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</tr>
<tr>
<td>≤ 2.5 kg</td>
<td>51</td>
<td>35</td>
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</tr>
<tr>
<td>&gt; 2.5 kg</td>
<td>280</td>
<td>21</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>4.6</td>
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<tr>
<td>Season</td>
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<td></td>
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<tr>
<td>Early dry</td>
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</tr>
<tr>
<td>Late dry</td>
<td>260</td>
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<td>Wet</td>
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<tr>
<td>Malaria: P. vivax</td>
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</tr>
<tr>
<td>Yes*</td>
<td>58</td>
<td>29</td>
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</tr>
<tr>
<td>No*b</td>
<td>645</td>
<td>13</td>
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<tr>
<td></td>
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<td>10.2</td>
<td>0.001</td>
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<tr>
<td>Malaria: P. falciparum</td>
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<td>Yes*</td>
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<tr>
<td>No*b</td>
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<td>2–4</td>
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</tr>
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<td></td>
<td></td>
<td>6.9</td>
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</tr>
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<td>Maternal education</td>
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</tr>
<tr>
<td>None</td>
<td>175</td>
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<td>236</td>
<td>22</td>
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<td>Secondary school</td>
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</tr>
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<td>1.8</td>
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</tr>
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<td>Sanitation</td>
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<tr>
<td>Ventilated pit latrine</td>
<td>382</td>
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<tr>
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<tr>
<td>No sanitation</td>
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<td>0</td>
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</tr>
</tbody>
</table>

Associations on univariate analysis. $\chi^2$ values are for linear trend except for ‘Parity’ and binary variables, which are simple $\chi^2$ tests. *-α-α homozygous α-thalassaemia; -α/αα heterozygous; αα/αα normal. *Children who suffered one or more episodes of malaria during the preceding 6 months as determined by active malaria surveillance. *Children who suffered no episodes of malaria during the preceding 6 months as determined by active malaria surveillance.
altered malaria risk in this population, we determined the incidence of malaria in children by anthropometric group before and after assessment. The results are summarized in Table 2. During the 6 months before assessment, the incidence of \( P. \) \textit{vivax} malaria was significantly higher in underweight than in non-underweight children. The same was found for wasting: the incidence of \( P. \) \textit{vivax} infection during the period before assessment was significantly higher in wasted [IR = 24 (12-52)] than in non-wasted children [IR = 9 (7-12); IRR = 2.2 (1-4.9); \( p = 0.05 \)]. The incidence of \( P. \) \textit{falciparum} infection was not significantly different between groups, suggesting that this was not a major cause of acute malnutrition in this population. No evidence was found that underweight or wasting altered the risk of malaria of either species during the subsequent 6 months.

**Stunting**

The prevalence and associations of stunting in the hyperendemic area are summarized in Table 1. Unlike underweight, on univariate analysis stunting was not significantly associated with age, season or \( \alpha^+ \) thalassaemia genotype, but was significantly associated with male sex, low birth weight and \( P. \) \textit{vivax} malaria. High maternal parity (5+ children) and no maternal education did not quite reach significance. Second, underweight and wasting were most common in children <5 years, in whom \( P. \) \textit{vivax} malaria is a dominant form of malaria. Whilst both conditions are usually most common in the youngest children in tropical communities, the association with age was strongest in the hyperendemic area, supporting the contention that malaria may be a factor in its aetiology.

**Discussion**

These data suggest that \( P. \) \textit{vivax} infection is important in the aetiology of malnutrition on the island of Espiritu Santo. First, prevalence of underweight, wasting and stunting were all higher in the South (hyperendemic area) than the East (mesoendemic). Other than malaria incidence, no significant differences could be found between children resident in these areas with regard to any of the variables discussed (Table 1) except anthropometric indices. Further, the populations were indistinguishable with regard to their HLA class 1 and 2 allele frequencies and dietary habits (T.W. and K.M., unpublished), making simple genetic or behavioural explanations unlikely. Within the hyperendemic area, underweight and wasting were both strongly associated with the dry season, when the incidence of clinical \( P. \) \textit{vivax} infection is highest. This relationship was opposite to what would have been expected if poor diet was the explanation, food being most plentiful during the dry season, and this seasonal variation was much less marked in the mesoendemic area (data not shown). Second, underweight and wasting were most common in children <5 years, in whom \( P. \) \textit{vivax} is the dominant form of malaria. Whilst both conditions are usually most common in the youngest children in tropical communities, the association with age was strongest in the hyperendemic area, supporting the contention that malaria may be a factor in its aetiology.

The most compelling evidence that \( P. \) \textit{vivax} is a major cause of acute malnutrition in this community comes from active malaria surveillance data. First, apart from age, the only parameter significantly associated with both underweight and wasting on logistic regression analysis was clinical \( P. \) \textit{vivax} malaria in the preceding 6 months. Second, the incidence of clinical \( P. \) \textit{vivax} malaria was significantly higher in underweight than non-underweight
children during this period. Furthermore, the IRR for P. vivax was highest in children <2 years old [3.7 (1.7–7.8), p < 0.0001], the age of peak P. vivax incidence. Perhaps surprisingly, the same analyses provided no evidence that P. falciparum was a cause of acute malnutrition in this population. However, this may be a feature of the epidemiology of malaria in this community, where P. vivax is the dominant parasite in the first 2 years of life. In keeping with observations from The Gambia, no evidence could be found from this study that either underweight or wasting either predisposed children to, or protected them from malaria, of either species.

Although stunting was strongly associated with residence in the hyperendemic area, it was not associated with P. vivax infection on multivariate analysis. However, stunting is a marker of chronic malnutrition, and it is likely that any association would be missed by a study of this duration. As stated previously, the populations of these two areas are genetically, behaviourally and nutritionally similar yet, remarkably, mean adult height is significantly lower in the hyperendemic than the mesoendemic area [mean difference (SE of difference) males 6.9 cm (1.8); p < 0.0001: females 4.8 cm (1.4); p = 0.001]. We speculate that this results from chronic malaria exposure in childhood and pregnancy, although other causes can not be excluded by this study.

We have shown previously that children with homozygous α + thalassaemia are predisposed to mild malaria in this community, and that this effect is most marked for P. vivax and in children <30 months old. Although homozygous α + thalassaemia was significantly associated with both underweight and wasting on univariate analysis, it was not associated on multivariate analysis, indicating that the association is mediated through P. vivax infection.

Although we believe these data argue strongly for a role of P. vivax in the aetiology of malnutrition on Santo, it is impossible to differentiate cause and effect using this approach. Furthermore, only a limited number of potential confounders were investigated, and it is possible that subtle differences in diet, behaviour or socio-economic factors could have increased the susceptibility of some children to both malaria and malnutrition. Nevertheless, it is well-recognized both that P. vivax is a potent stimulus to TNF secretion, resulting in serum levels exceeding those seen in even the most severe forms of P. falciparum malaria, and that TNF induces both anorexia and cachexia. Thus, the role of this organism in the aetiology of malnutrition is biologically plausible.

Because infant and child mortality rates were surprisingly low on Santo, our study was not large enough to examine the relationship between malnutrition and mortality. However, given that the relationship between WA Z score and relative risk of mortality remains remarkably constant between developing countries, we predict that P. vivax-induced malnutrition may be associated with significant mortality in Santo and other areas where P. vivax infection is common. On the other hand, we have also speculated that P. vivax infection may ameliorate the course of subsequent infection with P. falciparum, a process that could lead to reduced P. falciparum-associated mortality in communities where the two parasites coexist. Malaria control interventions which specifically target P. vivax control may therefore have an unpredictable effect on overall mortality, and should be monitored most carefully.

Acknowledgements

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References

7. D'Alessandro U, Olaleye BO, McGuire W, Langerock P,


Black Eyes (Hair and velvet)
Decayed Teeth (Japanese paper, cloves and chiffon)