Asthma and atopic dermatitis are associated with increased risk of clinical Plasmodium falciparum malaria

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ABSTRACT

Objectives: To assess the impact of atopy and allergy on the risk of clinical malaria. Design: A clinical and immunological allergy cross-sectional survey in a birth cohort of 175 children from 1 month to 14 years of age followed for up to 15 years in a longitudinal open cohort study of malaria in Senegal. Malaria incidence data were available for 143 of these children (aged 4 months to 14 years of age) for up to 15 years. Mixed-model regression analysis was used to determine the impact of allergy status on malaria incidence, adjusting for age, gender, sickness, cell trait and force of infection. Main outcome measures: Asthma, allergic rhinoconjunctivitis and atopic dermatitis status, the number of clinical Plasmodium falciparum malaria episodes since birth and associated parasite density. Results: 12% of the children were classified as asthmatic and 10% as having atopic dermatitis. These groups had respectively a twofold (OR 2.12 95%; CI 1.46 to 3.08; p=8×10-3) and threelfold (OR 3.15; 1.56 to 6.33; p=1.3×10-3) increase in the risk of clinical P falciparum malaria once older than the age of peak incidence of clinical malaria (3–4 years of age). They also presented with higher P falciparum parasite densities (asthma: mean 105.3 parasites/µL±SE 41.0 vs 51.3±9.7; p=6.2×10-5). Atopic dermatitis: 135.4±70.7 vs 52.3±11.0; p=0.014). There was no effect of allergy on the number of non-malaria clinical presentations. Individuals with allergic rhinoconjunctivitis did not have an increased risk of clinical malaria nor any difference in parasite densities. Conclusions: These results demonstrate that asthma and atopic dermatitis delay the development of clinical immunity to P falciparum. Despite the encouraging decrease in malaria incidence rates in Africa, a significant concern is the extent to which in the increase in allergy will exacerbate the burden of malaria. Given the demonstrated antiparasitic effect of antihistamines, administration to atopic children will likely reduce the burden of clinical malaria in these children, increase the efficacy of first-line treatment antimalarials and alleviate the non-infectious consequences of atopy.

INTRODUCTION

The World Allergy Organisation estimates that 40% of the world’s population is concerned by allergic diseases.1 In developing countries where Plasmodium falciparum malaria is endemic, prevalence of allergy is significantly lower, but is on the increase.2 T helper type 2 (Th2) cells, their related cytokines, IgE, eosinophils and mast cells (MCs) play a major role in allergic inflammation. Orientation of the immune response towards a Th1 profile is crucial for immunity.
to intracellular pathogens, whereas orientation towards a Th2 profile drives immunity to extracellular pathogens and antigens resulting in class switching giving rise to IgE-producing B cells. A role of the Th1/Th2 balance in the development of clinical malaria following infection by P. falciparum has been suggested by numerous studies. While it is recognised that acquired antiparasite immunity is IgG dependent, parasite-specific IgE also impact upon the clinical outcome of infection. For example, higher IgE but not IgG levels have been observed in patients with cerebral malaria than those with uncomplicated P. falciparum infection. The role of IgE, however, remains unclear.

The interplay between infectious agents and allergy is ambiguous. On the one hand, for example, severe respiratory syncytial virus infection in infants increased the risk of allergic rhinoconjunctivitis and allergic asthma. On the other hand, measles, hepatitis A and tuberculosis seemingly reduce atopy. Although, an atopic condition can increase incidence of disease, such as the case for the skin commensal Staphylococcus aureus in patients with atopic dermatitis, an atopic tendency per se does not generally lead to increased illness from infectious agents.

Genome-wide studies have identified chromosomal regions linked to clinical malaria, all of which overlap with those previously identified to be involved in atopic dermatitis, asthma, atopy and IgE levels, suggesting that common mechanisms may be involved in both pathologies. Chromosomal region 5q31 that has been repeatedly shown to be associated with control of parasite density and contains a cluster of cytokines, among which IL12B has been previously associated with psoriasis. The other regions, 13q13-q23, contain genes involved in innate immunity, particularly the interleukin 7 receptor, and several involved in tumour necrosis factor synthesis (C1q and tumour necrosis factor-related protein 3 (C1QTNF3)) and a gene involved in the complement system (C9).

Several additional lines of evidence support the concept that susceptibility to malaria and atopy may be related to similar immunological defects. In Ethiopia, a history of malaria was associated with atopy. A mouse model for human atopic disease was found to be very susceptible to murine malaria and a major locus for atopic disease mapped close to the region controlling parasite density. This region contains several candidate genes that have effects on T cell function.

Moreover, a direct effect of histamine in the malaria pathogenesis has been found using genetic and pharmacological approaches and increased levels of histamine are associated with the severity of disease in humans infected with P. falciparum and in animal malaria models.

To test the hypothesis that allergy impacts upon clinical P. falciparum malaria, we performed a clinical allergy cross-sectional study in the family-based longitudinal cohort from Senegal previously used for the genome linkage study and analysed the impact of asthma, atopic dermatitis, allergic rhinoconjunctivitis on the incidence of clinical P. falciparum episodes and the maximum parasite density during each episode.

METHODS

Population and outcome data

The malaria research programme conducted in Dielmo village in Senegal has been ongoing since 1990 as described elsewhere. In brief, between 1990 and 2008, a longitudinal study involving the inhabitants of the village of Dielmo, Senegal, was carried out to identify all episodes of fever. The study design included daily medical surveillance with systematic blood testing of individuals with fever and examination of 200 oil-immersion fields on a thick blood film for malaria parasites (about 0.5 µL of blood). Each individual was given a unique identification code and details of family ties, occupation and precise place of residence were recorded on detailed maps of each household with the location of each bedroom. All households were visited daily, absenteeism recorded and the presence of fever or other symptoms assessed. We systematically recorded body temperature at home three times a week (every second day) in children younger than 5 years, and in older children and adults in cases of suspected fever or fever-related symptoms. In cases of fever or other symptoms, blood testing was carried out at the dispensary by finger prick, and we provided detailed medical examination and specific treatment. Parasitologically confirmed clinical malaria episodes were treated according to national guidelines. From 1990 to 2008, four different drug regimens were implemented: quinine from 1990 to 1994, chloroquine from 1995 to 2003, fansidar (sulfadoxine-pyrimethamine) from 2004 to mid-2006 and artemisinin-based combination therapy (Amodiaquine-sulfadoxine-pyrimethamine; ACT) from mid-2006 to 2008.

Parasite positivity was established as follows. Thick blood films were prepared and stained by 3% Giemsa stain. Blood films were examined under an oil immersion objective at ×1000 magnification by the trained laboratory technicians and 200 thick film fields were examined to count the number of asexual and gametocyte parasite stages. Asexual parasite densities (per µL) were calculated by establishing the ratio of parasites to white blood cells and then multiplying the parasite count by 8000, the average white cell count per µL of blood.

Malaria transmission in Dielmo is intense and perennial. We conducted a cross-sectional survey to estimate the prevalence of symptoms related to allergic diseases among 175 children aged from 1 month to 14 years old who were born during the malaria research programme. Both the longitudinal and cross-sectional surveys were approved by the Ministry of Health of Senegal. Informed consent of the volunteers is renewed every year. More specifically for the cross-sectional survey, after informing about the procedures and the purpose of the
study, written informed consent was obtained from parents or guardians of children either by signature or by thumbprint on a voluntary consent form written in both French and Wolof, the main local language. Consent was obtained in the presence of the school director, an independent witness.

The family structure (pedigree) was available after a demographic census performed for every volunteer at his adhesion in the project. A verbal interview of mothers or key representatives of the household was used to obtain information on genetic relationships between studied individuals, their children, their parents and to identify genetic links among the population. The total pedigree comprised 828 individuals, including absent or dead relatives, composed of 10 independent families that can be subdivided into 206 nuclear families (father–mother couples with at least one child) with an average of 3.6 children each. Genetically related nuclear families occur because of multiple marriages and marriages among related individuals. Previous typing with microsatellites has enabled the construction of a pedigree based on Identity-by-Descent using MERLIN. The mean coefficient of inbreeding is 0.0008. Newborns since this original genetic analysis were added to the family of the parents in question. The 143 children, with allergy and malaria data, belonged to 61 nuclear families and comprised 30 singletons, 102 siblings and 11 half-sibs (yielding 55 half-sib pairs). The mean genetic relatedness (by pedigree) of the 143 children is 0.0114 (range: 0.0013–0.022).

### P falciparum clinical episodes

*P falciparum* malaria clinical episode phenotypes analysed were: (1) clinical *P falciparum* infections treated with antimalarial therapy and (2) the highest parasite density during the *P falciparum* clinical episode. A clinical *P falciparum* episode was defined as a clinical presentation with fever (axillary temperature ≥37.5°C) and/or other clinical signs suggestive of malaria associated with a thick blood smear positive for *P falciparum* and that was treated with antimalarial therapy. Repeated clinical malaria presentations within 15 consecutive days were not considered to be independent and were excluded from the analyses, unless there was a negative thick blood smear between two clinical presentations. We also excluded observations in any trimester for which the individual was not present for at least one-third of the time.

We calculated the quarterly incidence rate of clinical *P falciparum* episodes in children below the age of 15 years as the ratio of the total number of clinical *P falciparum* episodes during the trimester divided by the total number of person-trimesters surveyed. Incidence rate is expressed as cases per 100 person-trimesters (see online supplementary figure S1). This rate was used in the analysis to approximate the force of infection (exposure level) within the targeted population at the time of a given clinical *P falciparum* episode.

The total number of clinical presentations per trimester that were not attributable to *P falciparum* was tabulated. Repeated non-malaria presentations within seven consecutive days were not considered to be independent and were excluded.

### Allergic diseases and atopic status

The International Study of Asthma and Allergies in Childhood (ISAAC) diagnostic criteria have been shown to be reproducible, adequate and able to discriminate children with allergic diseases in different areas of the world. The standardised ISAAC questionnaire originally written in English was translated into French in compliance with ISAAC guidelines adapting it to the usual local customs following advice from local clinicians and paediatric allergologists (acknowledgements and see online supplementary technical appendix). The adequacy and reliability of the translated questionnaire had been previously confirmed by a pilot study on 30 randomly selected children in the same community. The questionnaire was completed by specially trained health workers during an oral interview conducted in Wolof with children and their mothers or guardians.

To assess the prevalence of allergic diseases in children, we used the positive and negative predictive values of the ISAAC questionnaire diagnosis criteria developed for subtropical countries. Each question was scored according to the medical diagnosis of paediatricians and paediatric allergologists. Positive or negative answers were thus graded on the basis of symptom sensitivity, specificity, frequency, location or early onset. For each allergic disease, three categories of symptom severity, severe, moderate and none, were defined as follows:

- **Asthma**—severe symptoms if the child had ‘wheezing or whistling in the chest before the age of two years’ and ‘more than three times’ or severe enough to ‘limit his/her speech’; moderate symptoms if the child had ‘wheezing or whistling in the chest before the age of two years’ and ‘in the past 12 months’; and none otherwise.

- **Allergic rhinoconjunctivitis**—severe symptoms if the child had ‘sneezing, runny or stuffy nose in the past 12 months’ and ‘more than five times a year’ and ‘itchy, watery eyes or tropical endemic limboconjunctivitis (TELC) in the past 12 months’; moderate symptoms if the child had ‘sneezing, runny or stuffy nose in the past 12 months’, and ‘itchy, watery eyes or TELC in the past 12 months’ and none otherwise.

- **Atopic dermatitis**—severe symptoms if the child had ‘scaly or exudating, crusted and pruritic patches in the past 12 months’ and ‘affecting any of the following characteristic areas: face, around the ears or eyes, folds of armpits or elbows or groin, behind the knees, under the buttocks’ and ‘onset of symptoms before the age of 2 years’; moderate symptoms if the child had ‘scaly or exudating, crusted and pruritic patches in the past 12 months’ and ‘affecting any of characteristic areas (see above)’, and ‘onset of symptoms before the age of 4 years’ and none otherwise.
The inter-relationships between variables reflecting the severity of symptoms of the three allergic diseases were used to identify children at high risk of atopy. The high probability group was defined by the prevalence of at least one of any severe symptoms or two of any moderate symptoms. The probable group was defined as those with moderate symptoms from one of the three allergic diseases and remaining children were classified in the unlikely group.

Helminths
Helminthic infections are common in this region and are known to modify the clinical course and outcome of both allergic diseases and malaria. We therefore carried out a helminth survey for 91 individuals present during the cross-sectional survey. Diagnosis was performed by stool examination by microscope and by the Kato technique to search for the presence of Ascaris lumbricoides, hookworms (Ankylostoma duodenale and Necator americanus), whipworm (Trichuris trichiura), Schistosoma mansoni and Strongyloides stercoralis. Examination for pinworms (Entobius vermicularis) was performed by the anal scotch-test. An anthelminthic treatment was proposed for all infested individuals.

IgE titles
Specific IgE titres were measured by ELISA as previously described. A panel of allergens of potential pertinence to the three classes of allergy were used: (1) salivary gland extracts (SGE) of two mosquito species present in the study cohorts, Aedes aegypti and Anopheles gambiae sensu stricto and (2) Plasmodium falciparum parasite extract were prepared as previously described; (3) House dust mite spp. Dermatophagoides farinae and Dermatophagoides pteronyssinus; (4) a mix of pollen allergens from five ubiquitous gramineae spp. (Cock’s-foot (Dactylis glomerata), Timothy grass (Phleum pratense), Sweet Vernal grass (Anthoxanthum odoratum), Perennial ryegrass (Lolium perenne), Kentucky Bluegrass (Poa pratensis)) (all from Stallergenes, France).

Statistical analysis
Statistical analyses were performed using R V.2.12.0 (The R Foundation for Statistical Computing, Vienna, Austria). To address the effect of allergic status on the number of days present on site during the trimester, trimestrial incidence of Plasmodium falciparum and age. Age was initially analysed as a continuous covariate. To assess the age-specific effect of allergy, age was categorised into two levels (<3.5 years of age and ≥3.5 years of age, based on the age of peak clinical incidence) and allergy class was nested within age class. The age threshold was varied from 1.5 to 5.5 years of age and the data reanalysed to assess at which age there was the strongest effect. The association of allergy classes with IgE levels was analysed by Box-Cox transforming the data and fitting a GLMM with a normal distribution.

RESULTS
Of the 205 eligible children aged under 15 years involved in the family-based longitudinal study, 175 (85.4%) participated in the cross-sectional survey to assess the prevalence of related symptoms of allergic diseases. All eligible children present at the time of the survey were included; no explicit refusal to participate was recorded. The study cohort was aged from 1 month to 14 years 11 months. The sex-ratio (male/female) was 0.94.

From 1994 until 2008, 143 of the children participating in the cross-sectional survey were present for at least 31 days in any trimester during the study period generating a total of 3093 person-trimesters of presence (see online supplementary table S1). There were 2065 treated Plasmodium falciparum clinical episodes (per individual: median 11, range 0–47; see online supplementary table S2). The age peak of incidence of Plasmodium falciparum episodes occurred at 3–4 years of age (figure 1). There were 1808 non-malaria episodes (median 12, range 0–37) (see online supplementary table S2). These non-malaria clinical presentations were associated with headache (38%), chills (32%), cough (13%), vomiting (11%) and diarrhoea (6%).

The prevalence of moderate or severe asthma symptoms was respectively 2.3% and 10.3% (table 1). The prevalence of moderate or severe allergic rhinoconjunctivitis symptoms was respectively 6.3% and 10.3%. The prevalence of moderate or severe atopic dermatitis symptoms was respectively 6.3% and 2.9%. On the basis of...
The risk of treated clinical *P. falciparum* infections was higher for children with high probability of atopy (OR 1.65; 95% CIs 1.20 to 2.26; p=0.002; table 2), after adjusting for age, sickle-cell trait and the exposure level. Gender was not found to be significant. Analysing the impact of atopy in children younger and older than the peak age of clinical incidence (3–4 years old) revealed that atopy increased the risk of *P. falciparum* episodes in children at an age greater than 3.5 years (OR 2.02, 1.39–2.93; p=2×10⁻⁴), but not in children of age prior to the peak clinical incidence (OR 1.38, 0.92 to 2.08; p=0.124; table 2). This increased risk resulted in an ever-increasing cumulative number of *P. falciparum* episodes with age beyond that of peak clinical incidence (figure 2; see online supplementary figure S2 for model predictions for comparison).

Analysis by allergy category revealed that asthma (severe or moderate) increases the risk of *P. falciparum* episodes (OR 2.12; 1.46 to 3.08; p=8×10⁻⁵) and this again only in children of age greater than 3.5 years old (OR 2.33; 1.50 to 3.61; p=1.5×10⁻⁴). Atopic dermatitis increased the risk of clinical malaria in children older (OR 3.13; 1.56 to 6.33; p=1.3×10⁻³) but not younger than 3.5 years of age (table 2). Allergic rhinoconjunctivitis was not associated with increased risk of clinical malaria at any age (table 2). The impact of atopy, asthma and atopic dermatitis can be clearly seen in the ever-increasing number of cumulative *P. falciparum* episodes beyond the age of the onset of clinical immunity in the population, 3.5 years of age (figure 2). There is no difference in the number of clinical malaria episodes prior to this age in individuals with or without an allergic condition. Analysis using different age thresholds (from 1.5 to 5.5 years of age) revealed similar OR for thresholds of 2.5, 3.5 and 4.5 years of age. The maximum OR for increased malaria occurred in children older than 4.5 years of age and with atopy or atopic dermatitis, whereas for the asthma group it occurred in children after 3.5 years of age (see online supplementary table S3).

There was no impact of any allergic disease on the number of non-malaria episodes by trimester (see online supplementary table S4).

The impact of atopy, asthma and atopic dermatitis on the maximum *P. falciparum* parasite density during a given clinical malaria episode mirrored that of the risk of *P. falciparum* episodes. Parasite density was significantly higher for children with allergic disease older than 3.5 years of age (table 3 and see online supplementary figure S3 for residuals of the fitted model). As the log-transformed data were left skewed, we additionally analysed using Box-Cox transformation and probit normalisation of the data. The results were qualitatively the same (see online supplementary text and figures S4–S8). Allergic rhinoconjunctivitis had no impact on the parasite density (table 3). Analysis using different age thresholds yielded similar qualitative conclusions as seen with the number of clinical episodes (see online supplementary table S3).

Individuals with moderate or severe symptoms of atopic dermatitis had significantly higher specific IgE

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**Table 1** Classification of asthma, allergic rhinoconjunctivitis, atopic dermatitis and overall Atopic status according to International Study of Asthma and Allergies in Childhood questionnaire in children aged 0–14 from a malaria birth cohort

<table>
<thead>
<tr>
<th>Asthma symptoms</th>
<th>N (F/M)</th>
<th>Per cent</th>
<th>n-Malaria (F/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>153 (73/80)</td>
<td>87.43</td>
<td>125 (59/66)</td>
</tr>
<tr>
<td>Moderate</td>
<td>4 (1/3)</td>
<td>2.29</td>
<td>4 (1/3)</td>
</tr>
<tr>
<td>Severe</td>
<td>18 (6/12)</td>
<td>10.29</td>
<td>14 (4/10)</td>
</tr>
<tr>
<td>Rhinoconjunctivitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>146 (64/82)</td>
<td>83.43</td>
<td>120 (52/68)</td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (8/3)</td>
<td>6.29</td>
<td>9 (6/3)</td>
</tr>
<tr>
<td>Severe</td>
<td>18 (6/12)</td>
<td>10.29</td>
<td>14 (6/8)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>159 (75/84)</td>
<td>90.86</td>
<td>128 (60/68)</td>
</tr>
<tr>
<td>Moderate</td>
<td>11 (1/10)</td>
<td>6.29</td>
<td>11 (1/10)</td>
</tr>
<tr>
<td>Severe</td>
<td>5 (4/1)</td>
<td>2.86</td>
<td>4 (3/1)</td>
</tr>
<tr>
<td>Atopic tendency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely</td>
<td>119 (56/63)</td>
<td>68.00</td>
<td>97 (46/51)</td>
</tr>
<tr>
<td>Probable</td>
<td>16 (8/8)</td>
<td>9.14</td>
<td>14 (6/8)</td>
</tr>
<tr>
<td>Highly probable</td>
<td>40 (16/24)</td>
<td>22.86</td>
<td>32 (12/20)</td>
</tr>
</tbody>
</table>

N is total number of children examined and n-malaria represents those for whom malaria data were recorded. F is the number of females and M the number of males.
titres against *A. aegypti* (p=0.004) and *A. gambiae* SGE (p<0.001). There were no detectable specific anti-*P. falciparum* IgE. Individuals with moderate or severe symptoms of allergic rhinoconjunctivitis did not have significantly higher IgE titres against the tested Graminae (p=0.28), although titres decreased with age (p=0.035).

There was also no effect of asthma on IgE titres against the house dust mite spp. tested (*D. farinae* p=0.60 and *D. pteronyssinus* p=0.27).

Only five individuals were infested with helminths (two *Ancylostoma*, one *Strongyloides*, one *Trichuris* and one *Enterobius*).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Impact of allergy status on risk of <em>Plasmodium falciparum</em> clinical episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age groups (3.5 years)</td>
</tr>
<tr>
<td>Atopy</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>&lt;3.5</td>
</tr>
<tr>
<td></td>
<td>≥3.5</td>
</tr>
<tr>
<td>Asthma</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>&lt;3.5</td>
</tr>
<tr>
<td></td>
<td>≥3.5</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>&lt;3.5</td>
</tr>
<tr>
<td></td>
<td>≥3.5</td>
</tr>
<tr>
<td>Rhinoconjunctivitis</td>
<td>Both</td>
</tr>
<tr>
<td></td>
<td>&lt;3.5</td>
</tr>
<tr>
<td></td>
<td>≥3.5</td>
</tr>
<tr>
<td>Age ≥3.5</td>
<td></td>
</tr>
<tr>
<td>Trimestrial incidence</td>
<td></td>
</tr>
<tr>
<td>HbAS</td>
<td></td>
</tr>
</tbody>
</table>

Shown are the p values and adjusted ORs with 95% CIs calculated from the mixed-model analyses. Values for the covariables age (≥3.5 years of age compared with <3.5 years of age), trimestrial incidence of *P. falciparum* clinical episodes and HbAS (β-globin sickle-cell trait; AS compared with AA) are those from the Asthma model analysis. For clarity significant covariables are shown in bold.

**Figure 2** Mean cumulative number of *Plasmodium falciparum* clinical episodes with age for the (A) asthma, (B) rhinoconjunctivitis and (C) atopic dermatitis classes and overall atopy class (D) (bold lines) compared with individuals without symptoms of each respective allergy type (thin lines). In all cases moderate and severe classes are combined and compared with individuals without allergy symptoms. Note there are no children older than 11 years of age with atopic dermatitis.
**DISCUSSION**

**Principal findings**

Establishing the allergic status of children up to the age of 15 years followed for malaria since birth, revealed an association of asthma and atopic dermatitis with susceptibility to clinical *P. falciparum* episodes. Importantly the increase in risk of malaria associated with these allergic conditions occurred after the peak clinical incidence of disease in the population, suggesting that they delay the development of clinical immunity to malaria.

**Strengths and weaknesses of the study**

The major strength of this study is the complete knowledge of the number of clinical *P. falciparum* malaria episodes each individual has had since birth and the exposure level per trimester over the 15 years covering the birth cohort. No other study has such detailed information for such a length of time. The major weakness of the study is the relatively small sample size, which would have reduced power to detect an association. In addition, although allergy diagnosis for children under 2 years of age is not considered reliable, there were only 15 individuals under 2 at the time of the allergy study of the 143 for whom malaria and allergy data were available.

**Meaning of the study**

Under intense malaria transmission, after repeated exposure to the parasite, children develop a clinical immunity whereby they tolerate elevated parasite densities without showing clinical symptoms. In this cohort, the population mean onset of clinical immunity occurred at 3–4 years of age. Although clinical immunity is accompanied by a reduction in parasite density, effective antiparasite immunity develops much more slowly with individuals achieving a state of premunition, whereby they maintain low-grade parasite densities in an asymptomatic state. We show here that children with clinically defined asthma or atopic dermatitis have an increased risk of presenting with *P. falciparum* malaria episodes requiring treatment once passing the age of peak clinical incidence. They also had higher parasite density during clinical episodes, suggesting a reduced ability to control parasite replication. The observed increase in clinical incidence of malaria in patients with asthma or atopic dermatitis is not likely to be the result of increased frailty of such individuals; these individuals did not come more frequently to the clinic with non-malaria symptoms. Our previous genome linkage study identifying chromosomal regions associated with malaria that overlap with those previously shown to be linked to asthma/atopy suggests that there may be a shared genetic basis to these pathologies rather than any causative effect of one on the other. This is consistent with the increased susceptibility to malaria of mouse atopic models.

**Comparison with other studies**

A previous study in Ethiopia (East Africa) found that a history of malaria (yes/no) increased risk of atopic Table 3  Impact of allergy status on the maximum *Plasmodium falciparum* parasite density during a clinical malaria episode

<table>
<thead>
<tr>
<th>Allergic condition</th>
<th>Age groups</th>
<th>Allergic status (no/yes)</th>
<th>Mean parasite density</th>
<th>SEM</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy</td>
<td>Both</td>
<td>N</td>
<td>76.3</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>131.0</td>
<td>36.4</td>
<td>0.0158</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3.5</td>
<td>114.3</td>
<td>23.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3.5</td>
<td>171.1</td>
<td>56.0</td>
<td>0.148</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>48.4</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>114.8</td>
<td>37.1</td>
<td>9.5×10⁻⁴</td>
</tr>
<tr>
<td>Asthma</td>
<td>Both</td>
<td>N</td>
<td>78.1</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>148.5</td>
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<tr>
<td></td>
<td></td>
<td>&lt;3.5</td>
<td>114.8</td>
<td>24.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3.5</td>
<td>171.9</td>
<td>74.5</td>
<td>0.167</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>51.3</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>105.3</td>
<td>41.0</td>
<td>6.2×10⁻³</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Both</td>
<td>N</td>
<td>82.6</td>
<td>15.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>93.9</td>
<td>38.9</td>
<td>0.605</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3.5</td>
<td>122.6</td>
<td>25.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3.5</td>
<td>133.9</td>
<td>63.5</td>
<td>0.425</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>52.3</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>135.4</td>
<td>70.7</td>
<td>0.014</td>
</tr>
<tr>
<td>Rhinoconjunctivitis</td>
<td>Both</td>
<td>N</td>
<td>81.5</td>
<td>14.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>111.4</td>
<td>39.0</td>
<td>0.570</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;3.5</td>
<td>118.8</td>
<td>25.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥3.5</td>
<td>166.3</td>
<td>69.9</td>
<td>0.537</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>54.6</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y</td>
<td>80.9</td>
<td>33.7</td>
<td>0.327</td>
</tr>
</tbody>
</table>

Shown are the back-transformed mean parasite densities per microlitre and SE measurements (SEM) estimated from the generalised linear mixed model analyses after taking into account the other covariables. Significantly different effects are shown in bold for clarity.

An important role in premunition. The higher parasite cytophilic immunoglobulins (IgG1 and IgG3), which are resistance to infectious disease in children. The dominant arm of the immune response enabling development of protective IgG, considered to be hence development of protective IgG, considered to be the link between malaria and atopy also interpreted the result from the perspective of the impact of malaria on atopy. They examined the reinfection rate with P. falciparum over a 5-year period in 91 children who were subsequently classified as atopic or not using skin prick tests (SPT) with house dust mite antigen. Their conclusion was that, as with measles and tuberculosis, malaria infection reduces atopy. However, the study lacked previous infection data since birth of the participating individuals and focused on atopy as determined by SPT against a single allergen. The case-control study of atopic dermatitis risk factors cited above found no overall association between allergen skin sensitisation and atopic dermatitis. We also found no evidence of increased IgE titres against house dust mites in the asthmatic or atopic dermatitis groups or against grass pollen in individuals with allergic rhinoconjunctivitis. Such differences likely reflect the different IgE reactivity profiles due to differences in allergen exposure in Africa. There was no evidence of antiparasite IgE in this cohort of children. We previously showed that circulating antiparasite IgE titres were strongly positively correlated with antimosquito saliva IgE, but became undetectable following malaria exposure, potentially being bound to effector cells. Only mosquito saliva, a known major local allergen, induced a specific IgE response at significantly higher titres in individuals with atopic dermatitis.

Although the immune effectors of clinical immunity are still poorly defined, there is strong evidence that acquired antiparasite immunity is IgG-dependent and cytophilic immunoglobulins (IgG1 and IgG3), which are capable of eliminating the parasites by opsonisation and/or by antibody dependent cellular immunity play an important role in premunition. The higher parasite density during symptomatic episodes observed in the asthma group suggests impaired development of acquired immunity. Impaired acquisition of immunity to malaria in children with asthma or atopic dermatitis may stem from their imbalanced Th1/Th2 response. Indeed, an atopic state may generate a tendency to develop a Th2 type immune response to P. falciparum. Dendritic cells that are oriented to a Th2 phenotype are more susceptible to orient the acquired immune response towards a Th2 profile. Orientation of the immune response towards a Th2 profile by asthma or atopic dermatitis would result in a poor Th1 response (and hence development of protective IgG), considered to be the dominant arm of the immune response enabling resistance to infectious disease in children.

Many studies have revealed an important role of histamine, a key downstream effector molecule in allergic reaction, in the outcome of a malaria parasite infection. Moreover, reports indicate that components of the innate immune system, including eosinophils, basophils and MCs, could play important roles in the pathogenesis of malaria. Increased levels of histamine in plasma and tissue, derived from basophils and MCs, notably following stimulation by IgE through the high affinity receptor FcεRI, are associated with the severity of disease in humans infected with P. falciparum and in animal malaria models. Chlorpheniramine, a H1 agonist reversed resistance to chloroquine and amodiaquine both in vivo and in vitro. Moreover, astemizole, another H1 agonist, was identified as an antimalarial agent in a clinical drug library screen. Finally, P. falciparum produces translationally controlled tumour protein, which is a homologue of the mammalian histamine-releasing factor that causes histamine release from human basophils.

Further research

Our results provide the first birth cohort study addressing the link between malaria and allergic diseases. They contribute to a growing body of evidence that the pathologies are related. ISAAC has revealed a steady but significant increase in prevalence rates of asthma and allergic diseases in Africa. While the majority of studies have focused on large cities, there is increasing urbanisation throughout Africa, as well as improved access to primary healthcare in many areas. A key concern for ISAAC is the extent to which such societal evolution will result in an increase in allergic diseases. Increased urbanisation in sub-Saharan Africa is changing the epidemiology of malaria and although resulting in a decrease in risk, will result in more severe clinical malaria in older individuals. Moreover, a large consumption of antimalarial drugs in the urban areas provides substantial drug pressure fostering the selection of drug-resistant parasites. Despite the encouraging recent decrease in malaria incidence rates, even in rural areas, an additional significant concern is the extent to which such an increase in allergy will exacerbate the burden of malaria. Given the demonstrated antiparasitic effect of antihistamines, administration of antihistamines to atopic children will likely reduce the burden of clinical malaria in these children, increase the efficacy of first-line treatment antimalarials and alleviate the non-infectious consequences of atopy. Clinical intervention studies should be envisaged.

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REFERENCES


Allergy and malaria


UNIT OF FUNCTIONAL GENETICS OF INFECTIOUS DISEASE

ENREGISTREMENT

Coding:

03/MM/YYYY Version: 1

ALLERGY MODIFIED ISAAC QUESTIONNAIRE

Place of study
Technician X
Technician X
Technician X

Research Institute responsible
Name of Institute
Principle investigator
Project manager

IDENTIFICATION

Date of questionnaire: [__] [__] [__] [__] [__] dd/mm/yyyy

Name of investigator: ..............................................................

Name of study supervisor: ............................................................

Child:

First and last name of child:

Identification code of child:

Date of birth:

Sex:

Village/town:

Identification code of Questionnaire:

Identification code of father:

Identification code of mother:

Weight: [__] [__] [__] (kg)

Height: [__] [__] [__] (cm)

Mid Upper Arm Circumference: [__] [__] (cm)

Person questioned:

Last name of person questioned: ..............................................................

First name of person questioned: ..............................................................

Relationship to child: Mother [1]; Father [2]; Brother/Sister [3]; Grand-parents [4]; Other [5];

If other, define: ........................................................................

FACTORs PREDISPOsing ATOPY

First days of life: Consultation of health records of child and maternity records of mother

1. How much did your child weigh at birth?

   <1500 g [1] [2500-3500] g [2];
   [1500-2000] g [3];
   [2000-2500] g [4];
   Record not found/NSP [5]

   [__] BIRTHWEIGHT

2. Until what age did your child breastfeed (exclusively or mixed)?

   Corresponds to the age of weaning of child

   < 6 months [1]; 6 – 12 mths [2]; 12 – 24 mths [3]; >24 mths [4]; NSP [5]

   [__] AGEWAN
3. Until what age did your child breastfeed **exclusively** without ever taking other aliments (fruits, vegetables, rice, meat, fish, etc.) or liquids (powdered milk, cow or goats milk, fruit juice, water, etc.)?  
   < 6 months ☐  6 – 12 mths ☐  12 – 24 mths ☐  NSP ☐  

### Illness and vaccination:
Consultation of health records of child

1. Has your child had the following illnesses?
   - Malaria: ☐ No ☐ Yes ☐ NSP
   - Tuberculosis treated: ☐ No ☐ Yes ☐ NSP
   - Helminths (oxyures, ascaris, taenia, etc.): ☐ No ☐ Yes ☐ NSP
   - Amoeba: ☐ No ☐ Yes ☐ NSP
   - Measles: ☐ No ☐ Yes ☐ NSP

2. Against what illnesses is your child vaccinated?
   - Yellow fever: ☐ No ☐ Yes ☐ NSP
   - Hepatitis B: ☐ No ☐ Yes ☐ NSP
   - Measles: ☐ No ☐ Yes ☐ NSP
   - Mumps: ☐ No ☐ Yes ☐ NSP
   - Rubella: ☐ No ☐ Yes ☐ NSP
   - Tuberculosis/BCG: ☐ No ☐ Yes ☐ NSP
   - Diphtheria/Tetanus/Pertussis/Poliomyelitis: ☐ No ☐ Yes ☐ NSP
   - Typhoid: ☐ No ☐ Yes ☐ NSP
   - Meningitis: ☐ No ☐ Yes ☐ NSP
   - Haemophilus influenzae type B (HiB): ☐ No ☐ Yes ☐ NSP

### Habitation:

1. Which of these animals / insects can be found in the **rooms** where your child lives (today and/or during his first year of life)?
   - Dogs in rooms today: ☐ No ☐ Yes ☐ NSP
   - Dogs in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP
   - Cats in rooms today: ☐ No ☐ Yes ☐ NSP
   - Cats in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP
   - Sheep in rooms today: ☐ No ☐ Yes ☐ NSP
   - Sheep in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP
   - Goats in rooms today: ☐ No ☐ Yes ☐ NSP
   - Goats in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP
   - Chicken, ducks in rooms today: ☐ No ☐ Yes ☐ NSP
   - Chicken, ducks in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP
   - Rodents (rats, mice, etc.) in rooms today: ☐ No ☐ Yes ☐ NSP
   - Rodents (rats, mice, etc.) in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP
   - Cockroaches in rooms today: ☐ No ☐ Yes ☐ NSP
   - Cockroaches in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP
   - Other in rooms today: ☐ No ☐ Yes ☐ NSP
   - Other in rooms 0-1yr: ☐ No ☐ Yes ☐ NSP

   If Others, define: ..........................................................

2. Which of these animals could be in **contact** with your child **at least once per week**

### Other:

- Malaria: ☐
- Tuberculosis treated: ☐
- Helminths (oxyures, ascaris, taenia, etc.): ☐
- Amoeba: ☐
- Measles: ☐
- Yellow fever: ☐
- Hepatitis B: ☐
- Mumps: ☐
- Rubella: ☐
- Tuberculosis/BCG: ☐
- Diphtheria/Tetanus/Pertussis/Poliomyelitis: ☐
- Typhoid: ☐
- Meningitis: ☐
- Haemophilus influenzae type B (HiB): ☐
- Dogs in rooms today: ☐
- Dogs in rooms 0-1yr: ☐
- Cats in rooms today: ☐
- Cats in rooms 0-1yr: ☐
- Sheep in rooms today: ☐
- Sheep in rooms 0-1yr: ☐
- Goats in rooms today: ☐
- Goats in rooms 0-1yr: ☐
- Chicken, ducks in rooms today: ☐
- Chicken, ducks in rooms 0-1yr: ☐
- Rodents (rats, mice, etc.) in rooms today: ☐
- Rodents (rats, mice, etc.) in rooms 0-1yr: ☐
- Cockroaches in rooms today: ☐
- Cockroaches in rooms 0-1yr: ☐
- Other in rooms today: ☐
- Other in rooms 0-1yr: ☐
- Other: ☐

### NAMEOTH:

- Malaria: ☐
- Tuberculosis treated: ☐
- Helminths (oxyures, ascaris, taenia, etc.): ☐
- Amoeba: ☐
- Measles: ☐
- Yellow fever: ☐
- Hepatitis B: ☐
- Mumps: ☐
- Rubella: ☐
- Tuberculosis/BCG: ☐
- Diphtheria/Tetanus/Pertussis/Poliomyelitis: ☐
- Typhoid: ☐
- Meningitis: ☐
- Haemophilus influenzae type B (HiB): ☐
- Dogs in rooms today: ☐
- Dogs in rooms 0-1yr: ☐
- Cats in rooms today: ☐
- Cats in rooms 0-1yr: ☐
- Sheep in rooms today: ☐
- Sheep in rooms 0-1yr: ☐
- Goats in rooms today: ☐
- Goats in rooms 0-1yr: ☐
- Chicken, ducks in rooms today: ☐
- Chicken, ducks in rooms 0-1yr: ☐
- Rodents (rats, mice, etc.) in rooms today: ☐
- Rodents (rats, mice, etc.) in rooms 0-1yr: ☐
- Cockroaches in rooms today: ☐
- Cockroaches in rooms 0-1yr: ☐
- Other in rooms today: ☐
- Other in rooms 0-1yr: ☐
- Other: ☐
3. Which of these aliments are usually stocked in the rooms where your child lives?

- Millet kept in room: □ No □ Yes □ NSP
- Sorghum kept in room: □ No □ Yes □ NSP
- Maize kept in room: □ No □ Yes □ NSP
- Rice kept in room: □ No □ Yes □ NSP
- Wheat kept in room: □ No □ Yes □ NSP
- Biscuits, pasta kept in room: □ No □ Yes □ NSP
- Manioc (root, flour) kept in room: □ No □ Yes □ NSP
- Cashew nut, ground nut kept in room: □ No □ Yes □ NSP
- Curdled milk kept in room: □ No □ Yes □ NSP
- Dried leaves (millet, quinquiliba, baobab, etc.) : □ No □ Yes □ NSP
- Other aliments kept in room: □ No □ Yes □ NSP

If Others, define: .................................................................

.................................................................NAMEOTHCB

3. Which of these aliments are usually stocked in the rooms where your child lives (today and/or during his first year of life)?

- Corrugated metal roof today: □ No □ Yes □ NSP
- Corrugated metal roof 0-1yr: □ No □ Yes □ NSP
- Thatched roof today: □ No □ Yes □ NSP
- Thatched roof 0-1yr: □ No □ Yes □ NSP
- Wooden roof today: □ No □ Yes □ NSP
- Wooden roof 0-1yr: □ No □ Yes □ NSP
- Cement roof today: □ No □ Yes □ NSP
- Cement roof 0-1yr: □ No □ Yes □ NSP
- Plaster roof today: □ No □ Yes □ NSP
- Plaster roof 0-1yr: □ No □ Yes □ NSP
- Other type of roof today: □ No □ Yes □ NSP

.................................................................RIMETTODAY

.................................................................RMET01YR

.................................................................RTHATDAY

.................................................................RTHAT01YR

.................................................................RWOOTOYDAY

.................................................................RWO001YR

.................................................................RCEMTOYDAY

.................................................................RCEMO01YR

.................................................................RPLATODYDAY

.................................................................RPLA01YR

.................................................................ROTHTODAY
4. Which of these objects are in the room where your child sleeps (today and during the first year of life)?

<table>
<thead>
<tr>
<th>Object</th>
<th>Today</th>
<th>0-1yr</th>
<th>0-1yr Today</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattress in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattress in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bed in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bed in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wardrobe in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wardrobe in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest, trunk in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest, trunk in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Table in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chair in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chair in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpet, rug in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpet, rug in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matting in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matting in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curtains in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curtains in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malagasy fire in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malagasy fire in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other objects in room today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other objects in room 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If other, define: ________________________________

5. On what type of bedding does your child sleep (today and during the first year of life)?

<table>
<thead>
<tr>
<th>Bedding</th>
<th>Today</th>
<th>0-1yr</th>
<th>0-1yr Today</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foam mattress today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foam mattress 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant fibre mattress (straw, etc.) today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant fibre mattress (straw, etc.) 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wool mattress today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wool mattress 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feather mattress today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feather mattress 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plastic matting today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plastic matting 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant fibre matting (straw, etc.) today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant fibre matting (straw, etc.) 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other type of bedding today</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other type of bedding 0-1yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If other, define: ________________________________

6. Does your child sleep on a pillow?

If No, go to question 8

<table>
<thead>
<tr>
<th>Pillows</th>
<th>Today</th>
<th>0-1yr</th>
<th>0-1yr Today</th>
<th>Name</th>
</tr>
</thead>
</table>

If other, define: ________________________________

7. Does your child sleep on a pillow?

If No, go to question 8

<table>
<thead>
<tr>
<th>Pillows</th>
<th>Today</th>
<th>0-1yr</th>
<th>0-1yr Today</th>
<th>Name</th>
</tr>
</thead>
</table>

If other, define: ________________________________

8. Does your child sleep on a pillow?

If No, go to question 8

<table>
<thead>
<tr>
<th>Pillows</th>
<th>Today</th>
<th>0-1yr</th>
<th>0-1yr Today</th>
<th>Name</th>
</tr>
</thead>
</table>

If other, define: ________________________________
If Yes, what type of pillow is it?

<table>
<thead>
<tr>
<th>Foam :</th>
<th>☐ No ☐ Yes ☐ NSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic fibres:</td>
<td>☐ No ☐ Yes ☐ NSP</td>
</tr>
<tr>
<td>Plant fibres (straw, etc.):</td>
<td>☐ No ☐ Yes ☐ NSP</td>
</tr>
<tr>
<td>Feather:</td>
<td>☐ No ☐ Yes ☐ NSP</td>
</tr>
<tr>
<td>Other type of pillow:</td>
<td>☐ No ☐ Yes ☐ NSP</td>
</tr>
</tbody>
</table>

If other, define: ________________________________

---

7. Do people smoke in the room where your child lives?

- Today: ☐ No ☐ Yes ☐ NSP
- From 0-1yr: ☐ No ☐ Yes ☐ NSP
- During the pregnancy of the mother: ☐ No ☐ Yes ☐ NSP

---

8. What type of heating and lighting are used in the rooms where your child lives?

- Heating and lighting by charcoal: ☐ No ☐ Yes ☐ NSP
- Heating and lighting by wood: ☐ No ☐ Yes ☐ NSP
- Lighting by candle: ☐ No ☐ Yes ☐ NSP
- Lighting by petrol lamp: ☐ No ☐ Yes ☐ NSP
- Lighting by flash light: ☐ No ☐ Yes ☐ NSP
- Lighting by solar: ☐ No ☐ Yes ☐ NSP
- Other types of heating and lighting: ☐ No ☐ Yes ☐ NSP

If other, define: ________________________________

---

9. Which of the following products are used or stocked in the rooms where you child lives?

- Insecticide (type Yotox, spirales, etc.): ☐ No ☐ Yes ☐ NSP
- Deodorants (aerosols): ☐ No ☐ Yes ☐ NSP
- Incense: ☐ No ☐ Yes ☐ NSP
- Detergents (type Cotol, etc.): ☐ No ☐ Yes ☐ NSP
- Petrol, diesel: ☐ No ☐ Yes ☐ NSP
- Other types of products: ☐ No ☐ Yes ☐ NSP

If other, define: ________________________________

---

**Diet:**

1. Has your child had diarrhoea without fever or abdominal pains (colic) following introduction of non-maternal milk in his diet (cow or goat’s milk, milk powder):

- ☐ No ☐ Yes ☐ NSP

   after a few months of consuming non-maternal (cow or goat’s milk, milk powder):

- ☐ No ☐ Yes ☐ NSP

---

2. Currently, how many times, on average, does your child eat the following aliments? The consumption of certain aliments is seasonal.

- Meat: ☐ Never ☐ <1times/week ☐ 1-2 times/week ☐ ≥1times/day
- Fish: ☐ Never ☐ <1times/week ☐ 1-2 times/week ☐ ≥1times/day
- Egg: ☐ Never ☐ <1times/week ☐ 1-2 times/week ☐ ≥1times/day
- Milk (liquid, powder, curdled): ☐ Never ☐ <1times/week ☐ 1-2 times/week ☐ ≥1times/day
- Banana: ☐ Never ☐ <1times/week ☐ 1-2 times/week ☐ ≥1times/day
- Mango: ☐ Never ☐ <1times/week ☐ 1-2 times/week ☐ ≥1times/day
- Melon: ☐ Never ☐ <1times/week ☐ 1-2 times/week ☐ ≥1times/day
### HISTORICAL SYMPTOMATOLOGY OF ALLERGIC REACTIONS

**Asthma:**

1. Has a doctor or nurse already said that you child has asthma?
   - No
   - Yes
   - NSP

2. Has your child already breathed noisily or had whistling in his chest whilst breathing?
   - No
   - Yes
   - NSP
   
   If No, go directly to question 6

3. During his first two years of life, has your child already breathed noisily or had whistling in his chest whilst breathing?
   - No
   - Yes
   - NSP
   
   If No, go directly to question 6
   
   If Yes, how many times (before 2 years of age)?
   - 1 time
   - 2 times
   - ≥3 times
   - NSP
   
   Between the last two ramadans, has your child already breathed noisily or had whistling in his chest whilst breathing?
   - No
   - Yes
   - NSP
   
   If No, go directly to question 5
   
   If Yes, at which moment of the year?
   - Rainy season
   - Dry season
   - Harvest time
   
   Has the noisy breathing of your child been such that it has prevented him from talking normally?
   - No
   - Yes
   - NSP
   
   Has your child already had a rasping cough at night that prevents him from sleeping normally?
   - No
   - Yes
   - NSP

**Rhinitis and allergic conjunctivitis:**

1. Has your child already had problems of a runny nose, or a sensation of a blocked nose, or an itchy nose, or sneezing, or loss of the sense of smell for more than a week?
irrespective of the frequency of these episodes? □ No □ Yes □ NSP

2. Has your child already had problems of a runny nose, or a sensation of a blocked nose, or an itchy nose, or sneezing, or loss of the sense of smell more than 5 times in one year, irrespective of the frequency of these episodes? □ No □ Yes □ NSP

Between the last two ramadans, has your child already had problems of a runny nose, or a sensation of a blocked nose, or an itchy nose, or sneezing, or loss of the sense of smell more than 5 times in one year, irrespective of the frequency of these episodes?

If No, go to question 4
If Yes, at what moment of the year?
Rainy season: □ No □ Yes □ NSP
Dry season: □ No □ Yes □ NSP
Harvest time: □ No □ Yes □ NSP

3. Has your child already had watery eyes, or itchy eyes, or an allergic limbo-conjonctivitis?

If No, go directly to question 1 in the section Eczema
Has your child had, between the last two ramadans, watery eyes, or itchy eyes, or an allergic limbo-conjonctivitis?

If No, go directly to question 5
If Yes, at what moment of the year?
Rainy season: □ No □ Yes □ NSP
Dry season: □ No □ Yes □ NSP
Harvest time: □ No □ Yes □ NSP

Eczéma:

Has your child already had skin problems with dry patches or seeping cracked patches and itching?

If No, the questionnaire has finished.
Between the last two ramadans, has your child had skin problems with dry patches or seeping cracked patches and itching??

If No, go directly to question 3
If Yes, at what moment of the year?
Rainy season: □ No □ Yes □ NSP
Dry season: □ No □ Yes □ NSP
Harvest time: □ No □ Yes □ NSP

1. Have these skin problems affected different parts of the body of your child?
Scalp: □ No □ Yes □ NSP
Face: □ No □ Yes □ NSP
Around the eyes and ears: □ No □ Yes □ NSP
Armpits: □ No □ Yes □ NSP

□ RHIN1WEEK □ RHIN5FAN □ RHIN2RAM □ RHINRS □ RHINDS □ RHINHT □ CONJALER □ CONJ2RAM □ CONJRS □ CONJDS □ CONJHT □ ECZEMA □ ECZEMARS □ ECZEMADS □ ECZEMAHT □ ECZESCALP □ ECZEFAC □ ECZEEYEEAR
<table>
<thead>
<tr>
<th>Location</th>
<th>No</th>
<th>Yes</th>
<th>NSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elbow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hands</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under the buttocks</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Groin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Behind the knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feet</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other part of body</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What age did your child have when these skin problems of dry patches, weeping cracked patches or itching appear for the **first time**?

- [ ] < 2yr
- [ ] 2 - 4 yr
- [ ] ≥ 5yr

Have your child’s skin problems ever been sufficiently important to prevent him from sleeping correctly or waking him up during the night?

- [ ] No
- [ ] Yes
- [ ] NSP

**Comments**: Note with reference to which questions these comments apply

<table>
<thead>
<tr>
<th>Comments</th>
</tr>
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<tbody>
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</tbody>
</table>
Pedigree-based genetic relatedness

The Genetic covariance between two individuals can be computed using the pedigree information. For individuals A and B, a given pair in a pedigree, the genetic covariance is computed as \( r(A,B) = 2 \times coancestry(A,B) \) where the coancestry between A and B is calculated referring to the method presented by Falconer and Mackay in 1996 (Falconer and Mackay 1996): 
\[
coancestry(A,B) = \sum_p (1/2)^{n(p)} \times (1 + I_{\text{Common Ancestor}})
\]
where \( p \) is the number of paths in the pedigree linking A and B, \( n(p) \) the number of individuals (including A and B) for each path \( p \) and \( I_X \) is the inbreeding coefficient of X also equal to the coancestry between the two parents of X, \( I_X \) is set to 0 if X is a founder.

Illustration: Consider, as an example, the pedigree below containing 18 individuals named \{A, B, ..., R\} for the calculation of genetic covariance’s.

Pedigree structure.

The genetic relatedness between individuals N and O is equal to 0.266. This value is calculated as followed:

The number of paths linking N and O from the pedigree structure above is \( p = 2 \).

As illustrated below:

- **Path 1** contains \( n(1) = 3 \) individuals \{N, K, O\} with K as the common ancestor. Inbreeding coefficient of K, \( I_K \), is the coancestry between the two parents of K (F and G) and is null because F and G are not genetically linked.

- **Path 2** contains \( n(2) = 7 \) individuals \{N, K, F, B, H, L, O\} with B as the common ancestor. Inbreeding coefficient of B, \( I_B \), is null because B is a founder.

Therefore, genetic relatedness between individuals N and O is:
\[
= 2 \times (0.5^{n(1)} \times (1 + I_K) + 0.5^{n(2)} \times (1 + I_B)) \\
= 2 \times (0.5^3 \times (1+0) + 0.5^7 \times (1+0)) = 0.266
\]
Defining an equivalent model design where individual effects are independent using the genetic relatedness matrix:

Let us rename $Y^* = l(\mu)$. $Y^*$ can be consider as a linearization of the phenotype through the link function $l$. The expected mean of $Y^*$ and the variance of $Y^*$ are:

(i) \[ E(Y^*) = E(X\beta + Z\gamma + \varepsilon) \]
    \[ = E(X\beta) + E(Z\gamma) + E(\varepsilon) = X\times E(\beta) + Z\times E(\gamma) + E(\varepsilon) \]
    \[ = X\beta \quad \text{(asymptotically)}. \]

(ii) \[ \text{Var}(Y^*) = \text{Var}(X\beta + Z\gamma + \varepsilon) \]
    \[ = \text{Var}(\text{fixed part}) + \text{Var}(\varepsilon) \]
    \[ = \text{Var}(Z\gamma) + \text{Var}(\varepsilon) \]
    \[ = Z(A\sigma_g^2)Z^T + \sigma_r^2 \]
    \[ = ZAZ^T\sigma_g^2 + I\sigma_r^2 \]

If individuals were independent, i.e. $A = I_N$, variance of $Y^*$ could be expressed as $ZZ^T\sigma_g^2 + I\sigma_r^2$. However, using linear algebra theory by the method “Cholesky decomposition of a matrix”, we can show that there is an equivalent expression of the variance of $Y^*$ corresponding to the modeling of data from independent individuals, having $\gamma^*$ as an equivalent vector of random effects and $Z^*$ an equivalent design matrix relating $\gamma^*$ to $Y^*$ so that:

\[ \text{Var}(Y^*) = Z^*(I\sigma_g^2)Z^* + I\sigma_r^2 \]

Where $Z^*(I\sigma_g^2)Z^*$ is then the covariance matrix of the equivalent independent random individual effects $\gamma^*$.

**Theorem: Cholesky decomposition of a matrix**

If $A$ is a symmetric positive-definite matrix, there is a triangular matrix $L$ so that $A$ can be written as $A = LL^T$. $L$ can be seen as the “square root” of the matrix $A$.

Note that the genetic relatedness matrix $A$ computed using the pedigree information (Falconer and Mackay 1996) is a positive-definite matrix, unless identical twins are in the pedigree in which case it would be positive semi-definite.

**Equivalent model with independent random effects:** We set $A = LL^T$ then:

\[ \text{Var}(Y^*) = Z(A\sigma_g^2)Z^T + I\sigma_r^2 \]

\[ = Z(LL^T\sigma_g^2)Z^T + I\sigma_r^2 \]
\[
\begin{align*}
ZL \sigma_g^2 + I \sigma_e^2 &= (ZL)^T \sigma_g^2 + I \sigma_e^2 \\
&= (ZL)(ZL)^T \sigma_g^2 + I \sigma_e^2 \\
&= (Z^*)(Z^*)^T \sigma_g^2 + I \sigma_e^2
\end{align*}
\]
(\text{where we set } Z^* = ZL)

Then, if we define \( \gamma^* = L^{-1} \gamma \), we can rewrite the model as:

\[
Y^* = X\beta + Z^* \gamma^* + e
\]

(because \( Z \gamma = Z(LL^{-1}) \gamma = (ZL)(L^{-1} \gamma) = Z^* \gamma^* \)), and the \( \gamma_i^* \) are independent, in other terms \( \text{Var}(\gamma^*) = I \sigma_g^2 \), as demonstrated below:

We assumed that \( \gamma \sim N(0, A \sigma_g^2) \). Then \( \gamma^* = L^{-1} \gamma \) is also distributed as a multivariate Normal with mean \( \text{E}(\gamma^*) = L^{-1} \text{E}(\gamma) = L^{-1} \times 0 = 0 \) and variance:

\[
\text{Var}(\gamma^*) = (L^{-1}) \times \text{Var}(\gamma) \times (L^{-1})^T
= (L^{-1}) \times A \sigma_g^2 \times (L^{-1})^T
= (L^{-1}L)(L^{-1}L)^T \sigma_g^2
= I \sigma_g^2
\]

The random effects are now independent and then the classical mixed model assuming independence between levels (here individuals) is applied, and the estimate of fixed effects obtained are fine, i.e. corrected for genetic relationships.

\textbf{References}

Supplementary Tables

Table S1 Number of person-trimesters contributed by number of children by age class and the number who had severe/moderate allergy symptoms, for whom malaria data were also available. AS – Asthma, AD – Atopic dermatitis, RC – Rhinocconjunctivitis. Shown also are the numbers of these individuals suffering from two or all three allergy conditions.

<table>
<thead>
<tr>
<th>Age group</th>
<th>N° person-trimesters</th>
<th>N° people</th>
<th>AS</th>
<th>AD</th>
<th>RC</th>
<th>AS+AD</th>
<th>AS+RC</th>
<th>AD+RC</th>
<th>AS+AD+RC</th>
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<td>7</td>
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<td>0</td>
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Table S2 Summary of total number of person-trimesters with non-malaria and symptomatic *P. falciparum* clinical presentations and total number of non-malaria episodes according to age class. Given are the number of people contributing to each type of presentation.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>&lt;3·5</th>
<th>≥3·5</th>
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</thead>
<tbody>
<tr>
<td>Total person-trimesters</td>
<td>1283</td>
<td>1810</td>
</tr>
<tr>
<td>People</td>
<td>126</td>
<td>113</td>
</tr>
<tr>
<td>Total <em>P. falciparum</em> symptomatic trimesters</td>
<td>963</td>
<td>1102</td>
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<tr>
<td>People</td>
<td>114</td>
<td>108</td>
</tr>
<tr>
<td>Total non-malaria episodes</td>
<td>754</td>
<td>1114</td>
</tr>
<tr>
<td>People</td>
<td>123</td>
<td>109</td>
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</table>
Table S3 Effect of changing age threshold on impact of allergy on the risk of clinical malaria and concomitant parasite density. Given are Odds Ratio with 95% confidence intervals, for clinical malaria episodes and the beta coefficient and standard error for parasite density. Corresponding P values are also given. Values are from the nested GLMM analyses.

<table>
<thead>
<tr>
<th>A. Malaria episodes</th>
<th>OR 95% CI P value</th>
<th>OR 95% CI P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy</td>
<td>above threshold</td>
<td>below threshold</td>
</tr>
<tr>
<td>1.5</td>
<td>1.80 (1.25-2.59)</td>
<td>1.57 (0.85-2.89)</td>
</tr>
<tr>
<td>2.5</td>
<td>2.00 (1.39-2.88)</td>
<td>1.23 (0.76-1.99)</td>
</tr>
<tr>
<td>3.5</td>
<td>2.02 (1.39-2.93)</td>
<td>1.38 (0.92-2.08)</td>
</tr>
<tr>
<td>4.5</td>
<td>2.10 (1.42-3.10)</td>
<td>1.41 (0.98-2.04)</td>
</tr>
<tr>
<td>5.5</td>
<td>1.64 (1.07-2.52)</td>
<td>1.67 (1.17-2.37)</td>
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</table>

<table>
<thead>
<tr>
<th>B. Parasite density</th>
<th>Age cut-off</th>
<th>beta coeff (se) P value</th>
<th>beta coeff (se) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopy</td>
<td>above threshold</td>
<td>below threshold</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>0.70 (0.27)</td>
<td>9.2x10-3</td>
<td>0.04 (0.35)</td>
</tr>
<tr>
<td>2.5</td>
<td>0.79 (0.26)</td>
<td>2.6x10-3</td>
<td>0.35 (0.29)</td>
</tr>
<tr>
<td>3.5</td>
<td>0.85 (0.26)</td>
<td>9.5x10-4</td>
<td>0.37 (0.26)</td>
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<tr>
<td>4.5</td>
<td>0.87 (0.25)</td>
<td>6.9x10-4</td>
<td>0.40 (0.23)</td>
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<tr>
<td>5.5</td>
<td>0.73 (0.27)</td>
<td>7.4x10-3</td>
<td>0.48 (0.22)</td>
</tr>
</tbody>
</table>

| Asthma             | 1.98 (1.29-3.03) | 1.46 (0.69-3.19) | 0.34 |
| 2.5                | 2.30 (1.49-3.55) | 1.15 (0.63-2.09) | 0.65 |
| 3.5                | 2.33 (1.50-3.61) | 1.50 (0.90-2.50) | 0.12 |
| 4.5                | 2.30 (1.48-3.59) | 1.76 (1.11-2.80) | 0.017 |
| 5.5                | 1.98 (1.22-3.22) | 2.06 (1.33-3.18) | 0.0011 |

| Atopic Dermatitis  | 2.05 (1.18-3.56) | 0.91 (0.42-1.97) | 0.80 |
| 2.5                | 2.49 (1.36-4.57) | 0.82 (0.44-1.53) | 0.53 |
| 3.5                | 3.15 (1.56-6.33) | 0.84 (0.49-1.46) | 0.54 |
| 4.5                | 3.79 (1.61-8.92) | 0.94 (0.57-1.57) | 0.82 |
| 5.5                | 1.33 (0.47-3.77) | 1.19 (0.73-1.96) | 0.49 |

| Rhinconjunctivitis | 1.04 (0.66-1.62) | 1.01 (0.51-2.01) | 0.98 |
| 2.5                | 1.01 (0.64-1.61) | 0.96 (0.55-1.68) | 0.89 |
| 3.5                | 0.95 (0.60-1.52) | 1.05 (0.64-1.72) | 0.85 |
| 4.5                | 0.87 (0.54-1.42) | 1.06 (0.68-1.66) | 0.79 |
| 5.5                | 0.81 (0.48-1.36) | 1.07 (0.70-1.64) | 0.74 |

| Asthma             | 0.66 (0.31) | 0.03 |
| 2.5                | 0.78 (0.30) | 0.01 |
| 3.5                | 0.82 (0.30) | 0.12 |
| 4.5                | 0.81 (0.29) | 0.017 |
| 5.5                | 0.72 (0.31) | 0.02 |

| Atopic Dermatitis  | 0.80 (0.37) | 0.03 |
| 2.5                | 0.77 (0.38) | 0.044 |
| 3.5                | 0.99 (0.40) | 0.014 |
| 4.5                | 0.98 (0.47) | 0.036 |
| 5.5                | 0.26 (0.61) | 0.67 |

| Rhinconjunctivitis | 0.36 (0.32) | 0.27 |
| 2.5                | 0.28 (0.33) | 0.40 |
| 3.5                | 0.31 (0.32) | 0.33 |
| 4.5                | 0.20 (0.32) | 0.53 |
| 5.5                | 0.10 (0.33) | 0.75 |

6
Table S4 Frequency of non-malaria episodes (number of days of presence divided by number of non-malaria episodes) according to allergic status and age group. The $P$ value is that from the GLMM analyses of the effect of allergic status by age group on the number of non-malaria episodes per person-trimester.

<table>
<thead>
<tr>
<th>Allergic condition</th>
<th>Allergic status (No/Yes)</th>
<th>Age group (years)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;3·5</td>
<td>&gt;3·5</td>
</tr>
<tr>
<td>Atopy</td>
<td>N</td>
<td>78·2</td>
<td>85·9</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>87·2</td>
<td>102·6</td>
</tr>
<tr>
<td>Asthma</td>
<td>N</td>
<td>79·6</td>
<td>87·3</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>82·5</td>
<td>100·2</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>N</td>
<td>80·9</td>
<td>88·2</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>73·4</td>
<td>101·9</td>
</tr>
<tr>
<td>Rhinconjunctivitis</td>
<td>N</td>
<td>77·9</td>
<td>88·3</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>94·9</td>
<td>91·8</td>
</tr>
</tbody>
</table>
Figure S1. Incidence of clinical cases per 100 person-trimesters in children under 15 years of age.
Figure S2. Cumulative incidence of clinical cases according to allergy class predicted by the statistical model.
Figure S3. Graphical control model for parasite density

These figures provide a graphical checking of model goodness of fit. Figure A is the scatter plot of the natural logarithm of the observed parasite density and is compared to Figure B, which is the scatter plot of the natural logarithm of the predicted parasite density by the model; on both figures A and B the y-axes give the values for the log of the parasite density. Figure C shows the distribution of the residuals with the predicted values and Figure D is the histogram of the residuals; both figures C and D show the residuals normally distributed around zero.
Analysis using box-cox transformation and probit normalization

The model we fitted on the parasite density ("pf_density") has used as outcome variable the natural logarithm of pf_density (equivalent to a Box-Cox for which the parameter is null). As shown on Figure S4 the distribution of log(pf_density) is not perfectly normal, it is left-skewed.

Figure S4. Histogram of pf_density and log(pf_density)

We add here the case for a Box-Cox transformation of the parasite density where the parameter is λ = 0.3, this parameter value was obtained as optimal using the R- function named "boxcox" from the "MASS" library. Then the Box-Cox transformation of the parasite density is y = (pf_density^0.3 − 1)/0.3 having the distribution shown on Figure S5 below.
With this Box-Cox transformed parasitemia as outcome variable, our results are maintained. Note that this distribution is not "perfectly" normal. However, the corresponding graphical control of the model adequation presented on Figure S6 below shows residuals more close to the normal distribution than those for log(pf_density) as outcome.
Figure S6. Graphical control of the model adequation for $y = \text{Box-Cox}(pf\_density, \lambda = 0.3)$

Although using a mixed model approach based on an extreme value distribution would provide a more robust validation of these results, the method we used incorporating pedigree information was developed through an R-package known as "pedigreemm" that allows just for a limited number of distribution laws, which do not include extreme value distributions like the Gumbel or Weibull distributions.

However, we tried the Probit normalization on the log($pf\_density$) to readjust its quantiles to those from a standard normal, and subsequently used the derived standard normal transformation of the log($pf\_density$) as outcome (see Figure S7 below, the three graphs presented in the first row of the graphs panel concern the log($pf\_density$) before Probit normalization and the three in the second row are for after Probit normalization. We can see on the histogram in blue color a good normal distribution of the $y$ variable.
Figure S7. Probit normalization of the log(pf_density)

The results we obtained after this Probit normalization of the log(pf_density) confirmed the same findings. Also, the corresponding graphical control of the model adequation presented on Figure S8 below, shows a good normal distribution of residuals from this model.
Figure S8. Graphical control of the model adequation after Probit normalization of the log(pf_density)