Quantification of the Proportion of Unfavorable Clinical Outcomes among Imported Malaria Patients According to the Degree of Semi-Immunity on Population Level: An Ecological Study

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Abstract. The protective effect of semi-immunity to alleviate clinical complications of malaria remains incompletely understood. This ecological study quantified the proportion of unfavorable clinical outcomes among patient populations with imported malaria as a function of the reported proportion of absent semi-immunity in a patient population. Group-level proportions were extracted from published studies on imported malaria. Linear regression analyses demonstrate a consistent positive trend between the average proportion of absent semi-immunity in patient populations of imported malaria and the proportion of unfavorable clinical outcomes therein. Regression equations provide a group-level estimate of attributable fractions of clinical complications resulting from absent semi-immunity to malaria.

During the past few years, the proportion of imported malaria attributable to immigrants and travelers visiting friends and relatives has increased consistently.1 Patients originating from endemic regions may differ from classical tourists from non-malaria endemic regions because of partially retained semi-immunity, which they acquired during several years of routine exposure to the parasite Plasmodium falciparum. As a consequence, fewer clinical complications are noticed among patients with semi-immunity. Despite this well-accepted association, only a limited number of high-validity studies on imported malaria have stratified clinical complications by immunity status. To collate all currently available evidence, we conducted an ecological study in which we quantified the average proportion of unfavorable clinical outcomes among patient populations with imported malaria as function of the reported proportion of absent semi-immunity in a patient population.

For this study, a comprehensive review of the work by Mischlinger et al.2 comparing semi-immune and non-immune travelers with imported malaria constituted the sampling frame for the selection of relevant literature. Additional literature was identified in reference lists of respective publications, and group-level data were extracted. The exposure of interest was the proportion of absent semi-immunity in a patient population of a published study on imported malaria. In addition, the proportions of the following unfavorable clinical outcomes were extracted: severe malaria, admission to the intensive care unit (ICU), and death. Linear multivariable regression models were applied to determine the association between absence of semi-immunity and either severe malaria, ICU admission, or death. To prevent heteroskedasticity, weighted linear regression was performed by including the proportion of absent semi-immunity as an analytical weight. Because of the apparent associations with absence of semi-immunity and unfavorable clinical outcome, the following variables were regarded as a priori confounders and therefore data were also collected: age, the proportion of adherence to chemoprophylaxis, and infection by P. falciparum.2,3 In the univariable analysis, gender was not associated with any outcome. To avoid selection bias, articles were excluded if an outcome served as an inclusion criterion in the original publication.

The proportion of patients with absent semi-immunity in a published article was regarded as the reported proportion of patients without previous exposure to malaria. If a publication did not report explicit information, the proportion of patients who were born and are normally residing in a non-malaria-endemic area was used as the surrogate proportion for the proportion of patients without previous exposure to malaria. The definition of severe malaria followed WHO criteria, unless stated otherwise in the original publication.4 Stata v. 16 (StataCorp, College Station, TX) was used for statistical analysis.

Fifty-six articles on imported malaria from 1987 to 2017 were included in the analysis. The majority of articles were published from Europe (82%), six articles (11%) from the United States, and one article (2%) each from Australia and the Middle East. Two articles (4%) covered more than one continent. The median percentage of people without semi-immunity against malaria was 36% (range, 0–88%). The median number of study participants in selected studies was 208 (interquartile range [IQR], 86–545), with a median age of 33 years (IQR, 30–37 years), and the median percentage of males was 66% (IQR, 59–72%).

The median percentage of malaria caused by respective Plasmodium spp. was 78.4% (IQR, 66.8–90.3%) for P. falciparum, 10.8% (IQR, 0.7–19.4%) for P. vivax, 2.4% (IQR, 0–5.2) for P. ovale, and 1.2% (IQR, 0–2.3%) for P. malariae. The median percentage of participants who reported having taken antimalarial prophylaxis was 21.6% (IQR, 16.0–39.0%). Among the overall study populations, the median proportion was 14.0% (IQR, 6.7–23.3%) for severe malaria, 6.2% (IQR, 4.1–11.8%) for ICU admission, and 0.3% (IQR, 0–1.1%) for a fatal outcome.

Results of univariable linear regression analysis indicated strong evidence for a positive correlation between proportion of absence of semi-immunity and the proportion of severe malaria in a population (r = 0.32x + 0.02; P = 0.002). Similarly, evidence was found in support of a positive correlation between absence of semi-immunity and a fatal outcome on population level (r = 0.023x + 0; P = 0.02). No evidence for such a correlation was detected for ICU admission (r = 0.06x + 0.08; P = 0.6) (Table 1). After adjustment for
The adjusted regression equation for severe malaria is:

\[ y = 0.32 \times (0.12 \text{ to } 0.51)x + 0.02 \times (-0.1 \text{ to } 0.13) \]

\[ P \text{ value} = 0.02 \]

The adjusted regression equation for ICU admission is:

\[ y = 0.06 \times (-0.18 \text{ to } 0.31)x + 0.08 \times (-0.07 \text{ to } 0.23) \]

\[ P \text{ value} = 0.6 \]

The adjusted regression equation for death is:

\[ y = 0.023 \times (0.004 \text{ to } 0.042)x + 0.01 \times (-0.01 \text{ to } 0.01) \]

\[ P \text{ value} = 0.02 \]

**Table 1**

| Outcomes         | n | Univariable regression equations | \( P \) value |
|------------------|---|----------------------------------|--------------|
| Severe malaria   | 38| \( y = 0.32 \times (0.12 \text{ to } 0.51)x + 0.02 \times (-0.1 \text{ to } 0.13) \) | 0.002 |
| ICU admission    | 18| \( y = 0.06 \times (-0.18 \text{ to } 0.31)x + 0.08 \times (-0.07 \text{ to } 0.23) \) | 0.6 |
| Death            | 47| \( y = 0.023 \times (0.004 \text{ to } 0.042)x + 0.01 \times (-0.01 \text{ to } 0.01) \) | 0.02 |

**Table 2**

| Outcome            | n | Restricted univariable regression equations* | \( P \) value | Multivariable regression equations | \( P \) value |
|--------------------|---|-----------------------------------------------|--------------|-----------------------------------|--------------|
| Severe malaria 27*  | 27| \( y = 0.36 \times (0.15 \text{ to } 0.58)x + 0 \times (-0.13 \text{ to } 0.12) \) | 0.027 | \( y = 0.42 \times (0.18 \text{ to } 0.65)x + 0.02 \times (-0.24 \text{ to } 0.27) \) | 0.001 |
| ICU admission 12*   | 12| \( y = 0.06 \times (-0.22 \text{ to } 0.35)x + 0.07 \times (-0.1 \text{ to } 0.35) \) | 0.64 | \( y = 0.15 \times (-0.17 \text{ to } 0.47)x + 0.16 \times (-0.18 \text{ to } 0.5) \) | 0.31 |
| Death 28*           | 28| \( y = 0.027 \times (0.002 \text{ to } 0.056)x + 0 \times (-0.02 \text{ to } 0.02) \) | 0.06 | \( y = 0.045 \times (0.016 \text{ to } 0.074)x + 0.015 \times (-0.017 \text{ to } 0.046) \) | 0.004 |

**ICU** = intensive care unit, \( y \) = regression coefficient (95% CI), \( x \) = constant (95% CI).

* Univariable regression variables were re-computed restricted to studies with available data on all confounders. Similar regression coefficients indicate that missing data did not influence the change between crude and adjusted regression coefficients.
commonly in published articles. Although ICU admission and death are specifically defined events, the WHO criteria applied for the definition of severe malaria have been changed repeatedly between 1987 and 2017. Because WHO criteria have been applied equally for semi-immune and non-immune patients, no differential misclassification is expected.

This ecological study provides the first model for quantifying the proportion of severe malaria and death as a function of the proportion of absence of semi-immunity in populations of patients with imported malaria. Findings of this report are potentially important for medical centers where patients with imported malaria are managed. We believe the results of our linear regression models might help clinical decision makers allocate adequate resources for the management of patient populations with imported malaria by estimating the average percentage of severe malaria and death based on the prevalence of absent semi-immunity in their patient population.

Further research is needed to verify such results at the individual patient level. Furthermore, to overcome the difficulties in defining semi-immunity, additional investigations on biomarkers are needed that reflect both the degree of individual exposure to *Plasmodium* spp. as well as the degree of protection from developing clinically apparent disease.

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