Humans become infected with malaria as a result of their exposure to blood-feeding infective *Anopheles* mosquitoes. Sporozoite-stage parasites inoculated by even a single infectious mosquito can cause human malaria infection and life-threatening disease. To estimate the intensity of malaria parasite transmission under field conditions, it is standard practice to determine the entomological inoculation rate (EIR), the product of the mosquito biting rate times the proportion of mosquitoes carrying sporozoites in their salivary glands.\(^1\) The EIRs are expressed in terms of average numbers of infective bites per person per unit time. Unlike most other parts of the world where it is difficult to determine EIRs because of exceedingly low sporozoite rates, many valuable studies of transmission have been conducted in Africa where sporozoite rates generally range from 1% to 20%.\(^2\) The EIRs in endemic areas of Africa range from < 1 to > 1,000 infective bites per year.\(^3\)

Malaria prevalence is simply the number of persons found to be infected with malaria parasites out of the total number of persons sampled. Normally, prevalence studies involve taking thick and thin blood smears from volunteers, staining the slides with Giemsa, and microscopically examining the slides to detect and count parasites. Most epidemiologic studies of malaria have measured prevalence in cross-sectional surveys or through longitudinal investigations of specific study populations. For many countries in Africa, historic data on malaria prevalence are available from surveys done by the Ministries of Health. Such data can be useful for mapping and evaluating patterns of endemicity, as illustrated by recent studies in Kenya where malaria prevalence data were available from > 600 surveys throughout the country.\(^4\) At all levels within the public health sector, assessments of malaria prevalence are commonplace for planning and implementing malaria control programs.\(^5\)

Fundamental to the development of sound malaria control programs is a basic understanding of relationships between malaria transmission by vector populations of mosquitoes (i.e., EIRs) and the outcome measures of transmission in terms of malaria prevalence, malaria incidence, the incidence of severe disease, and mortality.\(^6-9\) To gauge levels of malaria control necessary to achieve meaningful public health improvements in Africa, it will be necessary to quantitative-\(^{ly}\) define the extent to which site-specific EIRs must be reduced to correspondingly reduce malaria prevalence. The objective of this study was to examine relationships between EIRs and *Plasmodium falciparum* malaria prevalence in sub-Saharan Africa.

To obtain EIR and malaria prevalence data collected simultaneously at the same sites, literature searches were done to identify relevant studies that met *a priori* inclusion criteria. Studies were evaluated for appropriate entomological data according to the following inclusion criteria: 1) studies conducted over at least one year, 2) frequency of mosquito sampling at least monthly throughout the year or during periods of transmission for sites with seasonal patterns of transmission, 3) standard methods such as human-biting catches, pyrethrum spray catches, or Center for Disease Control light traps used for estimating biting rates, 4) dissection or ELISA methods used for determining proportion of sporozoite-infected mosquitoes, and 5) studies were conducted during periods when no mosquito control operations were in effect. For those sites where EIR data were available for more than one year, yearly average figures were used as provided in the papers.

Inclusion criteria for malaria prevalence data included 1) malaria prevalence determined by standard thick/thin blood smear techniques, 2) malaria prevalence reported by age classes of volunteers and sampling periods, and 3) malaria prevalence reported according to *Plasmodium* species. In the literature, various types of methods have been used for de-
terming and reporting malaria prevalence with respect to selection of volunteer groups, sample sizes of volunteers, methods for detecting and quantifying parasites, and reporting results by age groups. For this reason, the maximum prevalence for any designated age group was used as a single figure for each site. By selecting only the maximum prevalence, it was possible to standardize prevalence estimates across studies to evaluate the worst possible public health effect due to an associated annual EIR for each given site.

In some instances, single papers reported EIR and P. falciparum prevalence data from several sites that met the inclusion criteria. There were other situations where EIR and P. falciparum prevalence data for single sites were reported in different publications. Such data were included in the analysis only when it was clear that the EIR and prevalence data were obtained through simultaneous investigations at exactly the same sites. In one case, prevalence data from a Ph.D thesis was matched with published EIR data. It is important to note that the studies included in the analysis are a representative sample rather than an exhaustive account of the integrated entomologic and epidemiologic malaria field research done in Africa. Many studies were not included because they did not meet inclusion criteria or because the reported data could not be interpreted.

Data for each site were entered using SPSS for Windows (SPSS Institute, Chicago, IL). Besides EIR and P. falciparum prevalence data, other data included 1) the authors and date of publication, 2) country, 3) names of sites, 4) habitat types (i.e., savanna, coast, forest, urban, irrigation, highland), 4) technique used to determine mosquito biting rates, 5) technique used to determine malaria sporozoite rates, 6) age classes of volunteers relating to the prevalence data, and 7) any other specific notes. Data values representing the maximum malaria prevalence and the annual EIR for each site were plotted on linear and logarithmic axes. A box plot was used to show how the variability in malaria prevalence decreases with increasing intensities of transmission.

Figure 1 shows the relationship between annual EIRs and the prevalence of P. falciparum infection based on data obtained from 31 sites throughout Africa. The EIR data ranged from 0 to 702 infective bites per person per year, while the malaria prevalence data ranged from 7.0% to 94.5%. The presentation of data in Figure 1A shows that even sites with relatively low EIRs had malaria prevalence rates exceeding 40%. There were no examples of prevalence rates < 50% when EIRs exceeded 15 infective bites per year. Malaria prevalence was typically > 80% when EIRs exceeded 200 infective bites per year. As detailed in Figure 1B, 71.2% of the variance in malaria prevalence was explained by the logarithm of the annual EIR. The same trends were seen when data were examined according to countries in east and west Africa, and according to different ecologic habitats.

Figure 2 shows the same P. falciparum prevalence data in a box plot format according to EIRs divided into categories of 1–10, 11–100, and 101–1,000 infective bites per year. With the lowest annual EIRs, from 1 to 10 per year, the mean ± SD malaria prevalence was 38.9 ± 17.9% (range = 7.0–62.5%). With annual EIRs from 11 to 100, the mean ± SD malaria prevalence was 58.2 ± 24.9% (range = 13.5–87.2%). With the highest EIRs, from 101 to 1,000 per year, the mean ± SD malaria prevalence was 83.2 ± 8.3% (range = 70.0–94.5%). At the highest EIRs, we observed the lowest range in prevalence, which is consistent with saturating levels of infection in the human population. Interestingly, the one outlier point, where a prevalence of 13.5% was associated with an annual EIR of 14, was from Pikine, a city outside of Dakar, Senegal, where residents had ready access to antimalarial drugs.

Based on the analysis, the relationship between EIR and malaria prevalence in Africa is such that any detectable EIR is associated with prevalence rates of P. falciparum malaria large enough to seriously impact public health. It is obvious that high prevalence rates can even be seen with extremely low or non-detectable EIRs. For example, on the Kenyan coast, one site with an EIR of 0.001 and another where no infected mosquitoes could be found had P. falciparum prevalence rates of 44.7% and 49.3%, respectively. Such find-
ings are not surprising because both historic studies\textsuperscript{1,5,13-15} and the more recent studies of insecticide-impregnated bed nets\textsuperscript{16-18} indicate that substantial reductions in transmission intensity are necessary to reduce the prevalence of malaria infection in human populations. In some holoendemic areas, reductions in EIRs by 95% or more are required before seeing any decreases in the prevalence of \textit{P. falciparum} infection.\textsuperscript{19-21}

In Africa, many studies have demonstrated that standard vector control measures are useful for controlling and even eliminating malaria in certain areas where transmission levels are marginal.\textsuperscript{22} A foundation of malaria vector control is that actions to decrease vector-host contact through methods including larval habitat modification, insecticide treatment of larval habitats, spraying insides of houses with residual insecticides, insecticide-treated bed nets, or the use of repellents will have correspondingly beneficial outcomes in terms of reduction in morbidity and mortality. Effective vector control measures decrease the incidence of malaria infections because there is a linear relationship between EIRs and malaria incidence.\textsuperscript{23} In fact, studies in Saradidi in western Kenya showed that 74% of the variation in \textit{P. falciparum} incidence is explained by EIRs.\textsuperscript{23}

In establishing priorities for malaria control, an exercise that is being repeated in many African countries, it is necessary to define quantitatively how much control is necessary to achieve desired impacts. This is difficult because malaria prevalence alone is not a sensitive indicator of transmission intensity (Figures 1 and 2). The degree of control needed, whether it is achieved through integrated vector control, anti-malaria drugs, or vaccines, is clearly going to be different in situations where residents are exposed to 1, 10, 100, or 1,000 infective bites per year.\textsuperscript{9} Importantly, the analysis in Figure 1 indicates that it may not be possible to achieve dramatic decreases in the prevalence of \textit{P. falciparum} infection at sites in Africa unless control measures reduce EIRs to levels well below 1 infective bite per year.

A complex issue is whether there are any levels of malaria transmission in Africa that can be considered acceptable from a public health perspective. In addition to malaria prevalence, we also need to consider how reductions in EIRs will affect other important outcome measures of malaria, such as the incidence of severe disease and mortality. First, though reducing the EIR will lead to upward shifts in the age distribution of the incidence of infection by effectively increasing the average age at first exposure,\textsuperscript{24} older individuals apparently are better prepared to handle infections and to seek proper treatment than infants and young children.\textsuperscript{9} Second, reductions in seasonally high levels of EIRs will likely reduce densities of asexual-stage parasites in the blood stream;\textsuperscript{25-27} parasite density is a significant risk factor for severe disease and mortality.\textsuperscript{28} Third, the incidence of severe malaria due to anemia and to cerebral complications appears to vary as a function of transmission intensity and so reductions in EIRs may change the clinical presentation of disease states\textsuperscript{7,8,11,12,29} nevertheless, it is well documented that even EIRs less than 5 infective bites per year can be associated with incidence rates of severe disease > 25 per 1,000.\textsuperscript{11,26} Fourth, the genetic diversity of \textit{P. falciparum} parasite populations increases with levels of transmission by vector populations, and there is recent evidence that the dependence of incidence and parasite density on EIR may be partially mediated by effects on genetic diversity of parasites.\textsuperscript{30,31} Fifth, the extent to which EIRs affect the presentation of disease varies as a function of available treatment, health services, and vector control.\textsuperscript{9} Overall, reductions in the presentation of disease and mortality are likely easier to achieve than meaningful reductions in malaria prevalence, as already demonstrated by results of recent bed net trials across Africa.\textsuperscript{16-18}

While it has been suggested that reducing transmission may counter-intuitively lead to greater mortality due to loss of immunity,\textsuperscript{29,33,34} there is no direct evidence from longitudinal studies\textsuperscript{7,13} Caution is required in using proxy measures of transmission (i.e., the force of infection using malaria prevalence survey data)\textsuperscript{29} and not actual EIRs because malaria prevalence is not a direct indicator of transmission intensity (Figure 1). Loss of immunity due to decreasing transmission intensity is probably not a clinical concern until the point where control measures are achieving significant reductions in malaria prevalence because clinical immunity is determined by exposure to blood stages rather than sporozoites.\textsuperscript{35} We have observed that prevalence rates can exceed 40–60% even at the lowest observed EIRs as shown in Figure 1. From direct observations in Kilifi, Kenya, we know that even barely detectable low-level EIRs\textsuperscript{11,30} are sufficient so that natural immunity in children develops early in life and few children develop severe disease or die after the age of 6 years.\textsuperscript{8} We do not know of any examples in Africa or elsewhere where malaria prevalence rates of 40% or higher are not associated with the development of effective natural immunity. At sites where malaria control is working in Africa and elsewhere,\textsuperscript{9} there is no indication that current effective strategies for case detection, treatment, health education, or vector control should be changed regardless of longer-term potential reductions in natural immunity that are bound

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2.png}
\caption{Box plot showing increases in \textit{Plasmodium falciparum} malaria prevalence with increases in annual entomologic inoculation rates (EIRs) with EIR categories of 1–10, 11–100, and 101–1,000. Per category, the mean value is shown as a line inside the box, the 25th to 75th percentile is shown by the box, and the range of values is shown by the lines outside the box. In the case of the EIR category 11–100, a single outlier point is shown instead of the lower range value.}
\end{figure}
to arise when the immune status of individuals approaches that of non-immune individuals due to reduced exposure to infected mosquitoes.35

While malaria stratification according to ecologic zones is an important element of malaria control,14 it is important to note that the fundamental relationships between EIR and the prevalence of *P. falciparum* infection (Figure 1) will likely hold across diverse ecosystems in Africa. We did not find any examples anywhere in Africa where high EIRs were associated with low malaria prevalence rates. Malaria control programs, including the new World Health Organization Roll Back Malaria program,36 that seek to achieve substantial reductions in malaria-associated mortality should consider the need for integrated transmission control methods that emphasize achieving and maintaining effective reductions in transmission by mosquito vector populations.

In conclusion, we have documented the basic relationship between EIRs and malaria prevalence in Africa. One of the most important points is that unacceptably high levels of *P. falciparum* prevalence exist at very low levels of transmission by local vector populations. Even at the lowest EIRs, there are high rates of malaria prevalence and associated severe disease.3,11,30,37 Basic relationships between EIRs and malaria prevalence should be used to guide the development and implementation of malaria control programs in Africa. The analysis in Figure 1 and the associated stratification of the data in Figure 2 provide a benchmark for how reductions in malaria transmission intensity will lead to reductions in malaria prevalence. Our analysis indicates that substantial reductions in malaria prevalence are only likely to be achieved when EIRs are reduced to levels less than 1 infective bite per person per year. Across Africa, there are approximately 360 million people at risk for *P. falciparum* infection.38 In areas where the climatic suitability for transmission is marginal,39 and EIR levels are generally <5 infective bites per year, current tools for control may be sufficient for effectively reducing levels of malaria prevalence. However, in endemic zones where the climatic suitability for transmission39 and corresponding EIRs are higher, there is an obvious need for new tools for malaria transmission control that could be used in conjunction with already proven measures like insecticide-treated bed nets. It is clear that the EIR is a more direct measure of transmission intensity than traditional epidemiologic measures of malaria prevalence or hospital-based measures of infection or disease incidence. As such, field programs need to consider both entomologic and clinical assessments of the efficacy of transmission control measures.

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Authors’ addresses: John C. Beier and Gerry F. Killeen, Department of Tropical Medicine, Tulane University, 1501 Canal Street, Room 505, New Orleans, LA 70112. John I. Githure, International Centre of Insect Physiology and Ecology, PO Box 30772, Nairobi, Kenya. Reprint requests: John C. Beier, Department of Tropical Medicine, Tulane University, 1501 Canal Street, Room 505, New Orleans, LA 70112.

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