PNAS COMMENTARY

Modeling malaria elimination with changing landscapes, climate, and potentially invasive vectors

Huaiyu Tian[a,1]

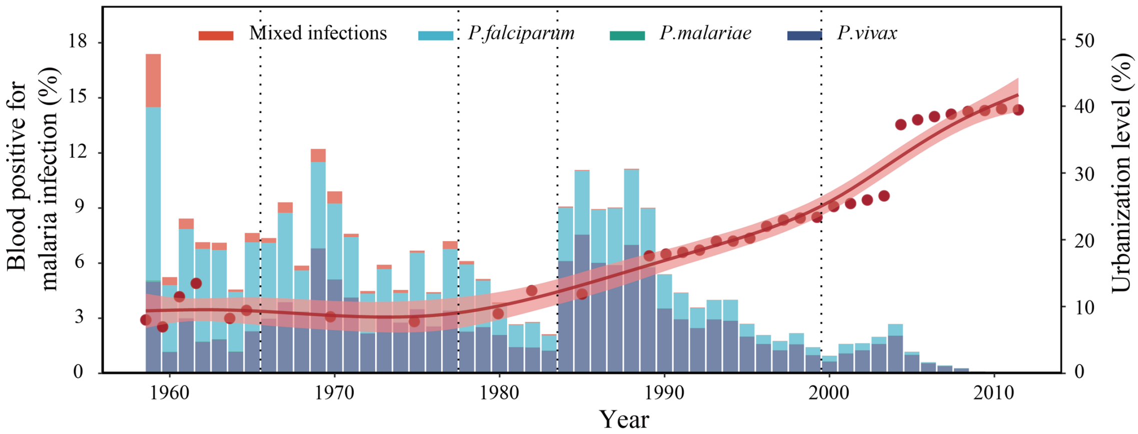

Fig. 1. Malaria epidemics in Hainan between 1959 and the elimination of endemic malaria in 2011. Hainan is a tropical island province in Southern China. Bars represent the annual malaria prevalence in the population measured using blood tests. Red dots correspond to the urbanization rate. Urbanization is defined as the percentage of the total population living in urban areas and is adjusted by the percentage of the nonagricultural population owing to changes in the official statistical category of "urban population" in 2005. The thick red line shows the fit of urbanization; 95% prediction ranges of regression are shown as red shaded areas. The vertical dashed lines indicate the timing of four major insecticides being successfully introduced since the 1950s: organochlorines, organophosphates, carbamates, and pyrethroids.

Malaria is one of the most ancient infectious diseases in human history. Eradication of malaria has long been a main global health initiative (1–3). To accelerate progress toward malaria elimination, the Global Technical Strategy for Malaria 2016 to 2030 (GTS) was adopted in 2015, with the aim of reducing the malaria burdens of both death and disease by at least 90% by 2030 (4). Although tremendous efforts have been made to control malaria over the past century, the disease remains one of the leading causes of morbidity and mortality worldwide (5). In particular, a rebound of malaria in sub-Saharan Africa accounted for 95% of all malaria cases and 96% of all malaria deaths worldwide in 2020 (6). Under these circumstances, the most worrying future scenario of malaria risk is the appearance of the invasive malaria vector, *Anopheles stephensi*, which was recently detected in Africa. Since the identification of the parasites that cause malaria, research has historically been focused on their biology as well as on the population ecology of mosquitoes that transmit malaria parasites (7). Short-term seasonal cycles and long-term trends of climate and land-use change can alter not only biological traits but also the contact between mosquitoes and humans, and hence, the transmission trajectories. In PNAS, Whittaker et al. (8) moved one step closer to understanding the uncertainty in future malaria risk by characterizing the impact of ecological factors on the invasion and establishment of *An. stephensi* across the Horn of Africa. The authors summarized the existing literature and presented evidence that variation in *An. stephensi* abundance is associated with temperature and patterns of land-use, with seasonality frequently differing between rural and urban settings. That important study sheds new light on a number of discussions in the environmental sciences related to global change and public health and provides a framework for invasive vector surveillance strategies in malaria control.

Accelerating Urbanization and Land-Use Change

Over 50% of the global population currently lives in urban areas, with the fastest urbanization rates seen in Africa. As a result, malaria-affected countries are expected to see more people moving into their urban areas. Concomitant land-use changes and population immigration, driven by the urbanization process, can have complex effects on shifting the risk of infectious diseases (9), such as rural urbanization, deforestation, and agricultural expansion and irrigation have been linked to the altered patterns of

Author affiliations: [a]State Key Laboratory of Remote Sensing Science, Center for Global Change and Public Health, College of Global Change and Earth System Science, Beijing Normal University, 100875 Beijing, China

Author contributions: H.T. wrote the paper.

The author declares no competing interest.

See companion article, "Seasonal dynamics of *Anopheles stephensi* and its implications for mosquito detection and emergent malaria control in the Horn of Africa," 10.1073/pnas.2216142120.

[1]Email: tianhuaiyu@gmail.com.

Published March 6, 2023.

malaria (10). Improvements in housing conditions, which usually accompanies urbanization, have been shown to be an important contributing factor to reducing the malaria risk (11–13). Over the past century, rapid urban development has largely accelerated malaria elimination in Hainan, a tropical island province of southern China, with fluctuations in the malaria prevalence with rapid urbanization and endemic turning points (Fig. 1). However, unplanned urbanization and the presence of invasive mosquito species that adapt to urban settings in malaria-affected countries may heighten the risk of malaria (14). Reports of rapid land-use change and species that amplify pathogens thrive in human-dominated landscapes have been accumulating for decades. *An. stephensi*, which is known to thrive in urban settings and mostly breeds in man-made water containers, could put population at new risk due to inadequate water supplies, waste management, dense population, and insufficient capacity of vector control and surveillance, especially in unplanned urban areas. Most recently, *An. stephensi* has been identified in multiple African countries as an invasive vector (15) incriminated in the resurgence of malaria outbreaks in Djibouti (16). Perhaps most intriguing, the meta-analysis of the population dynamics and adaptation of *An. stephensi* presented by Whittaker et al. (8) suggests the existence of a diverse range of temporal patterns between rural and urban settings, highlighting the urgent actions required to prevent malaria resurgence in sub-Saharan Africa, which previously occurred during the 1980s.

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Climate Change and Global Warming

As a climate-sensitive disease, the impact of climate change on malaria is of major public health interest (17, 18). Seasonal cycles are fundamental to malaria epidemiology. Variations mainly in temperature and rainfall can affect malaria incidence and transmissibility through the population dynamics of mosquito vectors and parasites or indirectly via other pathways (19). By analyzing environmental factors related to mosquito population dynamics, Whittaker et al. (8) in PNAS offer a fresh perspective that seasonal abundance of *An. stephensi* is associated with temperature but poorly predicted by rainfall. Owing to clear differences with the results obtained from analysis of dominant vectors across Africa, this finding again prompts the long-studied question of how future climate change will affect malaria transmission and geographic distribution. In light of previous theory, by estimating the optimal temperature range for malaria transmission, thermal response models (20) can help to explain the dependency between varying patterns of temperature and the changes in malaria incidence along altitudinal gradients across continents (21, 22). However, great uncertainties and controversies remain. Biological experiments, field surveillance, and population studies mainly analyze the currently dominant species. As such, mechanistic models linking climate variability to the biological response and ecological dynamics of mosquito vectors remain by far the most important tools for predicting malaria risk (23–25). Taken together, the disparate climate drivers identified for *An. stephensi* versus other dominant species in Africa imply a potential caveat regarding the scenarios of malaria risk predicted using previous climate–biological models.

Implications for Malaria Control

The patterns detected by Whittaker et al. (8) in their analyses are striking. The distinct patterns of *An. stephensi* abundance in rural and urban settings also raise interesting questions about the feasibility of and requirements for the effective control of malaria in the near future. Approaches to reduce the malaria burden in rural areas may not work or may be unsuitable in urban settings. Other challenges include the high population density and high levels of human mobility in urban settings (26) as well as rural-to-urban migration with malaria infection. Although some of the poorest countries have substantially reduced malaria transmission or even achieved malaria elimination, with some developing countries close to malaria elimination, the emergence and dissemination of invasive vectors that adapt to urban environments increase the risk of malaria resurgence and threaten the ultimate goal of malaria eradication.

Another key contribution of the novel study by Whittaker et al. (8) is to demonstrate the unanticipated challenges in combining knowledge about the temporal profiles of *An. stephensi* abundance with environmental data to predict future malaria risk with current entomological surveillance and vector control conducted in a stronger and more parsimonious manner. Most previous work has shown the importance of mosquito vector control in eliminating malaria, particularly the timing of vector control campaigns. For example, over the past century, indoor residual spraying has usually been implemented before the start of malaria epidemic season in Hainan (Fig. 1). However, several types of data are critical to test the proposed mechanisms (27–29). Causality has not been established from the inferred statistical framework between environmental conditions and the seasonal abundance of *An. stephensi.* Insecticide resistance profiles in malaria vectors are another important issue, and laboratory capacity remains scarce in many tropical countries (30). Going forward, such limitations suggest an urgent need for longitudinal entomological monitoring of invasive vectors in their new environments, given the above threats.

An. stephensi may not be the first and will not be the last invasive malaria vector in the 21st century. Owing to the rapid geographic expansion of *An. stephensi* and the potential replacement of efficient malaria vectors, particularly in Africa, it has proved challenging to anticipate malaria scenarios as targeted in the GTS (31). Changing epidemiological, environmental, and sociological conditions largely increase the complexity of malaria eradication. More powerful statistical and machine learning frameworks that can incorporate information of multiple driving factors, including the changing landscape, climate, and wide-ranging potential vectors, will be useful in optimizing the assessment of future malaria risk.

ACKNOWLEDGMENTS. This work was supported by National Key Research and Development Program of China (2022YFC2303803, 2021YFC0863400), Beijing Science and Technology Planning Project (Z221100007922019), National Natural Science Foundation of China (82073616), Beijing Advanced Innovation Program for Land Surface Science (110631111), Research on Key Technologies of Plague Prevention and Control in Inner Mongolia Autonomous Region (2021ZD0006), and Fundamental Research Funds for the Central Universities. I would like to thank Ziyan Liu for collecting the data in Hainan that have helped improve this Article.

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