Revista da Sociedade Brasileira de Medicina Tropical
Journal of the Brazilian Society of Tropical Medicine
Vol.:52:e20190308: 2019
doi: 10.1590/0037-8682-0308-2019

Mini Review

Do climate changes alter the distribution and transmission of malaria? Evidence assessment and recommendations for future studies

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Abstract

Malaria, a mosquito-borne infectious disease, is considered a significant global health burden. Climate changes or different weather conditions may impact infectious diseases, specifically those transmitted by insect vectors and contaminated water. Based on the current predictions for climate change associated with the increase in carbon dioxide concentrations in the atmosphere and the increase in atmospheric temperature, the Intergovernmental Panel on Climate Change predicts that in 2050, malaria may threaten some previously unexposed areas worldwide and cause a 50% higher probability of malaria cases. Climate-based distribution models of malaria depict an increase in the geographic distribution of the disease as global environmental temperatures and conditions worsen. Researchers have studied the influence of changes in climate on the prevalence of malaria using different mathematical models that consider different variables and predict the conditions for malaria distribution. In this context, we conducted a mini-review to elucidate the important aspects described in the literature on the influence of climate change in the distribution and transmission of malaria. It is important to develop possible risk management strategies and enhance the surveillance system enhanced even in currently malaria-free areas predicted to experience malaria in the future.

Keywords: Climate changes. Malaria. Infectious diseases.

INTRODUCTION

Malaria is a mosquito-borne infectious disease caused by the parasitic protozoans of the genus *Plasmodium* (*P. vivax*, *P. falciparum*, *P. ovale*, *P. malariae*, *P. knowlesi, P. cynomolgi*, and *P. simium*) and transmitted by female mosquito vectors of the *Anopheles* genus[1-5]. It is considered a significant global health burden at both global and regional levels[6,7]. The spatial distribution of malaria is largely influenced by climatic factors and ecological and socioeconomic factors, such as urban planning, land use, malaria treatment, and capacity of the healthcare system[8-10]. The influence of climate and socioeconomic changes on malaria's prevalence and distribution are being studied by researchers worldwide via projections that use different mathematical models (MMs) that consider different variables (e.g., altitude, temperature, humidity, Gini index, rainfall, humidity, and direction and speed of the winds) and predict the conditions for malaria distribution, incidence, transmission, and the costs associated with the treatment of new cases arising from climate change (CC)[11-16]. Most studies evaluating the effects of future CC are based on the Intergovernmental Panel on Climate Change's (IPCC) findings. In this context, we conducted a mini-review to elucidate the important aspects described in the literature on CC regarding

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Received 19 July 2019
Accepted 14 November 2019

the epidemiology and transmission of malaria and elucidated some of the effects of CC on anopheline mosquitoes and on the *Plasmodium* cycle in the vector. For review purposes, we reviewed the published articles. The identification of the articles was performed through a bibliographic search in the databases PubMed and SciELO Virtual Library, referring to the years 1994 to 2018 in English and Spanish. The search strategy used was as follows: (climate changes AND malaria) OR (temperature increase AND malaria) OR (humidity increases AND malaria) OR (climate change and Anopheles). From the paper evaluated, we made some recommendations for future studies of CC evaluation in the distribution and transmission of malaria worldwide, aiming to predict future impacts of CC on disease distribution. It is important that possible risk management strategies should be developed and surveillance system enhanced, including in the currently malaria-free areas predicted to experience malaria in the future.

Climate change and future climate scenarios and perspective of infection disease distribution

Global emissions of greenhouse gases (GHGs) from human activities have increased to >70% since the preindustrial period,[17,18] and in the face of CC in the late 1980s, the United Nations Environment Program and the World Meteorological Organization established the IPCC for a wide international network of scientists dedicated to assessing relevant scientific, technical, and socioeconomic information to understand the risks posed by CC worldwide and to propose CC scenarios for the future[19]. The Representative Concentration Pathways (RCPs), which are used to make projections based on population size, economic activity, lifestyle, energy use, land use patterns, and technology and climate policies, refer to the number of radiative forcing measured in watts per square meter per year by 2100[20].

The RCPs include a stringent mitigation scenario (RCP2.6), two intermediate scenarios (RCP4.5 and RCP6.0), and one scenario with very high GHG emissions (RCP8.5)[21]. RCP2.6 represents a scenario that aims to keep global warming likely below 2°C[22]. The RCP8.5 combines, among other factors, high population growth, high energy demand, and high GHG emissions in the absence of CC policies, corresponding to the RCP with the highest GHG emissions. This scenario includes radiative forcing beyond 8.5 W/m2 and carbon dioxide (CO_2) concentrations of 1,370 ppm up to the year 2100[23].

CC or different weather conditions patterns in different climatic scenarios are affecting the human health by increasing morbidity, mortality, and disabilities and through the emergence of diseases in previously non-endemic regions[24-26]. CC may impact infectious diseases' epidemiology and transmission, specifically diseases transmitted by insect vectors and contaminated water[27-29], such as dengue, malaria, hantavirus pulmonary syndrome, salmonellosis, cholera, and giardiasis[30-35]. CC includes alterations in one or more climate variables (such as temperature, precipitation, wind, and sunshine), and these changes may impact the pathogens, vectors, hosts, and their living environment mainly by altering survival, reproduction, or distribution of disease pathogens and hosts[36-38] (**Figure 1**). The impacts of CC must be understood in the context of several other forces that drive infectious disease dynamics, such as rapid evolution of drug- and pesticide-resistant pathogens, rapid global dissemination of microbes and vectors through expanding transportation networks, and deterioration of public health programs in some regions[39].

The IPCC concluded, with high confidence, that CC will cause higher frequency of infectious disease epidemics following floods and storms and anticipated that CC will have a mixed effect on the spread of malaria[40] based on vector biology and vector absence in regions that are currently extremely cold for survival[41,42]. Climate malaria models depict an increase in the geographic distribution of the disease as global environmental temperatures and conditions worsen[43-46]. Based on the current CC associated with the increase of CO_2 concentrations and increase in atmospheric temperature, the IPCC predicts that in 2050, malaria may threaten some previously unexposed regions of South America, sub-Saharan Africa (SSA), and China, thus causing a 50% higher probability of malaria[47].

Effects of climate change on malaria cases and their distribution: evaluating different theories and papers

The epidemiology of malaria is significantly complex and multifactorial[48], and understanding the association between climate and malaria is essential[41]. The association between climate warming and a malaria epidemic has been strongly debated, and recent evidence suggests that the incidence of malaria is increasing in colder regions of the world due to global warming[43,49-51]. However, the CC effects are potentially complex, and the implications for malaria risk in optimal transmission settings remain poorly defined[49-52]. It most likely depends on the ecology of the prevalent main vector species, the biology of the causative organism (*Plasmodium*), the resistance and immunity of the host, and climatic factors such as temperature, precipitation, and humidity[38] (**Figure 1**).

Babaie et al.[53] suggested that temperature, precipitation, relative humidity, and wind intensity and direction are the most important climatic factors affecting the growth and proliferation of *Anopheles*, the *Plasmodium* life cycle, and the prevalence of malaria. A series of studies associating temperature variations to incidences of malaria has been debated by several researchers, with particular emphasis on changes in the malaria distribution scenario, specifically in the African continent[43,54-61], although other studies haves been conducted in Asia[62,63], South America, and Latin America[64,65] (**Figure 2**).

Egbendewe-Mondzozo et al.[66] studied the association between malaria cases and climatic factors in 25 African countries that were observed over a period of 11 years. They performed an econometric analysis and found that the number of malaria cases per 1,000 people is significantly influenced by climatic factors, with the incidence of malaria generally increasing under CC. According to the authors, socioeconomic factors also significantly affect the number of malaria cases.

According to Jaenisch and Patz[67], Halimi et al.,[68] and Salahi-Moghaddam et al.,[69] the incidence of malaria is sensitive to

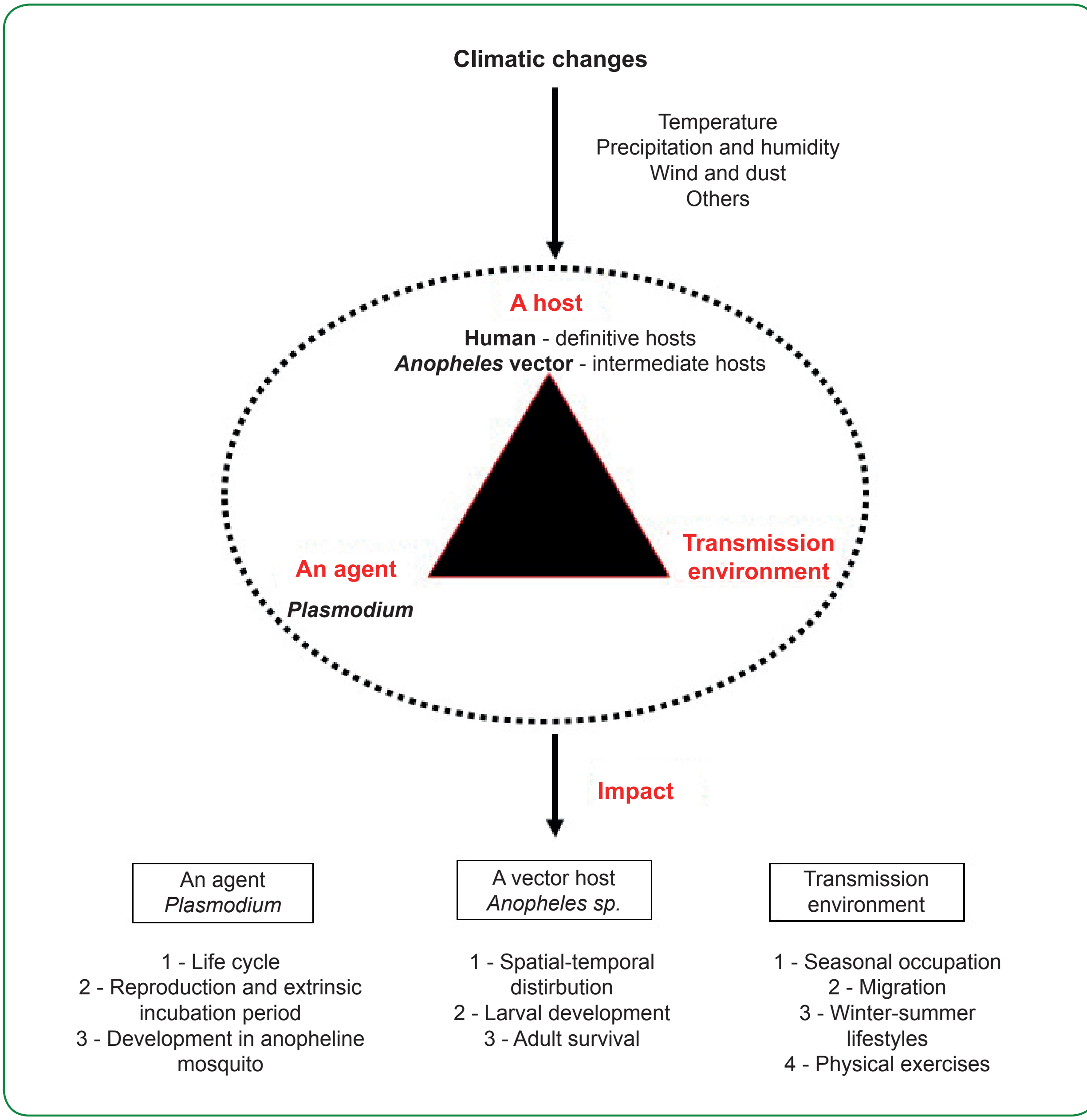

FIGURE 1: Association between climate change, malaria, and transmission environment. The climate change effect on human infectious diseases can be examined through its impacts on the three disease components: pathogen, host, and transmission environment.

short-term fluctuations in temperature and rainfall patterns, and with extreme precipitation, washing anopheline mosquito larvae from the breeding sites may lead to decreased incidence of malaria. Hay et al.[70] demonstrated that the mean temperature and precipitation did not change significantly over the past century in highland East Africa, where malaria incidence has increased. However, Pascual et al.[43] reanalyzed the temperature trend data in similar locations in East Africa between 1950 and 2002 and found that where there was an increase in the number of cases of malaria, the temperature increased by approximately 0.5°C in the last half of the twentieth century. They also evaluated the biological significance of this trend and conducted an active model on the population dynamics of mosquito vectors with time series of temperature.

Halimi et al.[68] showed that in Iran, precipitation has been the most important climatic factor associated with annual malaria changes; hence, the outbreaks of the disease had a high correlation with precipitation and humidity index and lower correlation with the annual temperature mean. A study

Topic	Location	Study Methods	Conclusions
Effects of climate change on malaria cases and their distribution	Ethiopia and Colombia49 East Africa43 African continent66 Guangzhou, southern China71 East Africa57 East Africa54 Sub-Saharan Africa78	MM	Evidence suggests that malaria may be increasing due to climate change.
	Iran53 Guangzhou, southern China71 Iran68 African continent66	SR MM GIS MM	The most important climatic factors in Anopheles proliferation are temperature, precipitation, relative humidity, wind intensity and direction, and hours of sunlight. These factors predominantly alter the distribution of the disease across the globe.
	African continent70 Iran69	MM	Place of residence and/or land use and coverage is an important factor in malaria distribution.
Effects of climate change on anopheline mosquitoes and the Plasmodium cycle in the vector	East Africa45 USA80	BR ESL	Temperature variations alter the vector's metabolic rates and vector capacity.
	USA82 USA83	ESL	Temperature effects modify the immune response of the vector.
	Western Kenya81 South West/Central China76 USA80	ESL MM ESL	Environmental changes interfere with the development of Plasmodium.

MM = mathematic model; **SR =** systematic review; **GIS** = geographic information system; **BR** = bibliography review; **ESL=** experimental study in laboratory.

FIGURE 2: Different aspects of climate change in malaria distribution and transmission over the globe.

conducted by Li et al.[71] via the analysis of CC in China between 2006 and 2012 showed the following through negative binomial regression: 1) each 1°C increase in temperature corresponded to 0.90% increase in the monthly number of malaria cases, 2) 1% increase in relative humidity led to an increase of 3.99%, and 3) an increase of 1 hour of sunshine led to a 0.68% increase in the number of malaria cases monthly.

MMs using equations with multiple climate variables and the biology of the *Plasmodium* in the mosquito vector that interferes with the epidemiology of malaria have been created. Over the last few decades, a number of MMs, typically statistical (using data and statistical approaches to correlate some climate variables with malaria incidence) or mechanistic (accounting for the detailed dynamic nonlinear processes involved in disease transmission, also sometimes referred to as "process based"), have been used to assess the likely impact of anthropogenic CC on malaria transmission dynamics and control[72].

Omumbo et al.[57] have indicated through MM that the increase in temperatures observed in the regions of East Africa has an effect on the epidemiology of malaria since the transmission of this condition depends on vector abundance, mosquito bite rate, vector survival, development rate, and environmental changes. Alonso et al.[54] developed a model that incorporated the population dynamics of the mosquito vector with the time series of temperature and found that a small increase in environmental temperature has an important but nonlinear effect on malaria transmission. Interestingly, temperature and precipitation exhibited nonlinear and synergistic effects on the incidence of malaria.

Parham and Michael[46] have developed a simple model of climate-related malaria transmission that provides insights into the sensitivity of disease transmission to changes in precipitation and temperature. These authors have shown that the development and analysis of such dynamic climate-based transmission models are crucial in understanding the rate at which *P. falciparum* and *P. vivax* can infect, expand, or disappear in the populations as local environmental conditions change. At fixed vector densities, *P. falciparum* and *P. vivax* differ by a few weeks in their rate of spread, with *P. vivax* spreading more rapidly than *P. falciparum*[73].

Beck-Johnson et al.[74] developed a temperature-dependent differential equations model structured in stages to better understand how climate determines the risk of malaria transmission. By including the complete life cycle of the mosquito in the model, it is revealed that the abundance of the mosquito population is more temperature sensitive than previously thought as it is strongly influenced by the dynamics of the life cycle of the mosquito at a juvenile stage whose vital rates are also temperature dependent. Additionally, the model they developed predicts a peak in the abundance of mosquitoes old enough to transmit malaria at high temperatures.

Studies evaluating the effect of future CC, based on the IPCC findings, show the role of different scenarios in the epidemiology and distribution of malaria. In a multimodel set, using variables predicted by the IPCC and based on five different global climate models, each run under four emissions and a single population projection. Carmine et al.[75] investigated the modeling uncertainty associated with future projections of populations at risk for malaria due to CC. Their findings show the global net increase in climate suitability and the net increase in the population at risk, but with large uncertainties. The model outputs indicate a net increase in the annual person-months at risk when comparing from RCP2.6 to RCP8.5 from the 2050s to the 2080s. Hundessa[76] projected the long-term future distribution of *P. vivax* and *P. falciparum* malaria in China using 10 years of malaria surveillance data and 26 global climate models under two emission pathways (RCP8.5 and RCP4.5). The results indicate that *P. vivax* and *P. falciparum* malaria will increase in China, but by a larger amount in the RCP8.5 scenario. Moreover, a principal component regression model, constructed by Kwak et al.[77] considering multicollinearity, shows an increase in the occurrence of malaria and the shortening of annual time of occurrence in the future.

Future climate data, generated from RCP4.5 CC scenario climate model, were applied to the constructed regression model to simulate future malaria occurrence and analyze the trend of occurrence and showed an increase in the occurrence of malaria and the shortening of annual time of occurrence in the future. According to Kibret[78], in SSA, the number of dams located in malaria areas is projected to increase in both RCPs. However, the number of cases will always be higher in RCP 8.5 than in RCP 2.6.

Effects of climate change on anopheline mosquitoes and on the *Plasmodium* cycle in the vector

Changes in vector body temperature due to variation in ambient temperature are able to significantly change the metabolic rates of insect vectors and the parasites they host[76,79]. Anopheline mosquitoes in environments with climatic warming effects have a higher metabolite rate, which in turn directly interferes with the development of larvae that take less time to mature[78]. Additionally, temperature increases promote the rapid digestion of blood supply, which in turn promotes a significant increase in fecundity, with the development of better reproductive fitness and a greater ability to produce more offspring[45]. Additionally, an increase in the ambient temperature can intensely increase the feeding frequency in the hosts and increase the annual temporal patterns of mosquito activity (particularly biting rates) and promotes a reduction in the time of sporogonic development of *Plasmodium* from an average of 14 days to 12.6 days[45].

Noden et al.[80] demonstrated that temperature affects the sporogonic development of *P. falciparum* in *A. stephensi* mainly by altering the kinetics of ookinete maturation. High temperatures (30ºC and 32ºC) are considered to significantly affect parasite densities and infection rates, interfering in the developmental processes that occur between fertilization of the parasite and ookinete formation, specifically during zygote formation and early maturation of ookinete. Okech et al.[81] demonstrated that in the experimental model for *P. falciparum* and *A. gambiae*, the prevalence of ookinete infection decreased with an increase in temperatures, while the mean oocyst intensities for infected mosquitoes increased with temperatures. Furthermore, they demonstrated that the success of infections reduced by 30°C and 32°C and resulted in greater losses during consecutive periods of development of the interstage parasite. These results show that the most significant impact of high temperatures occurs mainly at the transition between macrogametocytes and ookinetes, while the transition between oocysts and oocysts was apparently unaffected.

Temperature can shape the parasite's resistance and growth phenotype through indirect effects, which are still poorly studied, but they may interfere with the innate immune system of the mosquito and influence the development of the parasite cycle[82]. Suwanchaichinda et al.[83] investigated how larval nutrition and environmental temperature changes affect the melanization process in adults of *A. gambiae* after challenging with Sephadex beads and have shown that melanization progressively decreases as the temperature increases by 24ºC to 30°C[81]. Murdock et al.[82] emphasized that with *A. stephensi,* temperature change (ranging from 12°C to 34°C) is responsible for shaping variable cellular and humoral immune responses. The temperature was shown to significantly affect all measured immune responses, but in different ways. Unexpectedly, melanization, phagocytosis, and expression of defensin (an antimicrobial peptide) were all higher at 18°C (8°C below the standard breeding temperature for this mosquito). The expression of nitric oxide synthase reached its peak at 30°C, while the expression of the antimicrobial peptide cecropin was not directly affected by temperature. Based on these findings, it is possible to conclude that the immunological profile described during a *Plasmodium* infection is potentially different if the same experiment is conducted at different temperatures.

Although most studies available in the literature describe the association between high temperatures and the increase of malaria cases in certain regions of the globe, specifically in the African continent, Murdock et al.[84] demonstrated in the laboratory that temperature increases are capable of affecting the ability of *A. gambiae* and *A. stephensi* to transmit; increase in temperature reduces the rate and intensity of infection and increasing mosquito mortality, thus reducing the vector capacity of both species of mosquitoes[84]. These authors demonstrated that increases of 3°C from 27°C reduced vector capacity by 51%–89%, depending on the species, and at 33°C, the transmission potential was even lower for *A. stephensi* and completely blocked in *A. gambiae*. Additionally, these authors suggest that instead of increasing the risk, current and future warming may reduce transmission potential in existing high-transmission environments.

Recommendations for future studies

Assessing the potential change in the risk of malaria caused by CC and climate variability remains an important topic. The effects of CC on malaria appear to be multifactorial, and these distinct factors should be evaluated individually and in conjunction with modeling CC and malaria transmission to determine the factors involved in the incidence of malaria currently and in future climatic conditions as predicted by the IPCC. This will help to effectively control malaria; additionally, for greater impact, interventions could be synchronized with the most important climatic predictors of the disease. Furthermore, a better understanding of the association between precipitation patterns, temperature and humidity changes, and malaria cases and associated mortality is necessary to establish effective strategies for CC, involving the planning and implementation of appropriate control interventions for diseases. The distinct search allows decision-makers to assess changes in malaria in the different territories.

Furthermore, we would like to emphasize some important topics for elucidation in future research:

i) Development and validation of climate and ecosystem based on distinct early malaria epidemic prediction models.

ii) Malaria modeling at the regional or national scales and integrating regional environmental programs and socioeconomic variation[25], mainly in Latin America, where studies regarding malaria are insufficient.

iii) Assessment through multidisciplinary perspectives (life science, human science, and biophysics) of the qualitative factors that affect the transmission of malaria at different spatial and temporal scales, evaluating the interactions, synergism, and nonlinearity between the different factors involved in the transmission.

iv) Development of malaria transmission models to assess the risks posed by climatic and ecological changes. Observational, experimental, and modeling activities are all highly interdependent and must progress in a coordinated fashion[51].

v) Construction of the malaria transmission risk maps according to the IPCC forecast of future climatic conditions to provide an analysis guide for the planning and implementation of appropriate control interventions based on the research agenda for the elimination of malaria.

vi) Understanding the behavior of the malaria vector and the etiological agent in the face of CCs, predicted by the climatic scenarios provided by the IPCC, with special emphasis on the tropical countries of America.

vii) Association between temperature-induced variations in gene expression and functional resistance or malaria vector competence. Thus, the effects of temperature on the production of antimicrobial peptides and on the activity of the nitric oxide enzyme and phagocytosis of pathogens should be investigated under which mosquitoes are subject to *Plasmodium*.

Final remarks

Different studies were conducted to estimate the impact of future CC and population scenarios on malaria transmission at a global scale and to provide recommendations for future interventions and research. The research's results indicate that future climate might become more suitable for malaria transmission in the tropical regions. However, other factors such as land use change, population growth and urbanization, migration changes, economic development, and associated costs will need to be factored into future risk assessments for the treatment of the disease or for the determination of alternative treatments to block vector transmission through the use of mass treatment of the population.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Greenwood BM, Fidock DA, Kyle DE, Kappe SH, Alonso PL, Collins FH, et al. Malária: Progress, perils, and prospects for eradication. J Clin Invest. 2008;118(4):1266-76.
2. Bronner U, Divis PCS, Farnert A, Singh B. Swedish traveller with *Plasmodium knowlesi* malária after visiting Malaysian Borneo. Malar J. 2009;8(15):1-15.

3. Goh XT, Lim YA, Vythilingam I, Chew CH, Lee PC, Ngui R, et al. Increased detection of *Plasmodium knowlesi* in Sandakan division, Sabah as revealed by PlasmoNex™. Malar J. 2013;12(264):1-14.

4. Ta TH, Hisam S, Lanza M, Jiram AI, Ismail N, Rubio JM. First case of a naturally acquired human infection with *Plasmodium cynomolgi*. Malar J. 2014;13(68):1-7.

5. Brasil P, Zalis MG, Pina-Costa A, Siqueira AM, Júnior-Bianco C, Silva S, et al. *Plasmodium simium* causing human malaria: A zoonosis with outbreak potential in the Rio de Janeiro Brazilian Atlantic forest. Lancet Glob Health. 2017;5(1):1038-46.

6. Murray CJL, Rosenfeld LC, Lim SS, Andrews KG, Foreman K, Fullman N, et al. Global malaria mortality between 1980 and 2010: A systematic analysis. Lancet. 2012;379(9814):413-31.

7. Githeko A, Lindsay S, Confalonieri U, Partz J. Climate change and vector-borne diseases: A regional analysis. Bulletin of the World Health Organ. 2000;78(9):1136-47.

8. Semenza JC, Menne B. Climate change and infectious diseases in Europe. Lancet Infect Diseases. 2009;9(6):365-75.

9. Cyril C, Sari K, Joacim R, Adrian MT, Andrew PM, Felipe J. CG, et al. Impact of climate change on global malaria distribution. PNAS. 2014;111(9):3286-91.

10. M'Bra RK, Kone B, Soro DP, N'Krumah RTAS, Soro N, Ndione JA, et al. Impact of climate variability on the transmission risk of malaria in northern Côte d'Ivoire. PLOS ONE. 2018;13(6):1-15.

11. Ostovar A, Haghdoost AA, Rahimiforoushani A, Raeisi A, Majdzadeh R. Time Series Analysis of Meteorological Factors Influencing Malaria in South Eastern Iran. Journal of arthropod-borne diseases. 2016;10(2):222-36.

12. Yu PB, Tian HY, Ma CF, Ma CA, Wei J, Lu XL, et al. Hantavirus infection in rodents and haemorrhagic fever with renal syndrome in Shaanxi Province, China, 1984-2012. Epidemiol. Infect. 2015;143(1):405-11.

13. Mandal S, Sakar RR, Sinha S. Mathematical models of malaria - a review. Malaria Journal. 2011;10(202):1-19.

14. Traoré B, Sangaré B, Traoré S. A Mathematical Model of Malaria Transmission with Structured Vector Population and Seasonality. Journal of Applied Mathematics. 2017;1(2017):1-15.

15. Gurarie D, Karl S, Zimmerman PA, KIng CH, Pierre TGS, Davis TME. Mathematical Modeling of Malaria Infection with Innate and Adaptive Immunity in Individuals and Agent-Based Communities. PLOS ONE. 2012;7(3):1-13.

16. Kumar STPRCP, Reddy NNR. Factors affecting malaria disease transmission and incidence: a special focus on Visakhapatnam district. Int J Sci Res. 2014;5(1):312-17.

17. Pidwirny, M. [Internet]. Causes of Climate Change. Fundamentals of Physical Geography, [updated 2018 July 12; cited 2018 March 8]. Available from: http://www.physicalgeography.net/fundamentals/7y.html.

18. Steinberg TL. An Ecological Perspective on the Origins of Industrialization. Environmental Review. 1986;10(4):261-76.

19. IPCC, 2008: Towards new scenarios for analysis of emissions, climate change, impacts, and response strategies. IPCC Expert Meeting Report., Noordwijkerhout, The Netherlands, 34 p.

20. IPCC, 2014: Climate Change 2014: Impacts, Adaptation, and Vulnerability. Part A: Global and Sectoral Aspects. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press, Cambridge, United Kingdom and New York, NY, USA, 32 p.

21. IPCC, 2014: Climate Change 2014: Synthesis Report. Contribution of Working Groups I, II and III to the Fifth Assessment Report of the Intergovernmental Panel on Climate. Geneva, Switzerland, 151 p.

22. Vuuren DPV, Stehfest E, Elzen MGJD, Kram T, Vliet JV, Deetman S, et al. RCP2.6: exploring the possibility to keep global mean temperature increase below 2°C. Climatic Change. 2011;109(1):95-116.

23. Riahi K, Rao S, Krey V, Cho C, Chirkov V, Fischer G, et al. RCP 8.5 - A scenario of comparatively high greenhouse gas emissions. Climatic Change. 2011;109(1):33-57.

24. Moreno AR. Climate change and human health in Latin America: Drivers, effects, and policies. Regional Environmental Change. 2006;6(3):157-64.

25. Winchester L, Szalachman R. The urban poor's vulnerability to the impacts of climate change in latin America and the Caribbean. A policy agenda. Fifth Urban Research Symposium 2009.

26. Rodríguez-Morales AJ. Climate Change. In: Ogunseitan O, editors. Green Health: An A-to-Z Guide. The SAGE Reference Series on Green Society Toward a Sustainable Future. California: Paul Robbins; 2011. p.111-115.

27. Kuhn k, Campbell-Lendrum D, Haines A, Cox J. Using Climate to Predict Infectious Disease Epidemics. Geneva: World Health Organization; 2009. 56 p.

28. Tian H, Zhou S, Dong L, Boeckel TPV, Cui Y, Newman SH, et al. Avian influenza H5N1 viral and bird migration networks in Asia. PNAS. 2015;112(1):172-77.

29. Short EE, Caminade C, Thomas BN. Climate Change Contribution to the Emergence or Re-Emergence of Parasitic Diseases. Infectious Diseases: Research and Treatment. 2017;10(1):1-7.

30. Costello A, Abbas M, Allen A, Ball S, Bell S, Bellamy R, et al. Managing the health effects of climate change. The Lancet Commissions. 2009;373(1):1693-1733.

31. Yu PB, Tian HY, Ma CF, Ma CA, Wei J, Lu XL, et al. Hantavirus infection in rodents and haemorrhagic fever with renal syndrome in Shaanxi Province, China, 1984–2012. Epidemiol. Infect. 2015;143(1):405-11.

32. Epstein PR. Climate and health. Science.1999;285(1):347-8.

33. Kovats RS, Menne B, McMichael AJ, Corvalan C, Bertollini R. Climate Change and Human Health: Impact and Adaptation. Geneva: World Health Organization; 2009. 50 p.

34. Willox AC, Stephenson E, Allen J, Bourque F, Drossos A, Elgarøy S, et al. Examining relationships between climate change and mental health in the Circumpolar North. Reg. Environ. Chang. 2015;15(1):169-82.

35. Chretien JP, Anyamba A, Bedno SA, Breiman RF, Sang R, Sergon K, et al. Drought-associated Chikungunya emergence along coastal East Africa. J. Trop. Med. Hyg. 2007; 76(3):405-07.

36. Tian HY, Bi P, Cazelles B, Zhou S, Huang SQ, Yang J, et al. How environmental conditions impact mosquito ecology and Japanese encephalitis: an eco-epidemiological approach. Environ. Int. 2015;79(1):17-24.

37. Epstein PR. Climate change and emerging infectious diseases. Microbes Infect. 2001;3(1):747-54.

38. Wu X, Lu Y, Zhou S, Chen L, Xu B. Impact of climate change on human infectious diseases: Empirical evidence and human adaptation. Environment International. 2006;86(1):14-23.

39. National Research Council (US) Committee on Climate, Ecosystems, Infectious Diseases, and Human Health. [Internet]. Under the Weather: Climate, Ecosystems, and Infectious Disease. [updated 2019 March 05; cited 2019 March 10]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK222251.
40. Confalonieri U, Menne B, Akhtar R, Ebi KL, Hauengue M, Kovats RS, et al. Human health. Climate Change 2007: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press, Cambridge, UK; 2007. 391-431.
41. Caminade C, Kovats S, Rocklov J, Tompkins AM, Morse AP, Colón-González FJ, et al. Impact of climate change on global malaria distribution. PNAS. 2014;111(9):3286-91.
42. Yamana TK, Eltahir EAB. Projected impacts of climate change on environmental suitability for malaria transmission in West Africa. Environ Health Perspect. 2013;121(10):1179-86.
43. Pascual M, Ahumada JA, Chaves LF, Rodó X, Bouma M. Malaria resurgence in the East African highlands: temperature trends revisited. PNAS. 2006;103:(15):5829-34.
44. Delgado-Petrocelli L, Córdova K, Camardiel A, Aguilar VH, Hernández D, Ramos S. Analysis of the El Niño/La Niña-Southern Oscillation variability and malaria in the Estado Sucre, Venezuela. Geospat Health. 2012;6(3):51-7.
45. Afrane YA, Githeko AK, Yan G. The ecology of *Anopheles* mosquitoes under climate change: Case studies from the effects of deforestation in East African highlands. Acad Sci. 2012;1249(1):204-10.
46. Parham PE, Michael E. Modeling the effects of weather and climate change on malaria transmission. Environ Health Perspect. 2010;118(5):620-26.
47. IBRD. International Bank for Reconstruction and Development. 4º Turn Down the Heat. Why a 4ºC warmer world Must be Avoided. A Report for the World Bank by the Potsdam Institute for Climate Impact Research and Climate Analytics. Washington: IBRD; 2012. 84 p.
48. Nabil SA, Qader SS. Is global warming likely to cause an increased incidence of Malaria? Libyan J Med. 2009;4(1):9-16.
49. Siraj AS, Santos-Vega M, Bouma MJ, Yadeta D, Carrascal DR, Pascual M. Altitudinal changes in malaria incidence in highlands of Ethiopia and Colombia. Science. 2014;343(6175):1154-58.
50. Paaijmans KP, Read AF, Thomas MB. Understanding the link between malaria risk and climate. PNAS. 2009;106(33):13844-49.
51. Paaijmans KP, Blanford JI, Crane RG, Mann ME, Ning L, Kathleen V. et al. Downscaling reveals diverse effects of anthropogenic climate warming on the potential for local environments to support malaria transmission. Climatic Change. 2014;125(3-4):479-88.
52. Medlock JM, Leach SA. Effect of climate change on vector-borne disease risk in the UK. Lancet Infect Dis. 2015;15(6):721-30.
53. Babaie J, Barati M, Azizi M, Ephtekhari A, Sadat SJ. A systematic evidence review of the effect of climate change on malaria in Iran. J Parasit Dis. 2018;42(3):331-40.
54. Alonso D, Bouma MJ, Pascual M. Epidemic malaria and warmer temperatures in recent decades in an East African highland. Proc Biol Sci. 2011;278(1712):1661-69.
55. Bonora S, Rosa FG, Boffito M, Perri GD, Rossati A. Rising temperature and the malaria epidemic in Burundi. Trends Parasitol. 2001;17(12):572-73.
56. Loevinsohn ME. Climatic warming and increased malaria incidence in Rwanda. Lancet. 1994;343(8899):714-18.
57. Omumbo JA, Lyon B, Waweru SM, Connor SJ, Thomson MC. Raised temperatures over the Kericho tea estates: Revisiting the climate in the East African highlands malaria debate. Malaria Journal. 2011;10(12):1-16.
58. Pascual M, Cazelles B, Bouma MJ, Chaves LF, Koelle K. Shifting patterns: malaria dynamics and rainfall variability in an African highland. Proc Biol Sci. 2008;275(1631):123-32.
59. Craig MH, Kleinschmidt I, Nawn JB, Sueur DL, Sharp BL. Exploring 30 years of malaria case data in KwaZulu-Natal, South Africa: part I. The impact of climatic factors. Trop Med Int Health. 2004;9(12):1247-57.
60. Hay SI, Cox J, Rogers DJ, Randolph SE, Stern DI, Shanks GD, et al. Climate change and the resurgence of malaria in the East African highlands. Nature. 2002;415(1):905-09.
61. Githeko AK, Ndegwa W. Predicting malaria epidemics in the Kenyan highlands using climate data: A tool for decision makers. Glob Change Human Health. 2001;2(1):54-63.
62. Kim YM, Park JW, Cheong HK. Estimated effect of climatic variables on the transmission of *plasmodium vivax* malaria in the Republic of Korea. Environ Health Perspect. 2012;120(9):1314-19.
63. Lin H, Lu L, Tian L, Zhou S, Wu H, Bi Y, et al. Spatial and temporal distribution of *falciparum* malaria in China. Malar J. 2009;8(130):1-9.
64. Gagnon AS, Smoyer-Tomic KE, Bush AB. The El Niño southern oscillation and malaria epidemics in South America. Int. J. Biometeorol. 2002;46(2):81-9.
65. Prothero RM. Malaria in latin America: Environmental and human factors. Bull. Latin Am Res. 1995;14(3):357-65.
66. Egbendewe-Mondzozo A, Musumba M, McCarl BA, Wu X. Climate Change and Vector-borne Diseases: An Economic Impact Analysis of Malaria in Africa. Int J Environ Res Public Health. 2011;8(3):913-30.
67. Jaenisch T, Patz J. Assessment of Associations Between Climate and Infectious Diseases: A Comparison of the Reports of the Intergovernmental Panel on Climate Change (IPCC), the National Research Council (NRC), and United States Global Change Research Program (USGCRP). 2002;3(1):67-72.
68. Halimi M, Delavari M, Takhtardeshir A. Survey of climatic condition of Malaria disease outbreak in Iran using GIS. J. Sch. Public Health Inst. Public Health Res. 2013;10(3):41-52.
69. Salahi-Moghaddam A, Khoshdel A, Dalaei H, Pakdad K, Nutifafa GG, Sedaghat MM. Spatial changes in the distribution of malaria vectors during the past 5 decades in Iran. Acta Trop. 2017;166(1):45-53.
70. Hay SI, Guerra CA, Tatem AJ, Atkinson PM, Snow RW. Urbanization, malaria transmission and disease burden in Africa. Nature Reviews Microbiology. 2005;3(1):81-90.
71. Li T, Zhicong Y, Wang M. Temperature, relative humidity and sunshine may be the effective predictors for occurrence of malaria in Guangzhou, southern China, 2006-2012. Parasites Vectors. 2013;6:(155):1-4.
72. Eikenberry SE, Gumel AB. Mathematical modeling of climate change and malaria transmission dynamics: a historical review. J Math Biol. 2018;77(4):857-933.
73. Bi Y, Yu W, Hu W, Lin H, Guo Y, Zhou XN. Impact of climate variability on *Plasmodium vivax* and *Plasmodium falciparum*

malaria in Yunnan Province, China. Parasites Vectors. 2013;6(357): 1-12.

74. Beck-Johnson LM, Nelson WA, Paaijmans KP, Read AF, Thomas MB, Bjørnstad ON. The Effect of Temperature on *Anopheles* Mosquito Population Dynamics and the Potential for Malaria Transmission. PLOS One. 2013;8(11):1-12.

75. Caminade C, Kovats S, Rocklov J, Tompkins AM, Morse AP, Colón-González FJ, et al, Impact of climate change on global malaria distribution. PNAS. 2014;111(9):3286-91.

76. Hundessa S, Williams G, Li S, Liu DL, Cao W, Ren H, et al. Projecting potential spatial and temporal changes in the distribution of *Plasmodium vivax* and *Plasmodium falciparum* malaria in China with climate change. Science of the Total Environment. 2018;627(1)1285-93.

77. Kwak J, Noh H, Kim S, Singh VP, Hong SJ, Kim D, et al. Future Climate Data from RCP 4.5 and Occurrence of Malaria in Korea. Int. J. Environ. Res. Public Health. 2014;11(1):10587-605.

78. Kibret S, Lautze J, McCartney M, Nhamo L, Wilson GG. Malaria and large dams in sub-Saharan Africa: future impacts in a changing climate. Malar J. 2016;15(448):1-14.

79. Gillooly JF, Brown JH, West GB, Savage VM, Charnov EL. Effects of size and temperature on metabolic rate. Science. 2001;293(5538):2248-51.

80. Noden BH, Kent MD, Beier JC. The impact of variations in temperature on early *Plasmodium falciparum* development in *Anopheles stephensi*. Parasitology. 1995;111(5):539-45.

81. Okech BA, Gouagna LC, Walczak E, Kabiru EW, Beier JC, Yan G, et al. The development of *Plasmodium falciparum* in experimentally infected Anopheles gambiae (Diptera: Culicidae) under ambient microhabitat temperature in western Kenya. Acta Trop. 2004;92(2):99-108.

82. Murdock CC, Paaijmans KP, Bell AS, King JG, Hillyer JF, Read AF, et al. Complex effects of temperature on mosquito immune function. Proc Biol Sci. 2012;279(1741):3357-66.

83. Suwanchaichinda C, Paskewitz SM. Effects of larval nutrition, adult body size, and adult temperature on the ability of Anopheles gambiae (Diptera: Culicidae) to melanize sephadex beads. J Med Entomol. 1998;35(2):157-61.

84. Murdock CC, Sternberg ED, Thomas MB. Malaria transmission potential could be reduced with current and future climate change. Sci Rep. 2016;6(1):1-7.