NorCal Open Access Publications
Journal of Global Epidemiology and
Environmental Health
Volume 1; Issue 1
Lynn MK and Bossak BH

Research Article

Analysis of a Secular Trend in Malaria Incidence: Venezuela, 1959-2015

Mary K Lynn and Brian H Bossak*

Department of Health & Human Performance, The College of Charleston, Charleston, USA

***Corresponding author:** Brian H Bossak, Department of Health & Human Performance, The College of Charleston, 30 George St, Room 336, Charleston, SC 29424, USA, Tel: +1 8439531129; E-mail: bossakbh@cofc.edu

Received Date: 17 October, 2017; **Accepted Date:** 05 December, 2017; **Published Date:** 20 December, 2017

Abstract

El Niño-Southern Oscillation is a coupled ocean-atmosphere phenomenon that affects global weather patterns on a cyclical basis. The relationship between El Niño-Southern Oscillation and malaria has been studied in many countries where weather patterns are affected by this phenomenon. In nations where malaria rates continue to rise despite global initiatives to reduce the burden of disease, such as Venezuela, it is especially important to assess the influence of climatic variations on disease rates. We used a retrospective analysis of the confirmed number of malaria cases (1959 to 2015), along with sea-surface temperatures in the 3.4 region of the Pacific Ocean, to determine the relationship between El Niño-Southern Oscillation and malaria in Venezuela. We found no significant relationship between El Niño years and malaria case counts in Venezuela. We also found no significant correlation between three-month average sea-surface temperatures and malaria case counts. However, Pearson correlations showed a significant association between average annual temperature and malaria case counts, (r=0.502, p<0.0001). We also found a slightly negative correlation between annual governmental malaria expenditure and malaria case counts for the succeeding year in Venezuela, (r= -.295, p=0.04), and a positive correlation between the number of houses undergoing indoor residual spraying and malaria case counts in the succeeding year (r= .333, p= 0.018). The results of this study suggest that malaria case counts in Venezuela may be more associated with local temperature variability, rather than global scale El Niño-Southern Oscillation-driven climatic oscillations.

Keywords

ENSO; El Niño; Malaria; Southern Oscillation; Venezuela

Abbreviations

ENSO	-	El Niño Southern Oscillation
NOAA	-	National Oceanic and Atmospheric Association
SST	-	Sea-Surface Temperature
LL-ITNs	-	Long-Lasting Insecticide Treated Nets
IRS	-	Indoor Residual Spraying
ACT	-	Artemisinin-Based Combination Therapy
PAHO	-	Pan-American Health Organization
ANOVA	-	Analysis of Variance
USD	-	United States of America dollar currency

Introduction

Malaria is a vector-borne disease caused by *Plasmodium* parasites and carried by various species of *Anopheles* mosquito [1]. *Plasmodium vivax* is the primary parasite species historically responsible for the majority of malaria cases in Venezuela, and *Anopheles darlingi* the main vector [2,3]. Though the disease is both treatable and preventable, the World Health Organization (WHO), in its World Malaria Report 2016 identified 91 countries with endemic malaria, and almost half the global population still at risk for contracting the disease [4]. In the past few decades, global and regional initiatives, such as Roll Back Malaria have contributed to a decrease in the global disease burden [5]. Between 2000 and 2015, the global incidence of disease declined from 271 million in 2000 to 212 million cases in 2015 [4]. Global mortality rates also declined, from 864,000 in 2000 to 429,000 deaths in 2015 [4]. Preventative measures for malaria control, propagated by such international control programs, have put increased pressure on the use of LL-ITNs, IRS, and ACT with promising results [6]. From 2000 to 2014, the Americas experienced a 79% decrease in the overall malaria burden. All but two countries recorded reduced rates of malaria in the past few years, these exceptions were Haiti and Venezuela [7].

Malaria has long since been a major health issue in Venezuela [8]. In the first half of the 20th century, malaria mortality rates exceeded those of all other human pathogens, including influenza [8]. After 1945, large-scale insecticidal spraying along with other control efforts helped reduce epidemic periods and the overall malaria burden in the country, significantly reducing morbidity and mortality rates and fully eradicating the disease from central Costa-Cordillera for a period of time [2,8]. However, since the 1970's, there has been a resurgence of malaria in Venezuela [2]. A variety of factors, both environmental and socioeconomic in nature, have been associated with the spread of vector-borne disease such as malaria [9]. A link between epidemic malaria and drought in climates that are typically humid has been shown in previous studies [2]. Abrupt changes in the transmission rate of these diseases have been linked to natural disasters, as well as social factors like political unrest or military conflict [9].

El Niño-Southern Oscillation (ENSO) is an inter-annual climatic phenomenon occurring every two to seven years, which affects weather patterns globally [10]. The National Oceanic and Atmospheric Association (NOAA) classifies an El Niño event when Sea-Surface Temperatures (SST) in the 3.4 region of the Eastern Equatorial Pacific Ocean vary by + 0.5°C of the three-month running mean for five consecutive three-month periods [11]. An ENSO event consists of two cycles: El Niño with above average SST and La Niña, with below average SST [11]. ENSO events can affect temperature and rainfall patterns in equatorial regions of the world including East Africa and South America [10,12,13]. ENSO events are associated with drought and flooding that can lead to myriad agricultural, social, and human health issues [10,14]. The downstream effects of ENSO events can create environmental situations that are conducive to the breeding of mosquitos and rodents that carry vector-borne human pathogens [10,15]. There have been historical associations between regions with ENSO rainfall anomalies and periodic malaria epidemics [12]. ENSO-induced fluctuations of temperature and precipitation can have a serious impact on the intensity of disease risk based on vector abundance modeling [16]. The effects of ENSO on temperature and precipitation vary by region. Several studies have shown an association between ENSO events and increased incidence of malaria, typically with a lag period of about two to three months, in several regions of the tropics [17,18]. Strong evidence suggests a link between ENSO events and a higher risk of malaria in Africa; the majority of these studies examined the East African highlands of Uganda, Tanzania, and Rwanda [16,19].

In South America, studies, conducted in nations like Colombia, Venezuela, Guyana, and Peru also suggest a relationship between overall transmission of malaria during and after an ENSO [2,18,20,21]. In the past, malaria has been a large burden in the country of Colombia and the implications of ENSO events on this disease have been widely researched [19,21]. A 1997 study conducted on the relationship between ENSO events and deviation in the average confirmed number of cases of malaria annually, looked into the relationship between these parameters over a 32-year period. The results of the study showed an association between El Niño years and a higher than average number of confirmed malaria cases. This association was even higher in the second year of an El Niño cycle, suggesting a lag period between peak incidences after the onset of an ENSO event [18]. Another study regarding Colombia, looking into the association between ENSO and annual malaria cases, found a one degree increase in SST during an ENSO event to correspond with a 20% increase in the number of malaria cases in the country [19]. In Guyana, a retrospective study of ENSO SSTs and malaria epidemics in the country between 1956 and 1998 found a statistically significant correlation between the two events [21]. This same result was found in a retrospective study regarding Peru. Additionally, a prolonged epidemic in this country was reported between 1992 and 1995, which corresponded with a prolonged period of above normal SST in the Pacific Ocean [21]. A similar study of these relationships in Venezuela found a 37% increase in the number of malaria cases the year after an ENSO event occurred [2,18]. ENSO events in Venezuela are typically marked by periods of less than normal rainfall during an El Niño phase, and more than normal rainfall during La Niña [2]. Several studies have examined the association between ENSO events and malaria in this county [2,8,21]. These studies suggest a marked increase in malaria case numbers in the year following an El Niño event, with a lag period of one year [2,21]. El Niño events are associated with less than average rainfall near the Northern coast of South America, and studies suggest that epidemics typically occur in the year following a drought in Venezuela [2,21]. The 2015-2016 ENSO event was predicted to be the strongest in the past 36 years [15]. The goal of the present study was to examine the relationship between ENSO and malaria in Venezuela from the year 1959 to 2015.

Materials and Methods

To examine the possibility of an association between ENSO and malaria case counts in Venezuela, we followed the methodology of Bouma et al., in their 1997 study of malaria in Colombia. Bouma et al., (1997) examined confirmed cases of malaria from 1960 to 1992, along with select widely accepted years of El Niño, to determine any increase in malaria case counts above the five-year moving average during these years, as similarly shown in figure 1. A correlation between SST anomalies and malaria case counts was also used by Bouma et al., (1997) to assess any relationships, as similarly shown in figure 2.

Here, confirmed cases of malaria per year from 1959 to 2015 were obtained from the Pan-American Health Organization (PAHO). Data from 2016 were not available at the time this study was conducted. The 5-year moving average of malaria case counts was used to account for a secular increase in cases, and deviation from the moving average was defined as the percent error expressed as a ratio. SST anomalies in the Niño 3.4 region of the Pacific Ocean (from 5°N to 5°S and 170°W to 120°W) were used as SST values. Single-Factor Analysis of Variance (ANOVA) was used to determine if a relationship existed between malaria case counts between non-Niño years (Niño^0), the first year of an El Niño event (Niño^1) and the year after an El Niño (Niño^2). T-tests were carried out between Niño^0 and Niño^1 years, as well as Niño^0 and Niño^2 years to assess for any significant differences in malaria cases between these years. We used Pearson's correlation coefficient to assess for a relationship between Niño 3.4 SSTs and malaria case counts. We used three-month mean SSTs in Niño 3.4, January-March, April-June, July-September, and October-December for all years included in the study.

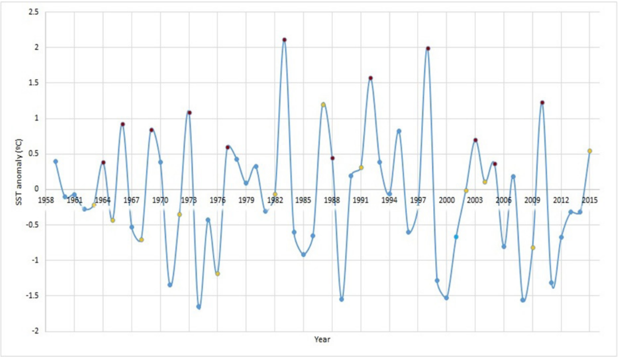

Figure 1: Average SST in the 3.4 region of the Equatorial Pacific from January through March of 1959 to 2015. Classification for ENSO years are shown by color. Yellow indicates Niño^1 year, red indicates Niño^2 year, and blue indicates a non-Niño year.

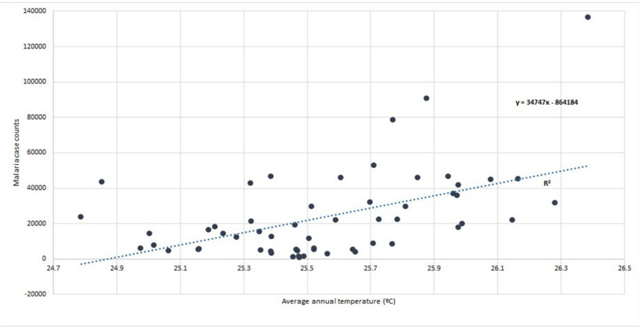

Figure 2: Scatter plot of annual malaria cases and annual average temperature in degrees Celsius from 1959 to 2015. Regression line (y= 34747x - 864184).

Defining an El Niño year can be somewhat ambiguous; we used three separate methods of classifying Niño years. The first method utilized the January through March average SST anomalies to classify these years, as in Bouma et al., (1997). We also used the NOAA definition of greater than or equal to + 0.5°C of the running mean for five consecutive three-month periods to classify Niño years. Finally, we used a list from NOAA of past Niño events to classify these years. The 12-month calendar period (year) following the years deemed as Niño years were classified as Niño^2 regardless of whether this was the second year of an El Niño event.

Monthly mean temperature and precipitation data for Venezuela (aggregated to country-level) from 1959 through 2015 was retrieved from The World Bank Group. Pearson correlation coefficients were assessed on these data to determine association with annual malaria case counts. To explore socioeconomic contributions to malarial disease burden, we also used annual government expenditures on combating malaria and annual number of dwellings undergoing IRS, retrieved from PAHO, to determine any association between these parameters and malaria case counts.

Results and Discussion

The results of this study suggest that ambient temperature, rather than ENSO cycles themselves, may be associated with malaria case counts in Venezuela. Figure 1 depicts the average January through March SST in the Niño 3.4 region of the Pacific Ocean from 1959 to 2015, with Niño year classifications indicated with different colors. Though the figure shows most Niño years located at the extremes of annual case counts, we found no statistically significant relationship between ENSO cycles and malaria case counts. Figure 3 depicts the reported number of cases of malaria for all 57 years (PAHO data), with a trendline representing the 5-year moving average of reported cases. As depicted, some designated Niño years far exceed the moving average; however, certain non-Niño years also far exceed this average, while other Niño years fall short of the trend. These results suggest that other factors aside from ENSO may play a greater role than expected in association with malaria case counts in Venezuela. To further analyze any association between ENSO parameters and malaria cases, we explored the deviation from the moving case average compared with SST anomalies in the Niño 3.4 region. Figure 4 depicts a scatter plot of the deviation in malaria case counts from the 5-year trend, along with average SST anomalies for the 57 years included in this study. The trendline in this figure indicates no association between the two parameters, as R^2= 0.003.

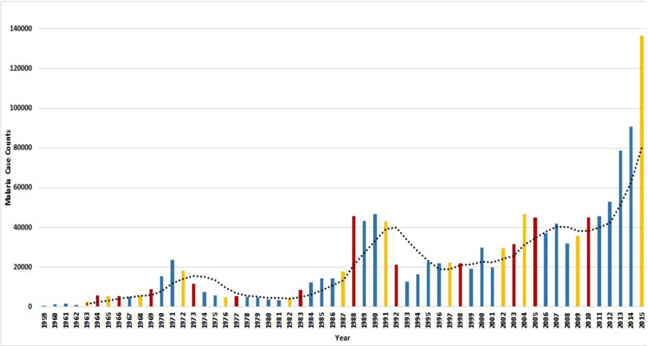

Figure 3: Annual reported number of malaria cases from 1959 to 2015. Classification for ENSO years are shown by color. Yellow indicates Niño^1 year, red indicates Niño^2 year, and blue indicates a non-Niño year.

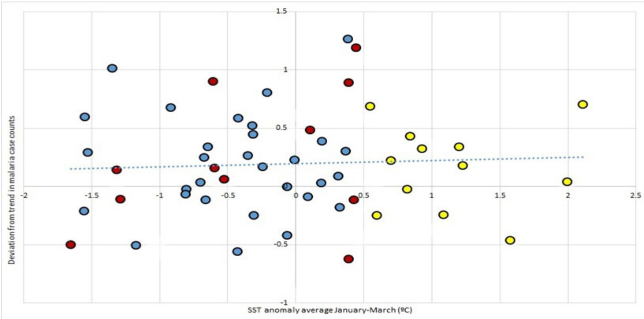

Figure 4: Scatter plot of the deviation in annual malaria cases (as defined by Bouma et al., 1997) in Venezuela from 1959 to 2015. The trendline is used to determine years that exceeded the average malaria case numbers. Classification for ENSO years are shown by color. Yellow indicates Niño^1 year, red indicates Niño^2 year, and blue indicates a non-Niño year. (R^2= 0.0029).

The results of our ANOVA using Niño year classifications suggest no association between those years deemed Niño years and higher malaria case counts. As indicated in table 1, Niño year classes defined by January through March SST anomalies showed no significant difference between year classes (F=0.109, P>0.97, d.f.= 4). We obtained similar results for Niño years determined by consecutive 3-month averages (F=0.324, P>0.72, d.f.=2) and those determined by NOAA's list of confirmed past events (F=0.329, P>0.72, d.f.=2). Thus, defining years classified as an El Niño year, as the year after an El Niño event, or as a neutral ENSO year, utilizing three different cited methods for doing so, yielded no significant associations with malaria case counts in the dataset available.

ANOVA

Source of Variation	F	F Crit	P-value	df
Niño Year Class	0.110	2.55	0.979	4
Niño Year Class'	0.325	3.17	0.724	2
Niño Year Class''	0.329	3.17	0.721	2

Table 1: Single Factor ANOVA among non-Niño years, Niño^1 years and Niño^2 years. Niño years for this analysis were determined by January through March SST anomaly above 0.5°C (Niño Year Class), by five consecutive three-month SST averages above 0.5°C ("Niño Year Class"), and by the NOAA list of previous Niño events ("Niño Year Class'').

We also tested each year classification separately to see if there was significant difference in malaria case counts between El Niño years, the year after an El Niño event, or neutral ENSO year, via two-sample T-tests. The results of the T-tests using non-Niño years and the first Niño years, revealed no difference in mean malaria cases between these years (P>0.6, P>0.5, P>0.5). Results of the T-test between non-Niño and the year after, or second year of a Niño, also show no difference in means (P>0.8 for all three*)*. These data are indicated in table 2.

T-TEST

t-Test: Two-Sample Assuming Unequal Variances				
Between Niño^0 and Niño^1 Years				
	t stat	**t crit two-tail**	**df**	**p-value two-tail**
Niño Year Class	-0.442	2.14	14	0.666
Niño Year Class'	-0.543	2.12	16	0.594
Niño Year Class''	-0.560	2.12	16	0.583
Between Niño^0 and Niño^2 Years				
	t stat	**t crit two-tail**	**df**	**p-value two-tail**
Niño Year Class	0.249	2.07	23	0.806
Niño Year Class'	0.241	2.05	27	0.811
Niño Year Class''	0.222	2.06	26	0.826

Table 2: Two-sample t-test assuming unequal variances between non-Niño years and Niño^1 years, and between non-Niño years and Niño^2 years. Niño years for this analysis were determined by January through March SST anomaly above 0.5°C (Niño Year Class), by five consecutive three-month SST averages above 0.5°C ("Niño Year Class"), and by the NOAA list of previous Niño events ("Niño Year Class'').

These results did not suggest an association between the reported number of malaria cases and ENSO cycles in Venezuela. The results of this study contradict certain of the existing body of literature that suggest an association between the two, with a one-year lag period before an increase in malaria case numbers [11,13]. Differences in our results and the results of other studies may have to do with ambiguity or variation in the possible ways to classify years as El Niño years. Pearson product-moment correlations between the Niño 3.4 SST averages from January to March, April to June, July to September, and October to December (for all years included in this this study) were analyzed for correlation with malaria case counts, as shown in table 3.

Pearson's Product-Moment Correlation

Parameter	R-value	t-stat	P-value	df
SST Anomaly				
Jan-Mar avg	-0.026	-0.193	0.848	2
Apr-Jun avg	0.173	1.30	0.198	2
July-Sept avg	0.198	1.50	0.140	
Oct-Dec avg	0.153	1.15	0.256	

Table 3: Pearson product-moment correlation between malaria case counts and 3-month average SST anomalies over the 57-year study period.

The results of this test were: January through March (r= -0.026, P>0.84), April through June (r=0.173, P>0.19), July through September (r=0.198, P>0.14) and October through December (r=0.153, P> 0.25). These results indicate no significant association between SST and malaria cases.

As our results revealed very little association between ENSO and malaria in Venezuela, we examined several other parameters to discern any relationship with malaria case counts in this country. The results of the Pearson's correlation between average annual precipitation and reported number of malaria cases showed a very slight negative correlation for the corresponding year and a slightly positive correlation with a one-year lag period and a two-year lag, depicted in table 4 (r= -0.03, r= 0.14, r=0.16). However, significance testing of these values indicates there is no significant association between rainfall and malaria case counts in this country (P>0.80, P>0.3, P>0.2).

Table 4 also shows the correlation between malaria case counts and average annual temperature at the country level in Venezuela. The results of this test indicate a moderately strong, positive correlation between temperature and the reported number of malaria cases for that year, (r=0.50, t=4.3, P<0.0001). The results of correlation between average annual temperature and malaria case counts for one-year and two-year lag periods, indicate a slightly weaker positive association, (r=0.44, t=3.65, P= 0.001 and r=.443, t=3.60, P=0.001 respectively). Results of significance testing indicate a significant positive correlation between average annual temperature and malaria case counts for all three tested year classifications. These results suggest that temperature may be a major contributor to the malarial burden of disease in Venezuela. Figure 2 supports this finding, as we found a slightly positive association between the parameters with R^2= 0.25.

Parameter	R-value	t-stat	P-value
Temperature			
corresponding year	0.502	4.30	<.0001
one-year lag	0.445	3.65	0.001
two-year lag	0.443	3.60	0.001
Precipitation			
corresponding year	-0.034	-0.25	0.803
one-year lag	0.140	1.04	0.305
two-year lag	0.161	1.19	0.239
IRS			
corresponding year	0.108	0.76	0.449
one-year lag	0.333	2.45	0.018
two-year lag	0.284	2.03	0.048
Govt Budget			
corresponding year	-0.218	-1.55	0.128
one-year lag	-0.295	-2.12	0.040
two-year lag	-0.244	-1.17	0.094

Table 4: Pearson product-moment correlation between malaria case counts and average annual country-level temperature, average annual country-level precipitation, average annual indoor residual spraying, and average annual government expenditure on malaria. For each parameter, Pearson's correlation was performed with the malarial case counts for the corresponding year, for a one-year lag, and a two-year lag.

We also examined sociopolitical factors for associations between malaria case counts and Indoor Residual Spraying (IRS), as well as malaria case counts and government expenditures toward combating malaria, table 4. Correlations on annual government expenditure towards malaria and malaria case counts, for all 50 years between 1959 and 2015, were not significant (r=-0.21, t=-1.55, P>0.1). The same result was found with a two-year lag in malaria case counts, (r = -0.29, t=-2.12, P<0.09); however, when this procedure was conducted with a one-year lag period for malaria cases, we found a significant slightly negative correlation between these parameters, and (r=-0.24, t=-1.71, P=0.04). This result was expected, as the amount of funding for anti-malarial interventions did seem to be associated with lower rates of malaria in the country. As more money is allotted to vector control efforts and public education regarding preventative measures, we would expect incidence to decrease in the country. The results of this study may indicate that programming and education conducted via government malaria budget, may have delayed benefits. We also assessed correlations between the annual number of houses undergoing IRS for the mosquito vector. There seemed to be no significant correlation between IRS and malaria cases from corresponding years, (r=0.108, t=0.763, P>0.1). The results of this test indicate a slightly positive significant correlation between malaria case counts one year and two years after IRS had occurred, (r= 0.33, t=2.45, P<0.02 and r=0.28, t=2.03, P<0.05, respectively).

The results of this study indicate that temperature may play a role in the number of annual malaria cases in the country of Venezuela. Though changes in temperature and precipitation result from ENSO cycles in certain regions of the globe, in the context of this study, the association between malaria case counts and temperature seemed to be independent of ENSO. Precipitation seemed to have no significant effect on malaria case counts in this study; however, such data was aggregated to the country-scale. While many studies have shown temperature and precipitation to be the principal limiting factors in malaria transmission in certain equatorial countries, in Venezuela, drought and temperature seem be of greater importance in the spread of disease. When drought occurs in typically humid climates, a lack of rainfall can create conditions in certain lakes and rivers that promote vector breeding and abundance [2].

This study indicates that sociopolitical and behavioral factors may also play a large role in the increased malaria case counts observed over the secular trend. Human behavior is a major factor in infectious disease transmission globally. Human behavior typically associated with drought may vary the amount of exposure to the vector, or the ability of the immune system to fight infection. Changes in time spent outdoors, and in water storage habits may also influence disease risk. Though our study did not assess human behavior, eliminating climate influences like ENSO and precipitation suggest that other factors may be at work. Future studies analyzing behavioral factors in further detail would be useful in expanding our understanding of parameters associated with malaria incidence in Venezuela. We hypothesized that malaria case counts would decrease as more houses were sprayed with insecticide. We also expected an increase in IRS to disrupt the life cycle of the vector and therefor influence vector abundance in the years following; however our analysis suggests that this was not the case. This study suggests that the number of houses undergoing IRS was not correlated with malaria case counts from the same year, and was positively correlated with malaria case counts one and two years following. This result may indicate an increase in insecticidal resistance to certain pesticides, or that the time of year when houses were sprayed was not conducive to disrupting vector reproduction. Government expenditure to fight malaria, seemed to be negatively correlated with case counts, as expected. With the political conflict occurring in Venezuela in the past few years, and the body of evidence existing between conflict and vector-borne disease, this is a feasible factor in the increase in malaria in this country. Further research should be conducted into social and behavioral factors that might influence the burden of disease in Venezuela, including: housing structures, factors of human exposure, use of LL-ITNs/ITNs, and other preventative measures. Additionally, insecticidal resistance should be further researched along with vector abundance of different mosquito species. The increased abundance of vectors infected with *Plasmodium falciparum* since the early 1990s, begs the need to explore how a change in parasite abundance may be affecting the overall burden of disease in the country [3].

Given that malaria case counts in Venezuela have more than tripled over the period of study, including a rapid increase in recent years (from 45,155 cases to 136,402 since the year 2010) [3], it is imperative that researchers investigate the different factors in this multifaceted issue to prevent further increases in disease spread and mortality in the future, particularly considering climate change predictions for the coming decades [22].

References

1. WHO (2017) Malaria. World Health Organization, Geneva, Switzerland.
2. Bouma MJ, Dye C (1997) Cycles of malaria associated with El Niño in Venezuela. Jama 278: 1772-1774.
3. PAHO (2017) Malaria Surveillance Indicators. Pan American Health Organization, Washington DC, USA.
4. WHO (2016) World Malaria Report 2016. World Health Organization, Geneva, Switzerland.
5. WHO (2016) Uganda. World Health Organization, Geneva, Switzerland.
6. Yeka A, Gasasira A, Mpimbaza A, Achan J, Nankabirwa J, et al. (2012) Malaria in Uganda: challenges to control on the long road to elimination: I. Epidemiology and current control efforts. Acta Trop 121: 184-195.
7. PAHO (2016) Health ministers adopt new plan for malaria elimination in the Americas. PAHO, Washington, DC, USA.
8. Griffing SM, Villegas L, Udhayakumar V (2014) Malaria control and elimination, Venezuela, 1800s-1970s. Emerg Infect Dis 20: 1697-1704.
9. Kilpatrick AM, Randolph SE (2012) Drivers, dynamics, and control of emerging vector-borne zoonotic diseases. Lancet 380: 1946-1955.
10. Kovats RS (2000) El Niño and human health. Bull World Health Organ 78: 1127-1135.
11. National Oceanic and Atmospheric Administration (2017) Equatorial Pacific Sea Surface Temperatures, Teleconnections. National Centers for Environmental Information (NCEI), NC, USA.
12. Bouma MJ, Siraj AS, Rodo X, Pascual M (2016) El Niño-based malaria epidemic warning for Oromia, Ethiopia, from August 2016 to July 2017. Trop Med Int Health 21: 1481-1488.
13. Mabaso ML, Kleinschmidt I, Sharp B, Smith T (2007) El Nino Southern Oscillation (ENSO) and annual malaria incidence in Southern Africa. Trans R Soc Trop Med Hyg 101: 326-330.
14. Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A (2003) El Niño and health. Lancet 362: 1481-1489.
15. Kogan F, Guo W (2017) Strong 2015-2016 El Niño and implication to global ecosystems from space data. Int J Remote Sens 38: 161-178.
16. Mouchet J, Manguin S, Sircoulon J, Laventure S, Faye O, et al. (1998) Evolution of malaria in Africa for the past 40 years: impact of climatic and human factors. J Am Mosquito Control Assoc 14: 121-130.
17. Kilian AH, Langi P, Talisuna A, Kabagambe G (1999) Rainfall pattern, El Niño and malaria in Uganda. Trans R Soc Trop Med Hyg 93: 22-23.
18. Bouma MJ, Poveda G, Rojas W, Chavasse D, Quinones M, et al. (1997) Predicting high-risk years for malaria in Colombia using parameters of El Niño Southern Oscillation. Trop Med Int Health 2: 1122-1127.
19. Lindblade KA, Walker ED, Onapa AW, Katungu J, Wilson ML (1999) Highland malaria in Uganda: prospective analysis of an epidemic associated with El Niño. Trans R Soc Trop Med Hyg 93: 480-487.
20. Mantilla G, Oliveros H, Barnston AG (2009) The role of ENSO in understanding changes in Colombia's annual malaria burden by region, 1960-2006. Malar J 8: 6.
21. Gagnon AS, Smoyer-Tomic KE, Bush AB (2002) The El Niño southern oscillation and malaria epidemics in South America. Int J Biometeorol 46: 81-89.
22. Patz JA, Githeko AK, McCarty JP, Hussein S, Confalonieri U, et al. (2003) Climate change and infectious diseases. Climate change and human health: risks and responses 6: 103-137.