VOLUME 00 NO 00

Environmental and anthropogenic factors associated with increased malaria incidence in South-Kivu Province, Democratic Republic of the Congo

R. N. Bigirinama[1,2], J. A. Ntaongo[3], D. Batumbo[3], N. A. Sam-Agudu[4,5], P. D. M. C. Katoto[6,7], L. N. Byamungu[8], K. Karume[9,10], J. B. Nachega[11,12,13,14]* and D. N. Bompangue[3,15,16]*

1 *Faculté de Médecine, Université Catholique de Bukavu, Bukavu, Democratic Republic of the Congo*
2 *Ecole Régionale de Santé Publique, Université Catholique de Bukavu, Bukavu, Democratic Republic of the Congo*
3 *Unité de Recherche et Formation sur l'Ecologie et le Contrôle des Maladies Infectieuses, Université de Kinshasa, Kinshasa, Democratic Republic of the Congo*
4 *International Research Center of Excellence, Institute of Human Virology Nigeria, Abuja, Nigeria*
5 *Department of Pediatrics and Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA*
6 *Département de Medicine Interne, Université Catholique de Bukavu, Bukavu, Democratic Republic of the Congo*
7 *Centre for Environment and Health, KU Leuven, Leuven, Belgium*
8 *Department of Paediatrics and Child Health, University of KwaZulu-Natal, Durban, South Africa*
9 *Département de Géochimie et Environnement, Observatoire Volcanologique de Goma, Goma, Democratic Republic of the Congo*
10 *Unité de GIS et Télédétection, Université Evangélique en Afrique, Bukavu, Democratic Republic of the Congo*
11 *Department of Medicine and Centre for Infectious Diseases, Stellenbosch University, Cape Town, South Africa*
12 *Departments of Epidemiology, Infectious Diseases and Microbiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA*
13 *The International Center for Advanced Research and Training, Bukavu, Democratic Republic of the Congo*
14 *Departments of Epidemiology and International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA*
15 *Direction de la Lutte contre les Maladies, Ministère de la Santé Publique, Kinshasa, Democratic Republic of the Congo*
16 *Laboratoire Chrono-Environnement, Université* de Franche-Comté, Besançon, France

Abstract

OBJECTIVE To examine environmental and human factors that affect the spatial and temporal dynamism of malaria in DRC's South-Kivu province.

METHODS In a cross-sectional study conducted between 1 January 2010 and 31 December 2015, spatial distribution was determined through thematic maps of malaria attack rate. SatScan ™ software and Monte Carlo test were used to identify spatial risk clusters. Temporal evolutions were analysed using the Cleveland algorithm. Generalized Additive Models for Location Scale and Shape and negative binomial regression were used to assess the independent human and environmental factors associated with incident malaria.

RESULTS The cumulative annual incidence of malaria increased from 10 968/100 000 in 2013 to 15 501/100 000 in 2015 (P for trend <0.001); malaria lethality increased from 0.1% in 2013 to 0.3% in 2015 (P for trend = 0.62). Between 2010 and 2015, 18 of 34 health zones consistently reported the highest attack rates, which ranged from 25 000 to 50 000/100 000. Four risk clusters areas were identified, with relative risk (RR) of 1.2 to 3.0, from which malaria was reported continuously during each year. Factors significantly associated with malaria cases were agro-pisciculture practices (Incidence Risk Ratio [IRR]: 1.96; 95% CI: 1.23–3.13) and the presence of a lake in the health zone (IRR: 2.48, 95% CI: 1.51–4.42).

CONCLUSIONS Malaria control in this setting must be intensified in peri-lacustrine areas and those in which the population is intensively engaged in standing water-associated activities.

keywords incidence, malaria, environment, Democratic Republic of the Congo

*Joint senior authors.

Introduction

Despite efforts to reduce incidence and mortality rates, malaria remains a major global public health problem [1]. In 2017, there were an estimated 219 million cases of malaria worldwide, three million more than in 2016 and four million more than in 2015; more than 90% of all cases occurred in sub-Saharan Africa in each reporting year [1,2]. According to WHO's 2018 Global Malaria Report, nearly 50% of global cases in 2017 were accounted for by Nigeria (25%), the Democratic Republic of the Congo (DRC) (11%), Mozambique (5%), India (4%) and Uganda (4%) [3]. WHO's 2018 report also identified DRC as one of 10 high-burden African countries that reported increased malaria incidence in 2017 versus 2016 [1–3]. In 2015, 38.7% of all medical consultations and 40.5% of deaths in DRC health facilities were due to malaria [4]. With an average of 145 897 cases per year between 2004 and 2014, South-Kivu province had the fourth highest malaria incidence among all 25 provinces plus Kinshasa [4–6]. In 2015, there were 1 059 372 malaria cases and 1734 (0.17%) malaria-related deaths recorded in the province [7,8].

Malaria control towards elimination by 2030, a goal put forth by WHO, is currently facing significant challenges, especially in high-burden African countries like DRC [1]. These include the recent emergence in Africa of *Plasmodium* strains resistant to artemisinin derivatives [9,10] and the resistance of mosquitoes to long-lasting insecticides used to treat bednets [11–13]. These challenges suggest re-evaluation of strategies for malaria control in DRC [14,15], such as epidemiological stratification of risk areas. Until 2015, this stratification was established in terms of 'epidemiological facies of malaria' following a typology defined by Mouchet and Carnevale and based on climate- ,relief- ,and vegetation-related characteristics specific to each area of malaria transmission [16].

Numerous studies report a direct relationship between malaria risk and the geo-climatic environment [17–19]. Recent planetary climate changes contribute to the complexity of malaria elimination [20,21], with climate variability during the last few decades measurably altering, extending and delocalising traditional malaria transmission zones [22,23]. In addition, changes in land cover related to human settlement and activities favouring the establishment of *Anopheles* breeding sites (such as market gardening, fishponds, rice paddies and dams) directly influence malaria transmission [20,24]. For example, a 2014 study conducted in South-Kivu demonstrated for the first time the presence of breeding sites of *Anopheles gambiae* at 1886 metres of altitude and adult mosquitoes in houses at a higher altitude [25].

Within an epidemiological area, malaria transmission is not homogeneous but dependent on factors such as landforms, soil and hydrography [21,26]. Little is known about how specific environmental and human factors influence the spatial and temporal distribution of malaria. Such knowledge will inform malaria control policies and practice in a more targeted and impactful manner.

We aimed to determine the environmental factors that influence spatial and temporal distribution of malaria in South-Kivu at the health zone (HZ) level.

Methods

Study design and setting

This cross-sectional study was conducted between 1 January 2010 and 31 December 2015. South-Kivu province is located in eastern DRC's mountainous region and extends between 1°44'13'' and 4°51'32'' east longitude and between 26°10'30'' and 29°14'10'' south latitude. The province covers an area of 64 851 km^2, average elevations within range from 645 m to >2500 m above sea level (Figure 1).

The climate is humid tropical tempered by altitude, with a nine-month rainy season. The vegetation is composed of upland forests, grassy savannahs, wooded bamboos and dense forests. South-Kivu encompasses Lake Kivu in the North and Lake Tanganyika in the South, which are connected by the Ruzizi River. There is a large network of smaller rivers throughout the province. The wide geo-climatic heterogeneity made South-Kivu a propitious choice for this study. In fact, based on malaria risk area typology [12], South-Kivu province houses all three of the DRC's malaria epidemiological facies (Figure 2).

Livestock rearing, plant agriculture and trading are the main income-generating activities in South-Kivu. Commercial fish farming was introduced in 1945 [27], and irrigated rice cultivation, introduced in 1950, is done at large scale by commercial farmers [28–31].

As a provincial health division, South-Kivu is organised into 34 health zones (HZ). In the DRC health system, the HZ represents the operational level of implementation of health promotion activities. This study aimed to describe malarial epidemiological peculiarities of each area according to its own environmental characteristics. Provincial coordination of activities under the National Malaria Control Program (Programme National de la Lutte contre le Paludisme or PNLP, from French) is

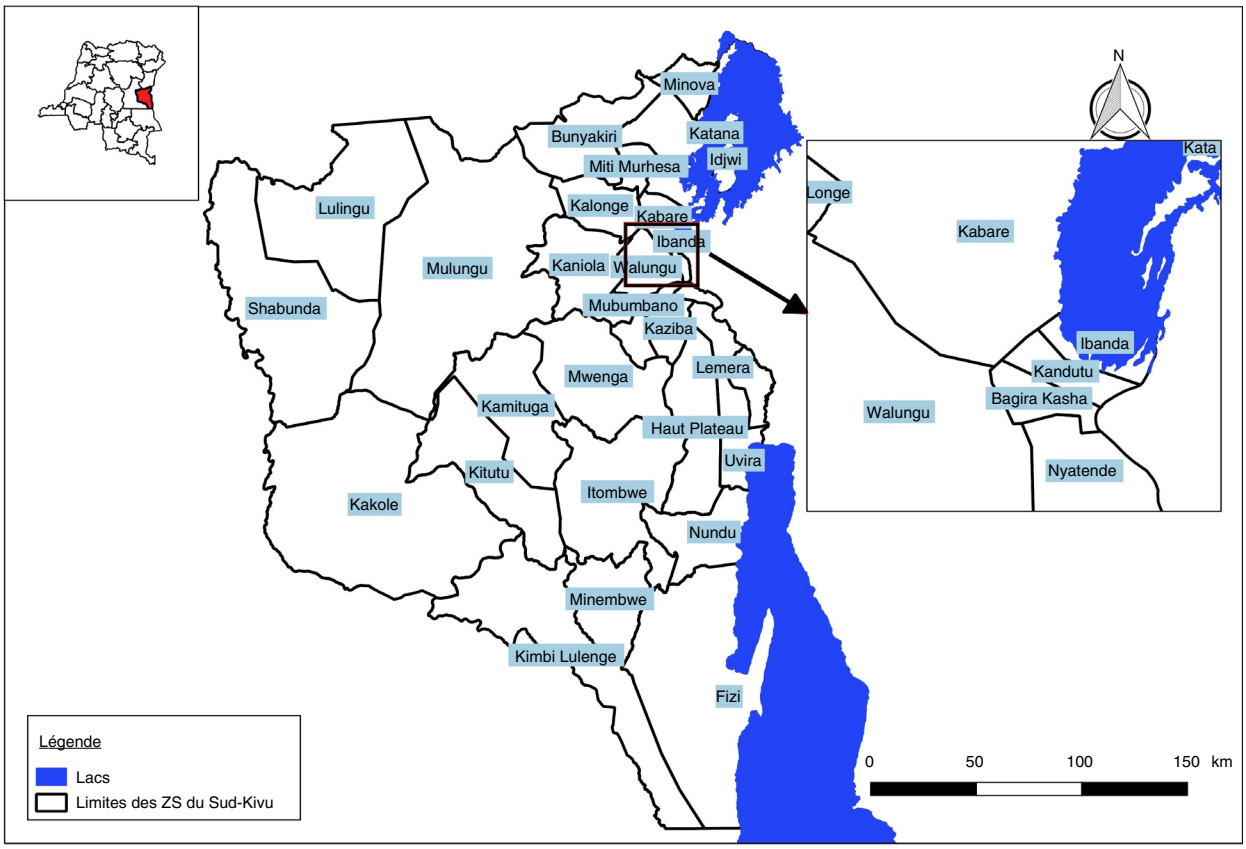

Figure 1 Health zones of the South-Kivu province (WGS 84-UTM 34S projection).

functional in South-Kivu. Syndromic and biological surveillance of malaria is conducted in HZs through the Public Health Ministry's Integrated Disease Surveillance and Response approach. Katana HZ is the South-Kivu's malaria sentinel site. Routine malaria biological monitoring occurs via Rapid Malaria Diagnosis Tests (RDT) and microscopic thick smear examination.

Weekly malaria case incidence and mortality data

We considered all data reported as malaria cases or malaria-related deaths from all 34 South-Kivu HZs between 1 January 2010 and 31 December 2015. This study period was chosen to better assess the influence of seasons on malaria transmission. The data were obtained from the Public Health Ministry's disease surveillance database. All cases met WHO's standard malaria case definition, which considers one/or both of the following: (i) suspected cases based on a typically evocative symptomatology and (ii) cases with biological confirmation of *Plasmodium* species in peripheral blood. The former definition has been preferred for epidemiological surveillance given that in DRC, many remote areas lack consistent access to biological diagnosis. Only since 2013, secondary to RDT scale-up, has there been an increase in the number of HZs able to perform malaria laboratory confirmation [32]. Malaria-related lethality was calculated as a percentage; that is, number of deaths attributed to malaria out of all malaria cases identified.

Demographic data

South-Kivu HZ population data applied in this study come from the National Statistics Institute of the DRC. These are projections made by the Institute based on population numbers recorded during the last DRC general census (1984) using an annual growth rate of 1.03% [33]. Eastern DRC is globally recognised as an area

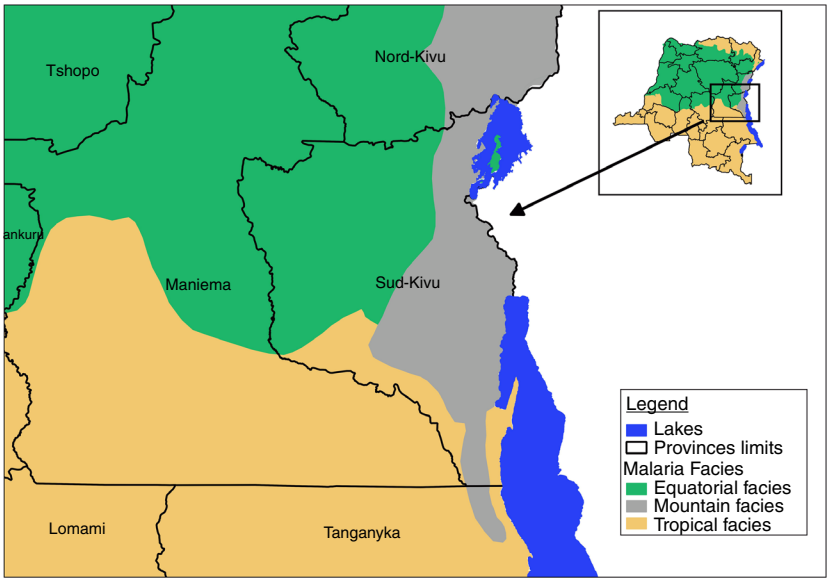

Figure 2 Epidemiological facies of malaria in South-Kivu (Mouchet J. et al., 1993).

currently in conflict. The 'mega crisis' concept has been recently proposed to characterise the country's current security, humanitarian, political, health and economic issues [34]. This situation explains one of the biggest limitations of our studies: the true number of internally displaced peoples (IDPs) in the DRC is unknown. Demographic data used do not consider these people, leading to some overestimation of disease rates since the population numbers on which these rates are calculated do not take IDPs into account.

Environmental data

The average altitude of each HZ was retrieved by remote sensing from the Shuttle Radar Topography Mission (SRTM) satellite image from the United States (US) Government's Satellite Observatory website [35] using Quantum Geographic Information System (QGIS) software (version 2.14.4). The altitude assigned to each HZ is the average of the altitudes sampled every 200 metres within the area [36]. Due to the absence of permanent weather stations covering all South-Kivu HZs, temperature and rainfall data were obtained from the Modern Era-Retrospective analysis for Research and Applications (MERRA) of the US National Aeronautics and Space Administration. MERRA data are represented by dots containing data projected on a South-Kivu map (Figure S1). Using QGIS software, we drew a 15-kilometre buffer around each data dot; the temperature and rainfall assigned to each HZ were the averages of the buffers that crossed the limits of the HZ. Since they impact *Anopheles* biology, the differences between the maximum and minimum daily temperatures were also considered. It should be noted that satellite imagery contains an intrinsic bias due to accuracy limits in distinguishing particularities of landscape's sub-units at finer scales. However, this choice was the most realistic given the context of the region; there is a virtual absence of measurement stations as a result of repeated armed conflict during the past three decades (only two of the 34 HZs have functioning local weather stations).

The main agro-pastoral activities traditionally conducted by households and/or large-scale farmers in South-Kivu (rice cultivation, fish farming and gardening) are operated in still water. Information on these activities was obtained from the 'Inspection Provinciale de l'Agriculture, Pêche et Elevage' (IPAPEL) of South-Kivu [37,38]. Only 18 out of 34 HZs are listed by the IPAPEL as practicing these activities in the specific context of semi-industrial exploitation for rice culture, and large tracts of land belonging to a single individual (generally a tribal chief) are used by small farmers grouped into cooperatives.

Using photo interpretation [39] from a 2017 map of DRC land use elaborated from a 30 m resolution Landsat satellite image, the habitat–vegetation interfaces were differentiated and the centroid of each point of human

presence calculated. The centroids obtained formed seedlings of points within each HZ, and the dispersion indexes of these points were calculated using the nearest neighbour method with QGIS software [40]. HZs in which the dispersion index was ≤ 1 were classified as 'zones with strong human presence and low vegetation coverage'. Those with an index > 1 were classified as 'zones with low human presence and highland areas covered by vegetation' [41,42]. We assumed that these parameters remained unchanged throughout the study period.

Malaria spatial distribution

The spatial distribution of malaria case incidence from 2010 to 2015 was determined from thematic maps representing attack rates per 100 000 inhabitants per year by HZ. Annual attack rate was calculated as the quotient of annual number of malaria cases in the annual average population of the HZ per 100 000 inhabitants. These maps were generated using QGIS software.

Spatial clusters analysis

We used SaTScan™ (version 9.2), a software that analyses spatial, temporal and space–time data using spatial, temporal or space–time cluster detection analysis [43,44]. Poisson's equation model was chosen, since our study is based on the identification of aggregates with particularly high numbers of cases of malaria under the null hypothesis (H_0) that the observed excess of cases is only due to random. For highlighting these aggregates, the maximum size chosen for the sliding window corresponds to the size for which 50% of the population included in the window is at risk; the minimum window size is zero. The *P*-value was generated using Monte Carlo replications. The number of iterations was set to 999 to ensure acceptable power for defining clusters. A *P*-value < 0.05 indicates statistical significance. The specific locations of clusters were calculated in terms of relative risk (RR). A cluster with RR > 1 indicates an increased risk compared with the risk outside that cluster [45].

Malaria temporal dynamics

The time series was analysed with Pro software R (version 2.15.0). A graphic representation of the chronological evolution malaria case incidence was developed and associated with a search for possible seasonal trends using the Cleveland algorithm [46]. In addition to studying the overall trend of the entire province, the time series of four HZs was decomposed. These zones were chosen according to representation in each of the four risk clusters highlighted in South-Kivu as well as having consistently complete weekly malaria data reports. The four zones were Shabunda for the north-west Block, Bunyakiri, north-east Block, Kamituga, central Block and Fizi, south Block.

Modelling

The association between malaria cases and environmental variables in each HZ was calculated by modelling using Pro software R. The Generalized Additive Models for Location Scale and Shape (GAMLSS) function was used to allow adjustment and accounting for the autocorrelation. Univariable and multivariable negative binomial regression were performed. The negative binomial model was build using the formula: Case tot = log (Pmoy) + a. Agrp + b. Lake + c. DT (where a, b and c are the values of the linear prediction coefficient for each variable; Tot Case = Total cases; Pmoy = Average population). In addition, we assessed the most explanatory binomial negative model based on Akaike criterion [47,48]. Variables with a *P*-value < 0.2 in univariable analyses plus variables assumed to have clinical or epidemiological significance were included in the multivariable model, and results were presented as incidence rate ratios (IRR) with 95% confidence intervals (CIs).

Results

Annual incidence of malaria cases

The cumulative annual incidence of malaria in South-Kivu increased from 10 967.61/100 000 in 2013 to 15 501.08/100 000 in 2015 (*P* for trend <0.001), and malaria mortality increased from 0.1% in 2013 to 0.3% in 2015 (*P* for trend = 0.62) (Figure 3).

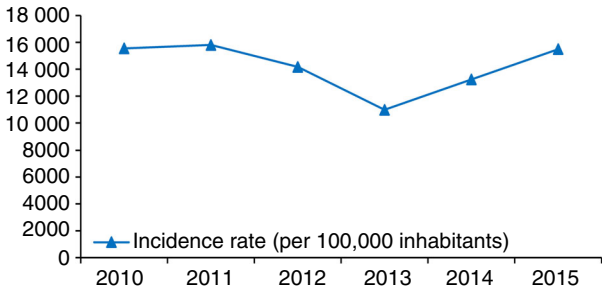

Figure 3 Annual reports of malaria cases in South-Kivu from 2010 to 2015.

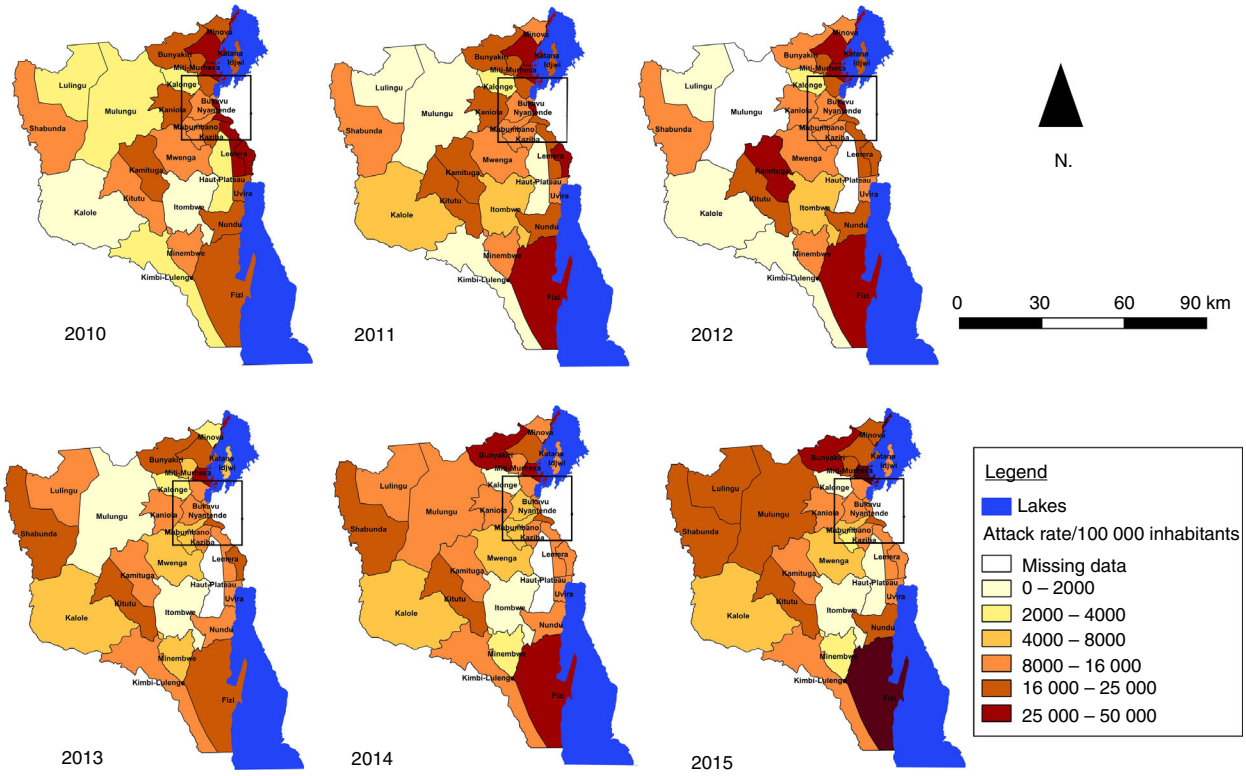

Figure 4 Yearly malaria attack rated from 2010 to 2015.

Spatial distribution of malaria cases in South-Kivu, 2010 to 2015

From 2010 to 2015, 18 of 24 HZs regularly reported attack rates ranging from 25 000 to 50 000/100 000 inhabitants (Figure 4).

Risk clusters

Each of the four malaria risk clusters identified had a relative risk (RR) between 1.2 and 3.0. Clusters with the highest risks were located on riverbanks (Figure 5).

Malaria temporal dynamics in South-Kivu

Time series analysis of malaria cases shows that *for each year*, malaria is reported consistently throughout the year in South-Kivu HZs (Figure 6). Fizi's peri-lacustrine HZ has a marked seasonal influence compared with other ecological areas, with the number of cases increasing significantly during the rainy season (Figure 7). Seasonal influence varies among the HZs.

Modelling environmental variables with malaria

In the multivariate model, factors independently associated with malaria cases were proximity to a lake shoreline (IRR: 2.48; 95% CI: 1.51–4.42) and local population practices of agriculture, fish farming or market gardening (IRR 1.96; 95% CI: 1.23–3.13) (Table 1). Malaria cases were significantly associated with areas bordering lake shorelines (IRR: 2.35, 95%CI: 1.43–3.86) within which the local population practices agriculture, fish farming or market gardening (IRR 1.93; 95% CI: 1.26–2.97) (Table 2).

Discussion

In our South-Kivu study setting, we found that malaria incidence has been increasing since 2013, despite ongoing malaria control efforts [4]. This corroborates concerns raised by WHO in its latest malaria report, citing a regression in malaria control [3], and raises questions regarding the effectiveness of current control and prevention strategies. Eighteen HZs, including Fizi, Katana,

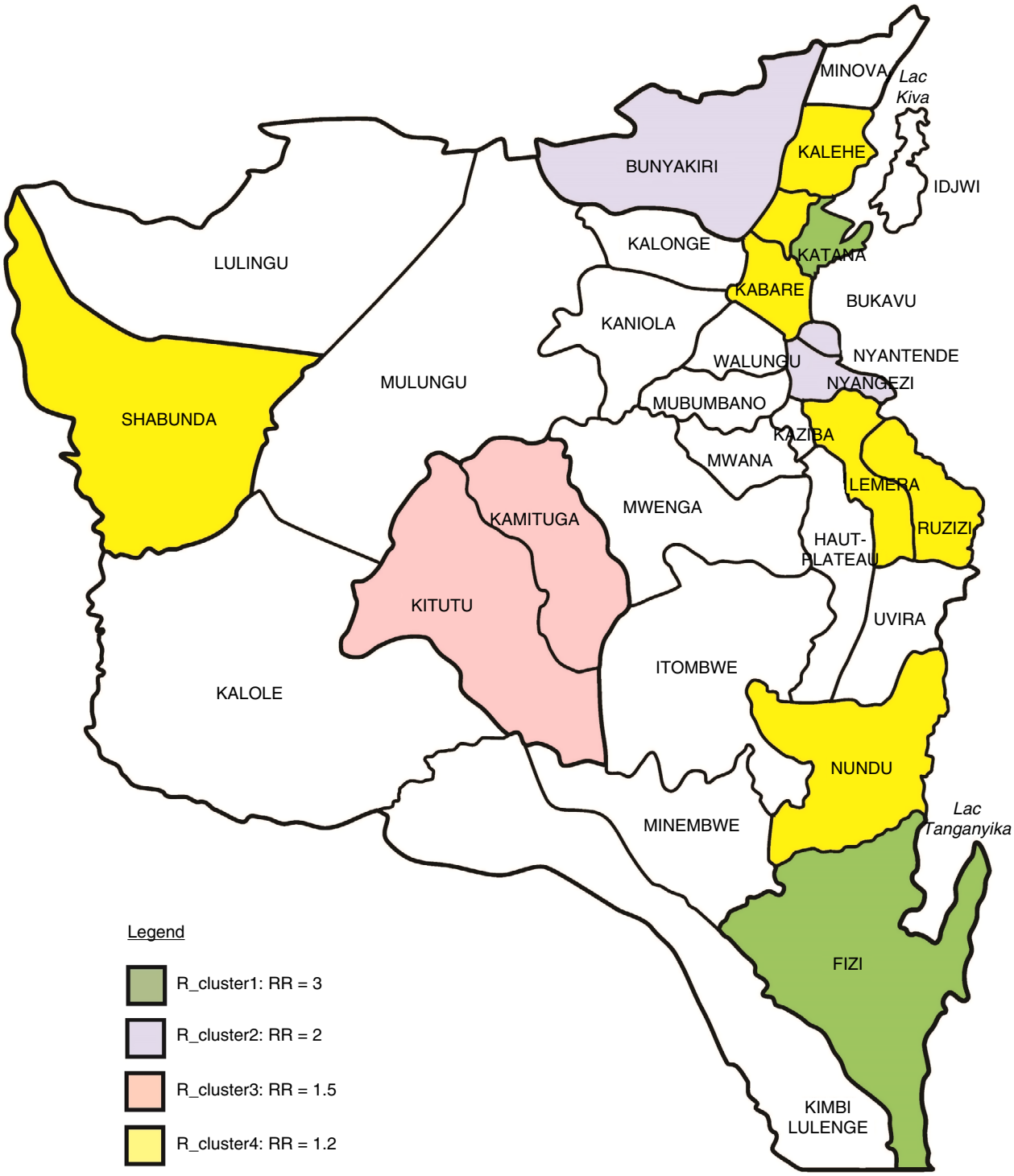

Figure 5 Malaria Risk Cluster Analysis in South-Kivu province, DRC.

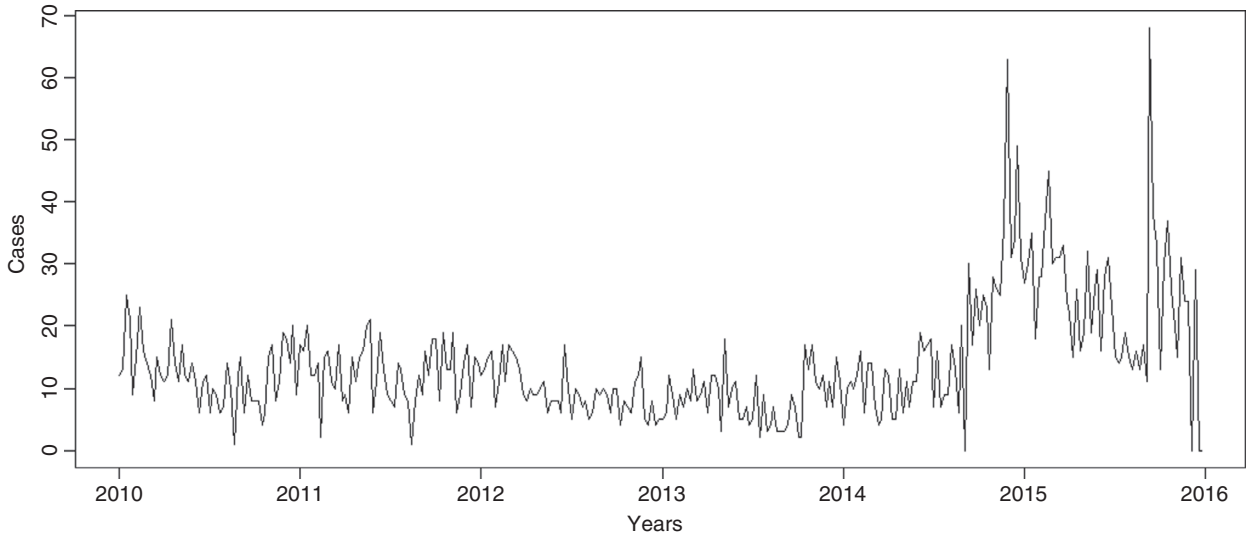

Figure 6 Time series, South-Kivu 2010–2015.

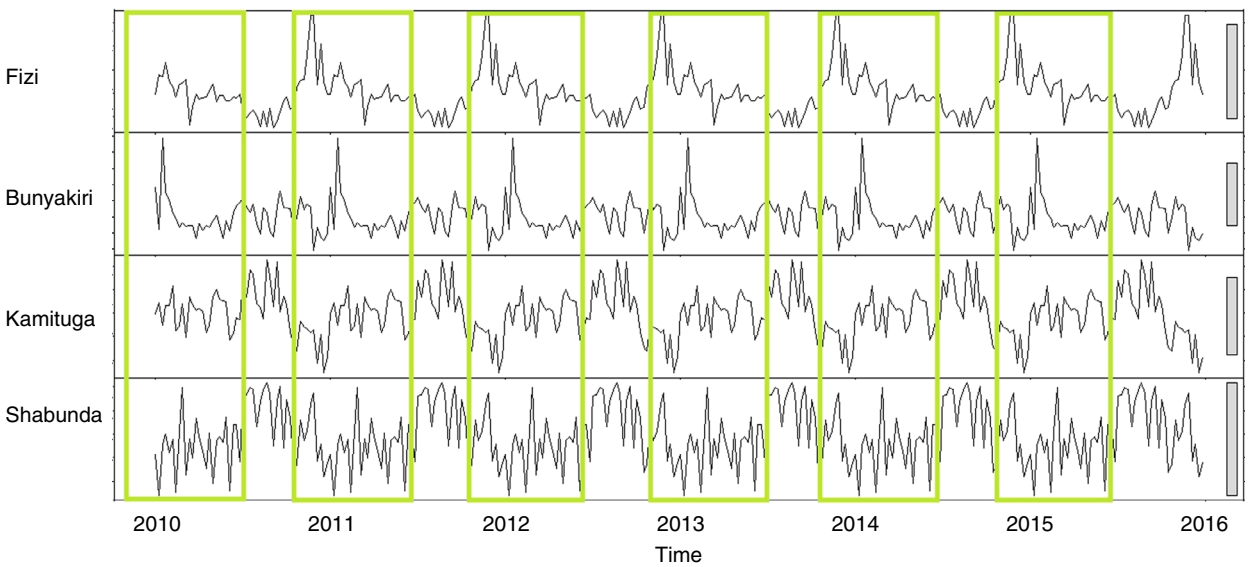

Figure 7 Time series decomposition of HZs belonging to a risk cluster, 2010 to 2015 (Green rectangles represent rainy seasons).

Bukavu, Shabunda and Kamituga, presented the highest attack rates during the six-year study period. In addition to the fact that these 18 HZs do not geographically overlap, we note that 15 of them are proximal to Lakes Kivu and Tanganyika.

Environmental factors such as the presence of lakes can explain the high incidence of malaria as determined by our predictive regression model; the map of risk clusters closely approximates the attack rate map. However, we should note that internally displaced people are not included in the denominator (population) but do contribute to the numerator (cases of malaria); this likely contributed to numbers recorded in the highest attack rate HZs, which have a strong presence of war refugees.

The time series analysis in South-Kivu province demonstrated that malaria presents an endemic picture rather

Table 1 Factors associated with malaria cases identified by negative binomial regression model

	Univariable (Unadjusted)		Multivariable (Adjusted)	
	IRR (95%CI)	*P*-value	IRR (95% CI)	*P*-value
Agro-pisciculture practices	1.18 (0.73–1.91)	0.511	1.96 (1. 23–3.13)	0.009
Presence of lake	1.82 (1.11–2.98)	0.024	2.48 (1. 51–4.42)	0.002
Max-Min difference of T° between 9°C and 12°C	0.52 (0.24–1.14)	0.112	0.59 (0. 26–1.33)	0.215
Max-Min difference of T° > 12°C	0.81 (0.32–2.07)	0.666		
T° between 17° and 20°C	1.33 (0.73–2.44)	0.359		
T° higher than 20°C	1.06 (0.54–2.07)	0.873		
Average rainfall between 1400 mm and 2700 mm per year	1.1 (0.56–2.14)	0.791		
Average rainfall between 2700 mm and 3400 mm per year	0.84 (0.43–1.65)	0.622		
Average rainfall >3400 mm per year	0.6 (0.28–1.26)	0.189	1.29 (0. 60–2.77)	0.516
Altitude between 1283 m and 1920 m	1.32 (0.73–2.36)	0.364		
Altitude > 1920 m	1 (0.53–1.92)	0.991		
Low land use	0.99 (0.61–1.61)	0.984		

CI, confidence interval; IRR, incidence rate ratio; T^0, temperature.

Table 2 The most explanatory binomial negative model based on Akaike criterion

	IRR	CI (95%)	*P*-Value
Agro-pisciculture practices	1.93	1.26–2.97	0.006
Presence of lake	2.35	1.43–3.86	0.002
Max-min difference of T° between 9°C and 12°C	0.6	0.28–1.32	0.215
Max-min difference of T° > 12°C	1.07	0.43–2.68	0.884

CI, confidence interval; IRR, incidence rate ratio; T^0, temperature.

than, as suggested in recent times, an epidemic picture [15]. Peaks observed in 2015 correspond to the three epidemics reported in Bunyakiri, Kalole and Minova [4]. Seasonal influence varies among HZs, but DRC malaria policies such as environmental sanitation or bednet distribution are conducted on a provincial or national scale. We did not find seasonal influence in urban areas, which agrees with some reports [49]. National epidemiological reports describe increasing changes in evolution patterns of malaria epidemiological facies, reinforcing the need to update these classifications at a much finer scale and include environmental and socio-cultural variables. The departure from this environmental classification in favour of an exclusively biological classification is therefore not recommended [14]. Unfortunately, there is a paucity of current scientific studies of these epidemiological phenomena in DRC.

An updated and refined eco-epidemiological classification would allow for appropriate customisation of malaria control efforts per the particular characteristics of each HZ. Our modelling results suggest that the presence of a lake and the existence of agro-fishing, market gardening, fish farming or rice cultivation are environmental factors which increase the risk of malaria within a HZ. Permanent water collections are favourable breeding sites for the *Anopheles* mosquito vector. However, although many authors describe the direct relationship between rice cultivation, fish farming, or market gardening and malaria [24,25,46], and others emphasise the non-constancy of that relationship [50]. According to Mouchet *et al.*, the implementation of rice cultivation in Burundi alongside the Ruzizi River in the 1980s led to an outbreak of malaria; prior to this, malaria was not a concern in this region [51]. Similarly, in northern Afghanistan, the introduction of rice culture led to malaria outbreaks caused by *Plasmodium vivax*. Conversely, in Burkina Faso, malaria is stable in the presence of rice cultivation in the Kou Valley [51]. In China, where *Anopheles sinensis* and *Anopheles anthropophagus* exist in rice farms, *Plasmodium vivax* malaria is observed in several provinces but not associated with morbidity [51]. Le Menach *et al.* similarly found that the relationship between stagnant water and malaria is not always straightforward. Indeed, adult female mosquitoes tend to aggregate around places where they oviposit, thus increasing the risk of malaria, regardless of the suitability of the habitat for larval development. Therefore, water body may be unsuitable for adult mosquito emergence, but still, be a source for human malaria [52].

Among the variables selected for modelling, it appears that only locally acting variables (lakes and agro-fishing practices) have a significant influence on malaria at the HZ level. Several other parameters can and could have influenced the incidence of malaria in our study area. These include (i) malaria control strategies such as

distribution and use of mosquito nets, intermittent preventive therapy and indoor residual spraying and (ii) environmental parameters such as massive felling of trees and significant influx of internally displaced people. A single study certainly cannot suffice to explore them all satisfactorily or to comprehensively explain changes in malaria epidemiology in a given area. What our study offers is provocative insight into shifts in malaria epidemiology in the context of geo-climactic changes and agro-pisciculture activities in our study area.

Our study highlights several important public health implications. Malaria remains an important threat in DRC. The malaria elimination plan for the next decade must associate detailed mapping of high-risk zones with related risk factors at different levels of intervention. This plan should target and prioritise anthropogenic and environmental factors that contribute to the persistence of malaria. Shifts in observed trends must also be considered. New classifications will allow interventions to be tailored to each HZ and its specific needs and therefore improve impact. Our study identified anthropogenic and environmental factors that might affect malaria risk at the operational level at each HZ. Malaria control in this setting must be intensified in peri-lacustrine areas and those in which the population is intensively engaged in standing water-associated activities. Future work involving diverse stakeholders as well as resident communities is needed to establish focal areas of high malaria risk and related predictive factors in the other provinces of DRC. In particular, the adoption of intermittent irrigation practices which elsewhere proved to be effective in the reduction of breeding sites following market gardening and rice cultivation. Furthermore, we recommend the inclusion of larvivorous fish species in fish breeding ponds as it was shown that it can inhibit vector multiplication [11,53].

Finally, to achieve the WHO 2030 goal of eliminating malaria in this post-conflict region, close collaboration between communities – including internally displaced people – researchers, policymakers and other stakeholders is necessary to improve the collection and application of surveillance data and to institute measures to protect populations living and working in high-risk health zones.

While informative, our study has some limitations: first, the unit of time considered in the study is the epidemiological week. The analysis method used does not account for time lags. Malaria cases recorded are not necessarily due to the weather phenomena of that week with regard to mosquito biology and malaria physiopathology. However, this time unit becomes interesting considering that our geo-climatic data were extracted by remote sensing on a daily unit time. Aggregation of these data over several additional days (from 7 to 10) allows us to minimise the bias that these data contain, given the fact that NASA provides prediction data from satellites on large quadrants. The bias would otherwise have been routinely corrected through linear regression for temperatures and double mass method for rainfalls using data extracted from local weather stations, which unfortunately are scarcely available in our study area. Second, some of the reported cases are suspected cases identified on the basis of the WHO operational definition, especially before 2013. This identification has been increasingly abandoned since 2013, and biological diagnosis is now more available in HZs with the scale-up of RTDs. Lastly, the population data used for the analyses are from the 1984 general census and extrapolated with a growth rate of 1.03 per year. This does not consider the many internally displaced persons linked to recurrent armed conflict in Eastern DRC during the past 25 years. Four years have passed between the time this study was conducted (2016) and publishing the data. However, our findings are still relevant: according to the WHO 2018 World Malaria Report, the malaria picture has not changed significantly in sub-Saharan Africa. On the contrary, the situation appears to be stagnant [3]. The Malaria Control Policies in the DRC stayed the same between 2010 and 2018. In addition, the time period between the data collection and publication does not represent a sufficient decline to observe major environmental changes that may affect our results. We therefore posit that a similar study conducted in 2019 would have produced results comparable to those obtained from 2015, as the context is essentially identical.

Conclusion

Agro-pisciculture practices and the presence of a lake in health zone are significantly associated with increased malaria morbidity and mortality in Eastern DRC. Evidence-based malaria control interventions in peri-lacustrine areas and in areas where individuals are engaged in standing water-associated activities need to be implemented and scaled-up in this setting. These could include intermittent irrigation, which has proved effective in reducing breeding sites after market gardening and rice cultivation, and introducing larvivorous fish in fish breeding ponds, which can inhibit multiplication of malaria vectors.

Acknowledgements

We are grateful to Professor Rostha Lohalo from the Department of Mathematics of the Université de Kinshasa for assistance with preparation and comprehension of data analysis and to Roger Kizungu from the

Department of Agronomy of the Université de Kinshasa for his help drafting the study design and better understanding the geo-climatic aspects of the study. We are also thankful for critical review of the manuscript by Professor Jef Van den Ende, University of Antwerp, Antwerp, Belgium, as well as editing services provided by Dr. Caroline Connor. Parts of the present work were presented at the International Center for Advanced Research and Training's 2017 International Research Symposium, 17 August 2017 to 19 August 2017. Jean B. Nachega is supported by the United States National Institutes of Health (NIH)/National Institute of Allergy and Infectious Diseases (NIAID), the Clinical Trial Unit (CTU) of the AIDS Clinical Trial Group (ACTG) at Stellenbosch University (Grant No. 2UM1AI069521-08); the University of Pittsburgh HIV-comorbidities Research Training Program in South Africa (NIH/Fogarty International Center [FIC], Grant No. 1D43TW010937-01A1); and the African Association for Health Professions Education and Research through grant (NIH/FIC, Grant No. 1R25TW011217-01). The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

References

1. [1]World Health Organization. World Malaria Report 2016. Geneva: WHO; 2016.
2. [2]World Health Organization. World Malaria Report 2017. WHO: Geneva, 2017.
3. [3]World Health Organization. World Malaria Report 2018. WHO: Geneva, 2018.
4. Programme National de Lutte contre le Paludisme (PNLP). Rapport annuel 2015 des activités de lutte contre le paludisme. Kinshasa: Programme National de Lutte contre le Paludisme; 2016.
5. Programme National de Lutte contre le Paludisme (PNLP). Rapport annuel 2013 des activités de lutte contre le paludisme. Kinshasa: Programme National de Lutte contre le Paludisme; 2014.
6. Programme National de Lutte contre le Paludisme (PNLP). Rapport annuel 2014 des activités de lutte contre le paludisme. Kinshasa: Programme National de Lutte contre le Paludisme; 2015.
7. National Programme, de Lutte contre le Paludisme (PNLP). Rapport, . des activités des sites sentinelles de lutte contre le paludisme dans la province du Sud-Kivu. Programme National de Lutte contre le Paludisme: Kinshasa, 2015, 2016.
8. National Programme, de Lutte contre le Paludisme (PNLP) Sud-Kivu. Rapport annuel, . *des activités de lutte contre le paludisme au Sud-Kivu*. Coordination Provinciale du Programme National de Lutte contre le Paludisme: Bukavu, 2015, 2016.
9. Lu F, Culleton R, Zhang M *et al*. Emergence of indigenous artemisinin-resistant *Plasmodium falciparum* in Africa. *N Engl J Med* 2017: **376**: 991–993.
10. Sutherland CJ, Lansdell P, Sanders M *et al*. Independent treatment failure in four imported cases of plasmodium falciparum malaria treated with artemether-lumefantrine in the United Kingdom. *Antimicrob Agents Chemother* 2017: **61**: e02382.
11. Benelli G, Beier JC. Current vector control challenges in the fight against malaria. *Acta Trop* 2017: **174**: 91–96.
12. Sokhna C, Ndiath MO, Rogier C. The changes in mosquito vector behaviour and the emerging resistance to insecticides will challenge the decline of malaria. *Clin Microbiol Infect* 2013: **19**: 902–907.
13. Toé KH, Jones CM, N'Fale S, Ismail HM, Dabiré RK, Ranson H. Increased pyearethroid resistance in malaria vectors and decreased bed net effectiveness, Burkina Faso. *Emerg Infect Dis* 2014: **20**: 1691.
14. PNLP. Plan stratégique national de lutte contre le paludisme 2016-2020. Kinshasa: Programme National de Lutte contre le Paludisme; 2016.
15. PNLP. Plan stratégique national de lutte contre le paludisme 2013-2015. Kinshasa: Programme National de Lutte contre le Paludisme; 2013.
16. Mouchet J, Carnevale P, Coosemans M*et al*. Typologie du paludisme en Afrique. Cahier Santé; 1993.
17. Thomson MC, Connor SJ, Milligan P, Flasse SP. Mapping malaria risk in Africa: what can satellite data contribute? *Parasitol Today* 1997: **13**: 313–318.
18. Zhou G, Minakawa N, Githeko AK, Yan G. Association between climate variability and malaria epidemics in the East African highlands. *Proc Natl Acad Sci USA*. 2004: **101**: 2375–2380.
19. Abeku TA, De Vlas SJ, Borsboom GJJM *et al*. Effects of meteorological factors on epidemic malaria in Ethiopia: a statistical modelling approach based on theoretical reasoning. *Parasitology* 2004: **128**: 585–593.
20. Patz JA, Olson SH. Malaria risk and temperature: Influences from global climate change and local land use practices. *Proc Nat Acad Sci* 2006: **103**: 5635–5636.
21. Patz JA, Hulme M, Rosenzweig C *et al*. Regional warming and malaria resurgence. *Nature* 2002: **420**: 627.
22. McMichael AJ,World Health Organization, éditeurs. *Climate Change and Human Health: Risks and Responses*. World Health Organization; Geneva, 2003; 322.
23. Bandibabone B, Zawadi M, Ntale M, Habamungu C, Ombeni B. Temporary evolutions of flies anopheles in high altitude region of Lwiro-Katana (Democratic Republic of the Congo). *Bull Soc Pathol Exot* 2016: **109**: 26–30.
24. Mabaso MLH, Craig M, Ross A, Smith T. Environmental Predictors of the seasonality of malaria transmission in Africa: the challenge. *Am J Trop Med Hyg* 2007: **76**: 33–38.
25. Bandibabone J, Ombeni L, Habamungu C, Bantuzeko C. Anopheles gambiae's located over 1800 miles of altitude at Lwiro in the East of the DR, Congo. *Int J Innov Appl Stud* 2014: **8**: 1187–1192.

26. Alemu K, Worku A, Berhane Y. Malaria Infection Has Spatial, Temporal, and Spatiotemporal Heterogeneity in Unstable Malaria Transmission Areas in Northwest Ethiopia. *PLoS ONE* 2013: **8**: e79966.
27. B. H. Organisation des Nations Unies pour l'alimentation et l'agriculture. Population (French Edition). 1950;5(4):764.
28. De Failly D.L'économie du Sud-Kivu. L'Afrique des Grands Lacs. 2000; Annuaire 1999–2000:30.
29. IPAPEL Sud-Kivu. Rapport annuel 2013 du bureau de production et de protection des végétaux. Bukavu: Inspection Provinciale de l'Agriculture Pêche et Elevage; 2014.
30. IPAPEL Sud-Kivu. Rapport annuel 2014 du bureau de production et de protection des végétaux. Bukavu: Inspection Provinciale de l'Agriculture Pêche et Elevage; 2015.
31. IPAPEL Sud-Kivu. Rapport annuel 2015 du bureau de production et de protection des végétaux. Bukavu: Inspection Provinciale de l'Agriculture Pêche et Elevage; 2016.
32. DLM. Guide technique pour la surveillance de la maladie et riposte, 2ème édition. Kinshasa: Direction de Lutte contre la Maladie; 2012.
33. National Statistics Institute, Democratic Republic of the Congo, Projections from 1984 Data (Not available Online).
34. Zarocostas J. Mega-crisis in DR Congo. *Lancet* 2018: **391**: 297–298.
35. United States (US) Government's Satellite Observatory website (Available from: https://earthobservatory.nasa.gov/.) [27 June 2019].
36. Heraude M, Boutet J. Guide d'utilisation QGis 2.8/2.14. Conservatoire d'espaces naturels de Picardie; 2016. 183 p.
37. IPAPEL Sud-Kivu. Rapport annuel 2014 des inspections territoriales de l'agriculture des territoires du Sud-Kivu. Bukavu: Inspection Provinciale de l'Agriculture Pêche et Elevage; 2015.
38. IPAPEL Sud-Kivu. Rapport annuel 2015 des inspections territoriales des territoires du Sud-Kivu. Bukavu: Inspection Provinciale de l'Agriculture Pêche et Elevage; 2016.
39. Lampin C, Bouillon C, Long-Fournel M, Morge D, Jappiot M. Caractérisation et cartographie des interfaces habitat-forêt Prévention des risques d'incendies de forêt - Guide méthodologique. 2010.
40. Chaikaew N, Tripathi NK, Souris M. Exploring spatial patterns and hotspots of diarrhea in Chiang Mai, Thailand. *Int J Health Geogr* 2009: **8**: 36.
41. Elkan C. (2011). Nearest neighbor classification. elkan@ cs. ucsd. edu, January, 11, 3.
42. Meunier-Nikiema A, Karama F, Kassie D, Fournet F.(2015). Ville et dynamique de l'offre de soins: Bobo-Dioulasso (Burkina Faso). Revue Francophone sur la Santé et les Territoires.
43. Kulldorff M. A spatial scan statistic. *Commun Stat Theory Methods* 1997: **26**: 1481–1496.
44. Kulldorff M. (2006). SaTScan^{TM} User Guide for version 7.0. SaTScan^{TM}. Accessed on August 13, 2007.
45. Bryan F, Manly J. *Randomization and Monte Carlo Methods in Biology*. Chapman and Hall: London, 1991, 281.
46. Cleveland RB, Cleveland WS, McRae JE, Terpenning I. STL: A seasonal-trend decomposition procedure based on Loess (with Discussion). *J Off Stat* 1990: **6**: 3–73.
47. Stasinopoulos DM, Rigby RA. Generalized Additive Models for Location Scale and Shape (GAMLSS) in R. *J Stat Softw* 2007: **23**: 1–47.
48. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. *J Roy Stat Soc: Ser C (Appl Stat)* 2005: **54**: 507–554.
49. Robert V, Macintyeare K, Keating J, et al. Malaria transmission in urban sub-saharian Africa. *Am J Trop Med Hyg* 2003: **68**: 169–176.
50. Dossou-Yovo J, Doannio JM, Diarrassouba S, Chauvancy G. The impact of rice fields on malaria transmission in the city of Bouaké, Côte d'Ivoire. *Bull Soc Pathol Exot* 1998: **91**: 327–333.
51. Mouchet J. L'écologie du paludisme. *In* Populations et environnement dans les pays du Sud [Internet]. Gendreau F, Gubry P, Véron J, Keyfitz N. éditeurs. Paris: Karthala; 1996 : 253-69. (Economie et Développement). (Available from: https://core.ac.uk/download/pdf/39853923.pdf) [24 Oct 2018].
52. Le Menach A, McKenzie FE, Flahault A, Smith DL. The unexpected importance of mosquito oviposition behaviour for malaria: non-productive larval habitats can be sources for malaria transmission. *Malaria J* 2005: **4**: 23.
53. Utzinger J, Tozan Y, Singer BH. Efficacy and cost-effectiveness of environmental management for malaria control. *Tropical Med Int Health* 2001: **6**: 677–687.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Mean Temperature and Rainfall Extraction Scheme on the MERRA Databank with QGIS.

Corresponding Author Rosine N. Bigirinama, Faculté de Médecine, Université Catholique de Bukavu, Avenue Michombero No. 02, Bukavu, Democratic Republic of the Congo. E-mail rosine.bigirinama@ucbukavu.ac.cd and **Jean B. Nachega**, Stellenbosch University, Faculty of Medicine and Health Sciences, Francie van Zijl Drive, Cape Town, South Africa. E-mails: jnachega@sun.ac.za or jnacheg1@jhu.edu or jbn16@pitt.edu

