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Vector-associated diseases in the context of climate change: Analysis and evaluation of the differences in the potential spread of tertian malaria in the ecoregions of Lower Saxony

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Abstract

Background: The outbreak of vector-associated diseases is determined by different factors. One of them is the existence of appropriate climatic conditions which influence the development of vectors as well as pathogens. Nowadays, accurate data on the occurrence of both vectors and pathogens are often not available in Germany, despite the coastal zones of Lower Saxony (Germany) being former malaria regions. Thus, the question arises, whether a new autochthonous transmission could take place due to the monthly mean temperatures of recent years taking into consideration the predicted increase in air temperatures according to the IPCC scenarios.
Methods: To model areas at risk, the transmission potential for new tertian malaria spreads in respect to temperature was computed in a GIS environment using the Basic Reproduction Rate (R_0) formula.
Results: We were able to corroborate that the risk of tertian malaria transmission is increasing as temperature is the determining variable of the mathematical model.
Conclusions: Lower Saxony is at risk of a new outbreak of tertian malaria assuming no other risk factors than temperature being of relevance.

Key words: climate change, epidemic control, GIS modelling, malaria, risk assessment

Introduction

An outbreak of diseases transmitted by vectors (intermediate or transport host, e.g., mosquitoes, rats or cockroaches) requires the following preconditions: a sufficiently dense vector population; the existence of causes of infection; the climatic conditions must grant a sufficient life span of the vector as well as the development of the pathogen in the vector; and there must be adequate habitats and host animals.

Infections can be introduced into another country from endemic regions in two ways: by vectors and by reservoir hosts; in the case of bluetongue disease it is spread by infected gnats or the import of infected ruminants. For example, gnats can drift on the wind or be introduced through goods and by passenger traffic (e.g., by planes, trucks, and ships). The phenomenon of vector transport by plane is particularly known from the so called airport malaria. Thereby infected Anopheles mosquitoes are carried over long distances from endemic regions to non-endemic regions and cause unexplainable and often delayed diagnosis of malaria infections, especially near the respective airports [1].

With regard to vector-associated diseases rising air temperatures entail, in Germany as well, the risk of

- introduction or rather spread and establishment of tropical vector-competent arthropods,
- development of the respective pathogens in indigenous arthropods whose vector-competence wasn't relevant since the air temperatures were too low for the development of pathogens so far
- increase of the population density of potential vector-competent indigenous arthropods.

In Germany, there is little up-to-date information on the existence and distribution of potential vectors as well as on pathogens potentially transmitted by these species. Furthermore, no systematic vector monitoring network is established yet to collect respective data [2]. Only data from the monitoring of vectors provides, in case of an epidemic, adequate information on species distribution and frequency and allow for development of appropriate strategies of epidemic control. Changes in environment, climate and human behaviour will undoubtedly increase the frequency and intensity of confrontations with vectors and vector-associated pathogens in the future.

The WHO recommends the systematic compilation of epidemiologically relevant data as well as the completion of studies on pests and vectors with the following crucial questions [3]: Which potential vector species can be found? What is their spatial and temporal distribution? Which pathogens are circulating? Where are regions at high risk of disease outbreaks? Which precautionary measures and what actions can be taken in case of disease outbreaks? Such data sets should be compiled in combination with scientific studies and a systematic long term monitoring.

In northern Germany (Lower Saxony), malaria was endemic until the early 1950s [4]. DDT application, drainage of wetlands as well as improved hygiene and health care finally allowed for the elimination of malaria in this area [5,6]. By contrast, the Anopheles vectors are still present in Lower Saxony. Wetland restoration as well as rising air temperature and precipitation increase the malaria risk by prolonging the potential seasonal transmission gate [2]. This is because besides endemicity of susceptible species among the ecological boundary conditions, climatic factors are particularly decisive for the epidemic spread of malaria [7,8].

The aim of the presented study was to investigate the impact of the variation of one of the factors affecting the potential transmission gate of the malaria pathogen *Plasmodium vivax* through the vector *Anopheles atroparvus*: The number of potential secondary infections (R_0) was calculated according to measured air temperatures for the periods 1947-1960, 1961-1990, 1991-2007, and with respect to the predicted air temperatures [9] for the years 2020, 2060 and 2100 (each one best and worst case scenario). In contrast to the study presented in [10] we differentiate the findings for the ecoregions of Lower Saxony. Each eco-region is defined by several ecological characteristics which are significant for the vector *Anopheles atroparvus* in terms of habitat requirements. Additionally, we used spatially and temporally more accurate data on air temperature as well as enhanced methods for mapping these temperatures for Lower Saxony.

Materials and Methods

Basic information on the genus Anopheles

Modelling and mapping of the potential temperature dependent malaria spread requires quantitative information on the ontology and ecology of the relevant Anopheles vector.

Anopheles (Diptera, Culicidae) is one of 41 mosquito genera. The females of 30-40 of the 430 Anopheles species transmit the malaria pathogen, Plasmodium to humans. Of the 16 European Anopheles species six occur in Germany [11], three of which were responsible for malaria transmissions till the post-war era (*An. atroparvus, An. maculipennis, An. messeae*).

Anopheles atroparvus transmits *Plasmodium vivax* [12] and is strongly correlated with the disease [13 -15]. *Plasmodium vivax* causes tertian malaria which is also called vivax malaria commonly known as ‚marsh fever' in the coastal regions of northern Germany [16]. The mosquitoes need 105 days with temperatures ≥ 14.5 °C to become infectious [12].

The risk modelling presented in this study refers to *Plasmodium vivax* because it is most relevant in north-western Germany [12-15]. *Anopheles atroparvus* occurs mainly in coastal regions in sea-, brackish- and freshwater [17]. The temperature threshold values needed for the aquatic stages of *Anopheles atroparvus* were adopted from the literature [12]. In the climate of the first half of the 20th century two to three generations of Anopheles grew up per annum in northern Germany [18,19]. In extraordinarily warm summers, like in 1947, up to five generations of Anopheles developed [18].

Data base

In addition to the physiological threshold values, information on historical Anopheles findings were available from literature as well [4,13,15, 20-27]. From 1985 these findings were supplemented by data from the database, Biological Archive of the Surface Waters of Lower Saxony' (Biologisches Archiv der Oberflächengewässer Niedersachsens – BOG Archiv). This BOG archive provides information on findings of Anopheles larvae which are not determined by the species level, so far.

Data on mean monthly air temperatures were compiled for those months being sufficiently warm for the development of Plasmodium vivax (T ≥ 14.5 °C)[28]. These data encompass measurements from 54 observation sites of the German Meteorological Service (DWD) for the months May till August in the period from1947 till 2007. To this end, monthly mean air temperatures were calculated for the periods 1947-1960, 1961-1990 (the last complete 30-year climate reference period), and 1991-2007. The maps of air temperature enabled the spatial linkage of the temperature data with the Anopheles findings and associated malaria incidences until the early 1950s and with the Anopheles findings documented in the BOG-archive since 1985. According to the scenarios of the IPCC [9], monthly air temperature means were added for 2020, 2060, and 2100 (for each one the best case and worst case scenarios), also including means for September and October due to the prolonged transmission gates. The future maps were generated in a GIS by adding the predicted values of rise in temperature to the temperature grid of the climate normal period 1961-1990. Thus, this procedure did not take into regard the spatial variation of the predicted temperature increase. This will be the focus of our upcoming investigations in which we use spatially differentiated temperature data for future climate scenarios from regionalised models.

Geostatistical surface estimations of temperature data

The locations of the Anopheles findings do not coincide with the air temperature observation sites. For a spatial linkage of punctual data on temperature and localities the temperature data were interpolated by means of regression Kriging [29]. This was performed by correlating temperature values with elevation data derived from the global elevation model GLOBE [30]. The correlation coefficients indicated a high (r = 0.75 to 0.83) and significant relationship between temperature measurements and altitude at the respective observation site. The regression model was used to calculate high resolution temperature maps (1 x 1 km²) for each month and period in a GIS. Finally, residual maps on the differences between measured and modelled temperature values were calculated by using ordinary kriging.

Ecoregions of Lower Saxony

Data on landscape characteristics were integrated by a map on ecoregions in Germany. This ecoregionalisation was derived from data on long-term (1961-1990) monthly means on precipitation, air humidity, air temperature, and global radiation as well as from maps on soil texture, elevation, and potential vegetation in using Classification and Regression Trees (CART) [31,32]. Each ecoregion is defined and mapped according to the respective characteristics of climate, altitude above sea level, soil texture, and vegetation. This helps evaluating whether and to what extent regions of long seasonal transmission gates coincide with those regions being adequate Anopheles habitats (e.g., wetlands).

Calculation of the potential spread of Plasmodium vivax

The kriging surface estimations of the air temperature were used for calculating the potential temperature-dependent spread of the malaria pathogen *Plasmodium vivax* hosted by *Anopheles atroparvus*. This was realised by estimating the possible number of secondary infections (R_0) using the basic reproduction rate formula [33-35] adapted by [28]:

$$R_0 = \frac{m * a^2 * b * p^n}{-\ln(p) * r}$$

- m Relative frequency of female *Anopheles atroparvus*
- a Number of blood meals per human and day
- b Ratio of female Anopheles atroparvus in which parasites can develop after ingestion of infected blood (in the absence of a value for Germany in literature, a mean value of 0.14 for England and the Netherlands was used)
- p Daily probability of survival of a female *Anopheles atroparvus* (p = 0.97 [12])
- n Duration [d] of parasite development in adult *Anopheles atroparvus* females $n = f_2 / (T - g_2)$
- f_2 Thermal sum in degree days (105 for the physiologically critical threshold g_2)
- T Average ambient temperature
- g_2 Minimum temperature for parasite development (14.5° C [12])
- r Recovery rate of malaria-infected people (1 / r = 0.0167 / day [10])

The calculation of R_0 provides the mean number of secondary infections caused by a single infected Anopheles individual when it meets a potential host population in which every member is susceptible for the agent. In case of $R_0 \geq 1$ malaria is spreading. In case of $R_0 < 1$ there is no risk of a malaria spread [35]. The determination of R_0 for all 48,000 grid cells (1 x 1 km^2) of the temperature surface maps in a GIS environment allows the mapping of potential malaria regions in Lower Saxony. The calculations were performed for the months June, July, August, and September for the periods 1947-1960, 1961-1990, and 1991-2007. For these periods also the lengths of the potential seasonal transmission gates were summed up in the GIS for all those grid cells where the R_0-value in Lower Saxony was ≥ 1.0 in the respective months. In addition, this was carried out for the years 2020, 2060 and 2100 on the basis of both an optimistic (best case scenario) and a pessimistic (worst case scenario) prediction of the future temperature development [9]. The results were assigned to an ecological land classification of Germany [31,32] to enable a landscape ecological differentiation of the modelling results.

Results

The calculations provided, amongst others, maps and data on the ecoregional differentiation of the number of potential secondary infections by *Anopheles atroparvus* (R_0) and of the length of the seasonal transmission gates allowing its reproduction. Quantity, period of occurrence and spatial distribution of the pathogen are major features of the epidemiological risk.

Table 1 gives an overview of the acreage of the calculated potential seasonal transmission gates of tertian malaria in Lower Saxony. The row ‚total' specifies the percentage of the respective ecoregion in relation to the whole area of Lower Saxony. Accordingly, ecoregion 43 (North German coastal heathlands) covers about 26 % of the area of Lower Saxony. The column 'total' contains the percentages of the coverage of the respective potential seasonal transmission gate (months) given for each investigated period. Accordingly, the period between 1947 and 1960 is dominated by a potential transmission gate of two months (81.7 %), whereas the area with a transmission of three months amounts for 16.1 % of the Lower Saxony territory. The inner cells of table 1 contain the percentages of the respective area of transmission length (0 to 6 months) for each ecoregion. Accordingly, from 1947 to 1960 24.1 % of the area of ecoregion 43 is characterised by a transmission length of three months, whereas such condition are found on 35.5 % of the area of ecoregion 47 (southern loess hills). In the three periods covered by measured values (1947-1960, 1961-1990, 1991-2007) the percentage with a two-month risk of transmission declines from 81.7 % to 28.3%, while the area with a maximum transmission period of three months increases from 16.1% to 70.8%. If the air temperature will increase by + 0.3 °C (2020, best case scenario)[9], 50% of the area of Lower Saxony would have a transmission period of two months and the other 50 % a three months transmission period. Considering a rise in air temperature of + 0.9 °C, the thermal conditions would permit an almost country-wide (94 %) three month transmission gate. In case of a temperature rise of + 1.4 °C (2100, best case) 21.5 % of Lower Saxony show a seasonal transmission gate of four months.

Table 1. Percentages of the potential temperature dependent malaria seasonal transmission gate according to the respective ecoregion of Lower Saxony

	Ecoregion*								total
	12	20	22	42	43	47	62	8	
1947-1960 (long-term annual mean: 8,3 °C)									
0	49.7	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.9
1	39.9	0.0	0.0	0.0	0.0	0.1	4.2	0.0	1.3
2	0.0	49.8	97.7	97.4	75.9	64.4	81.6	57.6	81.7
3	0.0	50.2	2.3	2.6	24.1	35.5	13.8	42.4	16.1
1961-1990 (long-term annual mean: 8,6 °C)									
0	98.9	0.0	0.0	0.0	0.0	0.1	5.6	0.0	2.0
1	0.0	0.0	0.0	0.1	0.1	0.0	7.5	0.0	0.7
2	1.1	4.3	100.0	84.9	60.9	39.5	84.6	1.3	68.8
3	0.0	95.7	0.0	15.0	39.0	60.4	2.3	98.7	29.3
1991-2007 (long-term annual mean: 9,5 °C)									
0	25.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4
1	26.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4
2	48.1	0.8	82.7	30.1	12.3	6.1	65.8	0.0	28.3
3	0.0	99.2	17.3	69.9	87.7	93.9	34.2	100.0	70.8
2020 b.c. (+0.3 °C)									
0	89.1	0.0	0.0	0.0	0.0	0.0	2.3	0.0	1.5
1	5.2	0.0	0.0	0.0	0.0	0.2	3.8	0,0	0.4
2	5.7	0.0	88.9	58.7	19.1	12.9	70.6	0,7	41.3
3	0.0	100.0	11.1	41.3	80.9	86.9	23.3	99.3	56.8
2020 w.c. / 2060 b.c. (+ 0.9 °C)									
2	94.8	0.0	5.9	2.2	3.2	1.5	17.4	0.0	6.0
3	5.2	100.0	94.1	97.8	96.8	98.5	82.6	100.0	93.9
2060 w.c. (+3.3 °C)									
3	70.1	0.0	0.0	0.0	0.0	0.0	0.5	0.0	1.2
4	22.6	0.0	11.8	1.1	0.0	1.4	22.6	0.0	4.5
5	7.3	100.0	88.2	98.9	100.0	98.6	76.9	100.0	94.3
2100 b.c. (+ 1.4 °C)									
2	85.0	0.0	0.0	0.1	0.1	0.0	2.3	0.0	2.0
3	15.0	80.4	71.7	80.0	90.9	55.6	83.3	40.3	76.6
4	0.0	19.6	28.3	19.9	9.0	44.4	14.3	59.7	21.4
2100 w.c. (+ 5.8 °C)									
4	50.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8
5	50.0	93.8	29.8	68.0	97.7	88.5	99.6	84.4	79.8
6	0.0	6.2	70.2	32.0	2.3	11.5	0.4	15.6	19.5
total	1.50	2.1	7.00	35.2	26.4	14.9	8.4	1.3	100.0

*percentage ≥ 1 % of Lower Saxony

b.c. = best case; w.c. = worst case.
The percentages in the columns indicate how much area of each ecoregion is covered by the respective transmission length (0 to 6 months) in each period of time. The last column ('total') describes the percentages of each transmission length in the whole country, whereas the last row ('total') reflects the acreage of each ecoregion compared to the territory of whole country.

Considering a rise of + 3.3 °C (2060, worst case), in almost 95 % of Lower Saxony secondary malaria infections would be possible during 5 months. In case of + 5.8 °C (2100 worst case) even a six month seasonal transmission gate is possible on about 19.5 % of Lower Saxony.

Each of the ecoregions in table 1 can be described with regard to the characteristics of the following features [32]: potential natural vegetation, soil texture, elevation, and climate (monthly mean precipitation, temperature, evaporation, and global radiation for the period 1961-1990). This basic ecological description of the landscape units can be supplemented by further information on features which are more variable in time, like, e.g., land use. Most of the Anopheles findings till the 1950's documented in literature (n = 155) were located in ecoregion 22 (coastal marshlands) (47.7 %) and in the old pleistocene hill lands (ecoregion 42) following southwards (25.2 %) (Figure 1). According to [31, 32] these marshlands (altitude 0-20 m above sea level) are characterised by a maritime climate with above-average precipitation in autumn and winter (up to 20 mm per month more than the country-wide average) and moderate temperatures (annual mean 8.6 °C), especially in winter (about 1 °C higher). In combination with a high number of waterbodies these conditions are favourable for mosquitoes and thus explain the high number of incidences of Anopheles in the 1950's. On the other hand, the percentage of a potential transmission length of three month increases from 16.1 % in 1947-1960 to 70.8 % in 1991-2007. Recent findings (n = 89) of Anopheles documented in the BOG archive concentrate in ecoregion 42 (62.9 %) which reflects a maritime climate as well (annual mean 8.9 °C) and additionally comprises a lot of ombrogenic bogs and fens being adequate habitats for mosquitoes, too. Due to cold weather conditions (mean annual temperatures 6.5-8.3 °C) the least possible annual transmission gate (0-1 months) for all periods can be found in the low mountain ranges in the south (ecoregions 12 and 62) with average altitudes ranging between 282 and 598 m above sea level.

The country-wide mapping of the potential seasonal transmission gate of tertian malaria is given exemplarily for the periods 1961-1990 and 1991-2007 in Figure 2. Whilst under the recent conditions the potential seasonal transmission gate amounts to three months (70.8 %, table 1), in 2100 the potential seasonal transmission gate varies between five and six months for the worst case scenario (Figure 3).

Figure 1. Ecoregions in Lower Saxony according to [31, 32] and localities of former malaria and Anopheles findings.

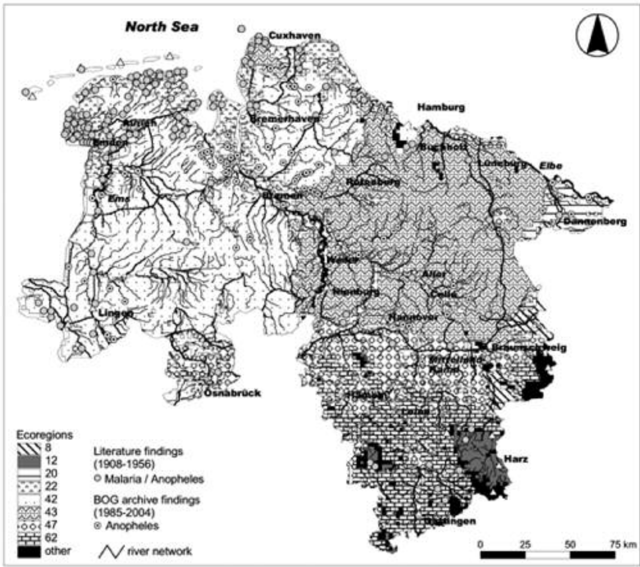


Figure 2. Potential seasonal transmission gates of tertian malaria for the periods 1961-1990 and 1991-2007.

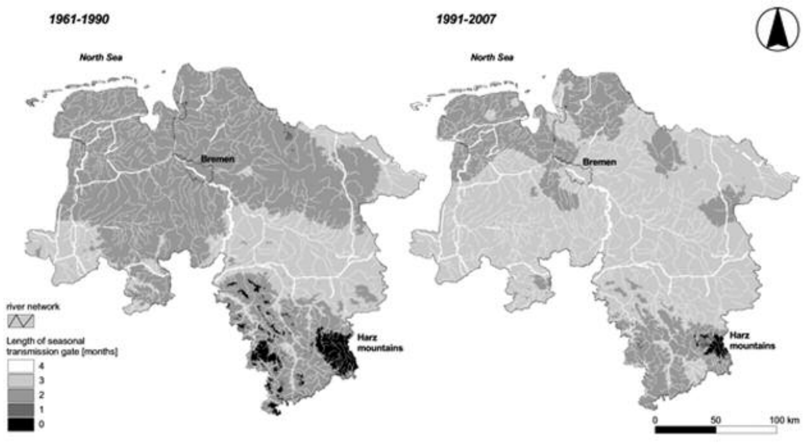
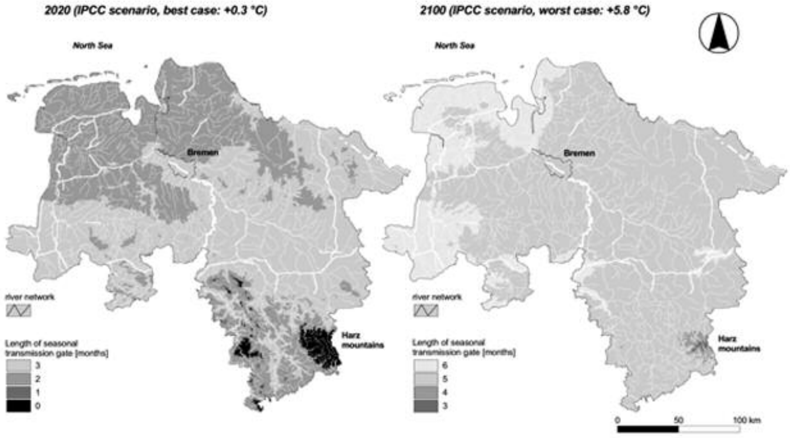


Figure 3. Potential seasonal transmission gates of tertian malaria according to the IPCC scenarios in 2020 (best case) and 2100 (worst case).



Discussion

Concerning the period from 1947 to 2007, similarity between former malaria zones and recent Anopheles findings listed in the BOG-archive can be revealed. Some areas mentioned there are exactly those which represent the highest risk of *Plasmodium vivax* transmission for all investigated periods. Recent studies provide evidence that *Anopheles atroparvus* and *Anopheles messeae* are still present in the coastal areas [36] as represented by ecoregion 22. It is this area where best case scenarios calculated a 4-month risk of transmission in 2060. Furthermore, it is also the area where tertian malaria occurred up to the 1950s [4]. If the pathogen is introduced and is still able to be transmitted by mosquitoes, transmission of tertian malaria could take place in Lower Saxony.

The presented risk prognosis is mainly determined by the model which is used for the mathematical estimation of the reproduction of the malaria pathogen and, thus, its probability of occurrence as a risk component. Like every model, this model does not reflect reality in its entirety and, consequently, the variety of influences affecting the reproduction of *Plasmodium vivax*. The model focuses on measured and predicted monthly mean air temperatures. Other driving factors are not taken into consideration. The model is not only incomplete with regard to known driving factors, it rather has to be assumed that the epidemiology of malaria is only deficiently known so far. Furthermore, the well-known problem of insufficiently documented data quality has to be considered. And finally, the interrelations between host, vector, parasite, and ecosystem characteristics (e.g., precipitation, air and soil temperatures, existence of breeding habitats) as well as hygienic status and health care are specified only inadequately [35,37]. Nevertheless, such models are understood as an approximation to reality which can help to identify areas at risk and initiate prevention [33].

Several studies deal with the question to what extent climate change is likely to increase the spread of vector associated diseases [35,38-40]. Whilst the increase in temperature has been proven meteorologically valid and statistically significant, there is no consensus on its epidemiological impacts. In some studies the relevance of air temperature is assessed to be not decisive [41,42]. However, it is not denied that the rise in temperature will affect the spread of malaria in Europe. In any case, it is clear that Lower Saxony is an area at risk for secondary malaria infections in terms of thermal conditions. Fading out other relevant influences besides air temperature one can culminate: in case of the recurrence and a permanent, autochthonous establishment of *Plasmodium vivax,* the possibility of a recurrence of tertian malaria is given [43]. Between 1999 and 2003, 150 imported cases of malaria occurred in Germany, which corresponds to 24.3 % of all cases registered in Europe [44].

In contrast to Germany, other European countries have drawn consequences from the proven risks and initiated investigations. The results confirm the epidemiological relevance of the rise in air temperature on the spread of malaria [28,45]. Germany should also confront this situation and intensify its research activities. Epidemiological research including landscape ecological approaches and modern GIS technology contribute to an appropriate risk assessment and to an accomplishment of preventative measures. Especially in Lower Saxony, the focus is not only directed on humans but also on livestock, being kept in high densities. A differentiation of environmental preconditions affecting the malaria spread was performed by intersecting the ecoregions of Lower Saxony with the transmission maps. For a more accurate spatiotemporal analysis of the risk potential, further influencing factors should be considered, e.g., by means of an intersection of maps on the distribution of natural and artificial water bodies (wetlands, temporary pools), precipitation, humidity as well as on population exposure and livestock density. Furthermore, the BOG survey established for investigating water quality and biology, essentially, was not performed country-wide nor investigated all waterbodies but concentrated on large water courses only. Depending on the respective sampler, not all Culicidae findings listed in the BOG archive were determined to the genus. This implies that the findings illustrated in Figure 1 represent just a fraction of the actually estimated Anopheles occurrence. Hence, the explanatory power of the statistical analysis regarding the relation between Anopheles findings and habitat conditions seems to be restricted and should rely on a systematic and consistent vector monitoring. This would further improve the spatial differentiation and, thus, the quality of the risk assessment. Socio-scientific investigations on ageing structure, leisure and recreation activities as well as livestock husbandry could further specify the information on potential host populations in space and time. Sensitivity analyses support the assessment of the relevance of different known factors for the calculation of the reproduction rate, like the number of blood meals or the lifespan of Anopheles. In further investigations the results of the regionalised climate prediction models REMO [46] and WETTREG [47] will be applied to the model on secondary malaria infections in order to achieve higher scientific quality and spatial resolution for the future.

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