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Climate-based seasonality model of temperate malaria based on the epidemiological data of 1927–1934, Hungary

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Abstract―The potential resurgence of malaria in the temperate areas of Europe due to climate change is an actual topic of epidemiology. Although several ecological forecasting models were built for the prediction of the potential re-emergence of malaria in the recently non-endemic areas of the world, the simulations are mainly based on the recent climatic thresholds of the tropical and subtropical vectors and *Plasmodium* parasites, mainly of *Plasmodium falciparum*. We aimed to reanalyze the primarily *Plasmodium vivax* caused autochthon malaria disease data of the past model period of 1927-1934 in Hungary to gain reliable knowledge about the climatic thresholds and the determinants of the malaria season for a temperate climate in a Central European country. Multivariable and simple linear correlation and regression was performed to analyze the malaria data of 96 months dividing the season a first and a second half parts of the year. Two models were built on the gained correlations using unstandardized and standardized correlation weights. It was found, that both in the first and second halves of the year, the ambient mean temperature was the most important predictor of the relative malaria incidence, while precipitation influenced the first half of the season. Summer sum of precipitation above 200 mm was found as one of the most important determinant of the absolute annual case number of benign tertian malaria. The unstandardized weights-based modeled malaria seasons returned well the observed autochthon malaria seasons.

Key-words: *Plasmodium vivax*, malaria, temperate climate, seasonality, archive data

1. Introduction

Malaria is one of the most important vector-borne diseases in the world affecting at least 3.2 billion people (*World Malaria Report*, 2005) and causing about 700.000 to 2.7 million people deaths per a year (*Patz* and *Olson*, 2006). The disease is caused by different *Plasmodium* species and transmitted by several *Anopheles* mosquitos. About 40% of the mankind live in malaria endemic areas (*Mendis et al.*, 2001). Once in the wide areas of Europe malaria was endemic, however, due to the active eradication programs of the 20th century, malaria became a non-endemic or rare disease in the old continent. Malaria was highly endemic also in Hungary, in the hearth of Central Europe, even to the mid-20th century, when the results of a combination of several actions, malaria became eradicated in the country. For example, in the 1920's, malaria caused six to eight thousand newly acquired cases per year in the continuous regions of the north-east and south-west parts of Hungary (*Lőrincz*, 1981–82). In the territory of the Kingdom of Hungary, the Ministry of the Interior adopted decree against malaria in 1901, but the malaria data was regularly collected from 1927 (*Szénási et al.*, 2003). The year of 1930 was a milestone in the history of the malaria in Hungary indicating the start of the active intervention, although the more intensive epidemiological interventions due to the start of the establishment of the observation stations in the endemic areas started only in 1937 (*Szénási et al.*, 2003). The intent public health efforts, the elimination of the wetland areas and the introduction of DDT led to the eradication of the malaria to 1956 in Hungary, although officially the WHO delivered Hungary to a malaria-free country in 1963.

In contrast to the recent epidemiological situation, the climate models predict the resurgence and worldwide increasing risk of malaria transmission due to the anthropogenic climate change (*Martens et al.*, 1999). It was found that small increases in temperature at low temperatures can increase the risk of malaria transmission substantially (*Lindsay* and *Birley*, 1996), although the potential effect of the changing climatic patterns are strongly influenced by socioeconomic developments and malaria control programs (*Martens et al.*, 1995). For example, in the East African highlands, the warming trend from 1950 to 2002 caused the parallel increases in malaria incidence, too. The rapid response of malaria to the changing temperatures patterns is understandable according to the fact that *Anopheles* mosquitos are highly sensible for the meteorological conditions, particularly to the air temperature. Temperature determines the time of the ontogeny and the questing activity of female mosquitos (*MacDonald*, 1957; *Jetten* and *Takken*, 1994). In addition, the highly complex ontogeny of *Plasmodium* parasites is also the function of the ambient temperature. For example, it is known that the lower temperature threshold of the ontogeny of *Plasmodium vivax* and *Plasmodium falciparum* are 14.5–16 and 18 °C, respectively (*MacDonald*, 1957). Even *Hackett* and *Missiroli* (1935) showed that the pattern of malaria season is in correlation with the latitude of a malaria endemic area, since the latitude essentially determines the annual temperature conditions with other factors, e.g., as the distance from the oceans and the altitude conditions. Before the 20th century, the 15 °C July isotherm appointed the northeast occurrence of the endemic malaria cases (*Menne* and *Ebi*, 2006). Precipitation is also an important factor of the malaria cases determining, with the temperature conditions, the dominance of the *Anopheles* species in Europe (*Kuhn et al*., 2002). In the Atlantic and continental climate zones of Europe, as the Central European region, *Anopheles atroparvus* van Thiel, in Eastern Europe *Anopheles messeae* Falleroni, and in the Balkan Peninsula *Anopheles superpictus* Grassi are the main potential vectors of the human pathogen *Plasmodium* species. Recently, seven *Anopheles* species are known from Hungary, although the presence of *Anopheles sacharovi* Favre is also possible in the southern border areas (*Tóth* and *Kenyeres*, 2012). The malaria pathogen transmission potential of the different *Anopheles* species are different, the members of the so-called Maculipennis complex (named after the *Anopheles maculipennis* Meigen malaria mosquito) are known to be the most important vector species. In Hungary, *Anopheles atroparvus, Anopheles maculipennis,* and *Anopheles messeae* are the plausible potential vectors of the *Plasmodium* parasites according to the historical data (*Szénási et al*., 2003). It is also known that before the eradication of the malaria in Hungary, *Plasmodium vivax* caused the 90% and *Plasmodium falciparum* the 10% of the malaria cases.

The resurgence of malaria in Europe is more than a fiction: *Plasmodium*-infected people introduced tropical malaria during the 1997 heat-wave in Germany (*Krüger et al*., 2001) and Italy (*Baldari et al.,* 1998), when local female *Anopheles* mosquitos bite infected passengers returning from endemic areas. The reverse case is also known, when introduced, infected malaria vectors caused malaria infection in the airport staff or the people living in the neighborhood of the airport (*Giacomini et al.*, 1997). However, the well-developed simulations provide information of the vector potential of the *Anopheles* species in the near future; there are no well-based evidences about the potential seasonality of malaria in the continental areas as the Carpathian Basin. In turn, seasonality and the determinants of the annual run of the disease season can be more important factors of the possibility of reemergence of malaria than the simple presence of the malaria vectors. Since either the tropical vectors or the parasites are not or only partly equivalent to their continental counterparts, the model results require further validation. According to the above described causes, only the historical data of an area in a temperate region can provide a reliable basis and model for the potential near future seasonality of malaria in the temperate regions, even the climate is changing. In contrast to the northern regions of Europe, where malaria spontaneously disappeared in the early 20th century (*Bruce-Chwatt* and *de*

Zulueta, 1980), in Hungary the malaria eradication was the consequence of the joint effort of public health services. Although, autochthon malaria cases were observed in Hungary from the medieval ages to the 1950's, the analyzable period is limited to the start of the regular data collecting activity and the start of the more active public health interventions in the second part of the 1930's.

Our aim was to analyze the autochthon malaria case data of Hungary after the start of the data collection, but before the pre-intervention era in the period of 1927 to 1934. While the threshold of the tropical vectors and parasites is well-known, the threshold of the extinct European strains is still debate (*Menne* and *Ebi*, 2006). We also aimed to gain information about the former seasonality patterns, the effect of the temperature and precipitation on the autochthon malaria cases and to build a phonological malaria seasonality model based on the results. In addition, the re-modeling of the adult female malaria mosquito season was performed for the studied period.

2. Methodology

2.1. Statistics and software

The multivariable and the simple linear correlation and regression were performed by the simple and multiple regression tool of VassarStats on-line statistical program (*Lowry*, 2004). Microsof Office 2010 Excel was used in the visualization of the graphs. ArcGis 10.0 software was used in the performance of the spatial data.

2.2. Climate data

Since the climatic and topographical conditions are very homogenous in the country, Hungary was considered in climatic sense as a homogenous unit. The daily mean temperature data were derived from the European Climate Assessment Dataset (*Haylock et al.,* 2008).

2.2.1. Temperature and precipitation data for the period 1927–1934

We gained the monthly mean temperature and the monthly sum of precipitation data from the dataset of CRU TS3.22 (land) model for 1901–2013. Average values were calculated from the 0.5° grid within the domain including almost the entire Hungary. The latitudinal range was 45.50°N–48.50°N, while the longitudinal was 16.00°E–23.00°E. The monthly mean temperature and the monthly sum of precipitation values were derived from the period of January 1927–December 1934.

2.2.2. Temperature and precipitation data for the period 1970-1999

We gained the mean daily temperature data from the dataset of E-OBS model (1950-now). Average values were calculated from the 0.5° grid within the domain including almost the entire Hungary (*Fig. 1*). The latitudinal range was 45.50°N-48.50°N, while the longitudinal was 16.00°E–23.00°E. The monthly mean temperature values were derived from the period of January 1970 – December 1999. The daily data was converted into monthly mean temperature values.

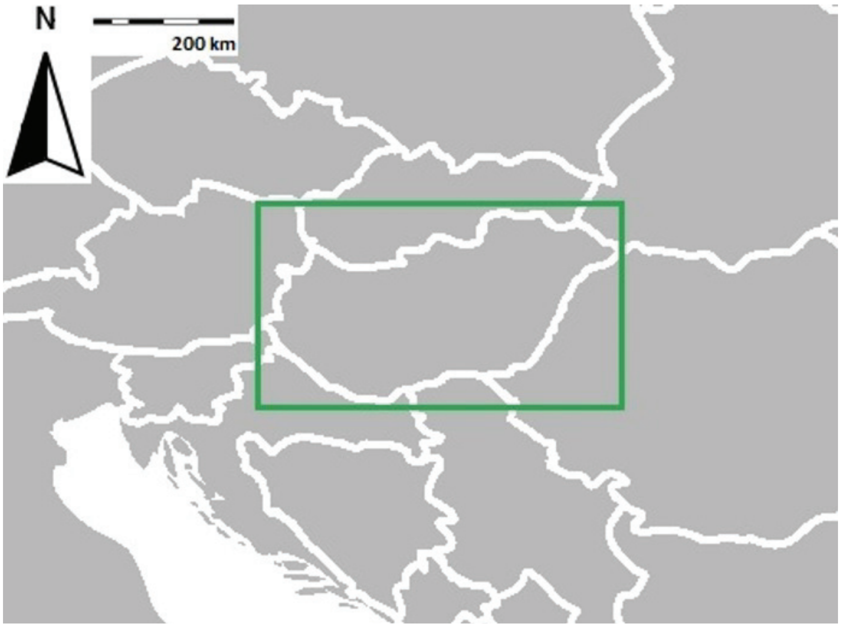

Fig. 1. The domain of Hungary in Central Europe.

2.3. Malaria data

2.3.1. Monthly autochthon malaria data of 1927-1934 in Hungary

The monthly malaria case number of 1927–1934 was based on the article of Zoltán Alföldy (*Alföldy,* 1935). The results of this study are shown in *Fig. 2 left*. Due to the lack of the written data, after the digitalization of the figure, the monthly case numbers were read directly from the figure using a precise covering grid. Although, malaria became a mandatory reportable disease in 1930 in Hungary, the regular collection of the disease started in the autumn of 1926. Since the data of 1926 is incomplete, in the latter analysis we neglected this data. Despite the fact that the studied eight years may seems at first inspect to be a short period, the absolute malaria case number showed a notable fluctuation. While the lowest malaria case number was observed in 1930 with less than 150 cases per year, the highest malaria case number exceeded the 1900 case per year value in 1934. Summer cases formed the most notable part of the annual malaria incidence with a synclinal pattern during the studied period (*Fig. 2 right*).

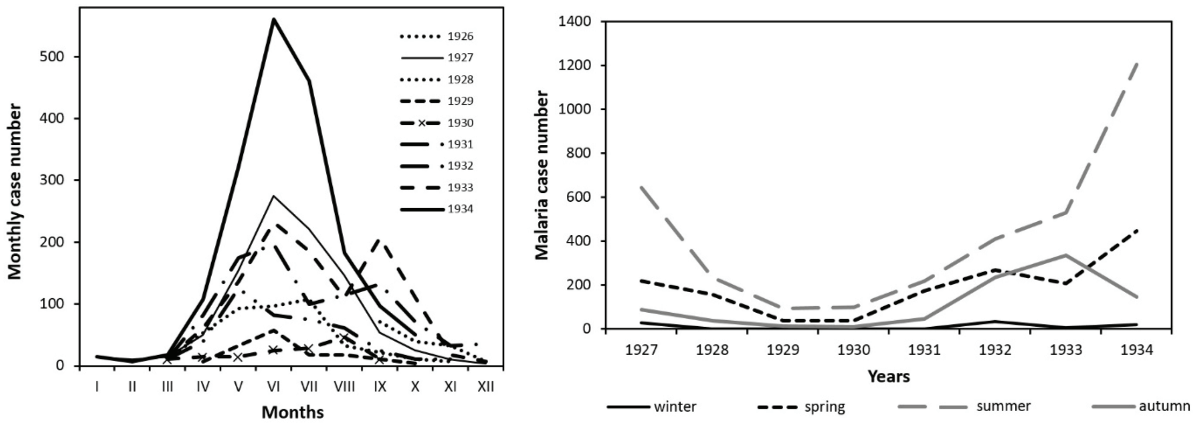

Fig. 2. Left: the autochthon monthly malaria cases in Hungary, in the autumn of 1926 and 1927–1934, *right*: changes of the number of the seasonal autochthon malaria cases in 1927–1934, Hungary.

2.3.2. Spatial data of the malaria cases of 1936 and its georeferencing

To show the former spatial occurrence of malaria in Hungary, the year of 1936 was selected as a characteristic example of the 1930's. In this year the malaria morbidity was 20.8 per 100.000. The spatial distribution data of the malaria cases of 1936 was based on the publication of *Szénási et al.* (2003) (*Fig. 3, Malaria morbidity in Hungary in 1936*). The original spatial data was displayed in the former "járás" (*processus*, the lowest-level administrative unit) system, which corresponds roughly to the present day NUTS4 district areas. We used the site appointing function of Google Earth imagery to mark the central points of the former NUTS4 areas. Each marked points were named after its case number interval. Six intervals of annual case number were used according to the original: the 1 to 5, 6 to 14, 15 to 29, 30 to 59, 60 to 149, and 150 to 284. We converted the designated spatial data into keyhole markup language (*kml*) file format (altitude or gamma intensity data). After opening the *kml* data, we converted them into shape file format in the ArcGIS 10.1 software. To create color images, we linked the points with the mean of the annual case number intervals. The different values were assigned to the referred points and were sorted into attribute table. We interpolated the values of the spatial data by the IDW interpolation function of the spatial analyst tool in the ArcGIS. The aquatic habitats illustrating cut off the second military surveying of the Habsburg Empire were derived from the Mapire homepage (*Mapire,* 2015), which is a digitized and georeferenced raster mosaic of the original individual sheets (*Molnár* and *Timár,* 2009).

2.4. Mosquito data

The relative abundance, *RA* (in %), value of the female imago individuals of *Anopheles messeae*, a member of the *Anopheles maculipennis* complex was gained from the three decades (1970's, 1980's, and 1990's) covering countrywide mosquito collecting data of *Tóth* (2004). We assorted the number of collected female mosquitos according to the months of the year and used the summarized monthly female mosquitos in the model. The number of the collected number of the mosquitos was termed as a relative abundance (*RA*). Since the monthly value of *RA* depends on the number of monthly trapping occasions, we used the quotient of *RA* and the number of the trapping occasions (termed as the normalized relative abundance value, *NRA*):

$$NRA = \frac{RA_i}{N_t}, \tag{1}$$

where *NRA* is the normalized relative abundance, RA_i is the the normalized relative abundance of the *i*th month of the year, and $N_t$is the the number of trapping occasions in the ith month of the year.

Since this number is based on the summarized amount of collected mosquitos, this data was utilized to build only a relative model predicting the seasonal run of the malaria mosquito season.

2.5. Modeling approaches

To analyze the phenology of the malaria season, two different approaches were used: a climate-based model and a vector (*Anopheles messeae*)-based model. In the first approach, we also used the temperature and precipitation data to predict, at first, the annual relative incidence (*RI*, in %) and after the percentage of the malaria case number according to the whole period's case number (*R*). Since, in contrast to the past malaria data, we used the 30 years summarized monthly number of the mosquitos, in the vector-based model only the temperature and the annual normalized relative abundance of the potential vectors (*NRA*, in %) were used. Both *NRA* and *RI* values mean the percentage of the monthly cases or number according to the annuals'. The *R* value was calculated according to the incidence values of the period of 1927–1934.

2.5.1. The first approach

The model was built to analyze the determinant climatic factors of the former run of the annual malaria case curve in Hungary and to reconstruct the curve in the studied period. At first, we calculated the relative case number values form the monthly cases, as in the period of 1927 to 1934. The case number of malaria showed the above described high variance, and the relative case number (relative malaria incidence, RI_m) values were used instead of absolute incidence or case number values as the basis of the model. The model was constructed to calculate the RI_m values of a certain month based on the monthly mean temperature (T_m) and the monthly sum of precipitation (P_m). Since RI_m may be related to the abundance of the actual questing, hungry active female *Anopheles* population, we hypothesized that malaria can positively correlate with the outdoor temperature and the precipitation. Our approach was that the annual RI is the amount of the monthly values of the temperature and precipitation dependent abundance related relative monthly malaria case numbers in the first (RI_{m1}; from the 1st to the 6th months) and second part of the year (RI_{m2}; from the 7th to the 12th months). Although the correlation between the relative monthly malaria incidence and the sum of the monthly precipitation values was negligible in case of the second part of the season, keeping the consistency of the model, precipitation was involved. RI is the product of the following equation:

$$RI = \sum_{i=1}^{6} RI_{m1} + \sum_{i=7}^{12} RI_{m2}, \tag{2}$$

where RI is the relative annual malaria incidence ,RI_{m1} is the relative malaria incidence (%) of the months of first half part of the year, and RI_{m2} is the relative malaria incidence (%) of the months of second half part of the year.

The monthly relative malaria incidence was described as a multivariable linear regression function of the T_m and P_m according to the gained coefficients of the multiple linear regression analyses in Eq.(3):

$$RI_m = a + \beta_1 T_m + \beta_2 P_m, \tag{3}$$

where RI_m is the relative monthly malaria incidence, a is a constant, $_{1,2}$ are correlation weights, T_m is the mean monthly temperature, and P_m is the sum of the monthly precipitation (mm).

Since the multiple linear regression analyses gave unstandardized and standardized coefficients, two groups of the models were built according to the used coefficients. $Model_a$ was built on the unstandardized, $Model_b$ on the standardized coefficients.

At the second step, we aimed to converse the output (the RI) of the relative annual model into the relative (R) values of the whole period. The conversation of the case numbers into incidence values was not considered to be necessary due to the relatively short period. Since the summer cases formed the more than 50% of the cases, the correlation between the summer precipitation and the summer malaria case number was analyzed. It was hypothesized that the ratio of the modeled summer case number according to the mean can be used as the multiplier of the annual case number:

$$R = RI_m \frac{N_{modeled\, summer\, malaria}}{N_{mean\, summer\, malaria}}. \quad (4)$$

2.5.2. The second approach

We used a simple linear model to gain correlation between the *NRA* values of the two *Anopheles* species and the mean monthly temperature of the period 1970–1999. Since the domain of the two sources of the temperature data was the same, we calculated the *NRA* values of the malaria mosquitos for the months of the period of 1927–1934. Finally, we compared the *RI* and *NRA* values for the studied period.

3. Results

3.1. The spatial occurrence of malaria in the 1930's

The historical malaria case data of 1936 shows that the former autochthon malaria cases in Hungary had three main focuses, the Upper Tisza region the northeast (*Fig. 3*.1), the river Drava in the southwest (*Fig. 3*.2a), and the south area of Zala hills, adjacent to the Drava valley (*Fig. 3*.2b). The endemic malaria focus in the Upper Tisza valley was partly related to the great Ecsed marsh. The central and northern parts of Hungary were malaria-free areas in 1936. The elevation of the Upper Tisza region focus is 101–118 m above sea level, in case of the southwestern former malaria focuses the topography is very heterogenic, the mean elevation is about 85–170 m, respectively (*Fig. 3,* upper map).The lower maps of *Fig. 3* show the most influenced autochthon malaria regions in 1936 according to the second military survey of the Habsburg Empire. Although the survey itself was carried out in the period from 1853 to 1873, the coverage with wetlands, oxbows, and marches did not differ notably from the conditions of the 1920's and 1930's. In the southern part of the Upper Tisza valley, the marshes formed the dominant potential aquatic habitats of *Anopheles* species, while in the northern part of the Upper Tisza and the Drava valley, these habitats were the oxbows and flood puddles.

3.2. The phenology of the autochthon malaria seasons from 1927 to 1934 in Hungary

The incidence of the autochthon malaria cases was the following: 1.17 (1927), 0.53 (1928), 0.25 (1929), 0.16 (1930), 0.53 (1931), 1.11 (1932), 1.33 (1933), and 2.29 (1934) per 10,000 inhabitants calculating with the population of Hungary according to the census of 1930 (8685109 inhabitants), respectively. The mean of the incidence values was 0.92, the variance was 0.4675, and the standard deviation was 0.7053 per 10,000 inhabitants. In the studied period, the malaria season in 6 cases had unimodal patterns (in 1927, 1928, 1929, 1930, 1931, and 1934), in 2 cases the season had bimodal feature (in 1932 and 1933). The maximum monthly case numbers were observed in May in 1 case (1931), in June in 5 cases (1927, 1928, 1929, 1930, and 1934), in August in 2 cases (1932 and 1933). In case of 1932, and 1933, a second seasonal peak was observed in September (*Fig. 4*).

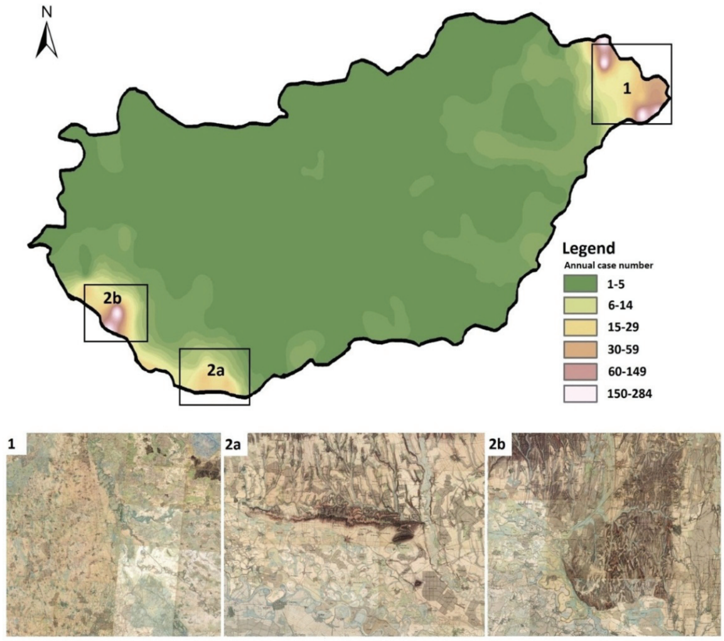

Fig. 3. Spatial distribution of the malaria cases in 1936. 1: Szatmár-Bereg plain, 2a: Drava Plain, and 2b: south Zala hills (upper map) are the most influenced autochthon malaria regions in the 1930's in the maps of the second military survey of the Habsburg Empire. Blue colors refer to the wetlands and rivers of the areas. **1**: the upper Tisza, **2a**: the Drava, and **2b**: the south area of Zala hills, adjacent to the Drava valley (lower maps).

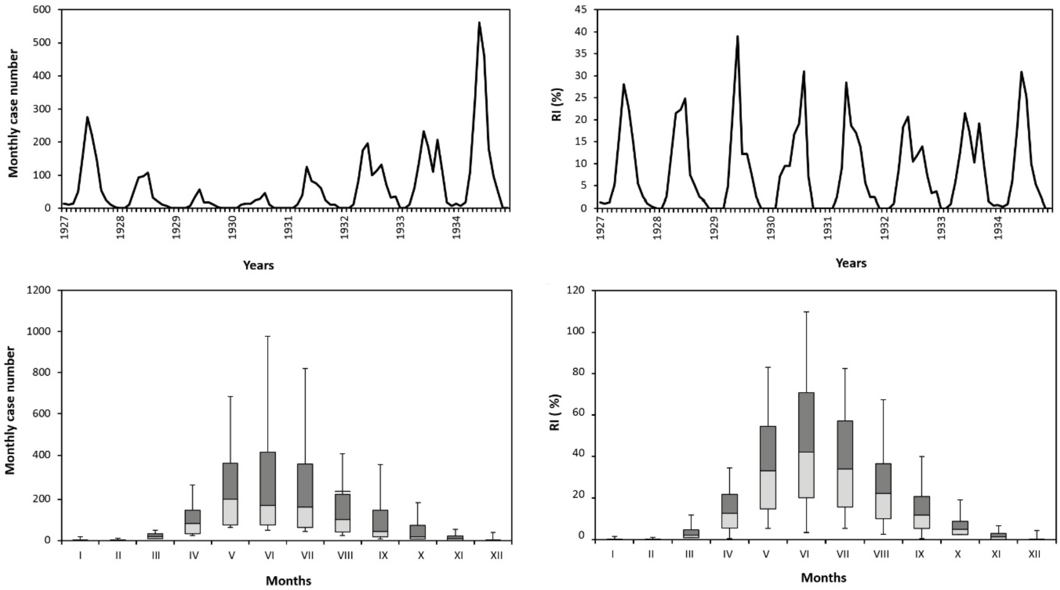

Fig. 4. Upper left: absolute monthly autochton malaria case numbers. *Left*: box and whiskers plots of the monthly case numbers of the years. *Upper right*: relative malaria incidence values. *Lower right*: box and whiskers plots of the annual proportion of the monthly case numbers of the years of 1927–1934 in Hungary.

The season started in March in general, although in 1929 and 1930, the malaria season started in April and May. The summer proportion of the cases according to the annual total case number were the following in the studied years: 1927: 65.69%, 1928: 54.54%, 1929: 63.41%, 1930: 66.66%, 1931: 49.59%, 1932: 43.23%, 1933: 49.00%, 1934: 66.21%. In general, the 57.29% of the annual cases occurred during the summer months in 1927–1934. The seasonal run of the malaria seasons show that the season started when the portion of the monthly malaria case number reached about the 5% of the annual cases. According to this criterion, the malaria season started in April except the year 1930, when the season started in March. The monthly mean temperatures, of the starting months were the following: 9.6 (1927), 10.3 (1928), 6.1 (1929), 6.2 (1930), 7.5 (1931), 9.5 (1932), 7.2 (1933) and 13.0 °C (1934). In general the start of the season occurred at 8.7 °C monthly mean temperature (SD: 2.37 °C). Using the same criterion for the end, the season ended in September in 1927–31 and 1934 and in October in 1932-33. The monthly mean temperatures of the last months were the following: 16.6 (1927), 15.9 (1928), 15.6 (1929), 16.8 (1930), 12.0 (1931), 11.9 (1932), 10.4 (1933), and 16.7 °C (1934). In general the end of the season occurred in 14.5 °C monthly mean temperature (SD: 2.6 °C). The absolute minimum temperature threshold of malaria in the begining and the end and of the season was about 5 °C mean monthly temperature (*Fig. 5 left)*. The peak season month occurred at the following mean temperature and monthly sum of precipitation conditions: 19.0 °C –76.7 mm (1927), 22.3 °C –21.3 mm (1928), 17.2 °C –79.0 mm (1929), 18.8 °C –92.7 mm (1930), 17.5 °C –42.1 mm (1931), 17.0 °C –52.5 mm (1932), 15.6 °C –102.4 mm (1933), and 17.7 °C –116.6 mm (1934) with a mean of 18.1°C (SD: 2 °C) and 72.9 mm (SD: 32.2 mm; *Fig. 5 right*).

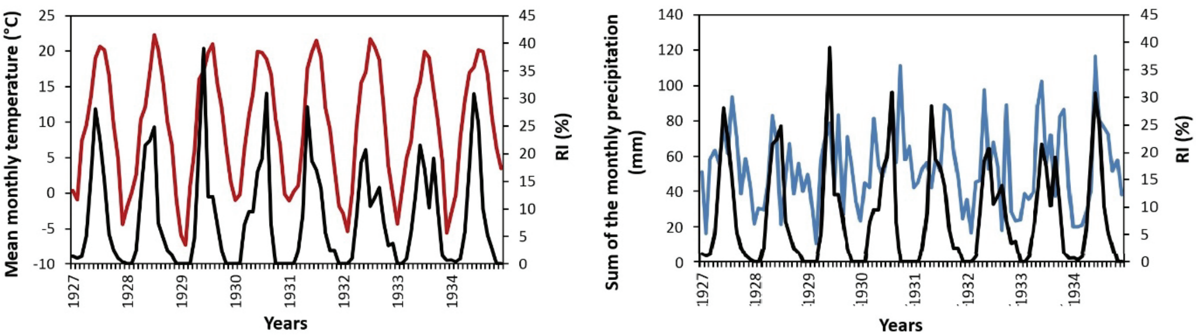

Fig. 5. Left: monthly relative malaria case number and run of the monthly mean temperature values. *Right*: the monthly relative malaria case number and run of the monthly sum of precipitation values.

3.3. Modeling approach 1

3.3.1. The first part of the year

Strong correlation was found between the *RI* and the mean monthly temperature values ($r^2 = 0.75$). We also found notable correlation ($r^2 = 0.5$) between the *RI* and the sum of the monthly precipitation in the first part of the year. The multiple r^2 of the regression was 0.78; the adjusted r^2 was 0.77 with a standard error of 4.7901. The value of the intercept is –2.5895. The correlation matrix and the gained regression coefficients can be seen in *Tables 1* and *2*.

Table 1. Correlation matrix of the results of the multiple regression in case of the months of the first half of the year; RI_{m1}: relative incidence of the months of first half in the year, T_m: mean monthly temperature, P_m: sum of the monthly precipitation

	T_m	P_m	RI_{m1}
T_m	1	0.656	0.866
P_m	0.656	1	0.71
RI_{m1}	0.866	0.71	1

Table 2. The gained regression coefficients; T_m: mean monthly temperature, P_m: sum of the monthly precipitation, *b*: unstandardized regression weights, *B*: standardized regression weights

	b	*B*	$B \times r_{TmPm}$
T_m	0.8904	0.7025	0.6081
P_m	0.1067	0.2487	0.1765

For the relative malaria incidence of the first six months of the year, RI_{m1}, the following equations can be written:

$$RI_{\mathrm{m1}} = -2.5895 + 0.8904T_m + 0.1067P_m, if\ T_{monthly}^{1927-1934} > 5\ °\mathrm{C} \quad (5.a)$$

$$RI_{\mathrm{m1}} = -2.5895 + 0.7025T_m + 0.2487P_m, if\ T_{monthly}^{1927-1934} > 5\ °\mathrm{C} \quad (5.b)$$

Eq. (5.a) is based on the unstandardized, while Eq. (5.b) is based on the standardized weights, where T_m is the mean monthly temperature and P_m is the sum of the monthly precipitation.

3.3.2. The second part of the year

Notable correlation was found between the *RI* and the mean monthly temperature values ($r^2 = 0.57$; *Fig.6 upper part*). In contrast, the correlation between the *RI* and the sum of the monthly precipitation was negligible in the second part of the season ($r^2 = 0.03$, *Fig. 6 lower part*). The multiple r^2 of the regression was 0.58; the adjusted r^2 was 0.56 with a standard error of 5.1746. The value of the intercept is 0.2607. The correlation matrix and the gained regression coefficients can be seen in *Tables 3* and *4*.

Table 3. Correlation matrix of the results of the multiple regression in case of the months of the second half of the year; RI_{m2}: relative incidence of the months of first half in the year, T_m: mean monthly temperature, P_m: sum of the monthly precipitation.

	T_m	P_m	RI_{m2}
T_m	1	0.313	0.758
P_m	0.313	1	0.168
RI_{m2}	0.758	0.168	1

Table 4. The gained regression coefficients; T_m: mean monthly temperature, P_m: sum of the monthly precipitation, *b*: unstandardized regression weights, *B*: standardized regression weights

	b	*B*	$B \times r_{TmPm}$
T_m	0.7727	0.7818	0.5924
P_m	–0.028	–0.0771	–0.0129

For the relative malaria incidence of the first six months of the year, RI_{m1}, the following equations can be written:

$$RI_{\mathrm{m1}} = 0.2607 + 0.7727T_m - 0.0280P_m, if\ T_{monthly}^{1927-1934} > 5\ °\mathrm{C} \quad (6.a)$$

$$RI_{\mathrm{m1}} = 0.2607 + 0.7818T_m - 0.0771P_m, if\ T_{monthly}^{1927-1934} > 5\ °\mathrm{C} \quad (6.b)$$

Eq. (6a) is based on the unstandardized, while Eq. (6b) is based on the standardized weights, where T_m is the mean monthly temperature and P_m is the sum of the monthly precipitation.

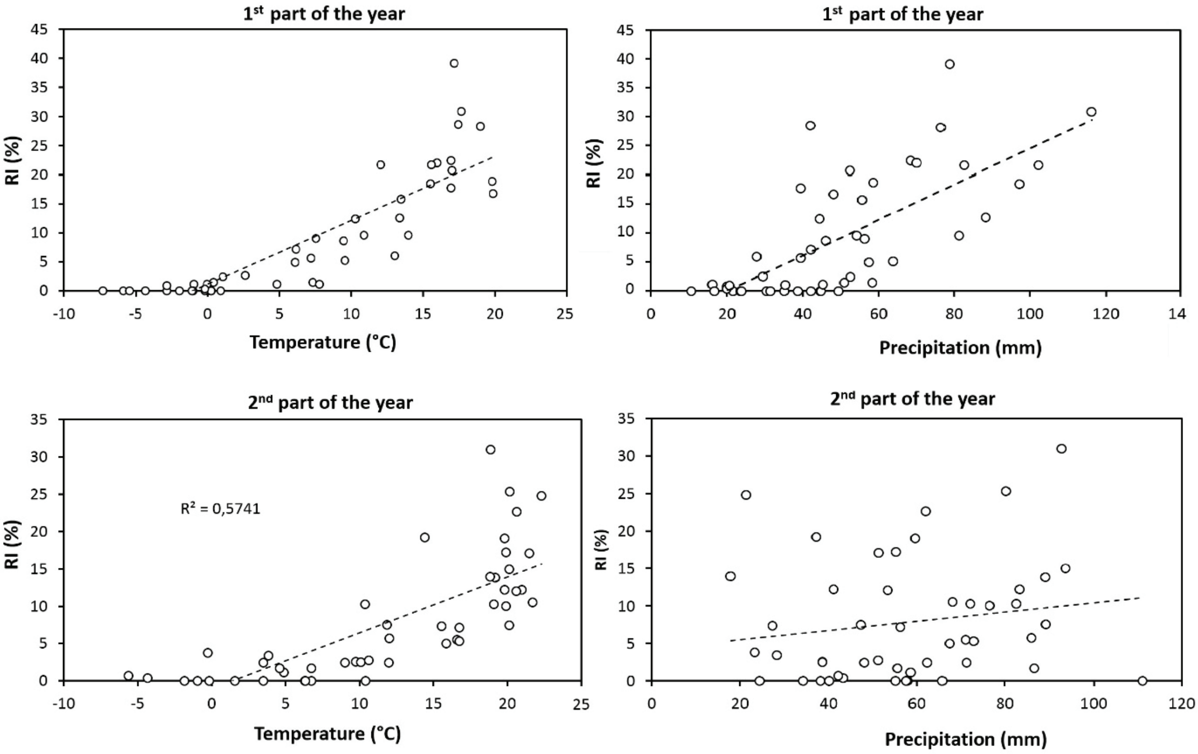

Fig. 6. Upper left: correlation between the monthly relative malaria case number and the run of the monthly mean temperature values in the first part of the year. *Upper right*: correlation between the monthly relative malaria case number and the run of the monthly sum of precipitation values. *Lower left*: correlation between the monthly relative malaria case number and the run of the monthly mean temperature values in the second part of the year. *Lower right*: correlation between the monthly relative malaria case number and the run of the monthly sum of precipitation values.

3.4. Modeled relative seasons

3.4.1. Correlation between the summer precipitation and the number of the summer malaria morbidity

Significant correlation was found between the sum of the summer precipitation and the summer malaria case number:

$$N_{malaria} = 23.437e^{0.0125\times P_{\Sigma ms}}, \tag{7}$$

where r^2=0.58 and p=0.3557. Results of the Eq. (7) are drawn in *Fig. 7.*

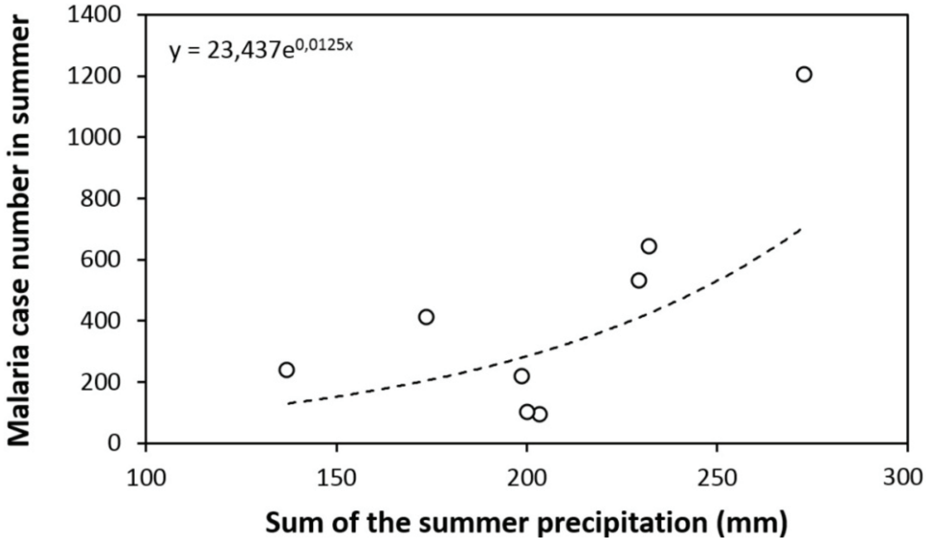

Fig.7. Correlation between the sum of the summer precipitation and the malaria case number in summer

Using unstandardized weights, the sum of the absolute errors is 3.7109, in case of standardized weights it is 4.3859 (*Fig.8 top*). The 12.5% of the malaria case numbers of the period of 1926–1934 occurred in a given year. The ratio of the real case number and the mean of the period were the following: 1927: 1.24, 1928: 0.38, 1929: 0.86, 1930: 0.83, 1931: 0.82, 1932: 0.60, 1933: 1.20, 1934: 2.06. The correlation of the relative malaria cases and the results of the model using unstandardized weights according to the linear and polynomial approximations are $r^2 = 0.6487$and $r^2 = 0.7247$, while in case of standardized weights these values are $r^2 = 0.311$ and $r^2 = 0.341$, respectively. The sum of the absolute errors in case of unstandardized weights was 70.78, in case of standardized weights 82.55, respectively. Although the model somewhat overestimate the relative case number of 1929 and 1930, it predicts the higher season peak values well in case of 1927, 1933, and 1934 (*Fig. 8* bottom).

3.5. The second modeling approach

3.5.1. The temperature dependent seasonality of Anopheles messeae in Hungary

The main part of the mosquito seasons of *Anopheles messeae* started in April and ended in October, however, a few numbers of individuals were collected also in March and November. The main parts (91%) of the female Anopheles maculipennis complex individuals were collected in months with more than 12 °C average temperature (*Fig. 9*).

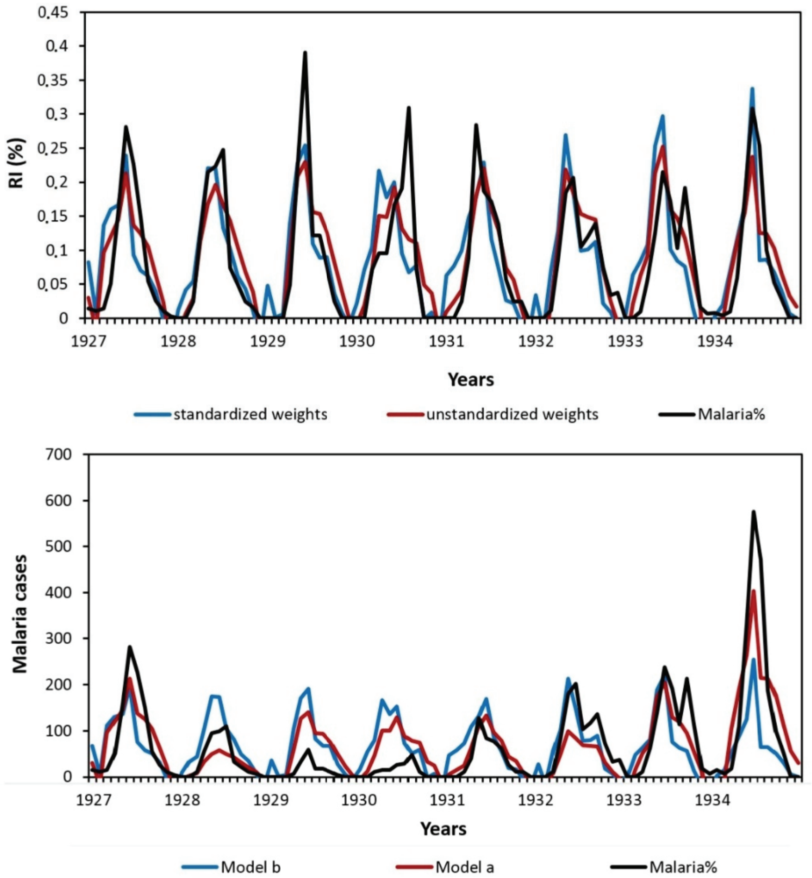

Fig. 8. Top: The observed and modeled relative autochthon malaria seasons according to the unstandardized and standardized weights. *Bottom*: the observed and modeled absolute autochthon malaria seasons according to the unstandardized and standardized weights.

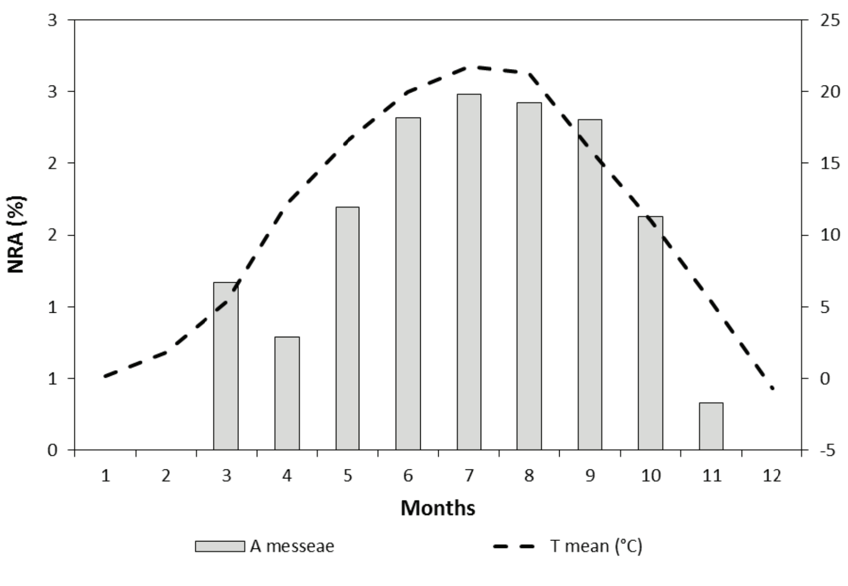

Fig. 9. Seasonality of *Anopheles messeae* and the monthly mean air temperature in the period of 1970–1999.

In case of the normalized relative annual numbers of *Anopheles messeae*, strong significant correlation were found with the monthly mean temperature ($r^2 = 0.89$, $p < 0.0001$). According to the correlation between the monthly mean temperature and the summarized relative (%) number of the collected female individuals of *Anopheles messeae* the following equation was gained:

$$NRA = 0.1147T_m + 0.0117, \quad (8)$$

where *NRA* is the normalized relative abundance (%) and T_m is the monthly mean temperature (°C).

3.5.2. The reconstructed Anopheles messeae seasonality in 1927–1934

Eq. (7) was replayed for the monthly temperature values of 1927–1934 and it was depicted with the relative (%) number of the observed autochthon malaria cases (*Fig. 10*).

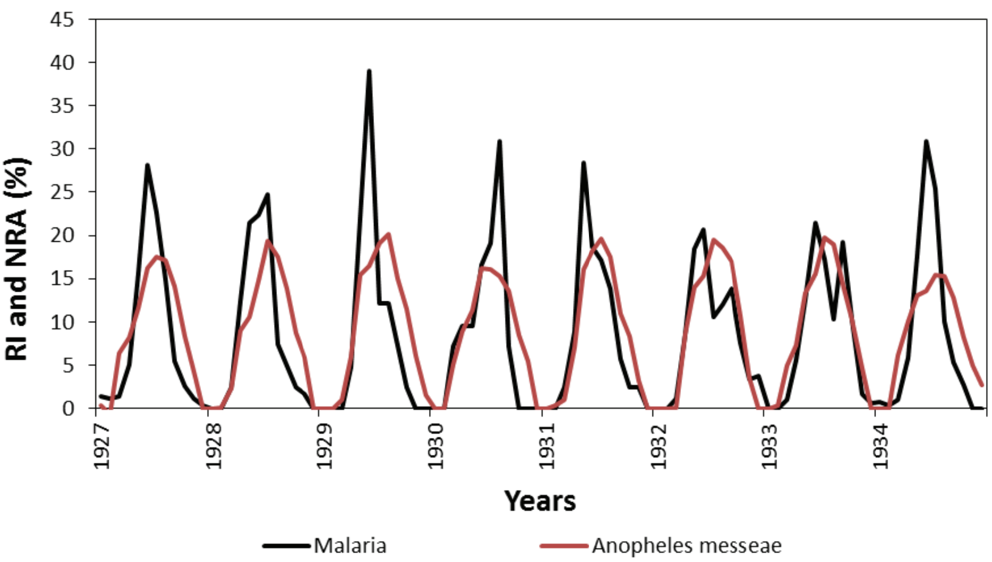

Fig. 10. The observed normalized relative malaria incidences and the modeled relative mean abundance values of *Anopheles messeae.*

4. Discussion

The reanalysis of the historical malaria data in the central part of Europecountry provides a unique feasibility to gain confident data about the former seasonality of the autochthon malaria in a temperate region of Europe. Historical maps show that the autochthon malaria cases occurred primarily in wetland areas or river basins and not at lakes as lake Balaton. The spatial occurrence of the cases was linked to two major aquatic habitats: marshes and the floodplain of the river valleys. It can be stated that the cases are accumulated in the water collecting area of medium-sized rivers as river Tisza, Drava, or river Körös. The salt lakes of the Danube-Tisza interfluve, the rivers and creeks of the Transdanubian mountain range were not affected by malaria in the studied period. It is plausible that areas with the extent presence of barely or not regulated river sections had the greatest risk for malaria endemicity. Although, the most notable focus in 1926–1934 were linked into south-western and north-eastern parts of Hungary, a major malaria endemic focus is plausible according to the historical records and the FY A Duffy blood group allele in the great plain of Hungary and the south parts of the Carpathian Basin. The recent presence of the local low FY A allele frequency in south Hungary, north Serbia, Vojvodina, and south western Romania (see *Howes et al.,* 2011) may refer to the former presence of a long-persistent malaria endemic area in the south-eastern part of the Carpathian Basin, since malaria resistance is linked to the Duffy-negative phenotype against *Plasmodium vivax* infection. In contrast, the recent distribution of sickle haemoglobin (HbS) allele frequency shows that *Plasmodium falciparum* caused malaria was endemic only in the South Balkan in the historical times (see *Piel et al.,* 2010) and it lacked from the Carpathian Basin which is consistent with the known sensibility of the parasite for cold conditions.

In the historical times, up to the middle of the 20th century, *Plasmodium vivax* was the predominant cause of malaria in the temperate parts of Europe, and *Plasmodium falciparum* persisted only in the Mediterranean coastal regions of the old continent (*de Zulueta*, 1994). The possibility of the overwintering of *Anopheles* mosquitos is not theoretical, since the lethal temperature for some members of the genus is below –15 °C (*Wallace* and *Grimstad*, 2002). It is plausible that relatively cold-resistant *Plasmodium vivax* was the main infectious agent of malaria in Hungary (*Szénási et al.*, 2003), which *Plasmodium* species outside of Africa recently accounts for more than 50% of all human malaria cases (*Mendis et al.*, 2001). *Plasmodium vivax* infection is a re-emerging malaria disease in the eastern part of the Mediterranean basin (*Andriopoulos et al.*, 2013). The occurrence of malaria is strictly limited by precipitation and temperature thresholds. For example, the temperature threshold of the digestion of blood meal in case of *Anopheles maculipennis* is 9.9°C, while the threshold temperature of the extrinsic incubation cycle of *Plasmodium vivax* is 14.5-15°C (*Martens et al.,* 1995).

The absolute minimum limits of the start and the end of the malaria season were about at the 5 °C mean monthly temperature values which are lower than the recent known, at least 14.5 °C ontogeny threshold of the *Plasmodium* species (*MacDonald,* 1957). It is in accordance with the gained, also about 5 °C minimum activity threshold of adult female *Anopheles messeae* individuals. These observations raise the possibility that the former malaria strains were much cold tolerant in the temperate regions of Europe – similarly to the vectors - than in case of the recent genetic lines of the tropical/subtropical regions.

In contrast to the recent tropical and subtropical examples, malaria in the temperate, continental climate of Hungary had mainly unimodal seasonality with a 3 to 4 months winter diapause. It is also notable that the also mosquito-transmitted, in Hungary recently endemic West Nile fever has a late summer - early autumn peak season with a very low and negligible case number in June (*Trájer et al.*, 2014). The clear difference of the seasonality of the two mosquito-borne diseases could be explained by the different reservoirs, which are birds in case of West Nile fever and humans in case of malaria. While active mosquitos can transmit malaria directly from human to human, West Nile fever epidemics can only break out after that the amount of the circulating virus reaches a given threshold prevalence level in the mosquito population. It should be added, that West Nile virus can overwinter in their mosquito vectors (*Nasci et al.*, 2001). It is somewhat surprising that while the mosquito population could increase during the summer season, the malaria incidence reached its annual peak already in early summer in most of the years. It is possible that infected mosquitos could overwinter in an increased number within the population, since *Plasmodium* infected mosquitos have increased longevity (*Vézilier et al.*, 2012).The observed June maximum in the majority of the years and the early and fast increase of the former malaria season support the hypothesis, that the infected overwintering female imago malaria mosquitos played a notable role in the transmission in the studied former autochthon malaria cases. Another possible interpretation of the former early outbreak and peak of malaria is the role of humans as reservoirs living in wetland areas, since the incubation period varies between 7 and 15 days in general, and the long incubation period can take several months (sometimes years) in case of *Plasmodium vivax* caused malaria without any effective treatment (*ECDC Epidemiological update,* 2013).

The found, 3 to 4 months winter diapause period of the potential vector mosquitos in the cold half of the year led the public health services to the successful intervention. *Szénási et al.* (2003) described that the infected people were re-treated in the spring of the next year, which practice was one of the most important cause of the eradication of malaria in Hungary.

Bismil'din et al. (2000) and *Kuhn et al.* (2003) concluded that there are strong link between the re-emergence of malaria and non-climatic factors. Climate change alone can be insufficient to trigger the reappearance of the autochthon malaria in an area. We found that precipitation is an important determinant factor of the relative incidence in the first half part of the year, and it influences significantly the summer incidence. This finding is in accordance with that rainfall has significant effect on the number of Anopheline vectors as e.g. *Anopheles gambiae* (*Koenraadt et al.*, 2004). We found that in the second half of the year, precipitation had no notable effect on the malaria incidence. Temperature played important role in the determination of the notable points (the start and the end) of the season although the absolute case number or the possible bimodality of the season was rather determined by the summer precipitation patterns. The effect of the summer precipitation sum above about 200 mm increased rapidly the summer, and consequently, the annual incidence of malaria. The gained similarity of the observed relative malaria and the modeled relative vector seasons confirms the former observations and hypotheses that the native members of Maculipennis complex, e.g., *Anopheles messeae* were the vectors of the malaria in Hungary. It can be concluded that our seasonality model can be well-adapted for the recent *Plasmodium vivax* malaria endemic areas of the world.

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