The Expected Impacts of the Anthroponitic Global Climate Change on the Potential Human Vector-borne Diseases in the Carpathian Basin and Europe

Ph.D.Thesis

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INTRODUCTION

The topic of my research was a subfield of climate change which is one of the most important, actual ecological problems of the globalized world. The increasing trend of the incidence of vector-borne diseases due to global warming, long-distance transport and travelling is a hot topic within Environmental Health and a specific consequence of globalization and the modern industry.The Hungarian literature relatively rich with publications deal with vector-borne diseases as Lyme borreliosis, tick borne encephalitis, but practically haveregional literature about the potential influence of climate on vector-borne diseases absent while this topic is a “hot potato” in the international literature.Emerging diseases as West Nile fever, canine leishmaniasis and human dirofilariasis cases in Hungary or Dengue and Chikungunya fever cases in the neighboring Croatia drew my attention to the importance of this topic. According to the foreign literature and the present range of the vector it is very likely that the Asian tiger mosquito will be the resident element of the Hungarian mosquito fauna to the mid of the 21stcentury. Because of the effect of climate change were verified on the climate of Hungary, these environmental health threats deserves an overall and wider investigation.The explanation of the high climate-sensitivity of the arthropod vectors is their ectothermic body temperature control and the high body surface/volume quotient. The rising seasonal average temperature can elongate the vegetation period and consequently the activity of arthropod vectors, increase the annual number of the generations and grow the size of their populations. In the case of many cold sensitive taxon this change will create the potential to be endemic in the Carpathian Basin.

AIMS

My aims were to study the effect of the influence of the changing seasonal and human activity patterns and the regional climate differences on the seasonal incidence of Lyme disease in regional and country level. Furthermore I modeled the potential expansion of eight important vector *Phlebotomus* species*and the Aedes albopictus* Skusemosquito, and the potential future geographical occurrence of twoimportant vector-borne diseases (leishmaniasis and West Nile fever) for the 2011-2040 and 2041-2070 periods in Hungary based on the climate suitability of the vectors in the case of the recent and projected climatic conditions using Climate Envelope Modeling which was run on the REMO climate model.

The specific question assumptions were the follows:

A) The influence of the mean temperature and other factors onthe incidence of Lyme borreliosis:

1.What was the trend of the Tick Borne Encephalitis, Lyme borreliosis and West Nile fever?
2.Does the Lyme season start have significant correlation with the start of and length of the season?
3.Why did increased the Lyme incidence and whether it was the consequence of a climate change or other factors?

4.Are there so notable regional climate differences within Hungary which can modify significant differences in the Lyme season?

5.Whetherdoes the weekly average temperature an essential predictor of the weekly incidence patterns of the Lyme season?

6.What are the reasons of the observation, while the Lyme season is unimodal in Hungary;the *Ixodes ricinus* tick season has a bimodal seasonality both in the other parts of Europe and Hungary?

7. How does human outdoor activity affect the run of the LB season?

8. Are there any correlation with the human outdoor activity and the mean ambient temperature?

B) The factors which determine the spatial-temporal occurrence of West Nile Disease:

1.Does have West Nile fever a stable geographical pattern in Hungary by year to year or the virus of West Nile fever is introduced by year to year to Hungary by birds?

2.What istheaverage weeklytemperature limit atthe outbreak of West Nilefevercases in Hungary?

3.Does have a correlation between the deviation of the mean of the annual West Nile fever numbers and the water level changes of the rivers in Hungary?

4. Climatic, geographical or bird migration patterns influence dominantly the European spatial occurrence of West Nile Virus?

C) The possibility of the emergence of new vector-borne diseases and its vectors in the Carpathian Basin due to Climate change:

1.Will the Asian tiger mosquito (*Ae. albopictus*) become the part of the mosquito fauna in Hungary to 2070 in Hungary and which areas?
2.Which potential vectors of leishmaniasis will conquest the Carpathian basin and the temperate regions of Europe 2070?
3.Do plant and animal species are good climatic indicators? Can we combine these indicators with each other?

METHODS

The weekly Lyme, West Nile fever data were gained from the EpidemiologicalSurveillanceSystem of Hungary. The weekly temperature data for the purpose of seasonal investigations and for modeling and studies in regional level were gained from the European Climate Assessment and Dataset. The climatic data for the Climate Envelope Modeling (CEM) purposes in the case of *Leishmania infantum*Nicolle, West Nile fever, *Ae. albopictus*, the studied eight*Phlebotomus* species and the climate indicator plant's potential future distribution were gained from the REMO model which was based onthe ECHAM5 global climate model and the IPCC SRES A1B climate scenario and has a 25km resolution.The distribution data of three Mediterranean ligneous specieswere gain mainly from the EUFORGEN database.The hydrological data of the river Tisza in the period of 2007-2012 were retrieved from the National Water Warning Network of Hungary. The population number of Hungary for the period 1998-2012 and the number of camping guest nights for the period of 2008-2012 were gained from the Central Statistical Office (KSH).The European distribution patterns of West Nile fever and leishmaniasis, the geographical range of the studied 8 *Phlebotomus* species were gained from the VBORNED dataset of the European Center of Disease Control.The Hungarian WNF data were derived partly from the VBORNETdataset, the Epinfo journal and from a publication of Krisztalovics et al. (2008).The ESRI ArcGIS 9.3 software was used for the preparation, management and editing of spatial and climatic data, modeling and presents the model results. The management of climatic data and preparation of the expressions for modeling were assisted by Microsoft Excel 2010 program and PAST statistical analyzer software. A model was built to analyze the differences between the observed unimodal run of the annual LB incidence curve and the bimodal activity of *Ixodes* ticks in Hungary and to reconstruct the incidence curve in the studied period. This model was based on the mean ambient temperature and the human outdoor activity was used for creating histograms (probability density function) and the cumulative distribution function of the climatic parameters, getting the percentile values of the parameters, and creating some statistical analysis of the model results.

For the distribution modeling, Climate Envelope Modelingwas applied.In the model I used monthly mean temperature, the monthly minimum temperature and monthly precipitation. These values were averaged for the period of 1960-1990, 2011-2040 and 2041-2070.

RESULTS

The highest LB incidence (23.04/100,000) were observed in 2010, the lowest (9.92/100,000) in 1999.Inthe period of 1998 - 2010 observed the 53.18% of the cases inthe 24th and the 36thweeks.The average LB incidence rate per 100.000 inhabitants was 11,597 in 1998-2003 and 15,268 in 2004-2010. Inthe studied period LB was the only disease which showed a significant increasing trend (p=0.0163).

According to theprevious observations I used the first week with 10°C mean ambient temperature which was followed by weeks with mean temperature warmer than 7–8°C as the onset of spring. During 1998-2010, this indicator day of the onset of spring shifted from the 113th day to the 89th day of the year defined by the linear regression model (p=0.0041), meaning a shift of 24 days. The last spring day with a minimum temperature under 0°C shifted from the 68th day to the 55th day by the linear regression. Only the year 2005 fell out of the 1 SD intervals. In the period of 1998–2010, this indicator week shifted from (the onset of the LB season) shifted from the 17th to the 13th week. A trend of -2.4 days per year was observed (p=0.0144). According to the linear trend, the expected start of the LB season of the years 2001 and 2008 fell out of the 1 SD intervals. I plotted the start of the vegetation period according to the function of the start of the LB season and we found a significant correlation (p=0.0177).

While the 47% of the annual LB case number occurred between the 15th and the 28th weeks in 1998-2001, in the period of 2007-2010 observed the 58% of the annual case number (9.85 per 100,000) in the same part of the year. Between 1998-2001 and 2007-2010 the difference between the mean annual case numbers was 5.81/100.000, so the 79% of the increment of the LB case number was the consequence of the increased case number of the 15-28th weeks. Analyzing the changing LB incidence rate of the 52 weeks of the year it was found that the pattern of the increment of the weekly LB cases were not homogenous, most of the increment occurred in the 15-28th weeks with significant trend in the 15-24th weeks with an unimodal maximum. This kind of change covered the 79% of the increment and occurred simultaneously with the above described shift of the LB season and spring. I found the greatest increasing trend in the case of the 23-25th weeks; e.g. in the 23rd week the linear coefficient was 6.64 and the significance of the increment $p=0.0002$. The curve of the linear coefficients run parallel with the annual LB curve to the 24th week, but the annual LB curve reached its maximum in not the 24th but in the 28th week.

In the case of the 3 analyzed southwestern counties the mean weekly temperatures of the winter months fluctuated near or above 0°C. In contrast in the 2 north and northeastern counties the mean weekly temperatures in winter were always below -1 or -2°C. I observed the greatest differences inthe mean temperatures in winter, late autumn and early spring, which differences sometimes reached the 1 to 1.5°C value. The mean weekly temperatures of the two regions met in the 13th week and from this time the difference between the weekly temperatures of the two regions were negligible. In the southwestern region the mean temperature of the winters was 1.2°C, in the northern counties this value was -0.3°C. The mean temperature of the winters changed simultaneously by year to year in the regions ($R^2=0.9554$). The first weeks without temperatures below 0°C started 2 weeks earlier in the southwestern region. By the above used definition of the start of spring I found that this point of the week shifted by 2.5 weeks into the earlier part of spring in the NE region (p=0.0172). Comparing the mean weekly LB incidences of the regions I found that the peak point of the LB season occurred 3 weeks earlier than in the NE counties (SW: 28th week, NE: 25th week) and I found a similar (3 to 4 weeks) difference in the run of the decreasing phase of the annual LB incidences. The start of the spring season also started earlier inthe SW region. Dividing the time scale into 2, same long periods (1999-2004 and 2005-2010) it was found that while the cumulative LB incidences showed a similar increment both of the regions (NE: 25.68%, SW: 30.55%) in the NE region the annual peak occurred one week earlier in the later period and in the SW region the change didn't reached the 1 week difference. Booth in the SW and NE counties the increasing trend of the LB case number were significant (p=0.0065 and p=0.0471), but in the SW counties the trend was much more continuous, since in the NE counties the incidence started to increase more rapidly only in the last 3 years of the period.

Assuming that the temperatures in May and June are very important in the life cycle of ticks, I studied the association between LB incidence and the mean temperature of these months. I divided the LB seasons into two groups according to positive or negative deviation from the mean temperatures of May and June for the 13 years. In the warmer years, the mean temperature of May and June was 19.02°C, and in the colder years it was 17.06°C, so I observed a 1.96°C difference between the late spring and early summer mean temperatures of colder and warmer years. In the years with a warmer late spring-early summer, the LB incidence curve reached the annual maximum point 2-3 weeks earlier and the descending phase of the curve started earlier.I found a strong association (R_0^2=0.7094, R_1^2=0.7118, and R_2^2=0.6859 between the weekly mean temperature values and the weekly relative (annual %) of the LB incidences using 0, -1, -2 weeks lags. Human activity in the nature (the number of the recorded camping guest nights) also showed a strong association with the mean temperature (R^2: 0.9329) except time of the summer holiday (from min-June to the late August). I calculated the observed/calculated ratio (multiplier) of the irregular week pairs to characterize the effect of the summer holidays on human activity.

The results of exponential regression is as follows: without HM with 0, -1, and -2 lags the calculated R^2 values of the regression was 0.7094, 0.7118, and 0.6859, respectively. With HM with 0, -1, and -2 lags the calculated R^2 values of the regression were 0.6708, 0.6617, and 0.6196, respectively. According to the model I reconstructed the LB seasons using the known human temperature-dependent activity in the nature and the temperature data of the 15 years. The R^2 of the three different approach were between 0.6247 - 0.6569. Autochthonous WNF cases are mandatory reported from Hungary from 2003.The changing WNF incidence rate didn’t showed any significant trend and the geographic distribution of the cases showed that the focuses of occurrence changed from year to year. In 2008 most of the WNF cases between May and September occurred mainly in riverside areas and wetlands mainly in the river bank of Tisza.The WNF showed a clear seasonality. About the ¾ of the cases occurred in August and September. In most of the years the season started in late July (e.g. in the 30th week in 2010) or August (e.g. in 2007, 2008). No cases were recorded between December to March and in June.

The averaged ambient weekly temperature of the 4 previous weeks before the first WNF case in 2008 was 21.6°C, 23.82°C in 2010 and 23.65°C in 2012. 78.6% of the cases in the period of 2004-2010 and 2012 occurred in August and September. In 2008 and 2010 the WNF cases terminated, when the weekly mean temperature dropped below 14.3-13.7°C, in 2012 after the penultimate case the ambient temperature dropped below 13.7°C and the last case occurred, when the mean temperature was 7.5°C. From the first stable week with 15°C or more ambient temperature to the first WNF case 19 weeks passed 2008, 14 in 2010 and 13 in 2012. I selected the weeks of the mean ambient temperature more than 15°C as the season of *Culex* mosquitoes. According to these observations we practically handled the period of May to September as the main time of the *Culex* season. The *Culex* season started in the 18th week of the year (in mid-April) in 2008 and terminated in the 37th week in the first quarter of September. In 2008 the observed WNF seasons 2 weeks exceed by 2 weeks the theoretical *Culex* season.The recent occurrence of visceral WNF is mostly restricted to the East Mediterranean areas and Eastern Europe. The model predicted the potential occurrence of WNF with the sporadic cases in the reference period to be greater than the observed current occurrence. Considering the current occurrence and the model result, East-Southeast Europe and the Carpathian Basin are highly vulnerable areas.

The predicted potential distribution of the aggregation of the Asian tiger mosquito, *Aedes albopictus*will contain the Mediterranean; most of the territories of Italy and some regions of the Balkan, and Spain with Mediterranean climate are included in the observed distribution. The modeled potential distribution seems to be greater in Western Europe and in the North Balkan and some parts of the Carpathian Basin. In the near future period expansion is predicted mainly in France, Spain, Croatia, Serbia, and Hungary. In the period of 2041-2070 significant expansion is projected in the Northern parts of France.According to the model the future potential distributions of the most important European *Phlebotomus* vectors show greater differences and none of the species fill their whole potential habitats. The main limiting factors are the winter minimum temperature, the summer mean temperature and surprisingly the summer precipitation which is an important limiting factor in the Atlantic areas. It is very likely that the recent distribution of the species is the consequence of a historical geographical isolation due to the cold mountainous and continental climate areas. *P. ariasi*Tonnoir and *P. perniciosus*Newstead have the greatest expansion potential in Western Europe and France may have a key role in the northern expansion of *P. ariasi* and *P. perniciosus*. In this aspect, Hungary may have a less significant role, while the surrounding mountains and the continental winters of the neighboring countries can inhibit the further northern expansion of sand flies. The model findings can explain the observed distribution of sand flies in southern Hungary and the autochthonous presence of the parasite. Climatically the recent presence of a *P. perniciosus*, *P. neglectus*Tonnoir és *P. papatasi*Scopoliin Hungary is comprehensible and it is very likely that in the near future the range of these species will reach the northern border of Hungary.

In accordance with the literature *P. ariasi* and *P. perniciosus* has the greatest potential for expansion and in the end of this century these species will reach the southern coastline of the Baltic Sea (49°N-59°N-ig).*P. papatasi* has a greatest adaptation capacity to expand under more continental climates than *P. similis* and *P. sergenti*Parrot and it is likely that *P. papatasi* will conquest the Carpathian basin in the 21st century.According to the cluster analysis of the ecological requirements of the species *P. ariasi*has a greater distance both ecologically and filogenetically (according to the literature) from the other species. It in accordance with the literature since *P. ariasi* is live in the Mediterranean mountainous areas while *P. perniciosus* colonize the coastlines of the western basin of the Mediterranean Sea.According to the CEM model Hungary seems to be a vulnerable area inthe aspect of leishmaniasis because the potential future climate of Hungary seems to be suitable for *P. ariasi*,a *P. neglectus, P. perfiliewi*Parrot, *P. perniciosus, P. tobbi*Adler and Theodor, while in the case of Germany and in general in the oceanic and northern areas of Europe „only" two species have a potential chance for expansion without the Benelux states where the summers are relative cold and rainy (>80-90mm precipitation in August). Using the activity data of sand flies of the relevant literature this activity period is predicted to elongate for the 2070's by 1 to 2 months in Hungary.The aggregated, observed and modeled distribution - and the climatic requirements - of the studied Mediterranean ligneous plantsshow significant resemblance with those of the studied *Ixodes* species. Hence it can be stated that these three plant species can serve as climatic indicators of the vectors of *L. infantum*. The predicted future distributions are not much more expanded than in the reference period. Expansion seems to be occurred in North-western France, South England and the Carpathian Basin. These results may confirm the co-use of different indicator taxa to verify the confidence of the models.

Theses

1.In the period of 1998-2010 the LB incidence doubled in Hungary which changes showed significant trend. The imported West Nile and TBE cases didn't show significant trend, but it is notable that WNF showed an increasing trend from 2003.

2.The start of LB season showed a significant correlation with the start of spring.

3.The start of spring shifted into the earlier periods of spring by 3 to 4 weeks and this change was parallel to the increment of the LB cases, so it is very likely that the increasing LB case incidence was the consequence of this change.

4.It is likely that one of the most important potential effects of climate change on LB can be the increase of the incidence due to the shift of spring and the lengthening of the vegetation period.

5.The temperature differences between the SW and NE counties have demonstrable influence on the seasonality of LB: the season starts earlier in the colder regions than in the SW counties and in the SW the season peak occurs later than in the NE counties and there is s 3 to 4 week visible difference in the run of the regions.A similar effect was found if the difference of the LB seasons was studied between the years with milder May and June periods than the average and with colder ones. According to the regional analysis it is possible that climate change affected in the last 13 years period more the colder region which manifested mainly in the shift and the peak of the LB season. It can be stated that the differences between the regional climates and the differences in the temperature patterns of late spring and early summer have a great influence on the LB seasonality: the start, the peak and the run of the season.

6.According to the model outcomesinthe critical spring-early summer period weekly mean temperature play a key role in the formation of the LB incidence run. In summer, human outdoor activity has a greater effect than the meteorological conditions on LB incidence. In this period the run of LB is mainly the consequence of the cultural, socio-economic conditions and these effects can mask the decreased seasonal activity in the mid- and late summer of *Ixodes* ticks.

7.Referring to the above mentioned facts LB seems to be an adequate and sensible human climate health indicator of climate change which is in accordance of the recommendations of the international literature.

8.It is likely that in the studied period (2003-2012) WNF doesn’t have a permanent geographic occurrence in Hungary; it is more likely that birds re-introduce the parasite by year to year.

9. The Hungarian WNF cases reach its maximum in late summer and early autumn and most of the cases the minimum required temperature is 15°C to development of *Culex* mosquitoswhich is in accordance with my observations that most of the WNF cases occurred above of 15-20°C. It is possible that mosquito populations require a minimum time to become infected by the migrating birds of enough numbers to have the chance to cause human infections.

10. The WNF case number in in correlation with the fluctuations of the water level of Tisza, but maybe due to the low amount of the years the correlation doesn't reach the significance level.

11. The recent distribution of WNF suggests that climate, topographically the run of the rivers, floods, the migrating routes of birds and the annual ontogeny of *Culex* mosquitoes together determine the occurrence of the disease. Most area of the European WNF occurrences are attached to the migration routes of birds from Africa. Continental climate it seems to be more suitable for the potential vector mosquitoes.

12. The invasion of *Ae. albopictus* is expected in Hungary for the end of the 21st century and Pannonia is predicted to be the most involved.

13. For the 21st century the northward expansion of 6 *Phlebotomus* species are expected from the studied 8 in Europe. Hungary is seems to be vulnerable area in contrast with England and Germany where only the invasion of *P. ariasi* and *P. perniciosus* are expected.The model outcomes are in accordance with the recent range of the sandfly species, the real distributions can be the consequence of the historical geographic barriers. Several species primarily live only in the western or in the eastern part of the Mediterranean basin. My findings show a similar, but more moderate picture about the future expansion of *Phlebotomus* species.

14. The geographicalpattern of *Phlebotomus* and Mediterranean plant species living in a similar habitat is very similar. It is very likely that climate models can produce more reliable outcomes with the use of different (plant and animal) indicator species. In the future could be useful to apply both plant and animal indicators in the CEMs.

LIST OF THE OWN PUBLICATIONS RELATED TOTHE THEME OF THIS DISSERTATION

Original articles in English

1. Trájer A, Mlinárik L, Juhász P, Bede-Fazekas Á. (2014) The combined impact of urban heat island, thermal bridge effect of buildings and future climate change on the potential overwintering of Phlebotomus species in a Central European metropolis.Applied Ecology and Environmental Research,12: 887-908.

2. Trájer A, Bede-Fazekas Á, Bobvos J, Páldy A. (2014) Seasonality and geographical occurrence of West Nile fever and distribution of Asian tiger mosquito. Időjárás-Quarterly journal of the Hungarian Meteorological Service, 118: 19–40.

3. Trájer A, Bobvos J, Páldy A, Krisztalovics K. (2013) Association between incidence of Lyme disease and spring-early summer season temperature changes in Hungary-1998-2010. Annals of agricultural and environmental medicine: Annals of Agricultural and Environmental Medicine, 20: 245-251.

4. Trájer A, Bobvos J, Páldy A, Krisztalovics K. (2013) Regional differences between ambient temperature and incidence of Lyme disease in Hungary. Időjárás-Quarterly journal of the Hungarian Meteorological Service, 117:175–186.
5. Trájer A, Bede-Fazekas Á, Hufnagel L, Horváth L, Bobvos J, Páldy A. (2013) The effect of climate change on the potential distribution of the European *Phlebotomus* species. Applied Ecology and Environmental Research, 11: 189-208.
6. Trájer A, Bede-Fazekas Á, Hufnagel L, Bobvos J, Páldy A. (2013) The paradox of the binomial Ixodes ricinus activity and the observed unimodal Lyme borreliosis season in Hungary. International Journal of Environmental Health Research, 24: 226-245

Other relevant articles in Hungarian

1. Trájer A (2014) Lepkeszúnyogok és klímaváltozás. Természet Világa, 145:505-508.
2. Trájer A, Mlinárik L, Juhász P, Bede-Fazekas Á. (2014) A klímaváltozás és a városi hősziget-effektus együttes hatása a lepkeszúnyog-fajok által terjesztett emberi megbetegedésekre. Iskolakultúra,24: 48-68.
3. Trájer A, Bede-Fazekas Á (2014) A klímaváltozás hatása a canine leishmaniasis vektorainak és azok növényi indikátorainak elterjedésére: The potential effect of climate change on future occurrence of the vectors of the canine leishmaniasis and the distribution of their plant indicators. Légkör, 59: 66-73.

4. Trájer A, Kacsala I, Padisák J (2013) A klímaváltozás várható hatása a szúnyogok és a lepkeszúnyogok, valamint az általuk terjesztett betegségek jövőbeli elterjedésére. Iskolakultúra, 13: 73-85.
5. Trájer A (2012) A változó klíma és a szúnyogok: Régi ismerősök és újonnan érkezők. Élet és Tudomány. 32: 998-1000.
6. Trájer A (2012) A klímaváltozás hatása a kullancsokra: trendek és várható következmények. Élet és Tudomány, 18: 553-555.
7. Trájer A (2011) Szúnyogok és a klímaváltozás. Természet Világa, 142: 219-221. In Hungarian.
8. Trájer A. (2011) Kullancsok és a klímaváltozás. Természet Világa, 142: 313-315.

Other articles in topic of climate change

1. Trájer A, Páldy A (2008) Az általános felmelegedés kliniko-farmakológiai vonatkozásai. Egészségtudomány, 52: 37-26. In Hungarian.
2. Trájer A, Páldy A (2008) Az általános felmelegedés gyógyszertani vonzata. Egészségtudomány, 52: 47-55. In Hungarian.