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Expected Impacts of the Anthropogenic Global Climate Change on the Potential Human Vectorial Diseases in the Carpathian Basin and Europe

Ph.D.Dissertation

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Motto: "…in the beginning of the malady it is easy to cure but difficult to detect, but in the course of time, not having been either detected or treated in the beginning, it becomes easy to detect but difficult to cure."

Niccolò di Bernardo dei Machiavelli (3 May 1469 – 21 June 1527): The Prince, Ch. 3.

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Contents

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention

CEM: Climate Envelope Modeling

CO_2: Carbon-dioxide

DWL%: percentage difference of an actual water level of a river from the mean level

DWNF%: water level range of the maximal and minimal case interval

ECHAM: a Global Climate Model developed by the Max Planck Institute for Meteorology

EM: erythema (chronicum) migrans (an early localized symptom of Lyme disease)

LB: Lyme borreliosis, Lyme disease

GCC: Global Climate Change (the recent global warming)

HM: human activity multiplier

IA: human activity independent tick activity

IPCC: Intergovernmental Panel on Climate Change

NE: regarding to the 2 studied north and north-eastern Hungarian counties

p: probability according to a normal (Gaussian) probability distribution model

ppb/ppm: pars per billion/million (gas concentration units)

PRUDENCE project: Prediction of Regional scenarios and Uncertainties for Defining European Climate change risks and Effects

r: correlation coefficient in linear regression analysis

RI: relative (%) Lyme disease incidence

rss: residual sum of squares in linear regression analysis

SRES: Special Report on Emission Scenarios (basic emission scenarios for the IPCC reports)

SW: regarding the 3 studied south-western Hungarian counties

TBD(s): Tick-Borne Disease(s)

TBE: Tick-Borne Encephalitis

Tmax: maximum ambient temperature

Tmean: mean ambient temperature

Tmin: minimum ambient temperature

VBD(s): vector or vector-borne disease(s)

VAHAVA report:Climate Change and Hungary: Mitigating the Hazard and Preparing for the Impacts

VBORNET: European Network for Arthropod Vector Surveillance for Human Public Health

WHO: World Health Organisation

WNF: West Nile Fever

WNV: West Nile (Fever) Virus

1.INTRODUCTION AND REVIEW OF LITERATURE

1.1. VECTOR-BORNE DISEASES IN THE GLOBALIZING WORLD

Global Climate Change (GCC) will affect many aspects of human health: the greater frequency of heat waves will increase the morbidity and mortality (Páldy et al. 2005), or can even modify the durability and the pharmacokinetics of drugs (Trájer and Páldy 2008a, 2008b). It is very likely that the GCC will modify the geographic range and incidence of several vector-borne diseases or environmental infectious diseases, including WNF, LB, dengue fever and human Hantavirus infections (Kovats et al. 2001, English et al. 2009). The current importance of these vector-borne diseases is smaller in Europe than in the low-income countries, particularly in Sub-Saharan Africa. The most important diseases are dengue fever and infections by other arboviruses (mainly flaviviruses), leishmaniasis, malaria, onchocerciasis, schistosomiasis and trypanosomiasis (Sutherst 2004). However, the protective role of the cold winters of the temperate climate may lose its importance. Due to the GCC, the importance of arthropod-borne diseases can increase by the end of the 21st century.Three groups of vector-borne diseases can be discerned: 1) the recently abundant ones; 2) the diseases of the past centuries, which have disappeared but can appear again, and 3) new, exotic diseases. Several new VBDs have been recognized in the past decades and many of them are spreading geographically and their frequency is increasing (Gratz 1999) due to the GCC and the effect of the rapid growth of human population and globalisation. The chikungunya outbreak in Italy, 2006, was a great example of the influence of globalisation on vector-borne diseases (Charrel et al. 2007). The emerging or re-emerging vector-borne diseases (hence: VBDs) are one of the major microbial causes of morbidity and mortality in the World (Gubler et al. 1998, ***Fig.1***).

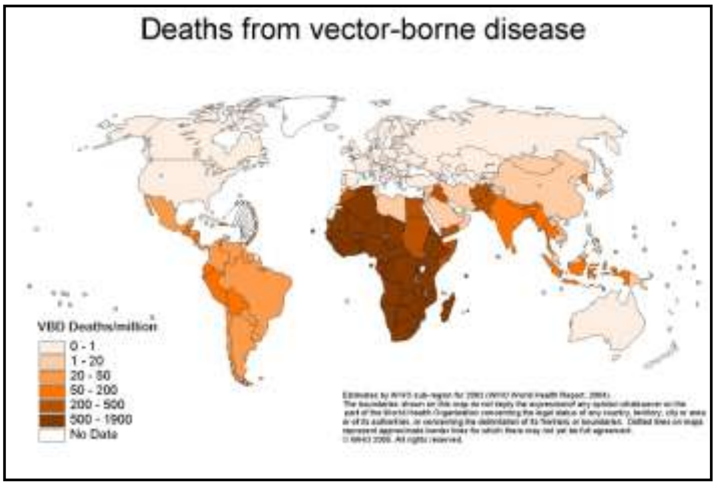


Fig.1. Worldwide deaths from VBDs (in: WHO 2008A)

Malaria alone causes at least 273 million cases worldwide every year (Rogers and Randolph 2000) and in 2001 malaria alone caused 1,103,000 deaths in the developing countries (WHO 2001). The WHO estimated that in 2010 approximately 660,000 to 1.2 million people died malaria (Nayyar et al. 2012)and malaria itself was the 5th in the top 5 causes of death (***Fig.2***) in the low-income countries in 2008 (0.48 deaths in millions - 5.2% of deaths; WHO 2008B).

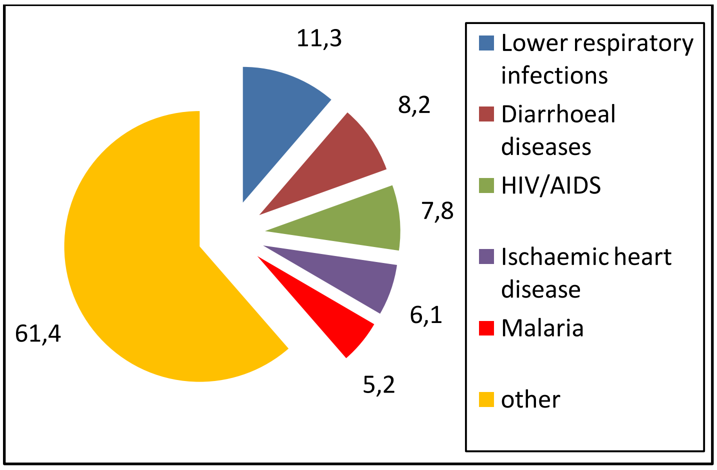
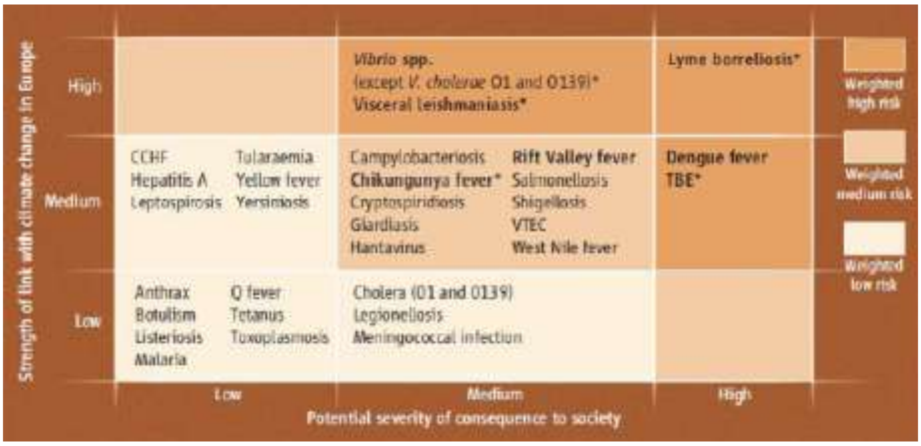


Fig.2. The top five causes of death low-income countries in 2008 (source: WHO 2008B)

Leishmaniasis have been detected in 88 countries with 350 million people threatened, and about 500,000 new cases of visceral leishmaniasis and 1–1.5 million new cutan leishmaniasis cases are observed every year (Desjeux 2004). In 2004 malaria caused 2.23% (20.4 per 100,000), leishmaniasis 0.09% (0.8 per 100,000) andTrypanosomiasis 0.08% (0.8 per 100,000) of worldwide deaths (WHO 2004). Although recently malaria cause most of the deaths by vector-borne diseases worldwide (Sachs and Malaney

2002), dengue fever and leishmanisis are the world's fastest spreading vector borne diseases (WHO 2008A).WHO estimates that 50 to 100 million dengue fever infections occur yearly, with 22,000 deaths (CDC factsheets: Dengue 2013). In general, the mortality rate of tick-borne encephalitis, which is autochthonous in Hungary is 1-2% (CDC factsheets:TBE 2013) but can be more, even 24% in some areas (Randolph 2001). The mortality rate of the Hantavirus pulmonary syndrome is 38% (CDC factsheets: Hantavirus).Several important vector-borne diseases have primarily canine hosts e.g. leishmaniasis or dirofilariasis. These so-called canine VBDs form a worldwide distributed group and the main hosts live in the immediate human environment (Otranto et al. 2009).According to the weighted risk analysis of climate change impacts on infectious disease risks in Europe (Lindgren et al. 2012; ***Fig.3***) cholera, leishmaniasis, Dengue fever, TBE and Lyme disease seem to be the most serious problems and note that all of them are vector-borne diseases-except cholera.



Strength of link with climate change in Europe

	Low	Medium	High
High		*Vibrio* spp. (except *V. cholerae* O1 and O139)* Visceral leishmaniasis*	Lyme borreliosis*
Medium	CCHF Hepatitis A Leptospirosis Tularaemia Yellow fever Yersiniosis	Campylobacteriosis **Chikungunya fever*** Cryptospiridiosis Giardiasis Hantavirus **Rift Valley fever** Salmonellosis Shigellosis VTEC West Nile fever	**Dengue fever** **TBE***
Low	Anthrax Botulism Listeriosis Malaria Q fever Tetanus Toxoplasmosis	Cholera (O1 and O139) Legionellosis Meningococcal infection	

Potential severity of consequence to society

Fig.3. The weighted risk analysis of the different zoonotic and vector-borne diseases according to their severity and projected expansion in Europe (in: Lindgren et al. 2012)

Among the vector-borne diseases TBE is one of the most numerous viral vector-borne diseases in the World and the most numerous flavivirus caused VBD in the temperate areas of the Northern Hemisphere including Europe (Suss 2008) (***AnnexSpreadsheet 1***). In 2007, 70 Congo-Crimean Haemorrhagic Fever cases were reported from Kosovo,geographically not too far from Hungary, with 4 deaths (Prajapati 2011). In 2012, a Dengue fever outbreak was reported from Madeira, Portugal (Sousa et al. 2012).Ticks are the main vectors of many serious diseases, such as Erlichiosis, Q-fever, LB, TBE, tularaemia, spotted fevers, and babesiosis and tick-borne diseases form an important group in the Northern Hemisphere within the group of the vectorial diseases (***AnnexSpreadsheet 2***).

1.2 THE PRESENCE AND IMPORTANCE OF VECTOR-BORNE DISEASES IN HUNGARY

The most common VBDs in Hungary are transmitted by ticks as Lyme disease or Lyme borreliosis (hence: LB; mandatory reportable from 1998 in Hungary the code 63/1997. (XII. 21. NM rendelet) government regulation and tick-borne encephalitis (hence: TBE; reportable from 1977) with about in the period of 1998-2010 more than 1016 (2007) and less than 2354 (2010) recorded cases per year (***Annex Spreadsheet 3***). Tick-borne diseases contributed toabout 99% of the recorded human VBDs cases without the sporadic cases in Hungary. It is possible that LB is underreported in Hungary, because in the neighboring country, Slovenia, the incidence of the disease was more than 100 per 100,000 (Rizzoli et al. 2011) during the past decade. Although the disease is not-noticeable at the European Community-level, about 85,000 cases are estimated to occur in Europe each year and in anotherneighboring country, Austria, alone. The annual number of the new LB cases reaches 14,000-24,000 (Lindgren and Jaenson 2006). In Hungary, LB formed about 96% and TB 4% of the recorded TBD cases in the last 15 years. While LB is an emerging disease in Hungary surprisingly the TBE showed a decreasing trend (Zöldi et al. 2013). Overall, 686 cases of TBE were reported from 2001 to 2010, so the annual incidence rates were between 0.5–0.8 per 100,000 in the period of 2001 to 2010 (Caini et al. 2012). Until 2013, 703 TBE and 13,606 LB cases were reported in Hungary (Zöldi et al. 2013), but it is very likely that both TBE and LB are underreported and also in the neighboring Austria (Jelenik et al. 2010). In fact, in 2007 a TBE outbreak occured involving 25 patients of 154 exposed persons by infected goat milk (Balogh et al. 2010). *Coxiella burnetti* were found in *Ixodes ricinus* Linnaeus (1758), *Dermacentor marginatus* Sulzer (1776) and *Haemaphysalis concinna* Koch (1884) from the forest of Börzsöny and Pilis Mountains, Hungary (Špitalská and Kocianova 2003). It can be assumed that most of the human Q-fever cases are not VBD. Human ehrichiosis, TIBOLA and babesisosis are sporadic or unrepresented in the record. Bartonellosis sometimes can be transmitted by ticks, but the parasite lacks from ticks in Hungary and only a small number of the fleas infected by *Bartonella* species (Sréter et al. 2004 and Sréter et al. 2006). Some diseases, like leishmaniasis (Farkas et al. 2011, Tánczos et al. 2012, Tánczos 2009) or the *Dirofilaria immitis* (taxonomy ID: 6287) caused dirofilariasis (Jacsó 2009) are only known in the case of the main host animals (mainly dogs) in Hungary, but endemic human cases have not been reported yet. Some introduced leishmaniasis cases from endemic areas are known in Hungary (Fok 2007 and Péterfi et al. 2010). *Babesia*species frequently infectdogs (Máthé et al. 2006, Földvári and Farkas 2005) and *Babesia microti* (taxonomy ID: 1133968) is present in the anthropophilic ticks in Hungary (Kálmán et al. 2003). Human babesiosis cases have also not yet been reported from Hungary. *Anaplasma phagocytophilum* Foggie (1949), the causative agent of the granulocytic ehrlichiosis (anaplasmosis) an emerging tick-borne pathogen among animals in Hungary, but the serological tests gave contradictory results in the suspected human cases (Lakos 2005). Spotless rickettsiosis (TIBOLA) cases caused by *Rickettsia slovaca* Sekeyova et al. (1998)sporadically were recorded in Hungary (Blanco and Oteo 2002, Raoult et al. 2002); Lakos et al. (2002) recognized the typical symptoms of TIBOLA on 86 patients with similar symptoms following by *Dermacentor*spp. tick bites. Some other diseases, such as Q-fever, tularaemia somethimes can also be transmitted by tick vectors, but these diseases are in most of the cases classical zoonoses with low annual incidence rates. It is notable that hard tick species may transmit the major part of the sporadic tularaemia cases; e.g. Ferencz (1997) collected 28 cases of human tularaemia within 2 years in Hungary. The vectors of leishmaniasis are present in the southern part of the Transdanubia region and the agglomeration of Budapest (Farkas et al. 2011, Tánczos et al. 2012). Imported cutaeous leishmaniasis cases are also known in Hungary (Péterfi 2010, Várnai 1985). Despite the fact, that WNF is an emerging disease in Hungary (Threat and Berencsi 2006) and sporadic *Dirofilaria repens* (taxonomy ID:31241) caused human dirofilariasis cases are also recorded (16 new cases were reported in 2001 and 2006; Fok 2007, Szénási et al. 2008, Pónyai et al. 2006), mosquito-borne diseases even with the imported malaria cases contributed only in about 1% of the recorded VBDs cases in Hungary. Malaria in the Middle Ages and even to the mid-twentieth century was a widespreadendemic disease in the Hungarian lowlands (Szénási 2003), but in the last sixty years only imported cases were reported (Melles and Jankó 2000), while the potential vector is the resident member of the mosquitoe fauna. By contrast, the West Nile Fever is an emerging mosquitoe-born disease in Hungary from 2003 (Krisztalovics et al. 2008). A similar, bird-carried virus, the 2005 Usutu virus was detected in organ samples of a blackbird, *Turdus merula* Linnaeus (1758), which was found dead in Budapest. The Usutu virus also has Eastern-African origin. Further cases were reported in 2007(Bakonyi et al. 2007). In the period of 1933-1943, the actual number of malaria cases was estimated as 10-100,000 per year in Hungary (Melles and Jankó 2000) and in the period of 1963-2001, 432 imported malaria case were registered in Hungary (Szénási et al. 2003). *Anopheles algeriensis*Theobald (1903), *A. atroparvus* Van Thiel (1927), *A. claviger* Meigen (1804), *A. hyrcanus* Pallas (1771), *A. maculipennis* Meigen (1818), *A. messeae* Falleroni (1926) and *A. plumbeus* Stephens (1828) are recently endemic malaria mosquitoes in Hungary (Kenyeres and Tóth 2012, Tóth and Kenyeres 2011).

1.3. GLOBAL CLIMATE CHANGE

1.3.1. THE CAUSES AND THE OBSERVED TRENDS OF THE RECENT CLIMATE CHANGE

The climate has always been in changeduring the history of Earth. The source of the energy and the main driver of the climate has always been solar energy; the role of the inner heat of the planet is of secondary importance. Different gases can absorb different spectraof light. Clouds and surfaces covered by snow and aerosols can reflect light thusshielding the land surface. Some gases (e.g. CO_2, methane and water vapour) can absorb infrared light. Water vapour is also a very effective and the most abundant greenhouse gas. As the concentrations of other greenhouse gases, CO_2, methane and dinitrogene-oxide have beenincreasing due to the human activity, the water vapour concentration may increase in a warmer world (Held and Soden 2000). Climate models also suggested that the increased convective activity due to global warming may also cause the increased evaporation of the oceans, but the increased convective activity may cause the drying of the upper troposphere (Shine and Sinha 1991). Before the first industrial revolution, starting around 1760, the atmospheric CO_2 content was some 280 ppm (pars per million). Only during the short period of 1880-1980 did the atmospheric CO_2content increase from 280 to 300 ppm mainly due to the burning fossil fuels (Te

1981). The Greenlandic ice cores showed that in the last 650 thousand years the atmospheric CO_2 content was not more than 300 ppm. In 2005, this amount was 379 ppm and by March 2013 it has already reached the 397.34ppm (Earth System Research Laboratory 2013). The 450 ppm concentration seems to be critical e.g. in the aspect of the acidification of the oceans (Mc Neil and Matear 2008). In the period of 1995-2005 the CO_2 content increased by 1.9 ppm per year (Pachauri and Reisinger 2007).According to the IPCC's 4th Assesment Report (Confalioneri et al. 2007), the increasing CO_2 content is mainly the consequence of human emissions and the changes in land-using techniques. The observed surplus of the atmospheric CO_2 content has been mainly released by the artificial fuel and coal combustion since the beginning of the industrial revolution (Revelle and Suess 1957). CO_2 is the most important greenhouse gas, warming the Earth's surface from -17°C to 15°C temperature by reducing outward radiation. CO_2 absorbs and emits infra-red (heat) radiation at wavelengths of 4.26 and 14.99 μm (Petty 2004). The most important sources of the atmospheric CO_2 are the burning of fossil fuels and the agriculture, including deforestation, and other natural environments (eg. the soil) which act as carbon-storages. The second most important greenhouse gas, methane, has a greater specific greenhouse effect than CO_2, but has a less concentration that CO_2. Before the 1760's, methane had a 715 ppb (pars per billion) concentration in the atmosphere (Pachauri RK and Reisinger 2007). In the last 650 thousand years the methanecontent fluctuated between 320-790 ppb. In 2005, the concentration of the gas was 1774 ppb (CDIAC, Solomon 2007). Dinitrogen-oxide is the third most important greenhouse gas. Before the 1760's dinitrogen-oxide had a 207 ppb concentration in the atmosphere. In 2005 the detected concentration of the gas was 319 ppb (CDIAC, Solomon 2007).In total, from the start of the industrial revolution the excess radiation thanks to the increased amount of the main greenhouse gases increased by 2.30 W $m^{-2}$and in the period of 1995-2005 alone the excess radiation by CO_2 showed a +20% increase (Pachauri 2007). The increase in the atmospheric aerosols caused a -0,5 W m^{-2} decrease in radiation. The whole anthropogenic excess radiation showed a 0.6-2.4 W m^{-2}(mean: 1.6 w/m^2) in the 20th century. The urban heat effect was negligible as a cause of global warming (Pachauri 2007).In the period of 1981-2005 the atmospheric CO_2 concentration increased by 10% in Hungary (Haszpra and Barcza 2005). From mid-1981 the 343 ppm increased to 383 ppm by the end of 2003, according to the measurement of the meteorological observatory of Hegyhát. The mean temperature of the vegetation season increased by 2.7°C in the period 1997-2003 (Haszpra and Barcza 2005). The increment of the CO_2 concentration was 1.65 μmol per year during 1981-1990, while in the period of 2001-2011 a 1.95 μmol per year linear increasing trend were observed. Nearly half (45%) of the 52.8 μmol increment from the industrial revolution occurred in the last 30 years (Haszpra 2012).The long-term trend of the annual mean temperature in the Northern Hemisphere in the period of 1906-2005 was 0.76°C per hundred years (+/-0.19°C) and it is important, that about two-thirds of the increase occurred since 1980, so the trend is exponential, since the rate of the increasing mean temperature over the last 50 years (0.13°C ± 0.03°C per decade) is nearly twice of that of the last one hundred years (Solomon 2007). The oceans absorbed 80% of the surplus heat in the period of 1961-2005. This fact can be explained by the great volume (about 1.37 billion [10^9] km^3 or 1.37×10^{18} m; Garrison 2007) of the cold and deep (the average depth of the World's oceans is 3,790 meters, e.g. the mean depth of the Atlantic ocean is: 3,926m; Garrison 2007) oceans and the high specific heat capacity of water c=4.1813J/(kg×°C), which means that to increase the average temperature of the oceans by 1°C (if $\rho=10^3$ kg/m3 at T=4°C; $M_{oceans}=1.37\times10^{21}$ kg) 1.37×10^{21} kg×[4.1813J/(kg×1°C)]=$5,7283\times10^{21}$ J energy is needed. By comparison, the total solar energy absorbed by the Earth's atmosphere, oceans and land masses per year is about $3,850,000\times10^{18}$ J and the Earth receives 174×10^{15} W (J s^{-1}) of incoming solar radiation which is $2,1024\times10^{22}$ J energy per year (Smil 2006). The above mentioned facts indicate that the oceans play the role of the main climatic buffer and can decrease the rapidity of GCC, but storing huge amounts of heat can make the trends permanent.

1.3.2. CLIMATE PROJECTIONS AND SCENARIOS

A wide range of projections were constructed for the prediction of the future level of global warming. The IPCC's SRES (Special Report on Emission Scenarios for IPCC; Nakicenovic et al. 2000 and Impacts, Adaptation and Vulnerability; Confalioneri et al. 2007) projections are the most frequently used scenarios to make models to predict the future climate. The SRES scenarios are reference scenarios, which mean that these scenarios are based on the continuously increasing atmospheric greenhouse gas levels.

Theauthors of the IPCC 4th Assessment Report (Confalioneri et al. 2007) used six potential emissions to construct six different scenarios projecting the future global mean temperature change (Leggett 1992). These scenarios are the following: the B1, which estimates the atmospheric CO_2 content to reach 600 ppm and the global mean temperature to increase to 1.8°C by the end of the 21st century. These amounts in the other scenarios are: B1: 600 ppm and 1.8°C, A1T: 700-800 ppm and 2.4°C, B2:800 ppm and 2.4°C, A1B: 850ppm and 2.8°C, A2: 1250 ppm and 3.4°C, A1F1: 1550 ppm and 4°C. Most of the models are based on the A1B scenario (Nakicenovic et al. 2000, ***Annex Spreadsheet 4***). Thus, the maps created by the model have importance not only for landscape architects and botanists (Czinkóczky and Bede-Fazekas 2012), but also for epidemiologists. The summer temperatures are predicted to increase by more than 2.5°C in the Mediterranean area, in Central Europe by less than 1.5°C and in Eastern Europe by about 1°C or less by 2050. The simulated warming is typically between 1.5°C and 2°C in most parts of Europe in winter. Although the precipitation in the Mediterranean area decreases by up to 50%, the precipitation increases in large, even the northern, parts of Europe in autumn and winter (Max-Planck-Institut 2007). As expected, the climate in the Carpathian Basin will be warmer, more arid, and will have extreme rainfalls more frequently in the colder half-year (Bartholy et al. 2007).In case of the Carpathian Basin, the global climate models (GCMs) are insufficient to predict the future changes. There are several regional climate models (RCMs), which can give a higher resolution, e.g. the RegCM model (Giorgi 1990). In 2010, the VAHAVA report and the PRUDENCE project summarized and synthesized the results of some regional climate models for Hungary. Most of the models were based on A2 or B2 scenarios and used the period of 1961-1990 as reference. The projected summer and autumn regional warming (1.7°C and 1.5°C, respectively) is larger than the annual increase (1.4°C), while the expected winter (1.3°C) and spring (1.1°C) warming is smaller than the annual temperature increase. The largest temperature increase is expected in summer, while the smallest in spring. In summer the expected increase in the daily mean temperature is 4.5-5.1°C (A2) or 3.7-4.2°C (B2) and the daily maximum and minimum temperatures in summer are expected to increase by 4.9-5.3°C (A2) or 4.0-4.4°C (B2), and 4.2-4.8°C (A2) or 3.5-4.0°C (B2) according to Bartholy and Pongrácz 2010. For spring, the expected temperature increase in Hungary is 2.8-3.3°C (A2) or 2.3-2.7°C

(B2). The annual precipitation sum is not expected to change significantly in this region, but it is not valid for seasonal precipitation changes, while precipitation is very likely to decrease in summer with a slight decrease of autumn precipitation and an also not too great increase in the winter precipitation. In summer, the projected precipitation decrease is 24- 33% (A2) or 10-20% (B2). In winter, the expected precipitation increase is 23-37% (A2) or 20-27% (B2).

1.4. ARTHROPOD VECTORS

1.4.1. THE COMMON PHYSIOLOGICAL CHARACTERS OF ARTHROPOD VECTORS

In the epidemiological terminology, vectors are organisms that can transmit infectious agents (eg. viruses, bacteria, protists, nematodes) from one still infected host to another potential one. In the case of hyperparasitism, a parasite is hosted by another parasite. For example ticks are the ectoparasites of vertebrate animals and Borrelia species are can be the endoparasites of both ticks (hyperparasite relation) and deers (simple parasite relation). Most of the vectors belong to the phylum of arthropods. Arthropods are ideal vectors for parasites (***AnnexSpreadsheet 5***) because of their huge population, small body size, rapid growth and generational change and in the case of insects; the ability of flying or bouncing is also an important benefit for the pathogens. Their poikilothermy and the consequential low metabolic rate allows these animals to require very little food to develop or to survive (ticks are one of the best example of bradymetabolism (creatures with low metabolic rate)). Many of the vector organisms are haematophagous, keeping contact with the circulation system of the animals/humans directly by the penetration of the skin and entering vessels. The most common arthropod vectors belong to the order Acari (eg. ticks and mites) and to the class Insecta (eg. fleas, mosquitoes). The members of the subphylum: Crustacea, cyclopoid copepods are the vectors of the nematode *Dracunculus medinensis* Linnaeus (1758), the agent of dracunculiasis. Within the class Insecta, the order Diptera has the greatest vector potential (eg. flies, sandflies, mosquitoes), but the role of some other members of the subclass Neoptera (fleas, lice) are also important as vectors. These organisms are mainly facultative ectoparasites like *Ixodes ricinus* (**Fig.4**). The reservoir animals of the pathogens are unfortunately frequently our domestic animals; e.g. dogs and cats are important carriers and hosts for the causative agents (leishmaniasis is an excellent example). Many of these pathogens and parasites are of great medical or veterinary importance. Most of the parasites actually are adapted to a particular vector for part of their developmental cycle, but the vector function essentially consists of transmission of the parasite to subsequent hosts. Arthropod vectors do not have any ability to control their body temperature by active heat-producing as mammals do. Poikilotherm organisms change their seasonal/daily activity according to the ambient environmental. Insects and ticks are little animals (in the range of mms to cms), having high body surface-body mass ratio. This situation allows rapid warming of the arthropod by solar irradiation ("Sun-bathing"), but also their quick cooling in cold environments or the consequence of the direct cooling effect of precipitation or wind. Furthermore, the high body surface allows the rapid escaping of the body water content by direct solar radiation, despite their waterproof exoskeleton, by their respiration system. While they are more or less easy prey for hunting animals they reproduce a large number of offsprings in every year. The questing, flying, moulting, pupation and reproduction activities are strongly related to the ambient temperature (Lactin et al. 1995, Logan et al. 1976) and other climatic factors.For more information about arthropod vectors see the excerpt in the ***Annex Text 1*** and ***2***: Arthropod vectors and Insect vectors.

Fig.4. Fed adult female hard tick individual.

Ticks have larval, nymphal and adult life stages. These life forms may feed on one, eg. *Boophilus annulatus* or two: eg. *Rhipicephalus bursa* Canestrini Fanzago (1878) or even three host species, eg. *Ixodes ricinus*, *Dermacentor marginatus* Sulze(1776), *Haemaphysalis punctata* (Canestrini Fanzago 1878), *Rhipicephalus sanguineus* Latreille (1806). The whole life cycle of *Ixodes. ricinus* usually takes 2–3 years to complete.

1.4.2.THE SEASONALITY AND THE LIFE CYCLE OF IXODES RICINUS TICKS

Ixodes ricinus is the most common vector of LB in Hungary and also the most common tick (Földvári and Farkas 2005). The new *I. ricinus* recruits delay their questing activity until the following spring in many parts of Europe, inter alia (Lees Milne 1951, Randolph et al. 2002). This may be true 'behavioural diapause' (Belozerov 1982). The main vectors for humans are infected adults and nymphs. There is strong association between Lyme disease in humans, the degree of nymphal *I. scapularis* Say (1821), abundance, and prevalence of *Borreliaburgdorferi* sensu lato infection in ticks (Nicholson et al. 1996). The main vectors for humans are infected adults and nymphs. Nymphs feed on their hosts 3-7 days long and their shading lasts for 2-6 months, the adults feed on the animals or humans 1-2 weeks (Kapiller and Szentgyörgyi 2001). It is important for modeling that ticks vary their questing activity in response to their immediate climatic conditions (Randolph 2008). From this fact,the natural development of ticks may be estimated by applying daily development rates to varying temperatures within the tick's habitat. Temperature should be measured as closely as possible to the microhabitat in which the tick undergoes its development. The cause of why nymphs are the most important transmitters of Lyme diseases is their small size (often less than 2 mm) and their seasonal co-activity with human beings, since they are most active in the spring months. Adult ticks are larger, they may reach a length of 11 mm and more likely to be discovered before the transmission of the parasite and they are most active during early spring and late autumn, when the human presence is low in the nature. According to the historical data and field collection studies, the seasonal activity of *Ixodes ricinus* is bimodal with a spring and fall peak in Hungary (Babos and Faragó 1964, Egyed et al. 2012). Földvári et al. (2007; ***Fig.5***), who collected ticks from dogs in the period of 2004-2007, and found that the *I. ricinus* season starts in March in Hungary, reaches its maximum in April and after dropping toits summer minimum in August and there is a second, less expressed peak in October. Széll et al. (2006) also observed that *I. ricinus* ticks were most active between April and June with an activity peak in April-May. In Hungary, there was a less marked increase of activity was also observed in September and October while the seasonality of LB doesn't show the bimodality of the seasonal activity of *I. ricinus* tick (Hornok 2009 A).

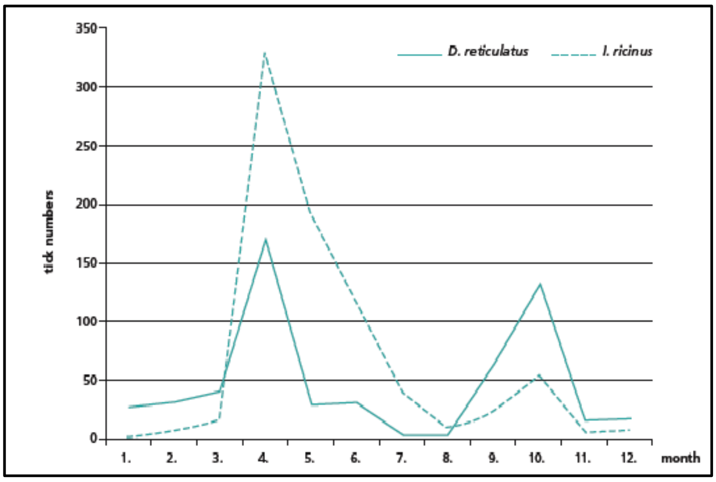


Fig.5. Seasonal occurrence of *I. ricinus* and *D. marginatus* adults on dogs according to months of collection (in: Földvári et. al. 2007).

To understand the seasonality of Ixodidae ticks it is important to know that the main vectors of the causative agent of LB, *Borrelia burgdorferi sensu lato*, take only one or a few very large blood meals per life stage to develop, which can take from weeks to even years (Randolph 2009) and the new recruit ticks delay their questing activity until the following spring in many parts of Europe, *inter alia* (Lees and Milne 1951, Randolph et al. 2002).The seed of the development and number of the questing nymphal *Ixodesricinus* nymphs depend greatly on the ambient temperature (Randolph 2009, Chauvin et al. 2009) because ticks are-as arthropods in general- poikilothermic animals. Between both the interstadial development rates of ticks and the daily questing, feeding rates of tick species can be described by non-linear relationships with temperature. Larval–nymphal simultaneous occurrence is statistically significantly associated with a particular seasonal land surface temperature profile (Randolph et al. 2000).

1.5. THE EFFECT OF GLOBAL CLIMATE CHANGE ON VECTOR-BORNE DISEASES

Vectors are sensitive to climatic conditions (Githeko et al. 2000, Hunter 2003, Rogers and Randolph 2006) and the best evidence for this fact is that most of the vbds show a distinct annual pattern, while vector-borne disease risk in humans is linked to climate variability so (Githeko et al. 2000) climate variability has direct effects on the epidemiology of vbds (Hunter 2003, Gubler et al. 2001). Changes in climatic patterns and in seasonal conditions may also affect disease behaviour in terms of distribution pattern, diffusion range, amplification and persistence in novel habitats (Ladányi and Horváth 2010). Higher temperatures can induce earlier flight of adult insects, eg.

Lepidoptera species (Kocsis and Hufnagel 2011). These changes can increase their population in recently inhabited areas and the mild climate in the temperate areas of Europe can facilitate the migration of these arthropod vectors to North (De la Roque et al. 2008). The GCC will also increase the chance of the vector-borne disease transmission the feeding/biting and fertility rate of the vectors, changing the seasonality of tick activity and the pathogen transmission, mosquitoes, sandflies, the susceptibility of vectors to pathogens, the incubation period of the pathogen (Hunter 2003, Patz et al. 1996). It is notable that the increasing CO_2 levels are usually unfavourably affecting the development of the insect larvae (Kocsis and Hufnagel 2011). Human influence may be a more important side of the interaction than the changes in the transmission potential in natural enzootic cycles (Randolph 2010) and hot, sunny summer weather and in general holiday times make an additional risk on human infection by stimulating people go to the nature (Šumilo et al. 2008). International travel also increases the risk of import of vbds (Gubler et al. 2001) as in the case of chinungunya disease happened several times, when travellers from developed countries with a temperate climate became infected with the virus in tropical/subtropical regions and returned home (Rezza et al. 2007).

1.6. CLIMATIC INDICATORS

As Kovats et al. (2007) stated the detection and then attribution of geographical and seasonal patterns of the vector-borne diseases to the GCC is an emerging task for scientists. For observing and detecting the effects of the GCC, one of the most adequate methods is using environment-sensitive indicator species. These indicator organisms can be used in different branchesof science, for example in agriculture, palaeoecology and to observe and predict the changing environmental human health patterns too (Subak 1999). The changing annual and inter-annual variability of the incidence patterns of vector-borne diseases and vectors may be the earlier effects of anthropogenic GCC (Subak 1999). Environmental health indicators are required to track the changes in health outcomes (English et al. 2009). Semenza and Menne (2009) suggest the use of a sentinel surveillance system collecting and analyzing a high quality and accurate data with exact geographical location tick-borne diseases as tick-borne encephalitis and LB. Not only animal species can act as good climate indicators, but plant species as well. It is importance for the future to find plant species that indicate the potential distribution of vectors and vector-borne diseases (Trájer and Bede-Fazekas 2013a and 2013b). Due to the GCC the phenological, physiological and genetic parameters, and also the distribution area of the plant species, and the stability of ecosystems seem to be changed in the future (Hughes 2000, Kovács-Láng et al. 2008). Several predictions were made for the future distribution of plants, including the European species (Berry et al. 2006, Bakkenes et al. 2006, Harrison et al. 2006, Peterson et al 2008, Bede-Fazekas 2012, Serra-Diaz et al. 2012). Since GCC can cause the expansion and the increasing abundance of insect populations (e.g. pests of plants) by changing the length of the vegetation period and making of the winter colds throughout Europe moderate (Ladányi and Horváth 2010). It can be useful to compare the reaction tothe GCC of the animal vectors of infectious diseases to the reaction of plant species. Since plants have a fix position and they do not have the ability to produce notable heat as warm-blooded animals do, they are the most sensitive and therefore the most suitable climate indicators. Other animals, such as sandflies, which are able to move, can avoid climatic extremities in man-made (Killick-Kendrick 1987and Killick-Kendrick and Killick-Kendrick 1987, Naucke 2002) and natural (Hanson 1961) shelters. In case of plants the climate affects them in their distribution area directly. Note, that sandflies are also poikilotherm organisms, just as plants are. Ligneous plants were studied as indicator species instead of herbaceous plants, since they are unable to react quickly to the small-scale changes of climate. Thus, the natural distribution and the area of introduction of these species are strongly influenced by the extrema of climatic parameters. Therefore their environmental demands can be well modelled based on their current distribution.

1.7. THE STUDIED VECTOR BORNE DISEASES AND ITS VECTORS

1.7.1. LYME BORRELIOSIS

LB is the most common arthropod-borne human infection in Hungary. LB is an emerging vector borne disease caused by the procaryotic *Borrelia*group, *Borrelia burgdorferi* (Johnson et al. 1984),*B.afzelii* (Canica et al. 1994)and*B. garinii* (Baranton et al. 1992). *B.burgdorferi* is the main cause of LB in North America, while in Europe more often the parasites of LB are *B. afzelii* and *B garinii.Borrelia* bacteria belong to the order Spirochaetales and the family Spirochaetaceae. The Lyme disease causing

Borrelia parasites can mostlybe transmitted to humans through the bite of infected ticks, eg. *B.burgdorferi* Johnson et al. (1984). *Borrelia* species have endoflagellums and they can move by a corkscrew motion quickly. They can reproduce themselves by asexual transverse binary fission which can explain their fast expansion in the organs. This spreading can be visible in the case of erythema migrans (hence: EM), the early localized symptom of *B. burgdorferi* infection.The castor bean tick, *Ixodes ricinus* is the main vector of*Borrelia* species in Western Palearctic (Eurasia, eg. in Europe), the taiga tick,*Ixodes persulcatu*s Schulze (1930) in Eastern Eurasia (from Russia to Japan), the blacklegged tick or deer tick, *I.scapularis* Say (1821)spreads LB in the northeastern, mid-Atlantic, and north-central United States, and the western blacklegged tick, *I.pacificus* Cooley & Kohls (1943) is the main vector of the disease on the Pacific Coasts of North America. The tick, *I.ricinus,* is also the primary European vector of Lyme borreliosis spirochaetes to humans (Jaenson et al. 2009). In our study area, in Hungary, the main vector is *I.ricinus* - castor bean tick (Halos et al. 2010, Hornok 2009). The reservoirs of *Borrelia. burgdorferi s.l.* are mammals or reptiles, but ticks are also reservoirs, since the transovarial transmission of the parasite from the pregnant adult females to larvae is also possible. Before adult ticks drop off they feed on larger mammals such as deers for 6–13 days or, if they have enough time to do it, even on humans. The nymphs feed on small to medium-sized mammals, but also in humans. The tick must be attached for at least 24 hours before the spirochaete can be transmitted to mammalian organisms (Piesman et al. 1987). Ticks can attach to any part of our body but they are frequently found in manually hard-to-reach or hidden from sight areas such as the navel, scalp, axilla and groin. Generally humans are infected by the immature ticks, called nymphs. Nymphs feed during the spring and summer months. Adult ticks can also transmit *Borrelia* species. Adult ticks are larger, they may reach a length of 11mm and more likely to be discovered before the transmission of the parasite and they are most active during early spring and late autumn, when the human presence is low in the nature because of the cold and wet weather conditions. The larvae have no role in the human transmission. There is strong association among LB in humans, the degree of nymphal *Ixodes scapularis*, abundance in the environment, and prevalence of *Borreliaburgdorferi* infection in ticks (Nicholson et al. 1996). The human activity in the nature is also a very important factor in the vector-host channel. Human behavioural responses to weather favourable for outdoor recreational activities, including wild mushroom and berry harvest, are influenced differently by national cultural practices and economic constraints (Randolph et al. 2008).

1.7.1.1. The predicted effects of Global Climate Change on Lyme borreliosis

The environmental sensitivity of the ontogeny of *Ixodes* tick species makes these organisms one of the most suitable GCC indicators. Lyme borreliosis (LB), which is the most common and important VBDs and TBDs in the temperate areas of Europe, is a highly recommended environmental health indicator of the GCC (English et al. 2009). The development highly depends on the ambient temperature, because ticks-as arthropods generally- are poikilothermic animals. Between both the interstadial development rates of ticks and the daily questing, feeding rates of tick species can be described by non-linear relationships with temperature. Larval–nymphal simultaneous occurrence is statistically significantly associated with a particular seasonal land surface temperature profile (Randolph et al. 2000). An important characteristic of ticks as vectors is their strategy of taking only one very large blood meal per life stage (i.e. larva, nymph and adult, Randolph 2008). The number of the questing nymphal *I. ricinus* nymphs and larvae are related with the seasonal variation of the maximum air temperature (Randolph 2009, Chauvin et al. 2009).*I. ricinus*entersdiapause in response to short daylength (Belozerov 1982). In temperate climates, ticks may be active from January suggesting that decreasing daylength beyond a certain level, may be the cause of diapause. (Randolph 2008). Therefore, daylight can play important role not only in the timing of diapause, but in the start of the tick season, too. Note, that parallel to the the increasing solar radiation the ambient mean temperature show consequently increasing trend. It is important for e.g. modeling that ticks vary quickly their questing activity in response to their immediate weather (Randolph 2008).In the past twenty years, studies found an increasing incidence of Lyme disease in Europe. Increases have been recordedin Poland, eastern Germany, Slovenia, Bulgaria, Norway, Finland, Belgium, Great Britain, and in the Netherlands (Smith and Takkinen 2006). In Sweden, the recent increasing prevalence of LB has been confirmed by serological tests (Kovats et al. 2000). The main vector *I. ricinus* has been observed to appear at higher latitudes and altitudes during the last 50 years on the old continent (Jaenson and Lindgren 2011).

In the neighbouring country, Slovakia, a significant increase in the incidence of early disseminated infection and late persistent infection of LB was observed from 1999 to 2008 (Svihrova et al. 2011, Randolph 2004). Regarding the seasonality of LB, the highest incidence in Slovakia was recorded from April to June and from September to November. In the south-western part of New York State (USA) the increasing distribution of *Ixodes scapularis*(deer ticks) wasobservedfrom 1990 to 1996 (Jaenson et al. 2009). According to the meta-analysis of Semenza and Menne (2009), incidence, prevalence, and distribution of the infectious disease are projected to shift in a changing environment. Astudy has assessed that the number of LB cases has been influenced by annual changes in population densities of *Ixodes scapularis* and has a corresponding change in the risk of contact with infected ticks (Falco et al. 1999). Previous studies suggested that the impact of the GCC on the spread of the European tick, *Ixodes ricinus*, has already had a noticeable effect (Randolph 2004, Lindgren et al. 2000). According to "The VAHAVA Report" the most obvious consequences and the most likely predicted effects of the GCC are the rising average and seasonal temperatures and the extension of the growing season in Hungary. Although some researchers found (Brewer et al. 2003, Subak 2003, Brownstein et al. 2003, Schauber et al. 2005, Ostfeld et al. 2006, Schulze et al. 2009) that precipitation or humidity can play a role in seasonality of tick-borne diseases, it seems to be that one of the most important abiotic factors is temperature (Randolph and Rogers 2000, Perret et al. 2003, Ogden et al. 2005, Daniel et al. 2008A, Ogden et al. 2008, Gray et al. 2009, Hancock et al. 2011, Wu et al. 2013) and human activity also can play an important role. The seasonal patterns of LB cases are a known consequence of two phenomena – the seasonal activity of ticks and the outdoor activity of humans.According to Randolph (2010) variation in human outdoor activities may influence positively on both the enzootic cycles and the degree of human exposure to the cycles of tick borne disease systems. In addition, health risks due to GCC differ between areas according to the rate of the development of health infrastructures, the primary climatic zone, the geographical position (Githeko et al. 2000).The geographic distribution is very important characteristic of the host and the vector populations and the human transmission of LB (James et al. 2010). Stafford (1998) found that the incidence of Lyme disease correlated positively with tick abundance which showed an increasing tendency since the 1990's in Europe (Randolph 2004, Confalonieri 2007). In

Hungary, as in Western Europe, *Ixodes ricinus* is the main vector of LB, but *Dermacentorreticulatus*is a common vector tick as well (Földvári et al. 2007). As a kind of external parasites, the complex three-stage onthogeny of *Ixodes* ticks occurs in the environment, the spatial-temporal distribution of ticks and in nature depends on climatic and ecological conditions (Estrada-Pena 2008). Kalluri et al. (2007) discovered a strong seasonal association between the time of the annual maximum of weekly LB incidences occurring during the summer and fall months when the nymphs are most active and the seasonal temperature and precipitation changes. Duffy and Campbell (1994) found that 4°C was the threshold of the activity of *Ixodes scapularis* in the milder winter days.According to Lindgren and Gustafson (2001) the threshold temperature of questing (food-seeking) tick activity was at 7-8°C and Perret et al. (2000) came to a very similar conclusion (between 6.6 and 8°C). Ambient temperature is one of the most important factor of the tick distribution and activity mainly in spring (when the relative humidity and soil moisture usually is appropriate for the ticks), but to explain the absolute annual LB case number, the ambient temperature is insufficient. For the prediction of the expected effects of the future GCC on LB it is essential to study the existing geographical differences in the LB seasons and to investigate the weekly, cumulative LB incidence rates based on the present regional climate differences and to observe the probable different seasonality of LB by regions.

1.7.1.2. The composition of the observed Lyme borreliosis cases by manifestation forms and the incubation period

LB has several clinical manifestation forms. The first one is the expanding rush of the early localized stage (3 days to 1 month post-tick bite), the EM with flu-like symptoms (eg. headache, fever, muscle pain). This symptom can be most likely connected to a given date, because rash occurs in approximately 80% of infected persons (Steere 2008) and the average appearance of the EM is 7-10 days. The different forms of LB have different incubation times. The main vectors for humans are infected adults and nymphs. Nymphs feed on their hosts for 3-7 days and their shedding lasts for 2-6 months.The adults feed on the animals or humans for 1-2 weeks and it may take some weeks or months, but in the case of EM (approximately 49% of the whole cases in Hungary, Lakos 1991) it needs 7-10 days on average, but it can extend to 3-4 month.

(Kapiller and Szentgyörgyi 2001, Lakos 1991, 1992, 1994, 1999, CDC-Lyme). The incubation time of the neurological manifestations (approximately 33% of the whole cases in Hungary; Lakos 1991) is the most similar to the ECM: 10-50 days, the median is 32 days (Lakos 1991). The longest incubation time (1-3 years) was found in the case of a rare symptom, acrodermatitis chronica atrophicans in Hungary (Lakos 1991). Most of the frank arthritis forms need to develop from several months to two years about one fifth of the LB cases in Hungary (Lakos 1991). Overall we can say that approximately 80% of the LB cases belong to a kind of manifestation form which has a 1 to 8 weeks long incubation period and most of the skin and neurological symptoms havea two to four weeklong latency.

1.7.2. WEST NILE FEVER

1.7.2.1. The causative agents of West Nile Fever and its vectors

WNF is a mosquito-bornezoonoticarbovirus caused disease. The West Nile Fever Virus (hence: WNV) itself belongs to the family Flaviviridae. The most common vectors of WNF are *Culex* species. Since the adult mosquitoes have good flying ability, their expansion can be rapid. They are vectors of many serious viral infections, such as WNF and Chikungunya disease which are re-emerging or emerging diseases in the Northern Hemisphere (Gould and Higgs 2009).

1.7.2.2. The geographical range of West Nile Fever in Europe

While the potential mosquito vectors of WNV live in the entire Holarctic biogeograpic zone, theoretically WNV may be endemic throughout Eurasia and North America. In contrast to the theoretical investigations historical presence of WNF was less abundant. Forthis reason I aimed to study the climatic requirements of the disease itself and not those of the potential vectors. According to Spielman (2001),*Culex* mosquito populations begin to proliferate when the water temperature exceeds 15°C during June, so the first stable week, when the ambient temperature reaches the 15°C can be used as the start of the WNF season.

1.7.2.3. The predicted effect of Global Climate Change on West Nile Fever

Many of the potential vectors of WNV are native in Europe. As is expected the climate in the Carpathian Basin will be warmer, more arid, and will have extreme rainfalls more frequently in the colder half-year (Bartholy et al. 2007). The increased frequency of heavy rainfall events, with the consequential floods may increase the incidence of mosquito-borne diseases and water-borne diseases (Hunter 2003). Many authors consider that the GCC still has an effect on the recent range and outbreaks of WNF epidemics (Platonov et al. 2008, Paz 2006) and/or will increase the geographical distribution in the future due to GCC (Semenza and Mene 2009, Gould and Higgs 2009) and the season length. Since according to Kilpatrick et al. (2008), Reisen et al. (2006) and Spielman(2001) the temperature derived transmission of WNV from *Culex* mosquitoes to humans occurs between 14–15°C, the ambient mean temperature of 15°C was handeled as the minimum temperature limit of the WNF season.

1.7.2.4. Other factors of the distribution: migrating birds, rivers, wetlands

Not only climatic factors determine the distribution of WNF. The principal vectors of the virus, WNV in Europe are *Culex pipiens* complex and *Culex modestus* (in Russia also ticks, while migrating birds are the most important reservoirs and propagators of WNV) (McLean et al. 2001, Reed et al. 2003). Mosquitoes transmit the virus to birds, and then the next generation of the virus will infect the biting mosquitoes.The mean water level and the changes of the water level of the rivers may have an important influence on the mosquito season.WNV (a member of Flaviviridae) originally was autochthonous in Africa prior tothe 1990’s and it was first isolated in 1937 in the Sub-Saharan WestNile territory of Uganda. Then the virus was isolated from humans, birds, and mosquitoes in Egypt (Nile delta) in the early 1950’s (Hubálek et al. 1999). It appeared at first in Europe in Albania in 1958 (Bárdos et al. 1959) and many of the early larger outbreaks were reported from the river deltas: from the Rhone delta in 1963 (Hannoun et al. 1964), the Rumanian Danube delta in 1971 (Topciu et al. 1971) and the Volga Delta in 1964 (Chumakov et al. 1964).Bird migration is the most important way of WNF/WNV introduction to the temperature areas (Malkinson et al. 2002, Reedet al. 2003). It is clear that rivers and riverbanks, coastal plains and deltas are the gathering and feeding places of migrating birds (Malkinson et al. 2002). In Hungary also most of the cases occurred near to riversides, mainly alongthe Tisza, Zagyva and Rába as was seen in 2008. (Krisztalovics et al. 2008).There are threemain migration routes between Africa and Eurasia (via Gibraltar, via Sicily, via Sinai) (***Fig.6A***) and one of them (***Fig. 6A***, red lines) makes connection between Eurasia and the Eastern Sub-Saharan Africa, e.g. the West Nile territory (***Fig.6B***), which is the most important migration route of the white stork (*Ciconia ciconia*Linnaeus 1758) (Berthold 2004) which bird species itself an important introducer of WNF (Malkinson et al. 2002). It seems to be that migratorybirds are the most important introductory hosts for the virus (Rappole and Hubálek 2003). According to Jourdain et al. (2007) the risk of the introduction of African pathogens, such as WNF into Mediterranean wetlands may be the highest from March to July, which is in accordance with the spring migration and breeding for birds.

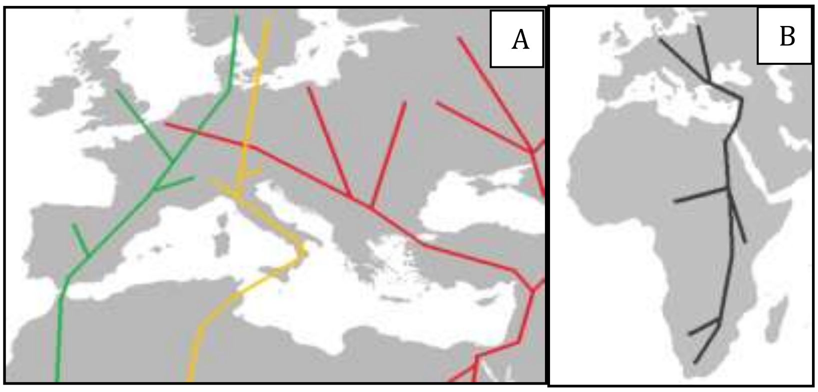


Fig.6A The simplified scheme of the main migration routes of birds between Africa and Europe. Red: Via Sinai per the Middle East from East Africa to Central and Eastern Europe, Yellow: Via Sicily per the Apennine Peninsula, Green: Via Gibraltar per the Hispanic Peninsula. The composite figure was mainly based on the migration routes of different birds of the homepage Global Register of Migratory Species. (**Fig.6B**) The right picture shows the eastern migration scheme route of white stark according to the Global Register of Migratory Species, *Ciconia ciconia* Linnaeus (1758). Note, that the West Nile territory is an important part of their migration route.

1.7.3. AEDES ALBOPICTUS MOSQUITO

Aedes (*Stegomyia*) *albopictus* Skuse (1984) originally indigenous to South-east Asia, islands of the Western Pacific and Indian Ocean and only in the last decades of the

20thcentury colonized Europe, the mid-east, Africa and the Americas (Gartz 2004). *Aedes albopictus* is considered the first in the case of the transmission of Chikungunya disease in the Mediterranean and also has an importance as potential vector of Dengue fever (Knudse et al. 1996), WNF, St. Louis encephalitis and filarial nematodes (Hochedez et al. 2006, Cancrini et al. 2003). In the Mediterranean Basin, the geographical expansionof the mosquito was observed during the past few decades, which can indicate the northward progressionof the mosquito and its parasites into other parts of the Old Continent (Knudse et al. 1996, Mitchell 1995). It is notable, that while the first observation of the establishment of *Ae.albopictus* in Italy was observed only in 1991 (Dalla Pozza and Majori 1992), the first outbreak of Chikungunya fever happened in 2007 in Italy (Rezza et al. 2007).Chikungunya virus belongs to the family Togaviridae and is usually transmitted to humans by *Aedes*mosquitoes (e.g. the Asian tiger mosquito). Before 2006 Chikungunya disease and the *Aedes* mosquitoes weremainly reported from the Sub-Saharan Africa, the Hindustan Peninsula and Southeast Asia, but now the vector, *Ae. albopictus*, is widely present in the Mediterranean Basin (in Spain, France, Italy, Slovenia, Croatia, Serbia, Bosnia and Herzegovina, Albania, and Greece; (Benedict et al. 2007, Scholte and Schaffner 2007). In the neighbouring countries of Hungary, the first observations of the tiger mosquito were recorded in 2006 in Croatia (Klobučar et al. 2006) and also in 2006 in Slovenia (Petrić et al. 2001). A few years earlier, in 2001 the presence of *Ae.albopictus* was suspected in Hungary, so in the last decades the spread of the mosquito was continuous in Europe (Scholte and Schaffner 2007).

1.7.4. LEISHMANIASIS

1.7.4.1. The worldwide importance, the hosts and the causative agents of leiahmaniasis

In the subtropical and tropical areas of the World, leishmaniasis is one of the most important human VBDs with more than 12 million infected people (Naderer et al. 2006) and an emerging disease in Europe (Shaw 2007). Two *Leishmania* species can threaten the human population of the EU: *L.infantum* and *L.tropica,* both endemic to the old Continent (Ready 2010).*L. infantum* is one of the causative agents of zoonotic visceral and cutan leishmaniasis in both humans and the reservoir animals (Ready 2010). *L.*

tropica cause anthroponotic cutaneous leishmaniasis. Members of the genus *Phlebotomus* (sandflies) are the primary vectors of the protozoan parasite genus *Leishmania* in the Old World. Other sandfly vectors of *Leishmania* parasites can be found in the subgenera *Larroussius* and *Adlerius* (Killick-Kendrick 1990). In the Mediterranean Basin, leishmaniasis is mainly a zoonosis, because the main reservoirs of *Leishmania* parasites are dogs (Shaw et al. 2003), foxes, rodents, but some studies showed, that cats and horses can be good reservoirs as well (Sánchez et al. 2000, Pennisi 2002, Köhler et al. 2002, Solano-Gallego et al. 2003), but an anthrogenic cycle is also possible (Alvar et al. 1997). The observed distribution of canine leishmaniasis (CanL) is similar to that of the human visceral leishmaniasis (Lindgren and Naucke 2006, Solano-Gallego et al. 2011). *Phlebotomus* species are the main vectors in Eurasia and *Lutzomya* species in the New World. These vectors in general have a wider area than leishmaiasis itself (Lindgren et al. 2004), so the expected future migration of sandflies due to the GCC does not imply a similar spread of the disease in to the northern regions of Europe.

1.7.4.2. The studied sandfly species

*Phlebotomus*species(sandflies)also belong to the suborder Nematocera as mosquitoes. To demonstrate the phylogenetical relationship between sandfly and mosquito species I present the taxonomic classification of the sandfly *Phlebotomus masc*ittii Grassi (1908)and the mosquito *Aedes aegypti* Meigen (1818):

Kingdom: Animalia	**Kingdom**: Animalia
Phylum: Arthropoda	**Phylum**: Arthropoda
Class: Insecta	**Class**: Insecta
Order: Diptera	**Order**: Diptera
Suborder: Nematocera	**Suborder**: Nematocera
Infraorder: Psychodomorpha	**Infraorder**: Culicomorpha
Family: Psychodidae	**Family**: Culicidae
Subfamily: Phlebotominae	**Subfamily**: Culicinae
Genus: *Phlebotomus*	**Genus**: *Aedes*
Species:***Phlebotomus mascittii***Grassi (1908)	Species:***Aedes aegypti***Meigen (1818)

Phlebotomus species are typical Mediterranean faunal elements (Aspöck et al. 2008). The geographic distribution of leishmaniasis is limited by the distribution of the different *Phlebotomus* species. *Phlebotomus (Larroissius) ariasi* Tonnoir (1921), *P. perniciosus* Newstead (1911), *P.tobbi* Adler and Theodor (1930), *P.perfiliewi* Parrot (1930) and *P.neglectus* Tonnoir (1931) are vectors of *Leishmania infantu*m Nicolle (1908); *Phlebotomus. papatasi* Scopoli(1786) is the vector of *Leishmania. donovani* Laveran et Mesnili (1903), *L. killicki* (Taxonomy ID: 40286), *L. tropica* (Wright 1903), *L. arabica* (taxonomy ID: 40284) and *L. majo*r (taxonomy ID: 5664); *Phlebotomus sergenti* Parrot (1917) can transmit *Leishmania tropica* and *L. major*; *Phlebotomus similis* (taxonomy ID: 132724) has the ability also to transmit the*Leishmaniatropica* (Minter 1989, Killick-Kendrick 1990, WHO 1984, Léger et al. 2000). The classification was based on the Systematic Catalog of Psychodidae homepage and the NCBI Taxonomy browser. The most common vectors of the parasite *Leishmaniainfantum* are*Phlebotomus ariasi* and *P. perniciosus* in Europe. Sandfly bites can be extremely irritating and cause secondary bacterial infections by the excoriated urticarias (Adler and Theodor 1957, Perfiliev 1966). The adult females of sandflies feed on blood. In the temperate areas of Europe the species can overwinter as third- or fourth -instar larvae (Ready and Croset 1980). In contrast to mosquitoes, the larvae of sandflies live in wet surfaces and feed on the microbial mats of rifts and wet stones, under dead leaves, but some species prefer the man-made environments (eg. ruins). Heat, humidity, and sufficient organic matter are the main requirements of the larval development of sandflies (Naucke 2002, Lindgren and Naucke 2006), while the increasing CO_2 levels are usually unfavourably affecting the development of the insect larvae (Kocsis and Hufnagel 2011). The taxonomy data were based on the NCBI taxonomy browser and Psychodidae homepage.For the overwiev of the transmitted parasites and the taxonomic classification of the studied sandfly species see the ***Annex Spreadsheet 6.***

1.7.4.3. Global Climate Change and leishmaniasis

According to Mahamdallie et al. (2011) and Esseghir et al. (2000) sandflies could follow the glacial climate variations during the Pleistocene (2,588,000 to 11,700 years ago) in the Mediterranean region and survived the glacials in refuges within Europe. Over the last decade the endemic regions of leishmaniasis have been spreading and the sharp increase of the human leishmaniasis was observed (Ready 2008).The northward expansion of the disease was also observed in North America (González et al. 2010). Using the climatic suitability model, Fischer et al. (2010.2011) predicted avery likely further northward expansion of the vectors of leishmaniasis in this century. One of the first signs of the establishment in a new area of leishmaniasis is that the parasite makes new autochthonous foci in the dog population (Ferroglio et al. 2005, Maroli et al. 2008). Despite the fact, that Germany is within a non-endemic region (Slappendel RJ and Teske E 1999), there are leishmaniasis cases reported from dogs and horses where some case history suggests autochthonous infections which verify the presence of sandflies within the heart of Central Europe (Köhler et al. 2002, Mencke 2011). In Hungary in 2007 and 2008 autochthonous *Leishmaniainfantum* CanL cases were observed in Tolna County (Tánczos et al. 2012). The presence of *Phlebotomusneglectus* and *P. perfiliewi* in Hungary is also verified (Farkas et al. 2011). The recent area of leishmaniasis is increasing: in Italy where *P. perniciosus* is the main vector of the parasite (Gradoni et al. 1980, Maroli et al. 1988, Bongiorno 2003) the northward expansion of visceral leishmaniasis (caused by *Leishmania infantum*) has been observed (Maroli et al. 2008). *P. perniciosus* spread to new continental climate areas due to either passive expansion from endemic localities and migration on small distances from neighbouring endemic areas (Ferroglio et al. 2010). Northward expansion of leishmaniasis has potential hazard from the recently autochthonous areas not only in Europe, but also in North America: Mexico and Texas (González et al. 2010). Models of climatic suitability have shown that we have to expect the presence of sandflies and leishmaniasis in Central Europe by the end of 21st century (Ready 2008, Fischer et al. 2010, Fischer et al. 2011a and 2011b). Ecological climate modeling seems to be useful to model the present and the potential distribution of the *Lutzomyia*spp.which are close relatives of the genus *Phlebotomus,*as well (Colacicco-Mayhugh et al. 2009). Travelling and long-distance transport are also can be an important determinant of the future abundance (Ready 2010). Rioux et al. (1985) found that the raising of temperature significantly increased the overall proportion of infected sandflies.

1.7.4.4. The climatic and microclimatic (habitat) requirements of sandflies

In contrast to mosquitoes, sandflies can lay their eggs directly on wet surfaces and they do not need open water surfaces. In Southwest Asia the distribution of *Phlebotomus papatasi* is highly dependent on temperature and relative humidity (Cross and Hyams 1996). According to Naucke (2007) and Lozán et al. (2008) the annual mean temperature of at least 10°C is considered to be suitable for the vector. *P. papatasi* prefer the areas where the mean minimum temperature is at least 16°C and mean maximum temperature doesn't exceed 44°C from May to October (Cross et al. 1996). In warm and wet environment *P. papatasi* can be found at elevations cca. 1 to1100 m above sea level (Belen et al. 2004). The larval stage of sandfly species needs a special microenvironment with sufficient organic matter, huge humidity and moderate temperature (Naucke 2002, Lindgren and Naucke 2006). In contrast to the complexity of the environmental requirements of the ontogeny of these insects, they can have their larval development in man-made environments (old buildings, rifts on the walls; Killick-Kendrick and Killick-Kendrick 1987, Naucke 2002) and in nature (surface of fallen dead leaves, forest floor; Hanson 1961). The larvae of different *Phlebotomus* species have different minimum temperature tolerances, usually it is between -4 – 5°C (Lindgren and Naucke 2006), but the adult individuals can survive in colder temperatures. The preferred humidity for adults is between 60-80% for *P. neglectus* and*P. perfiliewei*, and below 45% for *P. Papatasi and P. sergenti* (Lindgren and Naucke 2006). The differences in the environmental requirements between *Phlebotomus* species are noticeable in their different habitats: in France *P. ariasi* mostly live in the wet and mild climate of mountain forests, while *P. perniciosus* occupy the warm and drier Mediterranean coastal plains (Chamaillé et al. 2010). While the number of the days with suitable temperature for the reproduction and for the growing of the larvae, and the moisture index have a strong link with the ontogeny and growth of immature sandflies (Killick-Kendrick 1987, Oshagi et al. 2009), low temperatures and precipitation are expected to impose direct or indirect constraints on *Phlebotomus* distributions.

2. AIMS AND SCOPE

My aim was to studythe potential effect of the changing seasonal and human activity patterns due to climate change and the regional climate differencesondifferent vector-borne diseases as LB, leishmaniasis and WNF and the migration of *Aedes albopictus* mosquitoes in Europe and Hungary. In the case of LBthe effectsof climate change in the last decadeon the seasonality of LB also were studied. Our further aim was to study the influence of the ambient temperature and floods on WNF case number and to create a model to take into consideration the potential future distribution of WNV. It was also aimed to bind some indicator plants to the Mediterranean originated *Phlebotomus* vectors. Furthermore the potential expansion of some important vectors as *Phlebotomus ariasi*, *P. neglectus*, *P. perfiliewi*, *P. perniciosus*, *P. tobbi and Aedes albopictus*, and the potential future geographical occurrence of two important vector-borne diseases (leishmaniasis and West Nile fever) were modeled 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.

3. MATERIALS AND METHODS

3.1. DATA SOURCES

3.1.1. THE SOURCE OF THE DATA OF THE DIFFERENT VECTOR-BORNE DISEASES, ITS PARASITES AND PLANTS

Data on the weekly incidence of clinically, serologically identified LB cases for the period 1998-2012 were retrieved from the Hungarian National Epidemiological and Surveillance System (OEK 2013). While the Hungarian mandatory system does not distinguish between the infection forms the "case" was defined as any kind of early or late infection form of LB disease. The diagnosis in our database may be based on 3 main criteria: persons with typical EM symptoms, persons with late clinical manifestations (arthritis and/or cardiac, neurological disorders, late phase EM), and persons with laboratory confirmed LB with or without symptoms by ELISA, western blot or VlsE lipoprotein IR6 antibody serological tests. Since in the studied period LB showed an increasing trend with high variance, the weekly relative (percent per year) LB incidences were used in the model. It is very important to note that I retained the term "incidence" because originally the percentages of the weekly LB values werecalculated from weekly incidence values. Naturally the precise term of incidence (rate) is the number of new cases per population in a given time period. Hereinafter I will refer to the percent per year of the weekly LB incidences as weekly relative LB incidences (RI).The distribution data of *Leishmaniainfantum* were derived from observations in 2003 (Trotz-Williams and Trees 2003). The studied the following European *Phlebotomus* species: *P.ariasi, P. neglectus, P., P. perfiliewi, P. perniciosus, P. sergenti, P. similis*and*P. tobbi.* It were also examined the potential climatic requirements of *P. similis, P. sergenti* and *P. papatasi*, which are not vectors of *L.* infantum, but of other important *Leishmania* species in Southern Europe. Distribution of the *Phlebotomus*species in 2012 was obtained by VBORNET (2012).The Hungarian WNF data werederived from the Hungarian Epidemiological and Surveillance System and Epinfo (2010A) and Epinfo (2010B) and Krisztalovics et al. (2008). I could gain the geographical distribution data of the years 2008, 2010, 2011 and 2012. The European occurrence of WNF was also gained from the European Centre for Disease Prevention and Control homepage and from the European Disease and European Centre for Disease

Prevention and Control (ECDC) homepage (ECDC 2012 and 2011). Furthermore,it was also used a publication of the Eurosurveillance journal (Krisztalovics et al. 2008).The distribution data of *Aedes albopictus* was derived from the European Centre for Disease Prevention and Control's VBORNET (according to the 2012 September's stage) database (Medlock et al. 2012).

3.1.2. CLIMATIC DATA OF HUNGARY, EUROPE AND THE REMO CLIMATE MODEL

Since the climatic and the geographical conditions are very homogenous in Hungary, the Country was considered as a homogenous unit. The daily mean temperature data were derived from the European Climate Assessment Dataset (Haylock et al 2008, Tank et al. 2002). Average values were calculated from the 0.25° grid within the domain including almost the entire Hungary (***Fig.7A***). The latitudinal rangewas 45.77°N-48.56°N, while the longitudinal was 16.15°E-22.85°E. The weekly mean ambient temperature (T) values were calculated from the daily mean temperature data with the simple averaging method. Temperature values were derived from the period of 1.1.1998-10.31.2012. Regional differences in the weekly LB incidence were studied in two North-Eastern and three South-Western counties in Hungary. In this study I used descriptive statistics, the associations were analysed by linear and polynomial regression models.The European climate data were obtained from the regional climate model (RCM) REMO, which was developed in Hamburg (Jacob et al. 1997, Jacob et al. 2001). The horizontal resolution of the grid is 25 km (***Fig.7B)***. The model REMO is based on the ECHAM5 global climate model (Roeckner et al. 2003, Roeckner et al. 2004) and the IPCC SRES A1B scenario. The A1B scenario supposes very fast economic increase, worldwide population that peaks in the mid of the 21st century, and the introduction of innovative and efficient technologies (Nakicenovic and Swart 2000). The reference period of REMO is 1961-1990, the two future periods of modeling are 2011-2040 and 2041-2070. The horizontal resolution of the grid was 25 km. However the entire European Continent is within the domain of REMO, only a part (25724 of the 32300 points; ***Fig. 7B***) of the grid was used in the model.

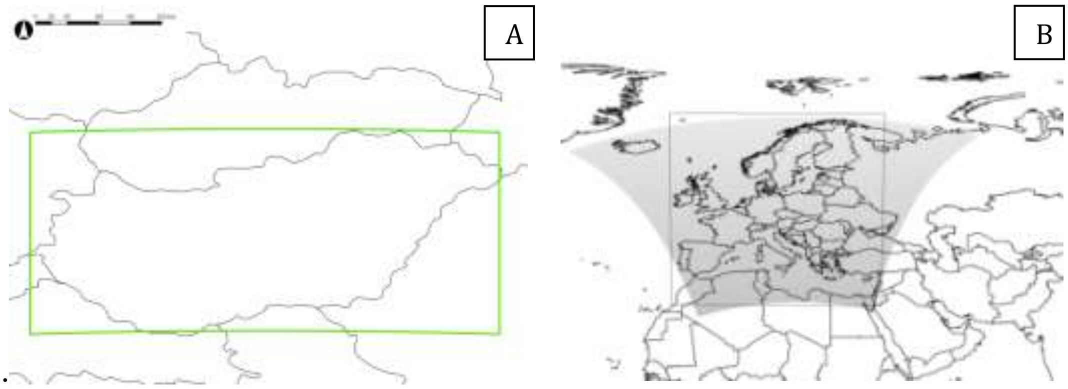


Fig.7A The “Hungary domain” and **Fig.7B** the “Europe domain” used in the CEM

Altogether 36 climatic variables were averaged in the 30-year-periods and used by the model: monthly mean temperatures (Tmean, °C), monthly minimum temperatures (Tmin, °C), and monthly precipitations (P, mm). Climate is the major driver of species distributions over Europe, and at the European coarse resolution, land cover is mainly driven by the climate, mainly by temperature and precipitation (Thuiller et al. 2004). The REMO model projects that the summer temperatures will increase by more than 2.5°C in the Mediterranean area, in Central Europe by less than 1.5°C and in eastern Europe by about 1°C or less by 2050. The simulated warming is typically between 1.5°C and 2°C in most parts of Europe in winter. Although the precipitation in the Mediterranean area decreases by up to 50%, the precipitation increases in large, even the northern, parts of Europe in autumn and winter (Max-Planck-Institut 2007).

3.1.3. THE HUNGARIAN POPULATION DATA

The population in 1998 was 10,280,000 and in 2012 was 9,958,000 inhabitants (-3.13% total decline per 15 year) (KSH 2013a). The population of Hungary was considered for the entire 15 years to be 10,000,000 inhabitants. The population of Hungary in 2012 was 9,958,000 (KSH 2013a). While the weekly percentiles of the annual LB incidences were used, the changing population didn not influence the model. The regional WNF incidence rate of 2008, 2010, 2011 and 2012 (5 years-long short interval) were studied.

3.1.4. CAMPING GUEST NIGHTS

The monthly guest nights data were derived from the KSH (2013b) database for the period of January 2008-October 2012. The data of guest nights spent at camping sites were used. The summarized annual guest nights were 491; 459; 380; 435; 436 (without the missing data of November and December) thousand, respectively.

3.1.5. THE USED CLIMATE INDICATOR PLANTS RELATED TO THE MODELING OF THE EUROPEAN RANGE OF THE MOST IMPORTANT PHLEBOTOMUS SPECIES

Climate change will affect the geographical distribution of the distribution of forest plants in Europe (Skov F and Svenning JC 2004).Three typical Mediterranean ligneous plants (***Fig.8***) were used as the geographical-climatic indicators of the studied sandfly species: *Juniperus oxycedrus* Linnaeus (1758) - (Prickly Juniper, Prickly Cedar, Cade Juniper), *Pinus brutia* or *Pinus halepensis subsp. brutia*Tenore (1811) - (*eng.*: Turkish Pine), and *Quercus ilex* L. (*eng.*: Holm Oak or Holly Oak). Distributions of *Juniperus oxycedrus*, *Pinus brutia*, and *Quercus ilex*Linnaeur 1758 were derived from Tutin et al (1964), EUFORGEN (2009), and Meusel et al. (1965), respectively. After a georeferencing process with 3rd order polynomial transformation, the digitization of the bitmap-format distribution maps were realized with the assistance of the digital NUTS3 polygon borders (GISCO 2013).

Fig.8. The habitus picture of the used indicator plants

3.1.6. THE HYDROLOGICAL DATA OF THE RIVERS TISZA AND DANUBE

The hydrological data of the river Tisza in the period of 2007-2012 were retrieved from the National Water Warning Network of Hungary (Hydroinfo 2013). The monthly water levels from May to September were averaged. To depict the annual amplitude of the water regime the difference between the annual maximum and minimum water levelswere used.

3.2. SELECTION OF THE TWO STUDIED HUNGARIAN REGIONS

Descriptive statistics, and linear, polynomial, exponential and Gaussian regression by PAST statistic analyzer (Hammer et al. 2001) and Microsoft Excel Solver add-in were used for this research. I selected counties with similar level of forestation, similar number of inhabitants and order of LB incidence. Forestation data wereretreiwed from a Hungarian data source (Erdőterület, erdősültség, 2006). The cumulative number of population of the three South-Western (SW) counties (Zala, Somogy, Baranya) was 1,002,977 inhabitants in 2010 and the number of population of the North-Eastern (NE) counties (Nógrád, Borsod-Abaúj-Zemplén) was 897688 inhabitants (KSH 2010) in the same year (2010). To calculate the LB incidences the population numbers of 2010 were used. The population ratio of the NE/SW counties was 0.895 - a slight difference (10.5%) exists between the two study regions. The mean forestation of the 3 SW counties: (27.74%) and the forest cover of the 2 NE counties (32.70%) is very similar, only a 15.16% difference exists (Komarek 2005). The difference between the cumulative LB incidences in period 1998-2010 of the 2 regions is not too high (NE counties: 298.99/100,000 and SW counties: 244.73/100.000), an 18.2% difference exists. So, the difference of the mean forestations and the cumulative LB incidences was similar: 15.16% - 18.2% for the 13 year period.

The plan view-like visualisations of the ***Annexed Charts1***, ***2***, ***3***, ***6*** and ***7***were prepared in ArcGIS 10.1 software.

3.3. MODELING STEPS OF THE RECONSTRUCTION OF THE LB SEASON

3.3.1. Modeling approach

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. The model was constructed to calculate the weekly relative incidence (*RI*) values of a certain week based on the weakly mean temperature (*T*) and the week number. Since the human and the tick activity are both positively correlated with the outdoor temperature,our first approach was that RI is the function of both a temperature dependent activity factor of ticks and humans (*A*), and a temperature independent component of activity (*IA*). *IA* may be related to the actual questing, hungry active tick population, and non-temperature climatic factors, and is the abstraction of the seasonality and population dynamics of ticks. Furthermore the human activity may have an additional effect in the summer holiday times (holiday multiplier, *HM*). The two approaches can be formed in simple equations (*Eq.*[1],*Eq.*[2]).

$$RI = A \times IA \qquad [1]$$

$$RI = A \times IA \times HM \qquad [2]$$

3.3.2. RELATIVE WEEKLY INCIDENCE AND THE TECHNICAL LYME BORRELIOSIS YEAR

The lowest LB incidence in the studied period was 9.93 per 100,000 in 1999 and the highest was 23.05 per 100,000 in 2010. Since in the period of 1998-2012 the incidence of LB nearly doubled, a variance analysis was made to analyze whether the trend was significant or not. In case of significant trend relative (%) incidence should be used instead of absolute incidence. At first, I calculated the LB incidence form the weekly cases. The occurrence of LB in Hungary can be highly underestimated since the number of patients affected at any one time could be as much as 10% of the population, (Bozsik 2004) and in the neighbouring countries the incidence was much higher during the past decade: the incidence of the disease has been more than 100 per 100,000 in Austria and more than 200 per 100,000 in Slovenia as Lipsker and Jaulhac(2009) described. Higher temperatures are needed for metamorphosis, egg hatching, between minimum 8-11°C (Daniel 1993) or 5-7°C (Campbell 1948). Perret et al. (2000) found that when the 5-days average of the daily maximal temperature was over 7°C tick questing activity was always observed. The nymphal activity starts when the maximum air temperature reaches about 10°C (Randolph 2009) or 8°C (Tagliapietra et al. 2011). It was found that in general the 11th week is the first stable spring week, with the T higherthan 5°C, which is not followed by a week with T less than 5°C (mean: 11.133; the week numbers are 13,12,12,10,8,12,11,11,12,9,12,12,11,11,11 for the 15 studied years, respectively). Technical years from the average start of the LB season were used from the 11th to the next year's 10th week in the calculation of *RI*. In conclusion the period of 03.16.1998-03.11.2012 were used for the modeling.

3.3.3. HUMAN OUTDOOR ACTIVITY

Human activity may have a great influence on the annual LB incidence (Šumilo et al. 2008, Randolph 2010). I found that many other accommodation types show clear seasonality, but camping was the most suitable approach, because the inside temperature of tents depends directly on the outdoor temperature and humans prefer the sunny, mild and windless days as ticks as well. The camping guest night data were used to describe the temperature dependence of the human willingness and seasonality to staying in nature.While the database contains monthly data linear interpolation were used for two weeks periods to gain higher resolution. The monthly mean temperature showed a strength correlation with the monthly number of camping guest nights. Our previous observations showed that without the July and August data the remained 10 month show a Gaussian-like run. A Gauss-curve was fit on the guest nights without the period of 13th to 18th two weeks (the omitted period showed an irregular run) by minimizing the sum of squared deviations by Microsoft Excel's Solver add-in. Because summer is the time of holiday activity, this irregular run can be the consequence of the holidays and the school holidays. After the Gaussiancurve was fitted, the observed/calculated ratio (multiplier) of the irregular week pairs could be calculatedto characterize the effect of the summer holidays on human activity. In case of the irregular two weeks, in the further calculations these ratios were used as a multiplier (hereinafter called holiday multiplier (*HM*)), while in the case of the non-irregular weeks the *HM*was thought as 1.

3.3.4. TEMPERATURE DEPENDENT ACTIVITY

The correlation between the *RI* and *T*was analyzed to determine an exponential connection (hereinafter called activity (*A*)). Theoretically the chance of the human LB-infection is related to both outdoor human and tick activity (*Eq.* [3]).

$$RI \sim A_{human} \times A_{tick} \qquad [3]$$

An exponential regression model was made without July and August on human camping (outdoor) activity and temperature. This finding showed that both human outdoor activity and *RI* showed a very similar, exponential correlation with temperature. Hence, I did not distinguish the temperature related tick and human outdoor activity, but summarized the temperature dependence in one variable (*A*). Our database is a mixture of early localized and disseminated, and late disseminated cases. The EM gives the base of our model since this can be directly tied to the time of the biting in most cases. Approximately 80% of the LB cases symptomatically belong to EM, the early, non-disseminate infection form (Steere 2008). An exponential regression model was made calculating with the weeks when the mean ambient temperature was more than 5°C and omitting the weeks with 0 LB cases to the peak of the LB season, practically to the 26th week. The *RI*was used only in the increasing phase (1st to 26th weeks) of the LB season, because (1) in spring the soil moisture and the air vapour content is relatively high due to the low evaporation of the previous seasons (low relative humidity is important limiting factor of tick activity); (2) the relative number of the primer manifestations can be higher than in the later part of the LB season; (3) in spring and early summer according to Széll et al. 2006 the activity of nymphs is the dominant. I was very important to remove the non-relevant, cold weeks from the data, where there is not real tick activity. Using this „false" LB incidence values may imply that there is no threshold for the tick activity. This removing method is useful to also avoid the false effect of the late manifestations of LB in winter time when calculating the temperature – LB incidence correlation. The weeklynumbers of the maximum of *RI* were 27, 27, 24, 26, 27, 25, 28, 25, 26, 24, 24, 27, 24, 29, and 28 for the studied 15 years, respectively (mean: 26.07). A linear regression was made to know whether a significant trend exists in the run of the annual maximum LB incidences in the studied period. The change in the time of the peak did not show significant trend. This result implicate that the 26th week can be usedas the peak of the LB season which did not change during the 15 years.

3.3.5. USING LAG

It is important to note, that the different forms of LB have different incubation times. The main vectors for humans are infected adults and nymphs. Nymphs feed on their hosts 3-7 days long and their shading lasts 2-6 months; the EM appear within 7-10 days on average, but it can take up to 30 days before the EM become visible. (Lakos 1991, Lakos 1992, Lakos 1994, Kapiller and Szentgyörgyi 2001, Bacon et al. 2008).There is a lag from tick biting to the observation and to the appearance of the case in the surveillance (report) system. To analyze the effect of the lag the 0, -1 and -2 week lagswere used. In addition it was studied whether the exponential regression is stronger in case of the *HM* is part of the expression (dependent variable is not *RI* but *RI/HM*).The temperature independent component of the activity (IA) was calculated by using polynomial regression of the *IA=RI/A* correlation. The aim was to find the correlation between the number of weeks and *IA*.Only the weeks from the 11th weeks with continuous periods were used, when the temperature was always more than 5°C. Three different approaches were made: (1) the effect of the summer holidays (*HM*) was not taken into consideration (*IA1*); (2) the effect of the summer holidays was added to the model and the entire year was regressed (*IA2*); (3) and a hybrid model (*IA3*) was made: only the period of the year was regressed when the *HM* had a visible effect on the run of the population curve (25th to 35th weeks), and the*IA1* curve was used beyond this period. Note that *IA3* is a composite function (not continuous). The modelled results and thenthe observed *RI* in the period of 03.16.1998 to 03.11.2012 were compared. An error evaluation (*R2* and summarized absolute error) was made to compare the different models. Three approaches wereconsidered: 1) $A\times P1$; 2) $A\times P2\times HM$, 3) $A\times P3\times HM$. The observed and modelled*RI*, the error and absolute error were displayedfor the entire analyzed period.

3.4. MODELING THE RECENT AND FUTURE OCCURRENCES OF *LEISHMANIA INFANTUM* AND THE DISTRIBUTIONS OF THE EUROPEAN *PHLEBOTOMUS* SPECIES

3.4.1. THE MAPPING PROCESS OF THE OBSERVED OCCURRENCES

Our model was run on the distribution of *Leishmania infantum*, and the eight *Phlebotomus* species, separately. I focused on the European distribution of sandfly species. It is known, however, that *Phlebotomus* species inhabit some North African territories too, such as *P. sergenti* (Depaquit et al. 2002, Lewis 1982), and *P. ariasi*, *P. papatasi*, *P. perfiliewi*, *P. perniciosus* and *P. tobbi* (Lewis 1982). The presence also of *Leishmania infantum* in North Africa was proven by Postigo (2010). The reason why I focused on the European sandfly populations was that there are few and sporadic sandfly species-specific detailed geographical data from North Africa and Asia Minor, while in Europe we have more reliable and actual data thanks to the surveillance systems of the European public health centres. Since the model studied the climate requirements only of the European *Phlebotomus* populations, it was able to project the shift of this part only. Only the continuous (not discrete) distribution data were taken into consideration where the force of infection was greater than zero. Weighting procedures were not used; the map of infection was reduced to a simple presence-absence map. The regions entitled as ‘indigenous’ and ‘recently present’ were utilized with the same weight. All the *Leishmania* and *Phlebotomus*distribution data were based on the NUTS3 (Nomenclature of Units for Territorial Statistics) regions, which are the third level public administration territories of the European Union. After a georeferencing process with 3rd order polynomial transformation, the digitization of the bitmap-format distribution maps were realized with the assistance of the digital NUTS3 polygon borders (GISCO 2012).

3.4.2. SELECTION OF THE DOMAIN WITHIN REMO AND THE CLIMATIC FACTORS

Although the entire European Continent is within the domain of REMO, only a part (25,724 of the 32,300 points) of the grid shown in 6 was used. For the distribution modeling, 36 climatic variableswere used: monthly mean temperature (Tmean, °C), monthly minimum temperature (Tmin, °C), and monthly precipitation (P, mm). Indirectly, seasonality, accumulated heat and some other climate parameters were used and the vegetation was used in the model in a more indirect way. Climate is the major driver of species distribution over Europe, and at the European coarse resolution, land cover is mainly driven by climate, mainly by temperature and precipitation (Thuiller et al. 2004).

3.4.3. THE USED SOFTWARES

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. PAST statistical analyzer software (Hammer et al. 2001) was used for 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.

3.4.4. CLIMATE ENVELOPE MODELING

Ecological modeling methods are utilized in ecology to predict how species, diseases or ecological structures will respond to global warming or other changes in the ecological environment. To project the possible impact of GCC on the distribution of the selected vectors *Aedes albopictus,* the 8 *Phlebotomus* species and the occurrence of the disease WNF the CEM method was used (Bede-Fazekas and Trájer 2013). About modeling vector-borne diseases see Hijmans and Graham and Hijamans 2006, Peterson (2006). A genetic algorithm, the GARP program, was used for modeling the distribution of leishmaniasis (Nieto et al. 2006), sandflies (Peterson and Shaw 2003, Peterson et al. 2004), and other species (Gómez-Mendoza 2007). There are programs for CEM, such as MaxEnt (Phillips et al. 2006), BioClim (Busby 1986, Nix 1986), and Domain (Carpenter et al. 1993). From among them MaxEnt was used for studying sandflies in North America (González et al. 2010), Europe (Chamaillé et. al. 2010), the Middle East (Colacicco-Mayhugh et al. 2010), but also for studying the Asian tiger mosquito (Medley 2010) and other insects (Strange et al. 2011, Bidinger et al. 2012). Fischer et al. (2011a and 2011b) also used CEM to model the future expansion of *Aedes albopictus*. CEM is based on statistical correlations between the observed distributions of species (e.g. *Ae. albopictus* mosquito) or occurrences of diseases (e.g. WNF) and environmental variables to define the tolerance, the limiting ecological factors (e.g. minimum/maximum of temperature, precipitation, the length of the vegetation season) of the species or the disease (Guisan and Zimmermann 2000, Elith and Leathwick 2009). Based on this bioclimatic envelope – using a selected climate scenario – one can predict the probable future range of a species/disease. The hidden and sometimes arguable idea of the CEM is assuming that climate plays a primary role on the present and future distribution of the species. (Czúcz 2010). For example in case of a vector infectious disease the long-distance transport, the migrating workers and travelling can play a very important role as the determinant of the real geographical occurrence (Walther et al. 2009; (Neghina et al. 2009). According to Thuiller et al. (2004) climate has the greatest influence on forming the geographical distribution of the species in

Europe. Three physical (climate) factors averaged in the 30-years periods were used: the monthly mean temperature (Tmean, °C), monthly minimum temperature (Tmin, °C), and monthly precipitation (P, mm) of the 12 months. This means 3x12 factors in the model. Cumulative distribution functions were calculated by PAST statistic analyzer (Hammer et al. 2001) for the selected 3×12 climatic parameters (Tmean, Tmin, P) and 10-10% from the extrema in the case of *Ae. albopictus* and 5-5% from the extrema in the case of WNF were neglected from the climatic values found within the observed distribution/occurrence. The selection of the amount of percentiles to be left from the climatic values was based on our former studies. The aim was to restrict the false positive error of the model result in a reasonably degree. The climatic data was refined by Inverse Distance Weighted interpolation method of ESRI ArcGIS 10 software. The modeling steps were the follows: first, the grid points within the distribution were quoted; second, the percentile points of the climatic parameters were calculated; third, the suitable percentiles of the climatic parameters were chosen; fourth, modeling phrases (3 strings) were created by string functions of Microsoft Excel 2007 for the three modeling periods; fifth, the ranges were selected where all the climatic values of the certain period were between the extrema selected in step 3.

3.4.5. MODELING STEPS IN CLIMATE ENVELOPE MODELING

Distribution of the eight studied *Phlebotomus* species was aggregated, and the model for this collectivedistribution was run iteratively to investigate the optimal amount of percentiles to left from the climatic values. Cumulative distribution functions were calculated by PAST statistic analyzer (Hammer et al. 2001) for the 36 climatic parameters. During the iterative modeling 0+0 to 19+19 percentiles were left from the lower and higher values of certain types of climate parameters (e.g. mean temperatures), while the other 2×12 climatic parameters were fixed at the extreme values (0-0 percentiles were left). In the meanwhile two types of error values were calculated: 1) false negative, 2) false positive. They were summarized with the same weights divided between them. The point of minimum (the optimal number of percentiles to be left) of the accumulated error function was searched. It was found that the precipitation parameter drew quite different error functions than the temperatures, therefore iteration was run to study the difference between the lower and higher part of the precipitation percentiles. The two extrema of the minimum and mean temperatures were fixed, and iteratively more percentiles from the minimum of precipitation values were left while the maximum was fixed, and vice versa. The result of model calibration based on the aggregated *Phlebotomus* distribution was used during the modeling of the species. Then the climatic data were refined by Inverse Distance Weighted interpolation method of ESRI ArcGIS 10 software. The modeling steps were as follows in case of certain species: 1) the grid points within the distribution (a few thousand × 36 data) were queried; 2) the percentile points of the 36 climatic parameters (101×36 data) were calculated; 3) the appropriate percentiles of the climatic parameters (2×36 data) were selected; 4) modeling phrases (3 strings) were created by string functions of Microsoft Excel 2007 for the three modeling periods; 5) the areas were selected where all the climatic values of the certain period were between the extrema selected in step 3.

3.4.6. THE CALIBRATION OF THE CLIMATE ENVELOPE MODEL

For calibrating our CEM a union distribution of the eight studied *Phlebotomus* species, the Asian tiger mosquito and the WNF occurrence was created and the model for this aggregated distribution was run iteratively to investigate the optimal amount of percentiles leaving out from the climatic values. Cumulative distribution functions were calculated by PAST for the 36 climatic parameters. During the iterative modeling 0+0 to 19+19 percentiles were left from the lower and higher values of certain types of climate parameters (e.g. minimum temperatures), while the other 24 climatic parameters were fixed at the extreme values (0-0 percentiles were left). In the meanwhile two types of error values were calculated: 1) internal – the ratio of the current distribution segment’s area not determined by the model, 2) external – the ratio of area outside the current distribution, determined wrongly by the model.

The error functions were accumulated, with the same weights divided between the two functions, and the point of minimum value was searched for. It should be noted that the North African model results were interpreted as external errors, in spite of the fact that the studied vector species live there, thus our model was calibrated to study only the European distribution segments. It was found that the precipitation parameter drew quite different error functions than the temperatures; therefore another iteration was ran to study the difference between the lower and higher parts of the precipitation percentiles. The two extremes of the minimum and mean temperatures were fixed, and was left iteratively more percentiles from the minimum of precipitation values while the maximum was fixed, and vice versa. The accumulated error functions (***Fig.9***) showed that leaving percentiles from precipitation and from the minimum of precipitation results in graphs having the minimum point at the origin.

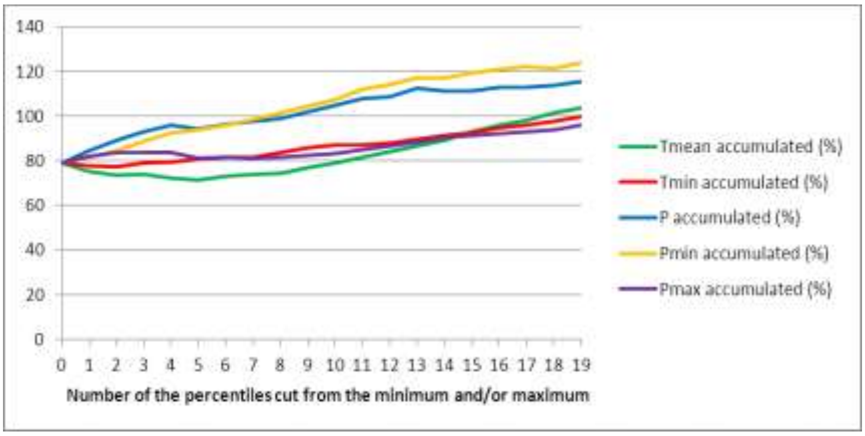


Fig.9. Accumulated errors of modeling while leaving percentiles from the minimum and maximum of mean temperature (Tmean), minimum temperature (Tmin), precipitation (P); from the minimum of precipitation (Pmin) and from the maximum of precipitation (Pmax)

Therefore, leaving percentiles from the minimum of precipitation values gives a worse model than without percentile leaving. According to the result of iterations, 5-5 percentiles are to left from the two extremes of mean temperature, 2-2 from the two extremes of minimum temperature, and 0 from the minimum and 8 from the maximum of precipitation.This result was used during the modeling of *Phlebotomus* species and *Leishmania infantum*. In the case of the WNF occurrence and the distribution of the *Aedesalbopictus* mosquito according to the result of iterations, 5-5 percentiles are to left from the two extremes of mean temperature, 2-2 from the two extremes of minimum temperature, and 0 from the minimum and 8 from the maximum of precipitation. Thus the model results are highly comparable with each other, but the models are not really sensitive to the characteristic of certain distributions. There may be noteworthy differences between observed and modelled current distributions, however e.g. *Phlebotomus* species are probably able to live and reproduce in territories with cooler climates, where it became extinct from in the Little Ice Age (Aspöck et al. 2008). The aforementioned model calibration technique shows numerous similarities with “area under the receiver operating characteristic (ROC) curve” (AUC), which is a plot of a test's true-positive fractions versus false-positive fractions (Hanley and McNeil 1982). The critical comments of Lobo et al. (2007) about AUC may refer also our calibration method. Although Cohen’s kappa measurement (Cohen 1960) is another way of model calibration, final Cohen’s kappa value of our model was calculated (0.54). For further error-based model calibration methods see Fielding and Bell (1997).

3.4.7. FURTHER MODELING STEPS

Before the running of the model on the distributions, the climatic data were refined by Inverse Distance Weighted interpolation method. Then the modeling steps were as follows in case of certain species: 1) the grid points were queried within the distribution (a few thousand × 36 data) with ArcGIS; 2) the percentile points of the 36 climatic parameters (101×36 data) were calculated by PAST; 3) the appropriate percentiles of the climatic parameters mentioned abovewere selected (2×36 data); 4) modeling phrases (3 strings) were created with the string functions of Excel for the three modeling periods, 5) the areas were selected where all the climatic values of the certain period were between the extremes selected in step 3. This last step was achieved by Raster Calculator function of ArcGIS. The raster results were converted to polygon type ESRI shapefile format. The order of the four layers (observed and modelled distributions) determined that the result maps are able to show the, mainly northward, expansion of the species, not the retreat from the southern parts (trailing edge) of the current distribution. Similar approach was made by Bede-Fazekas (2012).

4. RESULTS

4.1. THE FREQUENCY AND THE TRENDS OF THE VECTOR-BORNE DISEASES IN HUNGARY

The reported number of the known vector infections in Hungary was about 1600 cases per year in the period of 1998-2012. LB, TBE was the most numerous ones. I neglected to add the sporadic or mostly zoonotic VBDs diseases to the pie chart diagram while the total real case number transmitted by vectors is not known. Q-fever, tularemia and the parasite of the cat scratch disease sometimes also can be transmitted by vectorial arthropods, but the rate of this is not known. Most of the cases of TBE are VBD. It is plausible that almost the total number of the recorded LB, WNF and malaria cases were VBD. The WNF and the imported malaria cases together reached only about 1% of the amount of the vector infections in Hungary in the period of 2004 to 2012 (***Fig.10***).

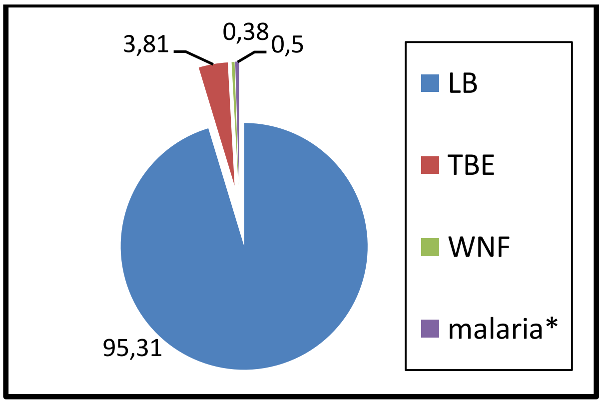


Fig.10. The pie chart of the 4 most important VBDs (LB, TBE, WNF with the imported malaria cases) in Hungary in 2004-2012.

4.1.1. LYME DISEASE

The annual number of the LB cases fluctuated between 992 (1998) and 2304 (2010) and it was about 95% all of the vector cases. In the period of 2000 and 2012 the annual case number of LB showed a significant (*p=0.0163, r=0.6478,rss=105.6104*) increasing trend (***Fig.11***). For the trend of the period of 1998-2010 see the ***Fig.23***.

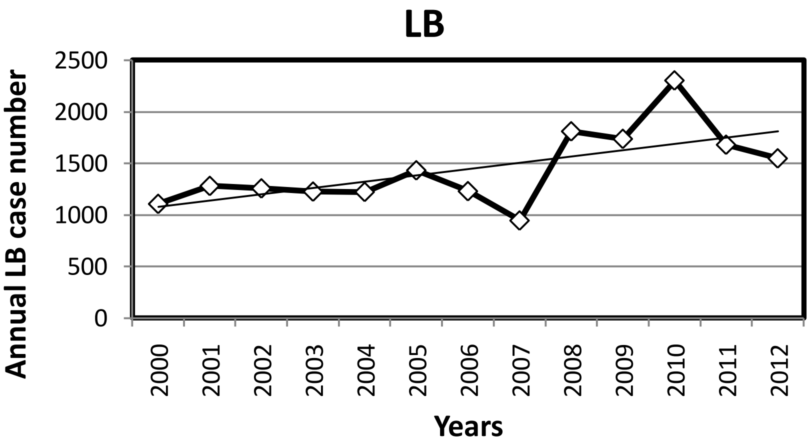


Fig.11. The annual number of the LB cases in Hungary; 2000-2012.

4.1.2. WEST NILE FEVER

In Hungary WNF is recently endemic; 34 cases were reported in the period of 2004-2009 (Krisztalovics et al. 2012, Epinfo 2010 A), 11 cases in 2010 (Epinfo 2010 B), 4 cases in 2011 and 12 cases in 2012 (ECDC, WNF maps 2012). From 2004 to 2012 annual number of endemic WNF cases never reached the 20 cases per year amount (the maximum 19 cases were reported in 2008) and always were fewer than 10 cases per year, but in the period of 2000 and 2012 the annual case number of WNF was low and highly variable (0-19/10 million) from year to year and showed a non-significant (*p=0.1457, r=0.5270, rss=49.7496*) increasing trend at 5% significance level (***Fig.12***).

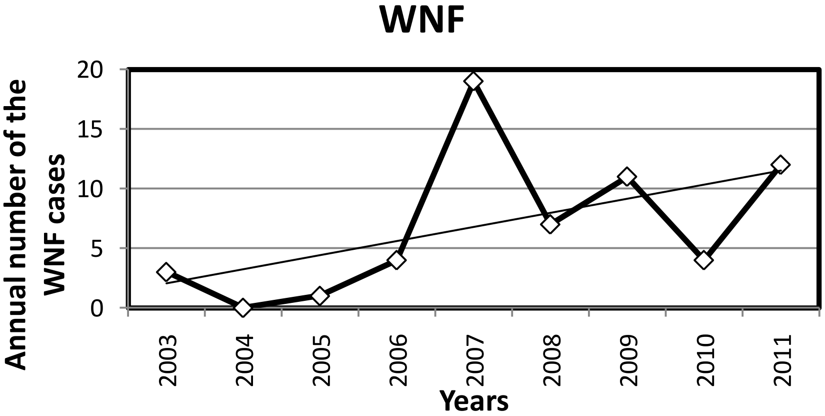


Fig.12. Annual case number of the WNF cases in Hungary; 2000-2012

In summary, it can be stated that LB is the most important vector-borne disease in Hungary with the highest annual case number and a significant increasing trend. WNF is also an emerging disease, but due to the short reported period and the relatively low case number the trend recently not significant.

4.2. THE ASSOCIATION BETWEEN LYME BORRELIOSIS AND CLIMATE IN HUNGARY

4.2.1. DESCRIPTIVE STATISTICS OF LYME BORRELIOSIS

A significant ($p<0.01$) increasing trend ($y = 0.5594x + 9.3829$; $R^2 = 0.4764$) of LB incidence was found in the period of 1998-2012, so I had to calculate the relative (%) instead of absolute LB incidence, since in case of same temperature value bound to significantly different incidences the calibration of the model would be problematic methodically. The LB incidences per 100,000 inhabitants in the order of the years were 10.92, 9.92, 11.08, 12.82, 12.58, 12.27, 12.24, 14.33, 12.31, 9.47, 18.11, 17.38, 23.04, 16.31, and 15.49 per 100,000 in Hungary. The difference between the biggest (2010) and lowest (1999) LB incidence was 13.12, which means, that the difference between 2010 and 1999 was 1,32 times higher than the incidence of 1999. In the studied period in summer from the 24th to the 36th weeks happened the 53.18% of the annual cases, but these values showed minor fluctuations: 68.38%, 54.43%, 49.32%, 50.46%, 52.98%, 52.24%, 52.92%, 56.08%, 56.79%, 41.22%, 51.23%, 53.05%, 49.83%, 60.02%, and 56.36%.

4.2.2. THE CHANGING SEASONAL AMBIENT TEMPERATURES AT THE COUNTRY LEVEL

The yearly mean temperature showed a non-significant increasing trend of 0.04°Cyear^{-1} according to the linear regression model during 1998-2010. In the summer, the increase was 0.043°C year^{-1}, in spring it was 0.04°C year^{-1}, in autumn the increase was the lowest 0.036°C year^{-1}, and it was the highest in winter 0.047°C year^{-1}. According to the linear regression model, the mean temperature growth was 0.52°C in summer during the analysed 13 years, from 20.83°C to 21.35°C. For the entire period, the spring growth was 0.48°C, the autumn growth was 0.44°C and the increase of the mean winter temperature reached 0.56°C. The seasonal variability was the highest in winter (3.44°C) which was 3.6-4.4 times higher than that of the other seasons (spring: 0.898°C, summer: 0.774°C, autumn: 0.944°C).

4.2.3. THE EXISTING TEMPERATURE DIFFERENCES BETWEEN THE SOUTHWESTERN AND NORTHEASTERN COUNTIES

The comparison of the monthly mean temperatures of the 3 southwestern and 2 northeastern counties (***Fig.14***) in 1998–2010 showed differences mainly in winter, early spring, and autumn periods. The biggest difference was that in the southwestern counties, the January mean temperature did not exceed the 0°C limit (***Fig.15***). In the case of Zala, Baranya, and Somogy counties (SW), the winter was milder than in the NE counties. While in the SW counties the mean weekly temperature of winter months fluctuated near 0°C, in the NE counties it sank to between –1 and –2°C. The two curves met at the 13th week of the year. The mean summer temperatures were the same in both regions, although autumn was milder in the SW counties. From November to the end of March, the weekly mean temperature differences of the examined 13 years reached 1°C.

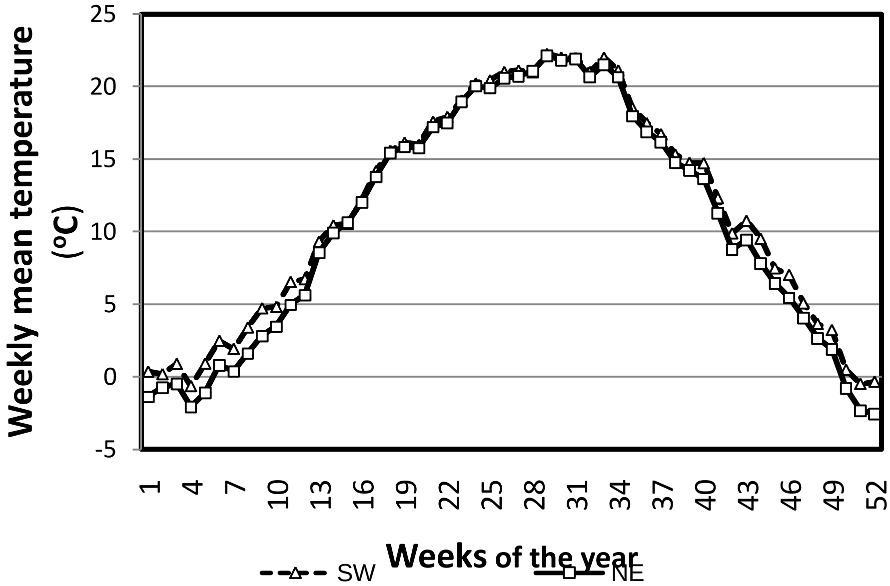


Fig.14. The weekly mean ambient temperatures in the SW and NE counties in Hungary, in 1998–2010.

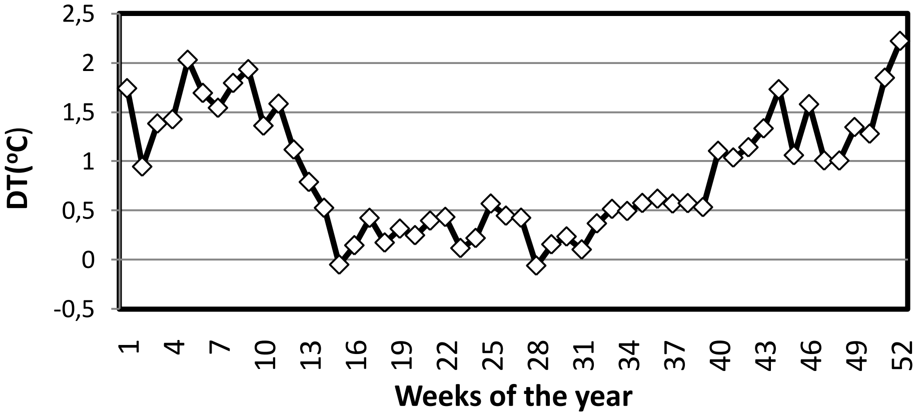


Fig.15. Differences in the weekly mean temperatures between the SW and NE counties in Hungary, in 1998–2010.

The mean winter temperature was 1.2°C in the 3 southwestern counties in period 1998–2010, respectively it was –0.3°C in the 2 NE counties, the difference was 1.6°C with a dispersion of 1.1°C (***Fig.16***). Due to the similar climatic influence and the small geographical distance (the nearest distance is about 100 km and the greatest distance is about 400 km), the correlation between the mean winter temperatures of the two regions was very strong ($p<0.0001$, $r=9.6635*10^{-1}$,$rss=2.5795$; ***Fig.17***).

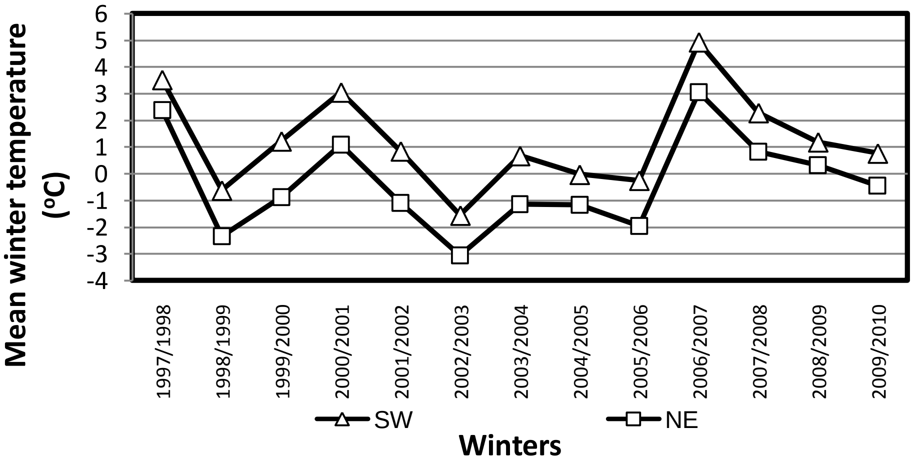


Fig.16. Mean winter temperatures in the SW and NE counties in Hungary, in 1998–2010.

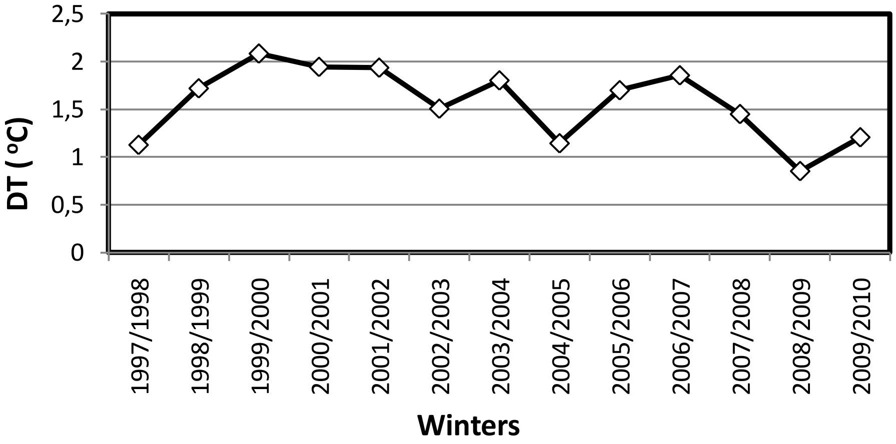


Fig.17. Differences in the mean winter temperatures between the SW and NE counties in Hungary, in 1998–2010.

4.2.4. THE SHIFT OF THE START OF THE VEGETATION PERIOD AND THE LYME BORRELIOSIS SEASON

Our observations showed that the incidence rate of 0.1 per 100,000 is a good indicator of the onset of LB season, and usually coincides with the first stable spring week with a mean temperature of 10°C, not followed by a week with mean temperature less than 7°C. 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 (*$p=0.0041$, $r=-0.8573$, $rss=48.2359$*), meaning a shift of 24 days (***Fig.18***). The last spring day with a minimum temperature under 0^{o}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.For the the plan view-like visualisation of the vegetation period's shift see the ***Annex Chart 1*** in the Annex.

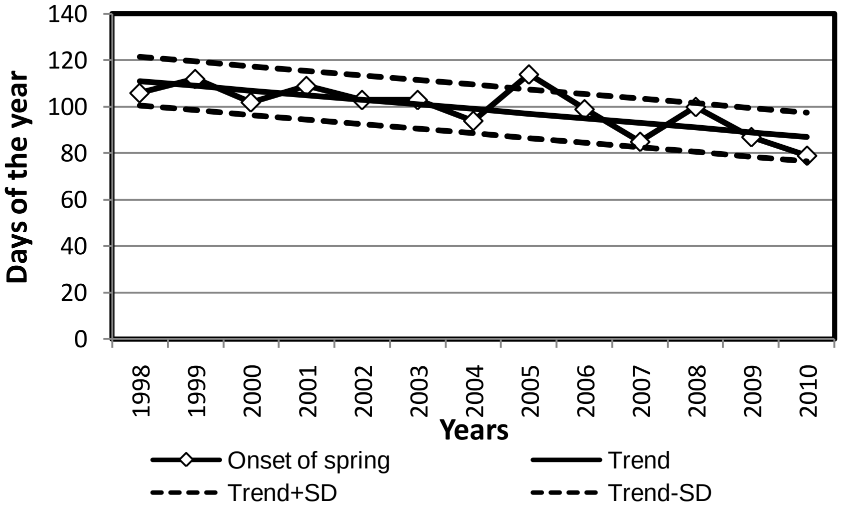


Fig.18. The change of the first day with 10°Cmean temperature followed by days with mean temperature warmer than 8°C(used as the onset of spring) in Hungary, 1998-2010

Our previous observations showed that the incidence rate of 0.1/100,000 is a good indicator of the onset of LB season, and usually coincides with the first stable spring week with a mean temperature of 10°C, followed by a week with a mean temperature not less than 7–8°C. Therefore the first week with 10°C mean ambient temperature which was followed by weeks with mean temperature warmer than 7–8°C was used as the onset of spring. During 1998–2010, this indicator week shifted from the 16.5th week to the 14th week of the year defined by the linear regression model (*p=0.0172*, *r=-0.7391*, *rss=82.5531*), in the case of the NE counties. However, this shift was not significant in the SW counties (*p>0.05,r=-5.4740*10-1,rss=127.4629*), where the indicator week shifted from the 14.2nd week to the 13.6th week of the year (***Fig.19***).

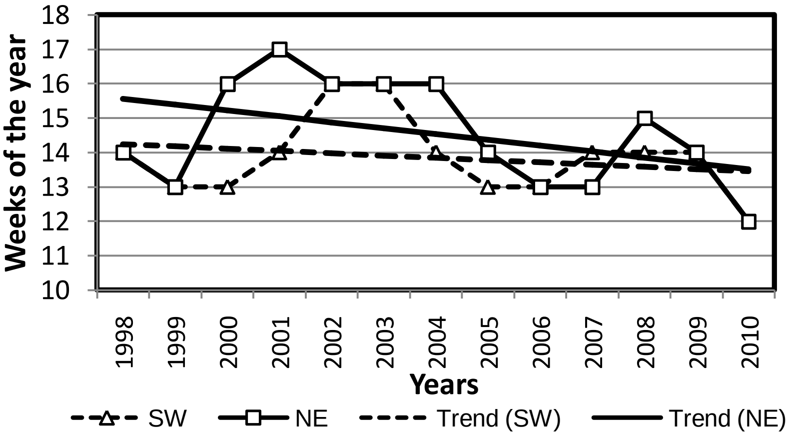


Fig.19. Shift of the start of the vegetation period based on the temperature>7–8°C requirement of the questing activity of *Ixodes*ticks in the SW and NE counties in Hungary, in 1998–2010.

During the 13 years analysed, the onset of the LB season shifted from the 17th to the 13th week (***Fig.20.***). A trend of -2.4 days per year was observed (*p=0.0144*, $r=-6.8972*10^{-1}$, *rss = 95.4191*). 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.For the the plan view-like visualisationsof the LB season's shift see the ***Annex Chart 2, 3*** in the Annex.

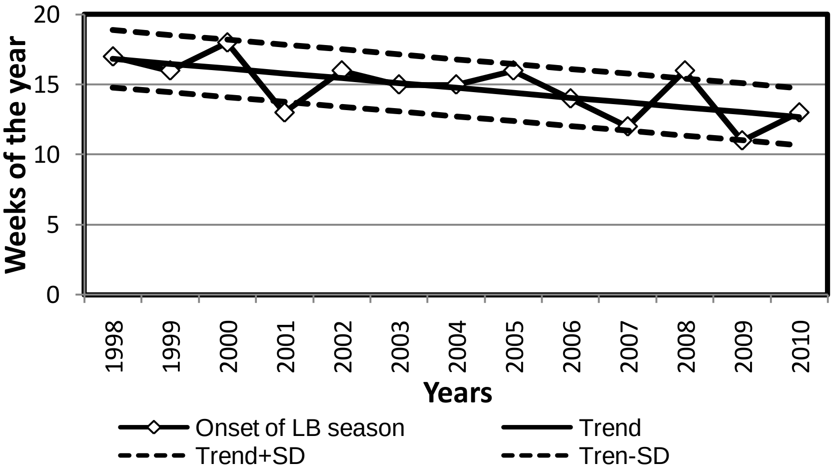


Fig.20. The change of the first week with LB incidence rate exceeding 0.1 per 100,000 in Hungary, 1998-2010

The start of the vegetation period was plotted according to the function of the start of the LB season and a significant correlation was found (*p=0.0177*, *r=6.4295*10-1*, *rss=29.5112*; ***Fig.21***).

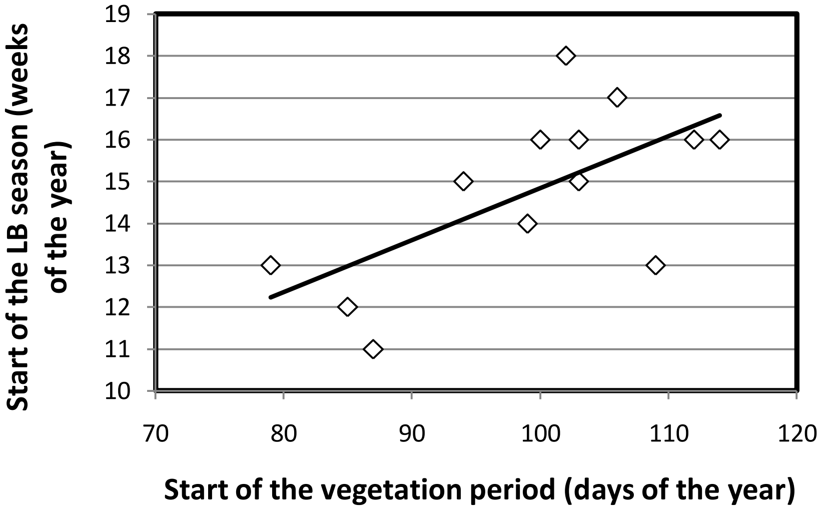


Fig.21. The correlation between the start of the vegetation period (by days) and the start of the LB season (by weeks).

4.2.5. THE CHARACTERISTICS OF THE AVERAGED WEEKLY ANNUAL LYME BORRELIOSIS CURVE AND MEAN AMBIENT TEMPERATURE

Analyzing the association between the mean weekly temperatures and LB incidence the lowest weekly incidence rates were observed in winter (the mean incidence in the 8th week, in February, was 0.02 per 100,000). The highest incidence rates occurred in summer, mainly in July in the 24th week, with a mean incidence rate of 0.83 per 100,000. Our observations showed that the LB incidence rate started to increase rapidly after reaching the weekly rate of 0.1 per 100,000, when the weekly mean temperature was around 10°C. The peak period of the weekly LB incidences of the 13 years was observed at weeks 23-28th followed by the highest weekly mean temperatures recorded at the 28-29th weeks. The increase of the incidence rate was more intensive from the 16th to the 23rd-24th weeks, the decreasing phase started from the 28th week. In each week between the weeks 23-28th, LB incidence rates exceeded 0.7 per 100,000; the mean of these values was 0.76 per 100,000; in contrast, the mean incidence of the preceding and following 5 weeks was much lower (0.45 per 100,000 resp. 0.58 per 100,000.; ***Fig.22***). The slope of the linear regression line of the increasing LB weekly incidence phase was +8.28 (P<0.0001) between the first week with a LB incidence of 0.1 per 100,000 (usually from week 16th) to the first week, when the incidence was greater than 0.8 per 100,000 (usually this occurred during the 24th week). The slope of the fitted linear regression line of the decreasing weekly LB incidence phase was –4.41 (P<0.0001) between the last week with an incidence of 0.8 per 100,000 (usually from the 28th week) to the last week, when the incidence decreased to 0.1 per 100,000 (usually this was recorded in the 43rd week). Accordingly, the absolute value of the slope of the increasing spring-early summer phase was 1.88 times greater than that of the late summer-autumn decreasing phase (***Fig.22***). A secondary autumn peak of incidence was not observed.

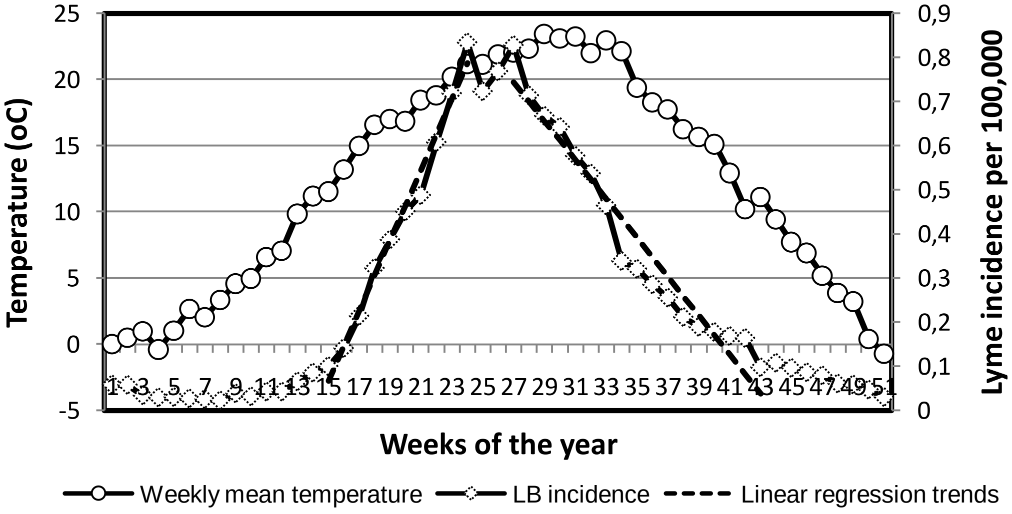


Fig.22. The weekly mean temperature and LB incidence rate and the linear regression trend of the increasing and the decreasing part of the annual LB incidence curve in Hungary, 1998-2010

4.2.6. TRENDS OF LYME BORRELIOSIS INCIDENCES

In the period of 1998-2010, the average annual incidence rate of Lyme borreliosis was 13.57 (SD=3.82) per 100,000 in Hungary. The lowest incidence rate, 9.47 per 100,000, was recorded in 2007, and the highest incidence rate 23.04 per 100,000, was recorded in 2010. The cumulative incidence rate was 176.47 per 100,000. The rates of lowest incidence were observed in the following three years, sorted by descending order: 1998, 1999, and 2007, respectively the highest incidence rates were recorded in 2009, 2008, and 2010 sorted in the same way. When the studied years were grouped into three periods (1998-2001, 2002-2005, 2006-2010) the average incidence rates per 100,000 were the following: 11.18, 12.85, 16.06, showing an increase of 15% and 43.6% compared to the first period. ***Fig.23***shows the change of annual Lyme disease incidence between 1998 and 2010. An annual significant growth rate of 0.71 per 100,000 was observed ($p=0.0049$, $r=7.2947*10^{-1}$, $rss=85.1514$). The SD of the entire 13 years was 3.84. According to the fitted linear trend, the expected incidence of the year 2007 was 15.18. The expected incidences of 2007 (9.47/100,000) negatively and in the case of the year 2010 (23.04 per 100,000) positively differed from the standard deviation of the points belonging to the trend.For the three-dimensionalvisualisations of the Lyme incidence seasons and trend in four weeks resolution see the ***Annex Chart 4*** and ***5*** in the Annex.

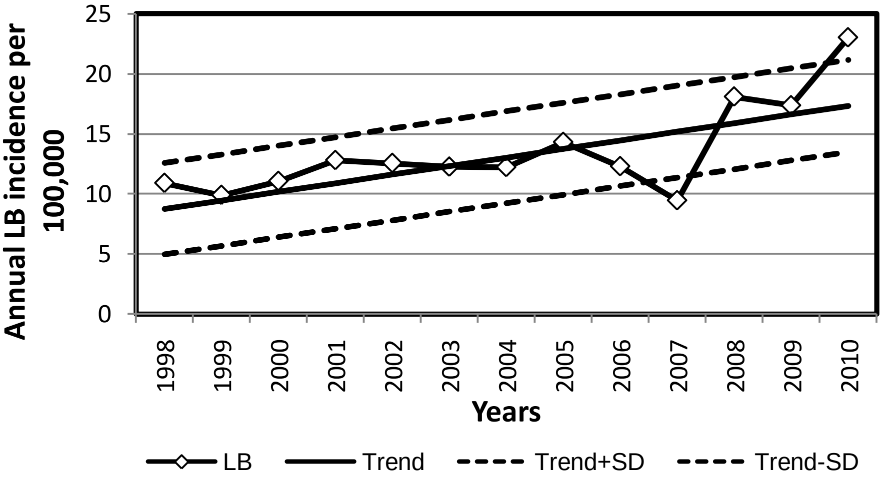


Fig.23. The annual Lyme disease incidence rate per 100,000 in Hungary in the period of 1998 to 2010.

The observed incidence rate of 2010 (23.04 per 100,000) was the opposite of the expected one (17.32 per 100,000), also falling out of the range of the standard deviation. Comparing the weekly incidences of LB between 1998-2001 and 2007-2010, a shift of three weeks was observed in the onset of the annual LB seasons (used the first week with 0.1 per 100,000 incidence rate as the start of LB season). The peak of the weekly incidence showed a similar change; it shifted 2-3 weeks earlier in the spring during the later observational period, and reached a higher maximum. Further, I compared the LB incidence curves of the periods of 1998-2001 to that of 2007-2010. 47% of the annual cases (5.26 per 100,000) occurred between the 15th and the 28th week in the period of 1998-2001, and 58% of the cases (9.85 per 100,000) were recorded in the same weeks in the period of 2007-2010. The total annual difference of LB incidence rate was 5.81 per 100,000 between the two periods (1998-2001 vs. 2007-2010), the difference between the number of cases of between the 15th-28th weeks was 5.26 per 100,000, so 79% of the difference occurred during the 15th-28th weeks. The trends of the LB incidence rate were examined for every week during the 13 years, which was found to be 0.07 per 100,000 per year; the total growth was 0.8 per 100,000 during 13 years (***Fig.24***). By using the linear regression coefficients of each week, the profile of the weekly coefficients of LB incidencecould be determined. From the 15th to the 28th week the increasing trend was significant and the maximum of the growth occurred between weeks 23rd-25th (linear coefficient at week 23rd was 6.64, P=0.0002; ***Fig.24***). The curve of the linear regression coefficients runs parallel with the curve of incidence until week 24, afterwards the former curve drops several weeks earlier (***Fig.25***).

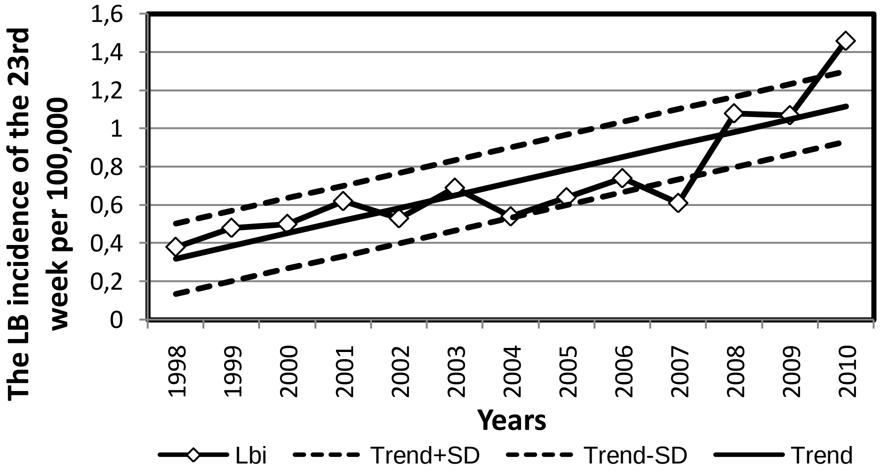


Fig.24. The trend of LB incidence rate per 100,000 at week 23rd in Hungary, 1998-2010

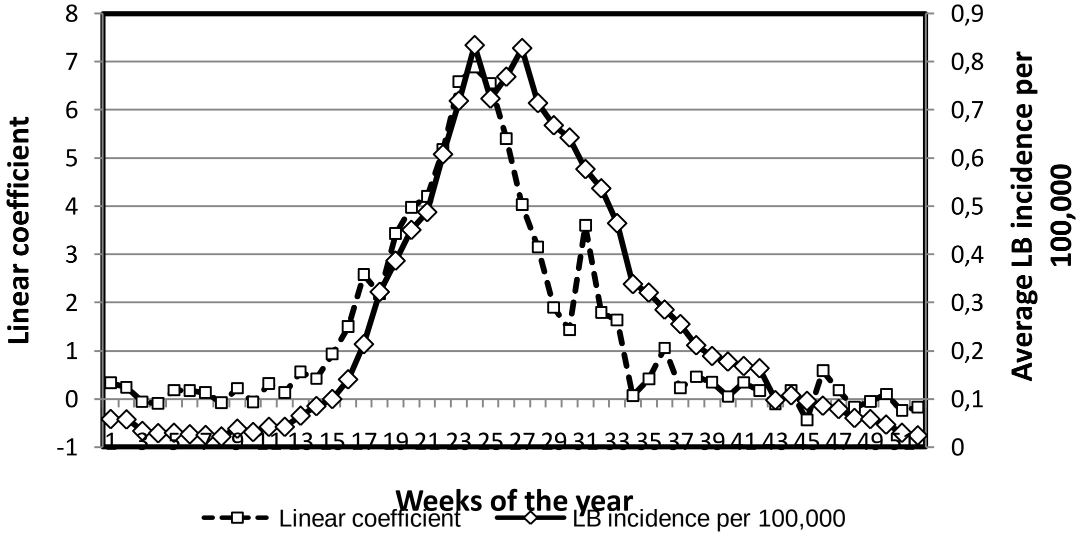


Fig.25. The weekly mean LB incidence of 13 years and the linear coefficients of the weekly LB incidence of the 13 years, Hungary 1998-2010

4.2.7. THE CHANGING REGIONAL LYME BORRELIOSIS INCIDENCES IN TWO HUNGARIAN REGIONS

The annual run of the LB incidences were compared in the case of 2 north-eastern (Nógrád and Borsod-Abaúj-Zemplén, hence: NE) and 3 south-western (Baranya, Somogy and Zala, hence: SW) Hungarian counties in the periods of 1999–2004 and 2005–2010. Comparing the periods by a polynomial regression model, the peak of the LB season shifted from the 28th to the 29th weeks in the NE counties, while in the SW counties this shift did not reach a one week difference. In the SW counties, the cumulative LB incidence was 118.3/100,000 in period 1998–2003 and 159.2/100,000 in period 2004–2010 (30.55% increase; ***Fig.26***). In the NE counties, the cumulative LB incidence was 92.2 per 100,000 in period 1999–2004 and 132.8/100,000 in period 2005–2010 (25.68% increase; ***Fig.26***). In periods 1998–2004 and 2005–2010, the percent increase of the cumulative LB incidences showed very heterogeneous trends in the different Hungarian regions. In both regions a growing trend could be seen, with *p=0.0065, r=6.9422*10-1, rss=94.2842*and in the SW and *p=0.0471, r=5.8264*10-1, rss=120.2152*in theNE counties, respectively. From 1998 to 2010, the trend was consistent in the 3 SW counties, however, no trend could be observed in the 2 NE counties before 2007, and each trend had borderline significance.

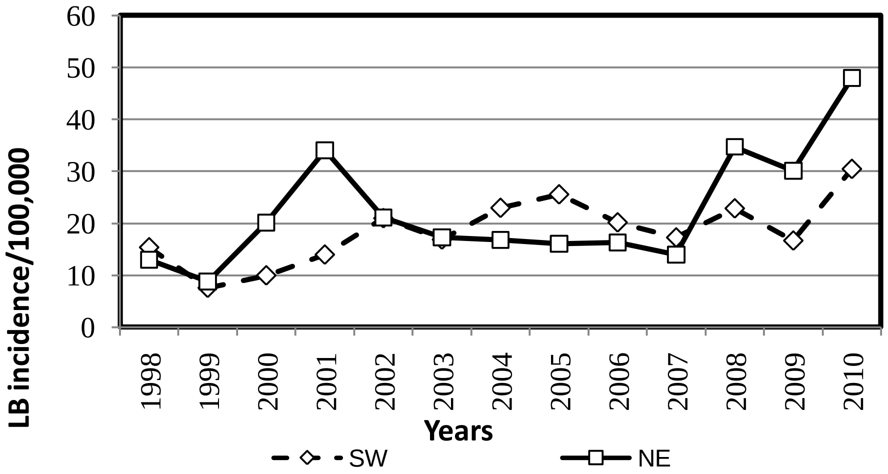


Fig.26. The annual cumulative LB incidence in the two studied regions (SW and NE), in 1998–2010.

The observations showed that the LB incidence rate started to increase rapidly after reaching the weekly rate of 0.1 per 100,000 from the 16th week and reached the peak period in the 23rd–25th weeks. Regional differences could be observed in the onset and peak of the LB incidence. In case of the 3 SW counties the weekly LB incidence reached 0.1 per 100,000 in the 11th week and in case of the 2 NE counties, in the 14th week. The LB incidence rate was more than 0.2 per 100,000 in the SW counties from the 15th week and in the NE counties from the 17th week, the start of LB season showed a 2–3 weeks difference (***Fig.27***).

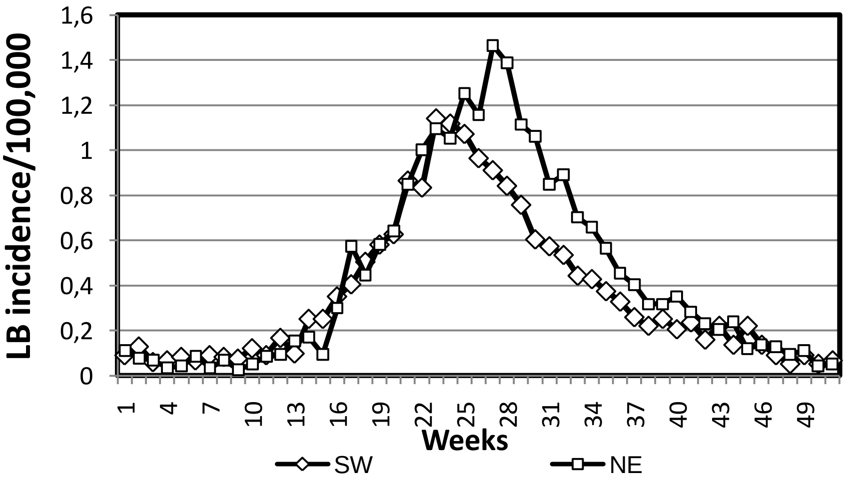


Fig.27. The average weekly LB incidences of the SW and NE counties in Hungary, in 1998–2010.

The peak of the annual LB curves reached its annual maximum in the 25th week in the SW counties, while in the case of the NE counties, this was observed on the 28th week, showing a 3 weeks difference in the peaks of the LB season by regions (***Fig.28*** and ***Fig.29***).For the plan view-like visualisations of the Lyme incidence profiles and trends in the SW and NE counties in 1999 to 2010 see the ***Annex Chart 6*** and ***7*** in the Annex.

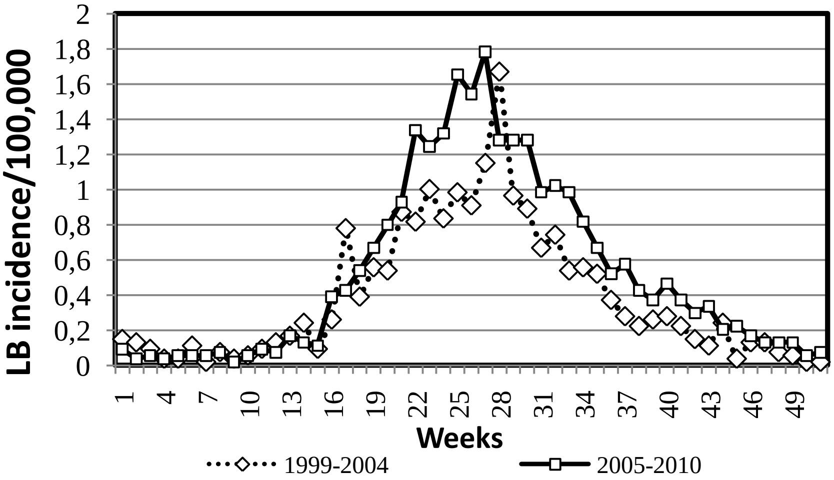


Fig.28. Average weekly LB incidences of the NE counties in Hungary, in the periods of 1999–2004 and 2005–2010.

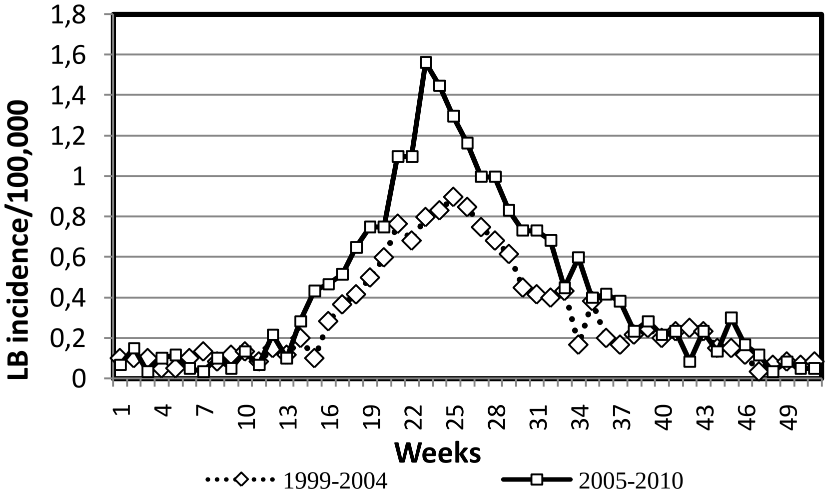


Fig.29. The average weekly LB incidences of the SW counties in Hungary, in the periods of 1999–2004 and 2005–2010.

4.2.8. THE INFLUENCE OF THE LATE SPRING-EARLY JUNE WEEKLY MEAN TEMPERATURES ON THE DATE OF PEAK LYME BORRELIOSIS SEASON

Assuming that the temperatures in May and June are very important in the life cycle of ticks, the association between LB incidence and the mean temperature of these months was studied. The LB seasons were divided into two groups according to positive (2000, 2002, 2003, 2007, 2008 years) or negative (1998, 1999, 2001, 2004, 2005, 2006, 2009, 2010 years) 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 a 1.96°C difference was observed 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 (***Fig.30***).

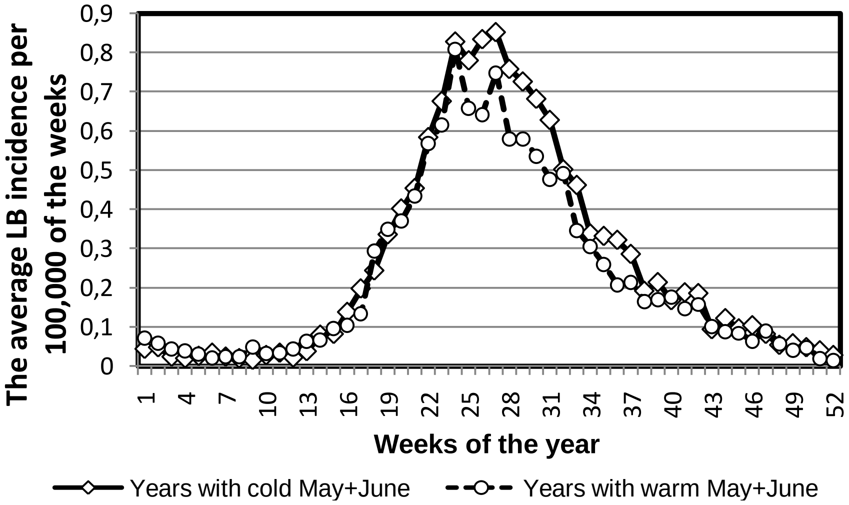


Fig.30. Weekly LB incidences divided into 2 groups according to positive or negative deviation from the mean temperature of May and June of 13 years, Hungary (1998-2010)

4.3. MODELING THE MAINLY TEMPERATURE-DERIVED RUN OF THE LYME BORRELIOSIS SEASON

4.3.1. HUMAN OUTDOOR ACTIVITY

After the Gaussian curve was fitted **(***Eq.*[4], *Eq.*[5]) the observed/calculated ratio (multiplier) of the irregular week pairs was calculated to characterize the effect of the summer holidays on human activity (***Fig.31***).

From mid-September to the next years' mid-June our model very strongly (R^2: 0.9958) follows the reported run of the camping guest nights.

$$A_{human} N(6.89; 1.82) \qquad [4]$$

$$A_{human}(hm) = \frac{939.74}{1.82 * \sqrt{2\Pi}} * e^{\frac{-(hm-6.89)^2}{2*1.82^2}} \qquad [5]$$

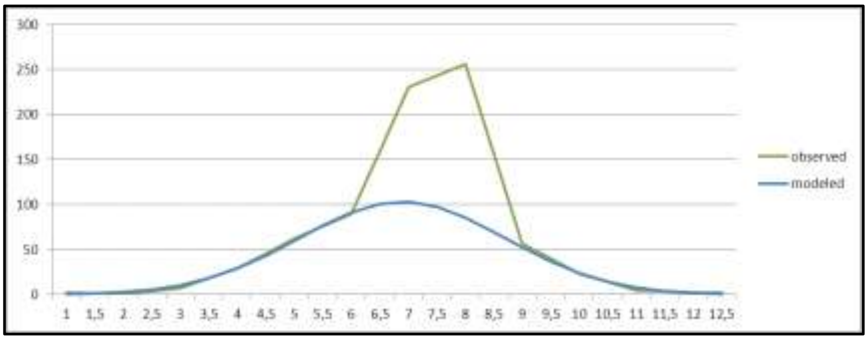


Fig.31. The difference between the modelled temperature-related camping activity and the observed surplus in the summer months.

While I were interested in the effect of the summer holidays on the human activity, *HM* was not calculated for the winter period (***Fig.32***). The peak multiplier (2.993) occurred in August, while the lowest occurred in the first half of September (1.080). In the entire July and August *HM* was above 2.00 (***Fig.32***, *Eq.*[6].).

$$HM(d) = \left\{ \begin{array}{c} 1.589;\ if d \in\ [167; 183[\\ 2.239;\ if d \in\ [183; 197[\\ 2.496;\ if d \in\ [197; 214[\\ 2.993;\ if d \in\ [214; 228[\\ 2.245;\ if d \in\ [228; 245[\\ 1.080;\ if d \in\ [245; 259[\\ 1;\ if d \notin\ [167; 259[\end{array} \right\} \qquad [6]$$

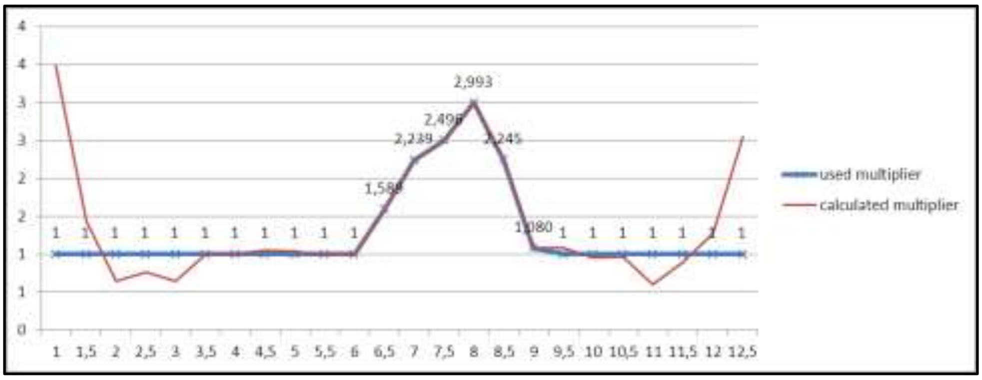


Fig.32. The calculated multipliers according to the modelled and observed camping activity.

4.3.2. TEMPERATURE RELATED HUMAN OUTDOOR ACTIVITY

Monthly camping guest nights and monthly mean temperature showed a strong correlation (R^2: 0.9329) in the period of 0.1.2008.-10.2012 (***Fig.33***, *Eq.*[7]).

$$A_{human}(T_n) = 3.445 * e^{0.058*T_n} \qquad [7]$$

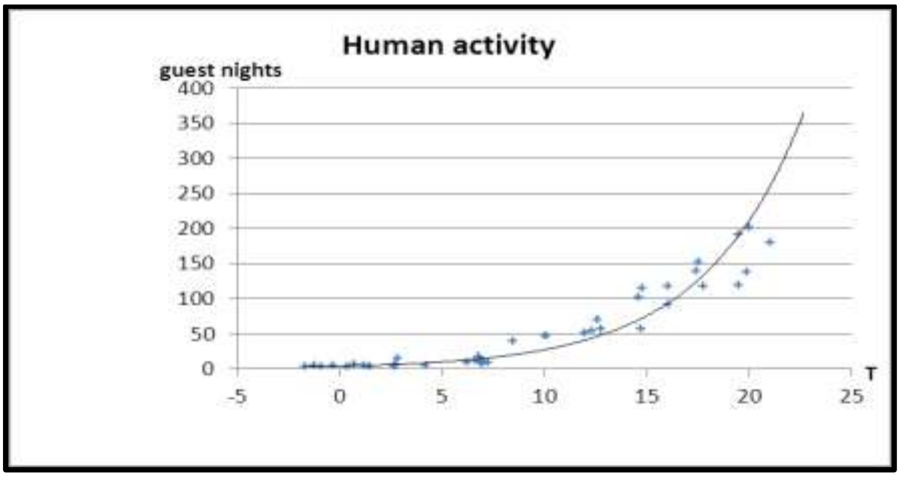


Fig.33. The correlation between the mean ambient weekly temperature and camping activity

The results of exponential regression is as follows (***AnnexChart 8***): 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. The strongest correlation weas selected (*Eq.*[8], without *HM* and with -1 week lag).

$$A(T_{n-1}) = 0.1057 * e^{0.1904 * T_{n-1}} \qquad [8]$$

4.3.3. TEMPERATURE-INDEPENDENT ACTIVITY

The results of the polynomial regression are given below in case of the three approaches. *Eq* [9] summarizes the result of the 1st approach (***Fig.34***), Chi^2: 209.44; R^2: 0.11; F: 20.17 (p<0.001).

$$IA_1(n) =$$

$$(-1.39995) + 0.378123 * n + (-0.0163487) * n^2 + 0.000208199 * n^3,$$

where n is the number of the week [9]

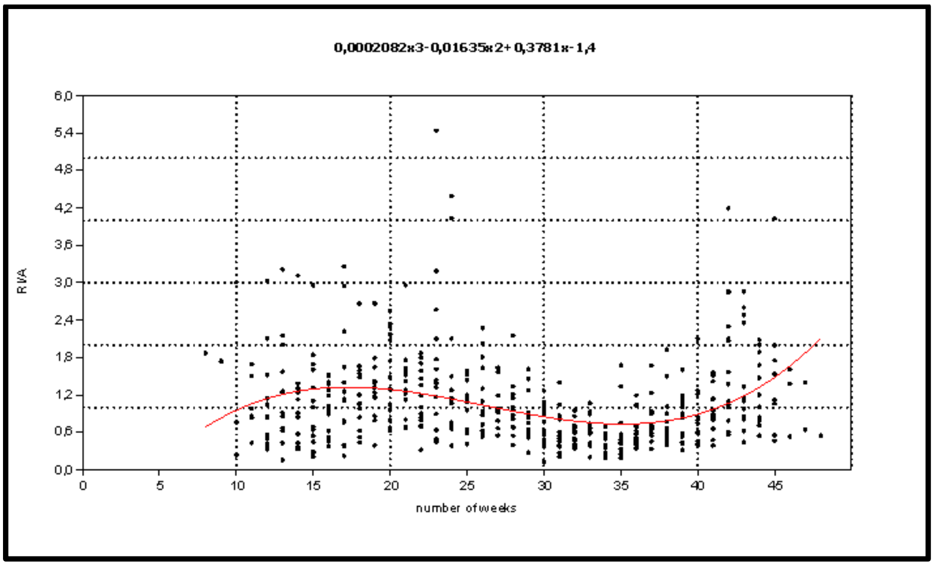


Fig.34. The temperature-independent activity

Eq. 10. summarizes the result of the 2nd approach (***Fig.35***), Chi^2: 213.96; R^2: 0.21; F: 42.69 (p<0.001).

$$IA_2(n) =$$

$$(-1.11633) + 0.374321 * n + (-0.0179289) * n^2 + 0.00024373 * n^3 \qquad ,$$

where n is the number of the week [10]

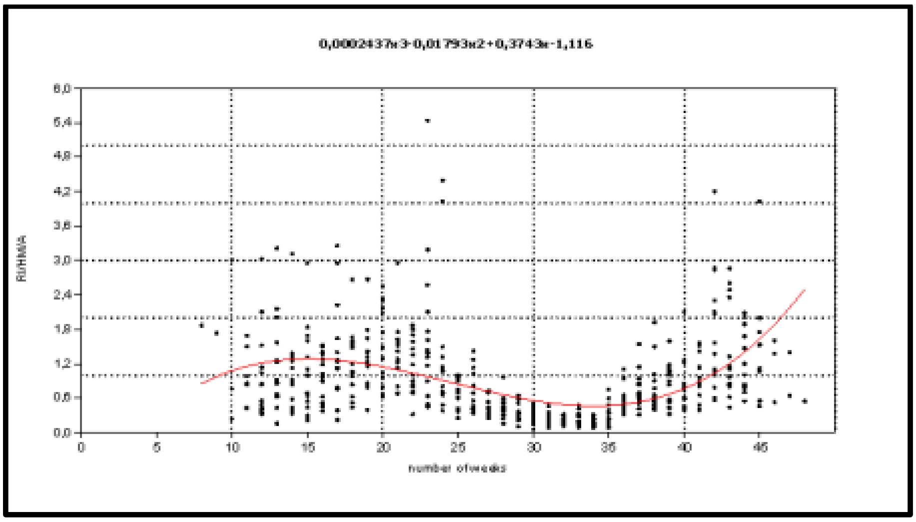


Fig.35. The temperature independent activity using the multipliers.

The *IA1* and *IA2* curves somewhat overestimate the point cloud in the summer. Since LB incidence is the mostly inaccurately modelled in the summer period (due to the high values and the influence of non-temperature factors), a second order regression was made separately for this period (***Fig.36***). *Eq.*[11] summarizes the result of the 3rd approach, Chi^2: 5.04; R^2: 0.45; F: 60.91 (p<0.001).

$$IA_3(n) = \left\{ \begin{array}{c} 9.11121 + (-0.542668) * n + 0.00827928 * n^2, if n \in [25;35] \\ (-1.11633) + 0.374321 * n + (-0.0179289) * n^2 + 0.00024373 * n^3, if n \notin [25;35] \end{array} \right\}$$

where n is the number of the week [11]

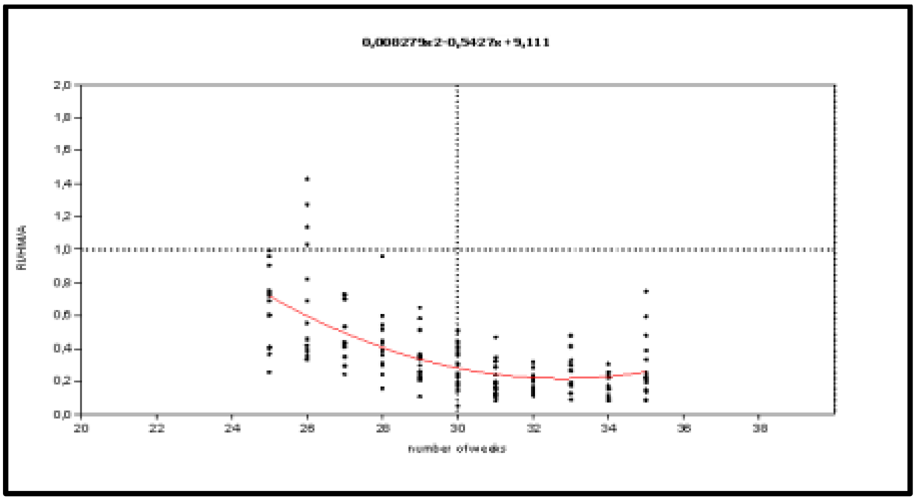


Fig.36. The temperature independent activity separately for the summer months.

4.3.4. THE RECONSTRUCTED LYME BORRELIOSIS SEASONS

Three different models were fitted to the curve of the observed RI and model suitability was calculated for the studied period. The first approach (***Fig. 37***) resulted in *Eq.*[12] R^2 is 0.6313 and summarized absolute error is 821.06.

$$RI_1(T_{n-1}, n) = A(T_{n-1}) * IA_1(n) \quad [12]$$

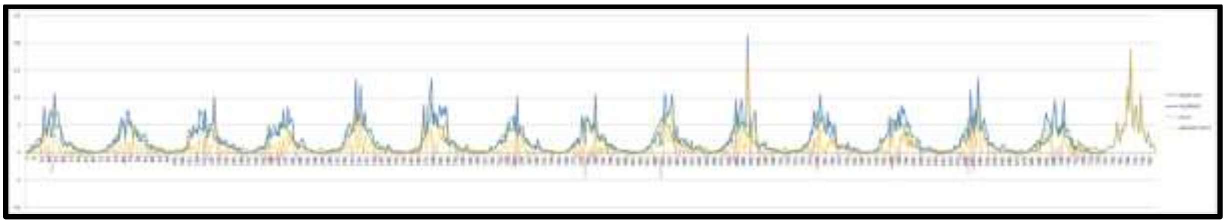


Fig.37. First approach.

The second approach (***Fig.38***) resulted in *Eq.*[13]. R^2 is 0.6247 and summarized absolute error is 685.35

$$RI_2(T_{n-1}, n) = A(T_{n-1}) * IA_2(n) \quad [13]$$

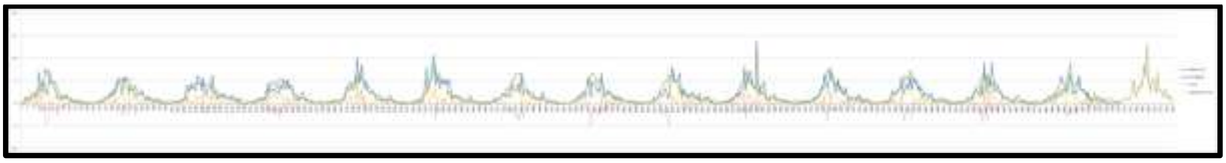


Fig.38. Second approach.

The third approach (***Fig. 39***) resulted in *Eq.*[14]. R^2 is 0.6569 and summarized absolute error is 774.23

$$RI_3(T_{n-1}, n, d) = A(T_{n-1}) * IA_3(n) * HM(d) \qquad (14)$$

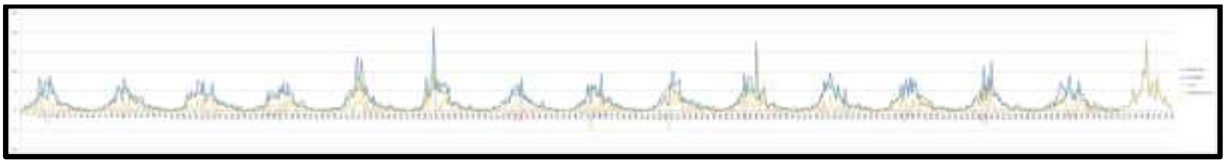


Fig.39. Third approach.

4.4. WEST NILE FEVER

4.4.1. THE REGIONAL DISTRIBUTION OF THE WEST NILE FEVER IN HUNGARY

The Hungarian regions are corresponds to the NUTS 2 statistical regions of the European Union. In 2008 and 2010-2012 (the geographical data of 2009 is missing) the highest WN incidence rates were observed in Northern Great Plain (NGP; 6.6×10^{-6}), in Southern Great Plain (SGP; 5.24×10^{-6}),in Southern Transdanubia (STD; 5.2×10^{-6}) andin Western Transdanubia (WTD; 5.01×10^{-6}). In Central Transdanubia (CTD; 3.62×10^{-6}), in Northern Hungary (NH; 2.48×10^{-6}) and Central Hungary (CH; 2.41×10^{-6}) the WNF average incidence of this 3 regions were about the half of the average incidence rate of NGP, SGP, STD and WTD. 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 (***Fig.40***).

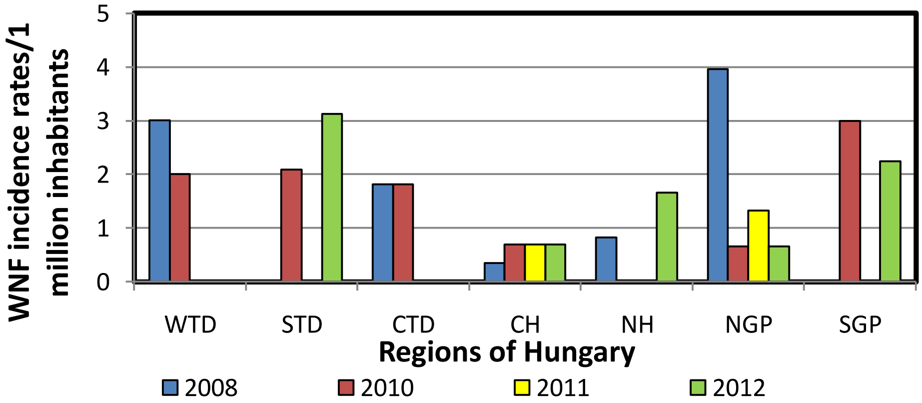


Fig.40. WNF incidence rates per 1 million inhabitants in the different Hungarian regions in 2008, 2010-2012 according to the population numbers of 2012. WTD=Western Transdanubia, STD=Southern Transdanubia, CTD=Central Transdanubia, CH=Central Hungary, NH=Northern Hungary, NGP=Northern Great Plain, SGP=Southern Great Plain.

4.4.2. THE SEASONALITY OF WEST NILE FEVER IN HUNGARY

The WNF showed a clear seasonality (***Fig.41***). 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.

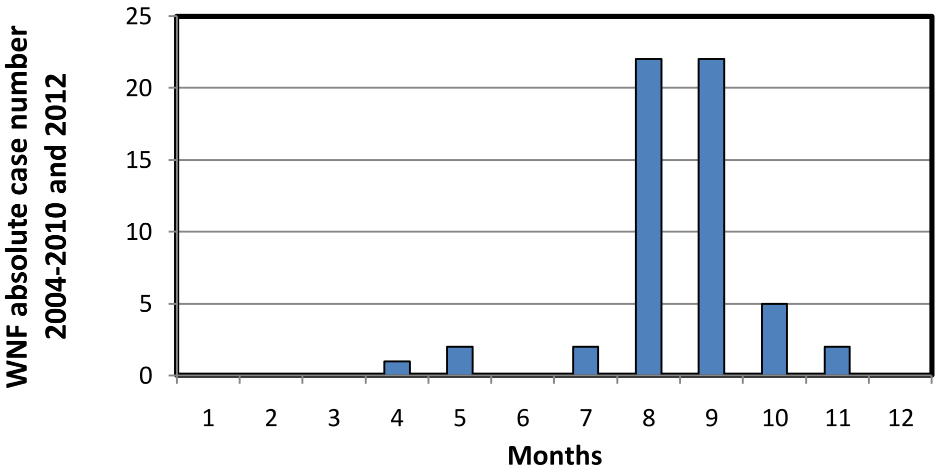


Fig.41. The seasonal distribution of the WNF cases in Hungary in the period of 2004-2010 and in 2012.

4.4.3. AMBIENT MEAN WEEKLY TEMPERATURE AND WEST NILE FEVER

In 2004-2010 and 2012 the 66.66% of the first symptoms of the disease cases occurred above 19°C and 84,84% above 16°C and the highest case numbers were observed between 21-21.9°C weekly mean ambient temperature (***Fig.42***). No cases were observed under 10°C. Note that the incubation period of the infection with WNV is thought to range from 3 to 14 days (CDC), but the probability distribution of the latency interval is not known.

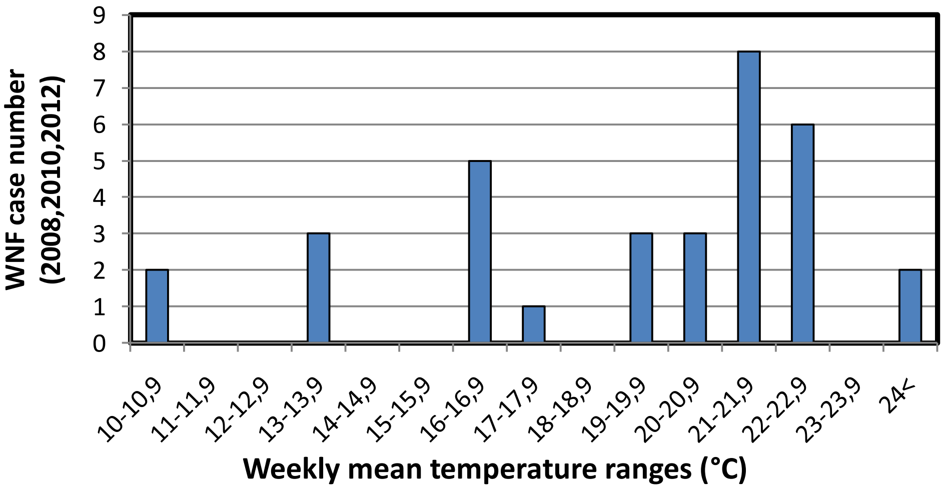


Fig.42. The frequency histogram of weekly ambient temperatures of 2008, 2010 and 2012 and the number of the WNF cases

4.4.4. EXAMPLES FOR WEST NILE FEVER SEASONS

The averaged ambient weekly temperature of the 4 previous weeks before the first WNF case in 2008 was 21.6°C (***Fig.43***), 23.82°C in 2010 (***Fig.44***) and 23.65°C in 2012 (***Fig.45***). 78.6% of the cases in the period of 2004-2010 and 2012 (weekly data from2011 are missing) 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. As I mentioned in the Methods, the weeks of the mean ambient temperature more than 15°C was selected as the season of *Culex* mosquitoes. According to these observations the period of May to September was practically consideredas 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 (***Fig.43***).

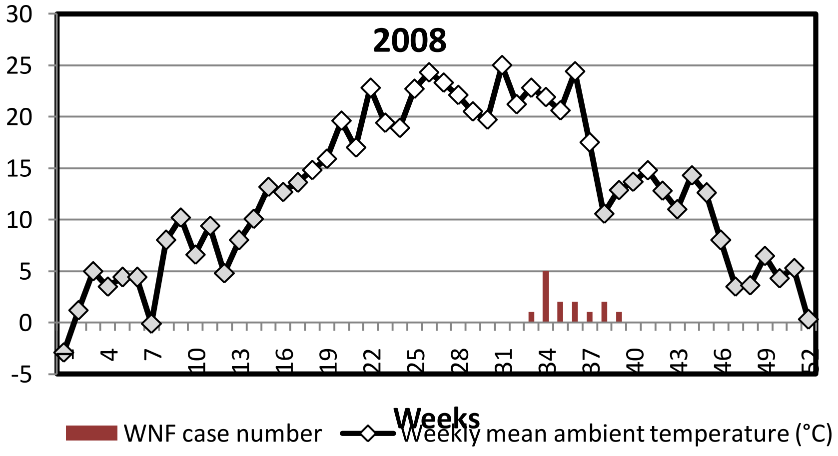


Fig.43. The weekly ambient temperatures in 2008 and the absolute number of WNF cases.

The light gray points mark the weeks, when the ambient temperature was less than 5°C.

In 2010 the *Culex* season started in the 20th week in the start of May and terminated in the 35th week in late August. In 2009 the the last case occurred in the last week of the theoretical season (***Fig.45)***.

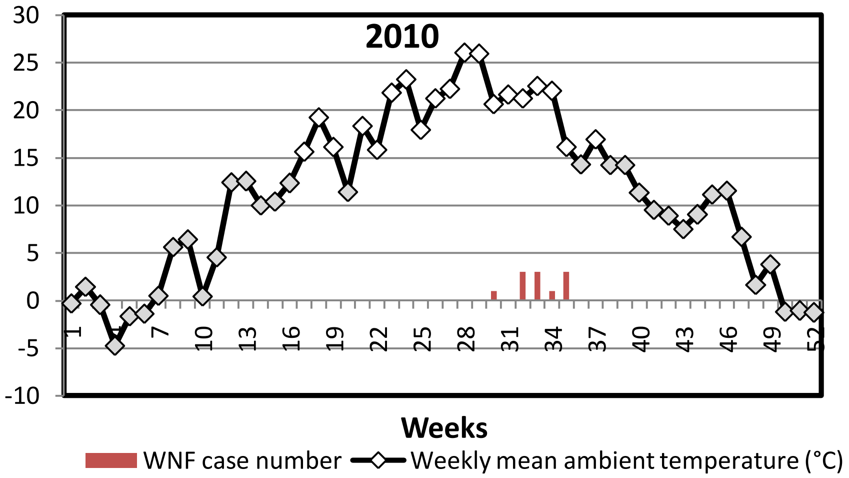


Fig.44. The weekly ambient temperatures in 2010 and the absolute number of WNF cases.The light gray points mark the weeks, when the ambient temperature was less than 5°C.

In 2012, the season started in the 16th week and terminated in the 43rd week in late October. In 2012 the last observed case exceed the theoretical season by 4 weeks, the previous case occurred 1 weeks before as the theoretical end of the mosquito season (***Fig.45***).

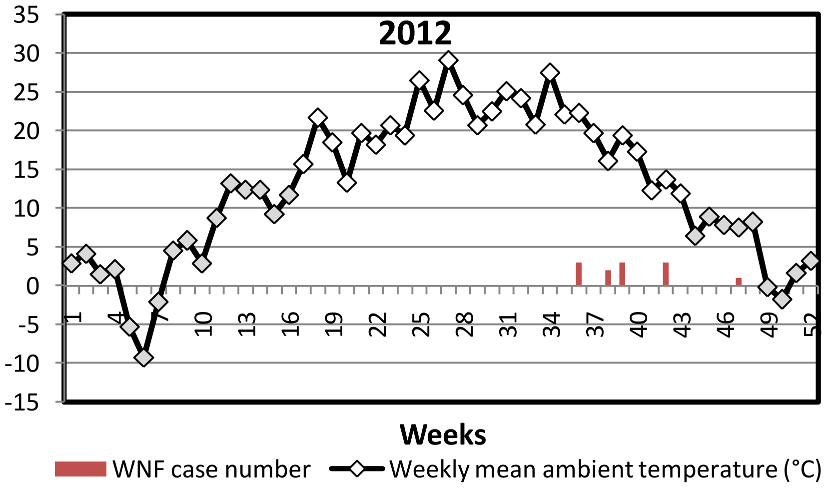


Fig.45. The weekly ambient temperatures in 2012 and the absolute number of WNF cases. The light gray points mark the weeks, when the ambient temperature was less than 15°C.

4.4.5. FLOODS AND WEST NILE FEVER IN HUNGARY

4.4.5.1. The presence of Chironomidae mosquitoes as wetland indicators and West Nile Fever

From the first observed human WNF in Hungary (2004)most of the cases were tied to the rivers Tisza, Raba, Drava, Zagyva, Körös and Hernád, and channels (e.g. East Main Chanel) and Lake Balaton. The river Danube had a smaller importance. For example from January 2008 to September 2008 8 WNF cases occurred in the Tisza valley and only 2 cases were observed in the Danube valley. Only 1-2 cases per year were matched to the river Danube. Since before 2007 the WNF levels were very low (in the period of 2004-2006 only 4 cases were observed) the period of 2007-2012 was used. Athough the Chironomidae mosquitoes are not vectors of WNF, since the larvae of these mosquitoes live in aquatic or semiaquatic environments Chironomidae mosquitoes are also tied to wetland areas, rivers and useful water quality indicators as well, while the larvae can live in polluted waters, too (Móra and Dévai 2004; Shaeter 1979). The larvae of *Culex* mosquitoes also live in aquatic habitats. In 2008 most of the WNF cases between May and September occurred mainly in riverside areas and wetlands (***Fig.46***).

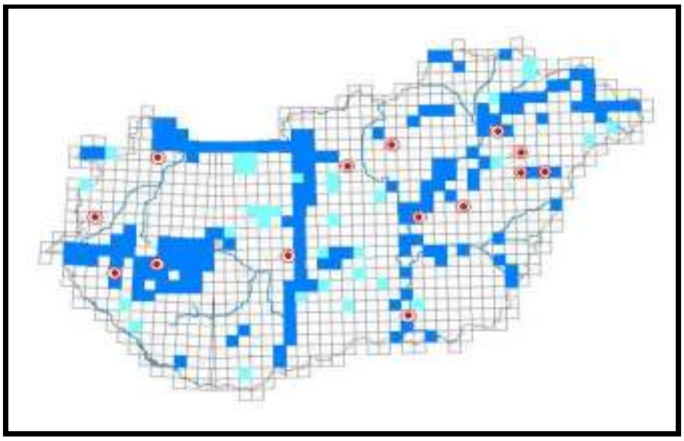


Fig.46. The confirmed presence of Chironomidae mosquitoes (dark blue), the non-confirmed, but expected presence of Chironomidae mosquitoes (light blue) (according to Móra and Dévai, 2004) and the occurrence of WNF in 2008 between may and September (n=14) in 2008, Hungary (red circles within red spot; according to Krisztalovics et al. 2008).

4.4.5.2. The amplitude of the water level changes of the river Tisza and Danube

The mean of the annual maximum and minimum water levels of river Danube was Δ=556cm, and for river Tisza it was 1.6 times higher: Δ=899cm. (***Fig.47***).

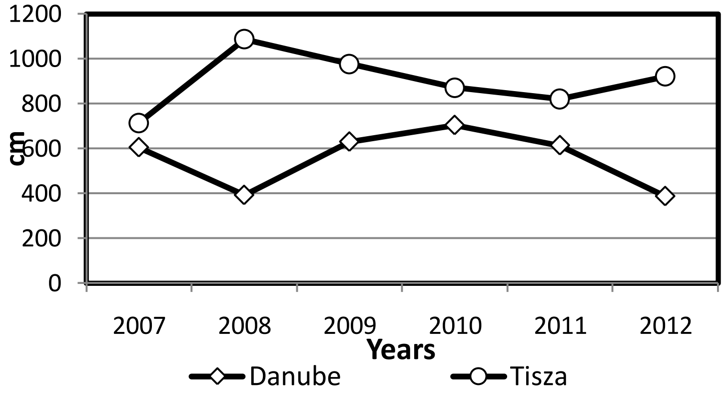


Fig.47. Differences between the annual maximum and minimum water levels of river Danube and river Tisza in the period of 2007-2010.

4.4.5.3. Water level of the river Tisza at Szolnok (2007-2012)

Since in the vicinity of the Danube the number of the observed WNF cases were negligible under the studied period, the river Tisza was selected as a typical representative of the rivers in Carpathian Basin, while the entire drainage basin of Tisza is within the Carpathian Basin and the water regime of the Tisza is the consequence of the previous and the same year's precipitation patterns of the Carpathian Basin. The average water levels of the Tisza between May and September in Szolnok (according to the long-time average, l) were the following: 2007 (l=-71 cm), 2008 (l=118.6 cm), 2009 (l=-108 cm), 2010 (l=454.6 cm) 2011 (l=-40.2 cm), 2012 (l=-99.6 cm). The mean of the 6 years long period was calculated, which was 42.4 cm (*m*). Thereafter the water level differences from the *m*ean were calculated: 2007 (Δ=-113.4 cm), 2008 (Δ=76.2 cm), 2009 (Δ=-150.4 cm), 2010 (Δ=412.2 cm), 2011 (Δ=-82.6 cm) and 2012 (Δ=-142 cm) and after this process the percentages were calculated according to the absolute range (-150.4cm[2009]; 412.2cm[2010]; absolute range=*562.6* cm as 100%): 2007 (-20.16%) 2008 (13.54%), 2009 (-26.73%), 2010 (73.26%), 2011 (-14,68%), 2012 (-25.28%).

4.4.5.4. West Nile Fever (2007-2012)

The case numbers in the studied years were the following: 2007 (n=4), 2008 (n=19), 2009 (n=7), 2010 (n=11) 2011 (n=4), 2012 (n=12). The mean of the WNF case numbers was 9.5 cases per year in the period. The differences of the cases from the mean were calculated (2007 (Δ = -5.5), 2008 (Δ = 9.5), 2009 (Δ = -2.5), 2010 (Δ = 1.5), 2011 (Δ = -5.5) and 2012 (Δ = 2.5) and after this process the percentages of the differences were calculated according to the absolute range of the maxima and the minima WNF cases (-5.5 [2007, 2011]; 9,5 [2008]; absolute range)=15 as 100%): 2007 (36.6%) 2008 (63.3%), 2009 (-16.6%), 2010 (10%), 2011 (-36%), 2012 (16.6%). The comparison of the changes of the water level of the Tisza in Szolnok and the WNF cases- showed that five years from the six years the same sign (less or more than the mean, 0%) of these percentages changed simultaneously except the year 2012 (***Fig.48***). The relative risk to the above-average number of WNF cases was 4 times higher when the mean level of the river Tisza was higher than the mean of the studied six year's (WNF>mean and water level>mean: 2 years, WNF<mean and water level>mean: 0 year, WNF>mean and water level<mean: 1 year, WNF<mean and water level<mean: 3 years).

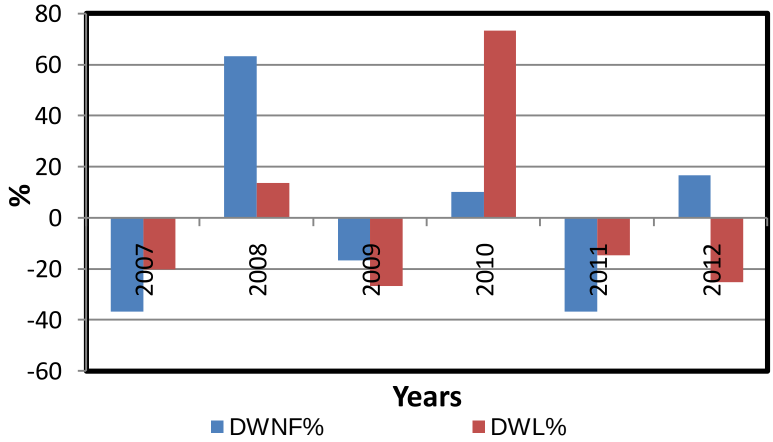


Fig.48. The percent difference of the May-September mean water level of the period 2007-2012 within the absolute water level range of the river Tisza at Szolnok (DWL%) and the percent difference of the annual WNF case number in Hungary within the absolute water level range of the maxima and minima case interval (DWNF%) in the period of 2007-2012.

4.4.6. THE PREDICTED OCCURRENCE OF WEST NILE FEVER USING CLIMATE ENVELOPE MODELING

The observed and predicted potential distributions of the WNF are shown in ***Fig.49***. 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. The major difference can be seen in Spain. Future expansion is expected principally in Asia Minor, the Carpathian Basin and the Balkan Peninsula, but the set of the affected countries is much larger: Spain, France and Hungary (mainly in the far future period), Serbia, Macedonia, Bulgaria, Romania, Ukraine, and Turkey. Considering the current occurrence and the model result, East-Southeast Europe and the Carpathian Basin are highly vulnerable areas. In the Western parts of Europe the primary limiting value is the minimum temperature in July (T min of July more than 20.9°C). It seems that the continental climate with warm summers and September isideal forthe WNF (T mean from June to September should be more than about 22°C). The WNF’s need for moderate summer precipitation (P July is less than about 80 mm).

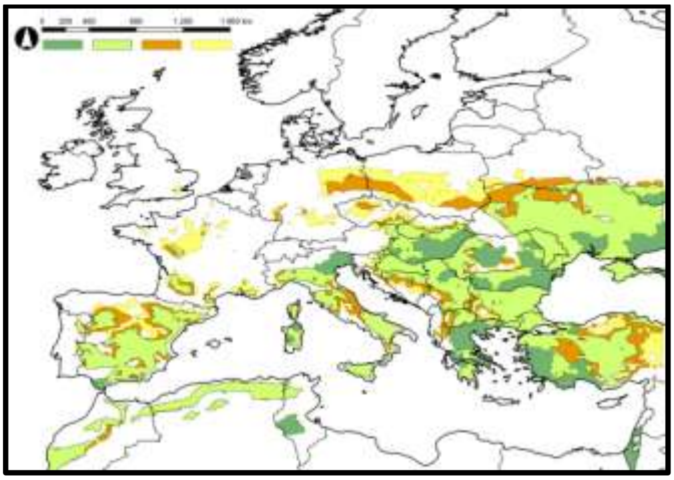


Fig.49. The recent (2010-2012) distribution of WNF (dark green according to the VBORNET database), the potential distribution area for the reference period (1961-1990, light green), the projected future distribution for the period of 2011-2040 (orange) and 2041-2070 (yellow)

4.5. THE PREDICTED DISTRIBUTION OF THE AEDES ALBOPICTUS MOSQUITO USING CLIMATE ENVELOPE MODELING

The observed and predicted potential distribution of the aggregation of the Asian tiger mosquito species are shown in ***Fig.50***. 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 modelled 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. The primary limiting value is the minimum temperature in January (T min should be more than about -2°C), *Ae. albopictus* prefer the relatively dry summers (P July less than about 6 mm).

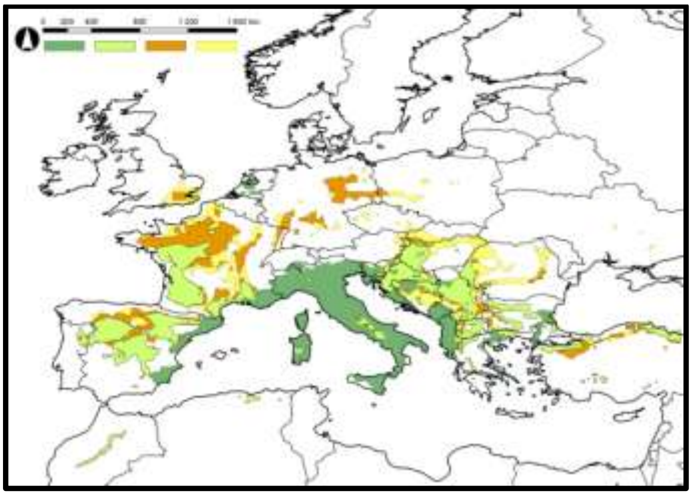


Fig.50. The recent (2012) distribution of the *Ae. albopictus* mosquito (dark green according to the VBORNET database), the potential distribution area for the reference period (1961-1990, light green), the projected future distribution for the period of 2011-2040 (orange) and 2041-2070 (yellow)

4.6. LEISHMANIASIS

4.6.1. THE RECENT AND THE PROJECTED DISTRIBUTIONS OF THE STUDIED *PHLEBOTOMUS* SPECIES AND THE GAINED CLIMATIC THRESHOLDS

It is very important to state in advance that the distribution maps described in the following pages are show only the potential future ranges of the species based on its climatic requirements and climate scenarios and there is no guarantee for wether these species will fill these areas or not in the future.

Based on the current distribution of the studied species the limiting climate values (monthly mean temperature, monthly minimum temperature, and monthly precipitation)were specified. These thresholds (***AnnexSpreadsheet 7***) characterize the climate tolerance and the potential distribution of the certain species; therefore they were used in the distribution modeling. Note that these values are not the observed extremes found in the distribution area, but the limiting values specified by percentile leaving. ***AnnexChart 9*** shows the model outcomes. The currently observed northern limit of *P. ariasi*'s distribution is near the 49°N latitude, but the area is mainly restricted to Spain and Southern France. Our model shows that the possible range is much wider, it reaches the 53°N latitude in Germany and in the UK. While the northern segment of the potential distribution expands to the German-Polish border, the southern segment contains almost the entire Balkan Peninsula and the Carpathian Basin, and in addition it includes, the whole Apennine Peninsula without Sicily. Beside the UK, Hungary, and Turkey, the major expansion from the potential current distribution can be observed in Germany (2011-2040), and in Poland, Bohemia, Slovakia, Romania, Moldova and Ukraine (2041-2070). *P. ariasi* is expected to reach the northernmost territories amongst the studied species: Denmark, Sweden, and Norway (59°30'N) can be affected in the far future. The limiting climate values: in the Benelux States and Northwestern Germany - max(PJul) < 87 mm and max(PAug) < 84 mm, in Northern Italy - max(PSep) < 93 mm, near the northern border of the eastern potential area - min(Tmean,Jan) > -0,5°C, and in the UK - min(Tmean,Jul) > 15,5°C and min(Tmean,Aug) > 14,7°C.Although the present distribution of *P. perniciosus* is very similar to that of *P. ariasi*,(the distribution of *P. ariasi* is slightly smaller),*P. perniciosus* seems to be less tolerant to the combination of cold summers and lowest winter temperatures than *P. ariasi*, since the modelled potential distribution of the former one is remarkably smaller, mainly in West Europe. Similarities can be seen in the projected suitable areas of these species for both the near and far future period; however Germany, Poland, and Bohemia are not as highly affected as in the case of *P. ariasi*. In contrast, in South-eastern Europe the modelled potential distributions both for the reference period and for the future periods have very similar shape in case of the two species. According to the results *P. perniciosus* will, as currently, still favour the low-altitude areas. Major expansion is expected in the UK, Germany, Hungary, Romania, Ukraine, and Turkey. The limiting climate values: in the Pyrenees, Northern and Eastern France, Northern Italy - max(PJun) < 84 mm, in Slovenia and in the Alps - max(PJul) < 78 mm and max(PAug) < 81 mm, near the northern border of the eastern potential area - min(Tmean,Jan) > 0,5°C and min(Tmean,Dec) > 2,1°C, and in the UK - min(Tmean,Aug) > 15,9°C.*P. sergenti* and *P. similis* are typical Mediterranean sandflies, the difference in their current distribution is that *P. similis* is restricted to the Eastern Mediterranean. According to our model, their suitable areas are highly overlapped in the reference period and in the future periods too. However, the modelled distributions of *P. sergenti* are, in all of the periods, slightly larger. By 2070, besides the mainly affected countries (Spain, Italy, Macedonia, Greece, and Turkey), Portugal, Albania, Romania, and Ukraine are also expected to offer suitable climatic conditions for these two species. The main limiting climate values are max (PJul) < 27 mm (both species) and max (PSep) < 36 mm (*P. similis*; Italy and Spain). In general, the lowest winter temperatures can restrict the northern border of the distributions.The current distribution, and therefore the environmental demand and the modelled distributions of *P. neglectus, P. papatasi*, *P. perfiliewi* and *P. tobbi* are similar; the distribution of *P. neglectus* and *P. perfiliewi* is almost the same. The latter ones are, in contrast to*P. papatasi,* absent from Spain, while *P. tobbi* is definitely restricted to the East Mediterranean. According to the modelled potential distribution in the reference period, all of these sandfly species could inhabit the Carpathian Basin, the Rumanian Lowland, the Balkans, Turkey, and the Iberian and Apennine Peninsula. Most of all, *P. papatasi* has occupied its potential area. Great northward expansion is not expected in case of these four species, only in France, Hungary, and Ukraine. The main limiting climate values are max (PJul) < 45 mm (*P. neglectus* and *P. papatasi*), and max(PJul) < 51 mm (*P. perfiliewi* and *P. tobbi*), min(Tmean,Jul) > 18.5°C (P. neglegtus; Northern Spain), and max(PSep) < 72 mm (*P. tobbi*; Italian coast, the Alps and the Pyrenees). In general, the lowest winter temperatures can restrict the northern border of the distributions.In the case of certain species the mean latitudes that limit their northward future expansion are as follows: 56°N – *P. ariasi*, 54°N – *P. perniciosus*, 48°N – *P. neglectus, P. papatasi, P. perfiliewi,* and *P. tobbi*, 46°N – *L. infantum*, and 44°N – *P. sergenti,* and *P. similis.* After examining the various *Phlebotomus* species the model result were evaluated based on the aggregated distribution of them. According to the differences between the aggregated current distribution of the *Phlebotomus*species and the modelled potential distribution of this group, the Po River Valley, Serbia, Hungary, the northern Rumanian Lowland, and the coastline of the Black Sea seem to be unsaturated with sandflies recently, while in the western European areas the resident sandflies almost completely fill their potentially suitable areas. The future northern expansion is expected in Britain, Germany, Poland, Bohemia, Slovakia, Hungary, Romania, Moldova, and Southern Ukraine (from 47°N to 49°N). The major expansion in the next 30 years can be seen in Germany, however in this country and in Poland expansion in the far future period is not predicted. In the period of 2041-2070 the major expansion is modelled in the UK and north to the Black Sea. A model validation was applied by comparing, for the reference period, 1) the model result based on the aggregated distribution, and 2) the union of the model result based on separate distributions (***Fig.51*** and ***Fig.52***). The area of the aggregated model results is slightly larger, but the difference can be seen mainly in the territories that were predicted as expansion of the aggregated species in the near future period (UK, France, Germany, Moldova, and Ukraine). An opposite type of overlapping is to be observed in Poland, Southern Slovakia, and Northern Hungary. It can be stated that the model was highly verified by this comparison.

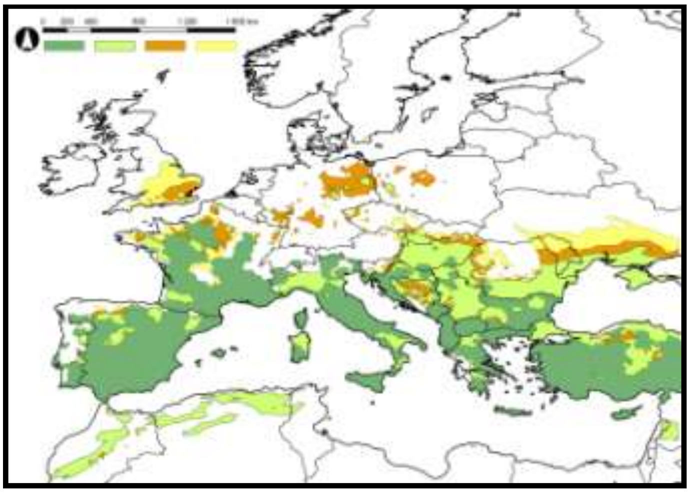


Fig.51. Current distribution (dark green), modelled potential distribution in the reference period (light green), and predicted potential distribution in the period of 2011-2040 (orange) and 2041-2070 (yellow) of the aggregation of the studied *Phlebotomus*species.

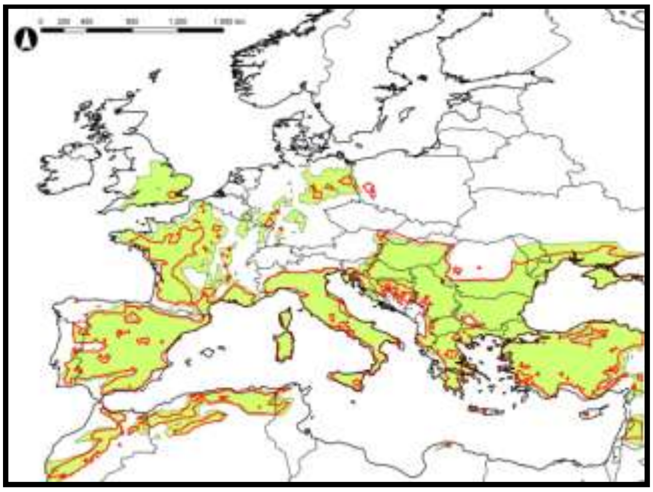


Fig.52. The model result based on the aggregated distribution of the eight *Phlebotomus*species (red contour) and the aggregated model results based on the individual distributions (green region). The model was run on the reference period (1961-1990).

4.6.2. LENGTH OF THE ACTIVE PERIOD

Our model resulted in the prolongation of the potentially active period. In the case of *P. neglectus* the number of months was 8, 8, and 9 in Athen, Greece, and 5, 6, and 6 in Pécs, Hungary in the period of 1961-1990, 2011-2040, 2041-2070, respectively. In the case of *P. papatasi* the number of months was 4, 4, and 6 in Athen, Greece, and 2, 3, and 4 in Szeged, Hungary in the studied three periods. In the case of *P. perniciosus* the number of months was 7, 8, and 8 in Málaga, Spain in the studied three periods, but no prolongation was found in Hungary in monthly resolution.

4.6.3. COMPARISON OF THE MODEL RESULTS

Cluster Analysis was used as the first statistical method for comparing the model results. The cophenetic correlation coefficient (Sokal and Rohlf 1962, Sokal RR, Michener CD 1958) value of the result was 0.958 (***Fig.53***). According to the analysis, *P. ariasi* is the sister group of the major complex of the other nine species with bootstrap value of 73 (the clustering was repeated 100 times). The most obvious group was formed by *P. similis* and *P. sergenti* with a bootstrap value of 83. It should be mentioned, that only these two species among the studied ones belong to subgenus *Paraphlebotomus* according to the conventional, but not proven (Alten, 2010) division of thegenera (Lewis 1982). The complex of the union distribution and *P. pernciosus* is, however, not so strong (bootstrap: 45), neither is the place of *Leishmaniainfantum* (bootstrap: 43).

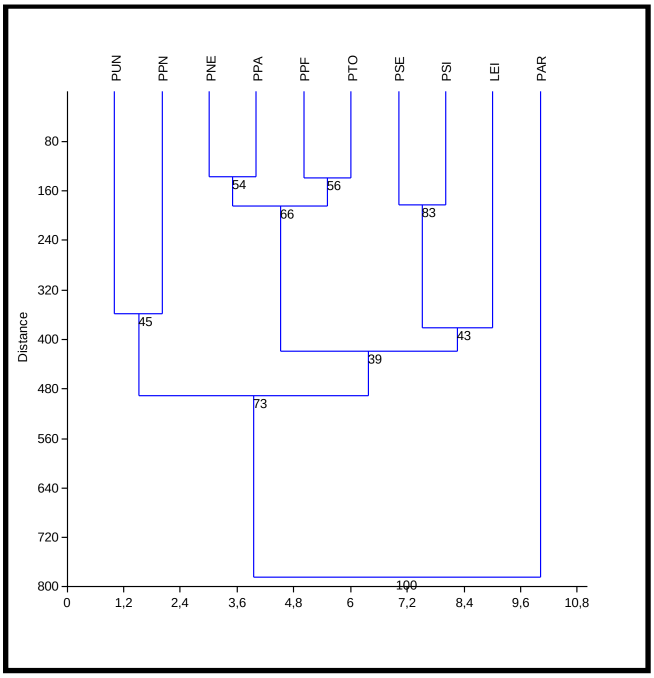


Fig.53. The result of the Cluster Analysis based on the presence-absence data with bootstrap values. Paired group method with Euclidean similarity measure was used. Abbreviations: LEI – *L. infantum*, PAR – *P. ariasi*, PNE – *P. neglectus*, PPA – *P.*

papatasi, PPF – *P. perfiliewi*, PPN – *P. perniciosus*, PSE – *P. sergenti*, PSI – *P. similis*, PTO – *P. tobbi*, PUN – unifieddistribution of *Phlebotomus*species

The NMDS result is related to the aforementioned results. The Shepard plot (Shepard 1962) shows good linearity, and the stress is only 0.01785, which indicates that there was a very small information loss during the dimension reduction in terms of the paired distances.

The Cluster Analysis put *Leishmaniainfantum* next to the group of *Phlebotomussergenti* and *P. similis* in the tree, which result is highly verified by the NMDS. In contrast, there is no evidence, that the species of the subgenus *Paraphlebotomus* are vectors of *Leishmania infantum*, rather they are bound to the parasite L. tropica (Ready 2000, Kamhawi et al. 2000, Depaquit et al. 2002). The distance between*L. infantum* and the aggregated *Phlebotomus* species is the greatest in the major complex. This may be the consequence of the fusion, because the sandfly species together contain the whole spectrum of the environmental tolerance of the eight species, and the present endemic areas of *Leishmania. infantum* are located in the relatively warm, southern part of Europe incorporating the distribution of *Phlebotomussergenti* and *P. similis*. The cluster of *P. perfiliewi, P. tobbi, P. neglectus,* and *P. papatasi* was proved by the NMDS. Since the NMDS is a good statistical method to ordinate the distances of the species, it is obvious that the larger distance from *P. ariasi* can be seen in case of the cluster of the four species mentioned above and the cluster of *P. sergenti* and *P. similis. P. perniciosus* and the cluster of four species are situated the nearest to the origin. The nearer the place is to the origin, the less summarized difference it has from the others (***Fig.54***). The result of the PCA can be seen on ***Fig.55***.

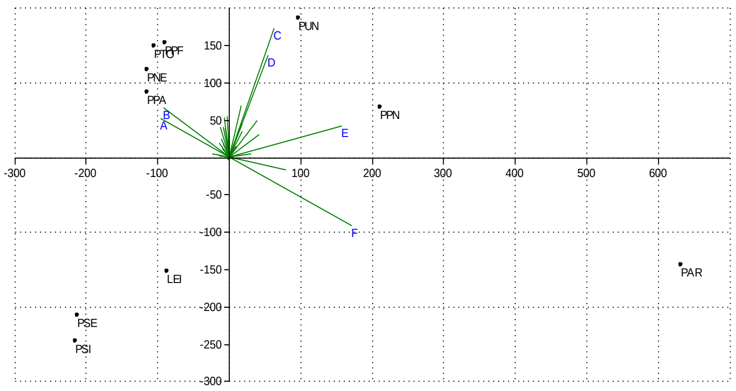


Fig.54. The biplot result of the principal component analysis (PCA). Abbreviations: LEI – *Leishmania infantum*, PAR – *Phlebotomusariasi*, PNE –, PPA *P. neglectus*– *P. papatasi*, PPF – *P. perfiliewii*, PPN – *P. perniciosus*, PSE – *P. sergenti*, PSI – *P. similis*, PTO – *P. tobbi*, PUN – union distribution of *Phlebotomus*species

The six major distinguishing variables were displayed in a map (***Fig.55***). The results are confirmed, since the plane stretched by the first and second components are responsible for the 72.08% of the variance, and only the first four components can explain more than 3% of the variance. The result of the PCA proved the former statistical conclusions. According to the biplot and the map displaying the six major variables it can be stated that 1) the cluster of *Leishmaniainfantum*, *Phleobotomussergenti*, and *P. similis* is segregated from the others mainly by the common absences of the three species; 2) the aggregated distribution is in the direction of the vector sum of variable as it was expected; 3) the variables C and D are reliable for the presence of the aggregated distribution and for the absence of cluster of *Leishmaniainfantum*.

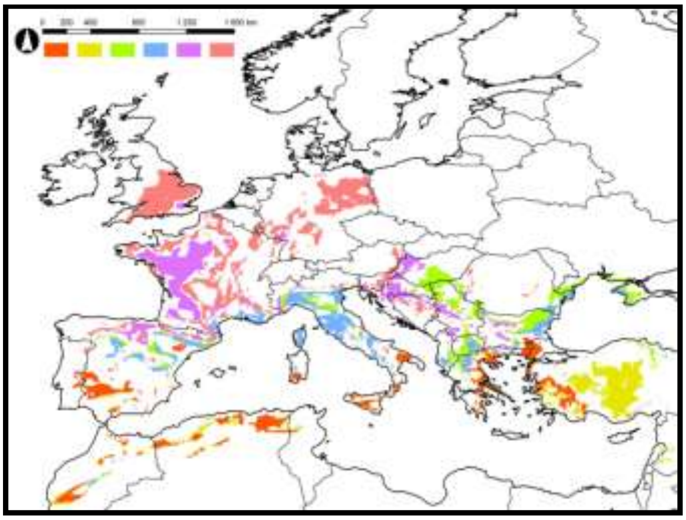


Fig.55. The area of the major distinguishing variables of the biplot PCA. A- orange, B-yellow, C-green, D-blue, E-purple, F-pink

These variables are bound mainly to the northern Mediterranean territories of Europe. They are adjacent to each other and include Northern Spain, Central Italy, Southern Hungary, Serbia, Albania, Macedonia, and Eastern Bulgaria; 4) the large distance of *Phleobotomus papatasi*'s cluster and *P. ariasi* is explained by variables A and B (absence of *P. ariasi*, presence of the cluster of four), and variable F (presence of *P. ariasi*, absence of the cluster of four); 5) variables A and B can be seen in the southern Mediterranean territories of Europe and in the western part of North Africa, including Southern Spain, Southern Italy, Greece, Western Turkey, Northern Morocco, and Northern Algeria. Note that the difference of the modelled and current distributions is mainly caused by the European input maps of our research. The principal difference is that variable B is displayed at Central Turkey, while the focal point of variable A is western than of variable B; 6) variable E is the most reliable of all for the presence of *P. perniciosus*, and is a neighbour of variable F in the map. They can be found mainly in the Atlantic climate (Southern Britain, France, and Germany) and in Western Hungary, Slovenia, Croatia, and Bosnia and Herzegovina.

4.6.4. THE POTENTIAL FUTURE COEXPANSION OF THE INDICATOR PLANTS AND *PHLEBOTOMUS* SPECIES

The aggregated, observed and modeled (***Fig.56***) distribution - and the climatic requirements - of *Juniperus oxycedrus*, *Quercus ilex*, and *Pinus brutia* show significant resemblance with those of the studied *Phlebotomus* species. Hence it can be stated that these three plant species can serve as climatic indicators of the vectors of *Leishmaniainfantum*. The observed distribution suggests that these indicators can tolerate a winter mean temperature not lower than 0°C, their cold tolerance is, however, known to be greater. According to the hardiness zones of USDA, *Juniperus oxycedrus* and *Quercus ilex* are hardy to -17.7°C, and *Pinus brutia* is hardy to -12.2°C. The modelled potential distribution in the reference period is larger than the observed one mainly in Eastern Europe. Territories with -1 - -2°C mean temperature in January is included. 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 (***Fig.57***).

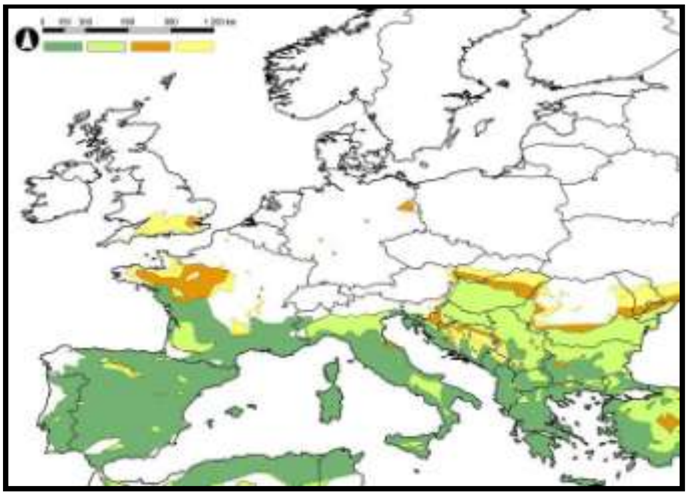


Fig.56. The aggregated, observed and modelled distribution of *Juniperus oxycedrus*, *Quercus ilex*, and *Pinus brutia*.

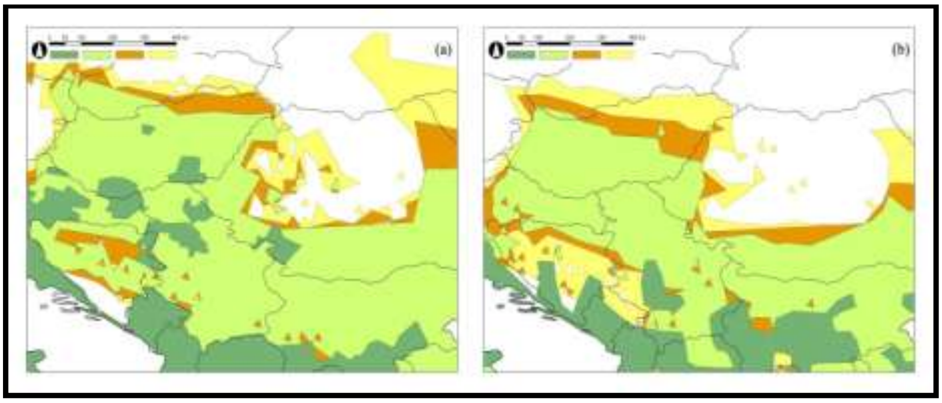


Fig.57. The aggregated, observed and modelled distribution of the studied *Phlebotomus*species (a) and *Juniperus oxycedrus*, *Quercus ilex*, and *Pinus brutia (b)*in the Carpathian Basin.

Future predictions for the period of 2011-40 and 2041-70 show similarities in case of the indicators and vectors. The selection of the indicators was verified by Cohen’s kappa measurement based on the distribution of the vectors and the indicators. Since the Cohen’s kappa value in case of the modelled distributions (0.7938) is much greater than in case of the observed distributions (0.6057), the similarities in the climatic requirements are greater than it was expected based on the observed ranges (***Fig.58***). It was concluded that the studied plant species can be reckoned as indicators of sandflies.

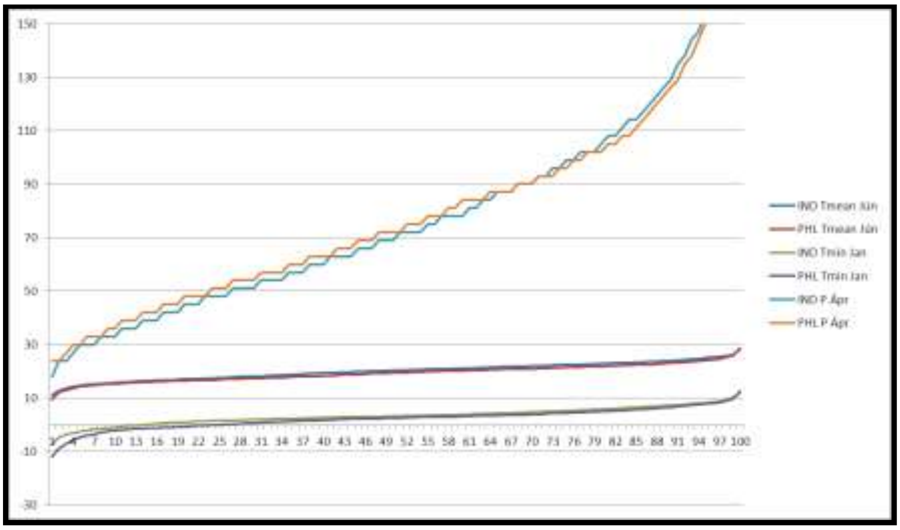


Fig.58. The Cohen’s kappa measurement based on the distribution of the *Phlebotomus* species (the vectors) and the studied plants (the indicators).

5. DISCUSSION

Our reporting system offers a possibility to study the basic associations between climatic and meteorological conditions and Lyme borreliosis.It was considered that 13 years is sufficient to find valuable correlations between Lyme incidence and climatic factors similar to Bennet et al. (2006) who analysed only 8 years in 1997-2003. The greatest annual LB incidences were reported in the last three years anda continuous increase was observed. The 79% of the growth of LB incidence occurred during these weeks in the later period of 2007-2010. Our findings are in accordance with the statement of the IPCC 4th Assessment Report (Confalioneri et al. 2007) in which was stated that the recent climatic change may affect the abundance, seasonality and geographical distribution of VBDs and are in accordance with our previously discussed observations that the shift of the start of the spring season caused the similar shift of LB season. Acorrelation was found between the weekly ambient temperature and weekly Lyme incidence from the 1st or10th to the 23rd-24th weeks (from the start to the peak phase of LB incidence) with a low dispersion. The peak of the annual LB incidence shifted about 2-3 weeks earlier as the season start. It is very important to note that the difference between the start of the increase of LB incidence and the onset of spring may be more than the observed difference of 2-3 weeks due to the lag between the tick bite and the appearance of EM. This lag is usually between 1-3 weeks; in most of the cases not more than 1 week. Nevertheless, based on our analysis, the coincidence is good between the onset of the major LB disease season and that of a stable 10°C or higher daily temperature, while the starts of a lower activity may starts at 5°C. This result is in accordance with the findings of Perret et al. (2000) describing that the threshold temperature of questing (food-seeking) tick activity is at 7-8°C, the lag between the start of the annual tick season and the observation of the first new primary cases would be, approximately not more than 2 weeks in spring (Lindgren 2001). Perret et al. (2000) found that when the 5-day average of the daily maximal temperature was over 7°C tick questing activity was always observed. On the other hand ticks were always collected when the temperature reached or exceeded 10.5°C and at temperatures ranging between 6.6°and 8°C, questing ticks were only occasionally collected. Based on thiesedata, this period is considered as the start of the activity of Ixodidae ticks. In Europe, the start of spring shifted to 2 weeks earlier during the calendar year, and the vegetation period became longer by two weeks between 1980 and 2001 (Ogden et al. 2005). From 1960 to 1995, the vegetation period shifted to 12 days earlier between the latitudes 45-70^{o}N (Beniston 2001). In our study, the 24-day shift in the start of spring during the 13 years seemed to be an overestimation, the shortness of the analysed period may explain the observed changes; however, this might be a real trend. A non-significant increasing trend was observed in the mean temperature of all seasons while the rise phase of the LB cases occurred from March to June what is consistent with the observations of Hornok (2009B) in Hungary who found that the activity of the *I. ricinus* nymphs was the greatest in the same period. Since a significant correlation was found between the start of the vegetation period and the start of the LB season it is plausible that the trend of increasing temperature and the earlier onset of spring were related to the increasing annual LB incidence and the earlier start of LB season. Randolph (2004) warned that the GCC is not necessarily the only cause of the emergence of tick borne diseases; the changing socio-political environment and habitat structure in the former socialist countries are important factors of the changes as well. In Hungary, the highest incidence was observed at the turn of June-July, but, for example, in Estonia the annual LB curve reached its maximum incidence in August, due to the different climatic conditions (Beniston etb al. 1998).The trend of increasing LB incidence was steady during the 13-year period in Hungary, except for the irregular years of 2007 and 2010. In 2007, the most severe heat wave was recorded in the history of Hungarian meteorological observations, in Budapest the daily mean temperature was higher than 30^{o}C for five days, and the mean daily temperature reached 27^{o}C for more than one week.In 2010, the summer was unusually wet, and the annual LB incidence was significantly higher than the expected value.The activity of ticks during hot summer days is restricted to morning and late-afternoon hours- In case of an extreme hot weather in July of 2007 in Hungary, it is probable that the weather conditions caused very similar avoidance behaviour for people and ticks, which reduce the possibility of human infection. In contrast Šumilo et al found (2008) that hot, sunny summer weather and in general holiday times make an additional risk on human infection by compelling people to take excursionsin the nature. Summarizing the above concerned facts the extreme hot summers and heat waves may moderate the effect of the GCC like in the case of the Hungarian heat wave in 2007, but one single event is not sufficient to assess the effect.To clarify this problemthe influence of the human presence in the nature was analyzed to better understand the start and bimodality of the LB season. Temperature plays a very complex and controversial key role in the influencing of tick-human connection by increasing the questing activity of ticks and human outdoor activity as well by increasing the evaporation and causing lower relative air humidity. The latter has a negative effect on tick activity, but sunny and dry summer days have a positive effect on human outdoor activity (Šumilo 2008, Randolph 2008).The development of the IA showed a pronounced summer depression, probablydue to the effect of the summer drought on tick activity. After the modification of the polynomial IA curve by HM, the remaining curve is mainly exempt from the additional human influence. Since our model used this empirically recognized equation, the model contains indirectly some kind of correlation between tick activity and the summer environment. Although the spirochaetae have an important role in the infection chain, the temperature requirements of the parasite may rather depend on the temperature of the blood meal than the ambient temperature, since the temperature optimum of *Borrelia burgdorferi* parasite is between 33-37°C (Barbour 1986, Heroldová et al. 1998, Hubálek et al. 1998, Hubálek 2009) and the maximum temperature is 41°C (Hubálek et al. 1998). The Hungarian National Health Center gives the weekly, monthly and annual sums of the data. The Hungarian LB data does not allow the differentiation between early and complicated symptoms. The early localized infection is 70% of the whole recognized LB cases in the USA (CDC Lyme), and according to a sampling (with n=1784) this is very similar in Hungary (Lakos 1999). Therefore a major part of the reported LB cases may be EM, the annual LB data was handled with the latency characteristics of the EM. This simplification, of course, doesn't allow the modeling of the non-EM cases of the year and consequently the exact modeling of the entire year. The onset of the late disseminated infection and other LB related complications can be much longer, months to years, than the onset of EM.According to the CDC the seasonal peak of the EM reaches its peak in July and August, while the maximum of the neurological manifestations appear in August and September in the USA. Creating the correspondence between the spring-early summer ambient mean temperature and relative LB the non-EM cases influenced the model less, because of their longer latency. There is a lag between the biting and the report of a case, while: 1) there is 3 day-30 days (the average is between the first to second weeks) from the biting to the observing of EM and the serology can confirm the suspect of the disease within 1 week. Note that the IgM antibodies have a diagnostic value only in the first 3 months of the infection and the non-EM symptoms usually have a longer latency than EM. From the above mentioned facts it is difficult to fit the cases of a reporting week to the real time of the tick biting, when the individual infected by the parasite. Searching for the spring-early summer correlation between mean temperature and LB incidence the 1 week lag gave the best results in the model, which is in accordance with the character of the latency of the disease and the report system. It is interesting that similarly one week lag was found in case of tick-borne encephalitis (TBE; Daniel et al. 2008B).The same weekly mean ambient temperature value was used for the entire country, because the topography of Hungary is largely homogeneous: only 2% of the country is situated higher than 300 m above sea level, the range of the elevation is between 77.6-1014 m. The country is not bisected by higher mountains and the entire studied area belongs to the Pannonian biographical region.The domain of the grid of the climatic data were derived from is somewhat greater than Hungary. Since the part of the Carpathian Basin situated within this domain is topographically homogenous, the difference between the domain of climatic and LB data is not significant. As in other countries of the European Union summer is the main time of the holidays. In Hungary in the last decades (eg. the studied period) the school holiday started in mid-June and ended in the end of August. It is very conspicuous that without July and August the camping activity (derived from the camping guest nights) is highly temperature-dependent and depends on the income of the households. From this fact human and tick activity show a similar correlation from March to the end of May and from September to late October and the holiday period from July to August form an additional risk to human infection. Although the studied period is greater than the period of the camping data, our aim was only to determine the nature of the correlation of camping/human outdoor activity and temperature and to calculate the multiplicative effect of the summer holidays. Since it was found that human activity is exponential function of temperature as well as the LB which is determined by both the human and tick activity, distinguished use of human and tick activity could not improve the model. Our previous assumption was that human outdoor activity has a strong correlation with temperature in spring and fall. The results verified our assumption. It was confirmed that the irregular additional summer human activity can explain the high LB incidence in July and August, in accordance with Šumilo et al. (2008), Randolph et al. (2008), and Estrada-Peña et al. (2008). Sinceit was observed that the LB season is occurred between the 10th to the 48th weeks of the year, applying any multiplicative effect of human activity (HM) out of this period is useless. Also note that in the case of low values of guest nights in winter calculating multiplicative HM is inaccurate. At first inspection, it seems that the most serious insufficiency of the model is that temperature was handled the as it were the only meteorological factor influencing the incidence of human LB. It is well known, that temperature and humidity theoretically are equally important in influencing the tick activity. In case TBE, which has the same vector as *Borrelia burgdorferi* s.l. has, in the Czech Republic a very strong correlation was found between the mean ambient temperature and incidence (Daniel et al. 2008A and 2008B). Using the precipitation or humidity data of the regular meteorological stations seems to be inappropriate for characterizing the natural environment of ticks, where the evaporation, the transpiration of plants and the penumbra create a balanced, relatively wet, windless environment with decreased solar radiation, which can provide the existence of dew even in a dry period. Another problem is that many classic meteorological stations are positioned in subsequently urbanized areas. The first phase of the LB season was analyzed in case of determining the temperature – activity relation, because in this time, from late February to mid-June soil moisture and the air humidity is high or moderate thanks to the low evaporation and freeze of the cold season and the probable effect of the decreasing size of the still hungry, questing tick population is not too high, as the second tick activity peak in fall also shows. The other reason is that in spring most of the cases belong to the EM. While according to historical data and field collection studies, the seasonal activity of *Ixodes ricinus* is bimodal with a major spring (March to June) and minor fall (September to November) peak in Hungary (Babos et al. 1964, Széll et al. 2006, Egyed et al. 2012), the seasonality of LB doesn't show bimodality in Hungary (Hornok 2009A and 2009B).After eliminating the human influence and the temperature-related activity from the model a bimodal point cloud was gained, which was regressed to a third order polynomial curve. This curve shows many similarities to the observed annual *Ixodes* tick activity in Hungary:1) the curve is similar to the bimodal summarized activity of adults and nymphs; 2) the spring-early summer peak is longer – and more important –

than the fall peak; 3) the first peak follows the known run of the activity period of nymphs, which may reflect also the spring activity of adults; 4) the second peak is very similar to the run of the activity period of adults. Note that the newly moulted ticks of all stages are thought to emerge in the autumn of each year (Randolph 2002); 5) the curve clearly shows the late summer depression of tick activity. Since the input of the model was not the number of field collected *Ixodes* ticks but the observed LB incidence, I could not distinguish the infection caused by adults or nymphs. The IA curve includes the climatic and non-climatic factors which may influence the LB except temperature-related human and tick activity and the multiplicative effect of holidays in summer. Since the modelled RI curves show a run similar to the observed RI curve, and the calculated R^2 values were relatively high, our analysis by distinguishing the temperature dependent activity, effect of summer holiday and temperature independent activity was proved. In accordance with Randolph (2010)it was found that the summer holiday has great influence on human infection with Lyme borreliosis (LB). Despite the fact that the raw weekly LB data in Hungary seem to be unimodal, the bimodality of the tick season was demonstrated known from the Stafford et al. 1998 and Széll et al. 2006 and by using the originally unimodal LB data. May and June are very important months in the life-cycle of ticks. During these months, the vegetation has the most intensive development and the amount of tick metamorphosis and egg laying activity is the highest. In our study, the LB seasons were divided into two groups according to positive or negative deviation of the years from the mean temperature of May and June. In case of the warmer late spring-early summer years, the LB curve reached the annual peak 2-3 weeks earlier and the descending phase of the curve started earlier also. This observation can be explainedif we note that the maximum activity of nymphal life-stage occurs during late spring and early summer in the temperate climatic zone. In case of a VBDs in general, higher temperatures accelerate the development of individual ticks, the ovulation and the metamorphosis, increase the population density and abundance.Due to the technical problems with the sensitivity of the tests the and personal diagnostic difficulties (LB is a great imitator of other cardial, neurological etc. diseases) and last but not least the relatively late first isolation of the pathogen and the discovery of the connection between the pathogen and the clinical manifestations the real cumulative prevalence of the disease in the living population is could be the 10% of the full population (approxymately1 million person) in Hungary (Bozsik 2004). In the analysis, I faced tosome problems that are difficult to solve. First, the incubation periodof LB from the infection to the onset of the primary symptoms is usually one to two weeks. Ideally, we should reconstruct the most likely date of infection (the exact time of tick bite). If we separate the primary cases from the secondary ones, we could statistically reconstruct the weekly incidence of the primary cases. Unfortunately, medical doctors often neglect to fill in the questions concerning the circumstances of the beginning of the disease. Consequently, we cannot separate the early localized infections from the early disseminated infections and late persistent infections, so the incidence of primary LB cases may be underestimated.A period of 13 years is a very short time to recognize a possible long-term natural fluctuation such as a changing tick population density or infection patterns with *B. burgdorferi*. The weekly incidence depends on several additional factors, for example the behaviour of the people, and the rate of infected ticks, host animals, etc. Anothershortcoming of this study is the uncertainty of the reporting system, which may modify the association between temperature and the weekly incidence of LB. Another important problem is that we cannot reconstruct the bias due to the changes in laboratory testing. The diagnostic activity, the knowledge of medical doctors and reporting habits may have also changed. The main impact of the GCC on ticks may be a change of their abundance and population, the rate of their LB infection level and the changing trend of their seasonal behaviour and life-cycle, but we only know the changing incidences of the disease. These problems should be kept in mind in the evaluation of the association between the increasing trend of LB incidence and the similar trend of the length of the vegetation season. We may suppose that a systematic error due to improving laboratory detection or a strict reporting discipline, would affect homogenously the approximate LB incidence every week during the year. It would be difficult to explain the observed significant increasing trend between the 15th and the 28th weeks, which correlates well with the shift of the vegetation period and can explain 79% of the increasing annual LB incidence, too. The daily mean temperature data on country level was used. Due to the relatively homogenous geographic circumstances of the country, the aggregated temperature data can characterize the different parts of the country. The associations can be further studied on a regional level when the effect of the changing ecological habitat and the abundance of the vector and host of the disease can be taken into consideration. In the southern part of Europe summers will become warmer and drier, so the GCC will likely affect the abundance and seasonal activity of the ticks more than in northern Europe where the geographic extension may show a greater change. In Hungary, the average LB incidence rate during 1998-2010 was only 13.57 per 100,000 per year, so it is very likely that LB is underreported, however, the difference in forest cover is notnegligible. In Hungary, the forestation is only 19.2% (Hungarian Ministry of Rural Development 2012), in Slovenia, 58.5% (Forestry Institute of Slovenia 2012) and forests are the greatest habitats for ticks. It is plausible that the GCC will decrease the availability of water for the vegetation in Hungary (Somogyi et al. 2008). Further studies are needed to clarify more precise associations. It would be useful to carry out a regional analysis in Hungary to search for differences of LB incidences between the counties with different regional climates. It is also desirable to know the proportion of the early and the later infections.Based on the associations, we may predict the future changes in the annual distribution of the incidence in relation to the GCC. The follow-up of the seasonal, monthly, or weekly changes of LB incidence may be more informative than changes in annual incidence with respect to changing climate and the vector, host and pathogen biology. More information can be gained if monthly or weekly changes of the incidence are correlated with meteorological factors. For routine purposes, temperature is the easiest accessible variable; therefore it seemed to be a first-level aim of the study to investigate whether a relationship between weekly incidence and weekly temperature can be revealed in different climatic regions within a country. Several supported the assumption that the number of the questing *Ixodes ricinus* ticks is related with the seasonal variation of the maximum air temperature (Randolph 2009, Chauvin et al. 2009).LB has been positively correlated with higher summer temperatures in the UK, with a greater number being reported in southwestern regions than in northern areas (Subak 1999). As a first step the association of temperature and LB was analyzed at the regional level. Although the selected two Hungarian regions that have a good contrast concerning their annual mean temperatures mainly in the colder half-year, the sums of annual precipitation of these regions are similar (550–700 mm or more; in period 1970–2000). In the centre of the Hungarian Great Plain, where the annual precipitation sum is the lowest in the Carpathian Basin (550–500 mm or less than 500 mm/year; in period 1970–2000), the annual LB incidences are too low to compare with the wetter Transdanubia region, even in the early summer period. For example, in 1998–2010 the annual LB incidences in the western part of Transdanubia were 4–10 times higher than in the southern part of the Great Plain. For these reasons I could not make contrast between the wetter and drier Hungarian counties. I did not find a significant correlation between the mean temperature of winter and the following annual LB incidence, which is consistent with Schauber et al. (2005), who found that the mean temperatures for the prior winter showed weak or inconsistent correlations with Lyme disease incidence. Although in the analyzed 2 NE counties the onset of spring shifted from the 16.5th week to the 14th week significantly, the peak of the LB season shifted from the 28th to 29th weeks. Our findings are consistent with Széll et al. (2006), who found that *I. ricinus* ticks are most active between April and June. In the 3 SW counties, this indicator week shifted from the 14.2nd to the 13.6th week non-significantly, and the peak of the LB season shifted less than one week. The differences between the onset and the peak of the weekly LB incidence curves can be explained by the regional differences of climate such as the different mean winter and autumn temperatures, since the peak activity of *I. ricinus* is influenced by their local environment (HornokandFarkas 2009).As described above, in the NE counties the increasing trend of LB incidence started later, but the shifting trend of the spring to the earlier weeks was more rapid than in the SW counties. It remains still open, why a significant shifting trend of the start of spring was not visible in the SW counties, why a slow, but significant increasing trend was observed in the LB incidence rate. According to (Bennet et al. 2006 and Walsh-Haehle 2010) the monthly mean summer precipitation, the number of summer days with relative humidity more than 85% or the soil moisture in summer (AshleyandMeentemeyer 2004) and the Palmer drought index (Schauber et al. 2005) are as important predictors of LB incidence as the monthly mean summer temperatures. Our further aim is to study the expected correlation between the summer precipitation and LB in Hungary, which would be an important additional factor to predict the future of the annual profile of LB incidence in Hungary.Lyme borreliosis is probably present for a long time Hungary, even though the first isolation of Lyme spirochetae from humans were publicated in 1985 (Lakos et al. 1985) and from ticks in 1991 (Lakos et al. 1991). However it must be kept in mind that the first publication which confirmed that Lyme disease is a spirochaetosis was only published in 1982 (Burgdorfer et al. 1982). Compared to the LB, WNF is a relatively new (from 2003) vector-borne disease in the Carpathian Basin. The comparison of the recent and the predicted future distribution of a vector and VBDs, at first aspect, may seem to be problematic, but the recent geographic range of WNF is cannot be explained without the climate factors. There are differences between the influences of the major rivers on the WNF occurrence, since alongthe larger Danube less WNF cases were observed in every year than alongthe smaller, but more natural rivers as Tisza and its tributaries, which have backwaters, wreaths and high amplitude water level changes. The greater river level fluctuation can play an important role to create appropriate conditions for mosquitoe populations (Rozendaal 1992). The year of 2012 was studied separately and it was found, that the contradiction was apparent, since most of the cases occurred in Transdanubia and not in the Tisza valley thanks to the extraordinary low water level of the Tisza in this year. According to Epstein (2010) the epidemic of WNF is ecologically similar to that of the St. Louis encephalitis, since these two VBDs are connected to long and hot, dry (continental) summers with occasionally wet summers, when the case number is generally the highest. Saint Louis encephalitis virus is also transmitted to humans by the bite of an infected mosquitoand the symptoms of the disease are similar to the WNF.Extreme summer rainfalls are favoured by the WNF and the increasing amount of extreme meteorological events are one of the consequences of the GCC (Fay et al. 2008, Meehl et al. 2000). In 2010 the 25% of the whole cases of the period of 2003-2010 were observed which year was unusually wet; -the total annual rainfall was two times higher than either annual rainfall of the last 100 years.Nevertheless,I cannot arrive to conclusions based on the observations of a single year. In the case of the *Aedes* mosquito, the connection between the climate and the geographic distribution is theclearest. According to the VBORNET (2012) database the recent occurrence of WNF in Europe is mainly similar to the migration route of white stork from the East Sub-Saharan Africa (e.g. Uganda, by via Sinai) to Central and Eastern Europe. Although climatic factors alone cannot explain the observed occurrence of WNV, they indicate that dry and warm summers, heavy rainfalls can enhance the population density of *Culex* mosquitoes (Reeves et al. 1994, Reiter 2001). According to SellersandMaarouf (1990) warm winds may carry infected mosquitoes from the dry riverbanks to northern areas. The above described extreme weather events are specific to continental climate conditions, where the disease occurredrecently. The seasonality of WNF may correspond to the spring-early summer migration of birds (Jourdain et al. 2007), in the sense that time needs to ensure a sufficient number of mosquito contaminate with the virus for the chance of human transmission. In contrast to e.g. *Culex pipiens* or *C.modestus*,*Ae. albopictus* mosquito prefers the more balanced conditions and milder winters of subtropical coasts of the Mediterranean Basin. Higher summer precipitation seems to be a major limiting factor in the model for *Ae. albopictus*, which is in accordance with the study of Alto and Juliano(2001) who found that Asian tiger mosquito populations occurring in warmer regions are likely to produce more adults as long as water bodies (e.g. in containers, little ponds) do not dry completely. It was found, that *Ae. albopictus* does not prefer the wetter climate of the oceanic areas of Western Europe which matches the findings ofAlto and Juliano(2001) who found that the populations of the mosquito in cooler regions produce less adults with the variability of precipitation. Our model findings are highly in accordance with the findings of Fischer et al. (2001) who projected the future expansion of *Ae.albopictus* mosquito to the end of the 2060's to France andthe western part of the Carpathian Basin. Since a threedays to two weeks latency is plausible (CDC WNF), the mosquito bites may occurred by initially higher weekly mean temperatures. Floods have a very important role in modifying mosquito abundance. Rivers which have more or less preserved, more natural floodplains - as the river Tisza - and have can offer better conditions for mosquitoes than the highly regulated rivers. It is plausible, that recently birds re-introduce the WNV into Hungary every year.Opinions differ whether climate is by itself sufficient or even the most important factor for explaining species distributions (Dormann 2007). According to Kennewick et al. (2010) the most important limit of the distribution of sandflies is the winter average and minimum temperatures and the cold and rainy summers. Note, that absolute climatic values and extremes rather than averages may explain the limits of distribution better (Kovács-Láng et al. 2008). The modelled potential area in the reference period, if there isn't a major geographic barrier between the inhabited and the unpopulated areas, is greater than the observed one. This difference is apparent in case of *Phlebotomus ariasi* in France and in cases of the *P. neglectus*, *P. papatasi*, *P. perfiliewi* and *P. tobbi* in the Carpathian Basin and in the

South-western countries of the Balkan Peninsula. Themodel is likely to overestimate the possible habitat of a species, but leaving percentiles of the limiting climate values can slightly reduce the overestimation. The modelled and observed distributions are similar in case of *P. papatasi, P. sergenti,* and *P. perniciosus* in the western Mediterranean Basin, and *P. similis* in the eastern Mediterranean Basin. Our model was somewhat validated by the fact that the distribution of the *Phlebotomus*species in the area of the Atlas Mountains were displayed in the model fairy well even though the model originally didnot include North Africa.Nonetheless, the fact that current distribution data of Africa were not considered by the model can cause problems in observation of the shift in the southern areas of Europe (trailing edge). The modelled retraction in Southwest Spain, coastal parts of South Italy and Greece, and Southwest Turkey is thought to be the blunder of the model. The significant retraction in the Atlas Mountain can, however, be a real result. The length and the average temperature of the warm season are important factors. Our model finds, in contrast with the results of Fischer et al. (2011a), that the Benelux States may not be suitable for *Phlebotomus*species, because they donot favour the short, relatively cold and rainy summers (Kennewick et al. 2010). Fischer et al. (2011a) expected no migration from thesouth-eastern direction, which is strengthened by our results. The range of suitable areas differs between the two species, which is consistent with Fischer et al. (2011b). In contrast of Fischer et al. (2011b) it was found that to the end of the 2060's Central and Western Europe will be only suitable for *P. ariasi* and *P. perniciosus*, and not for *P. perfiliewi* and *P. neglectus*. The long-distance transport and travelling can play a very important role (Walther et al. 2009), as can be shown in case of the migratingworkers and their and tourists' pets (Neghina et al. 2009). Therefore the modelled discrete potential distributions may be inhabited by the vectors without assuming continuous migration routes. Each of the selected eight sandfly species showed expansion according to the prijections of REMO model, but the size of their potentially inhabited area increase can be very different for the various species. Our results are consistent with the projections of Fischer et al. (2011a, 2011b) in the sense that the Central European climate will become more and more suitable especially for *P. ariasi* and *P. perniciosus*, the species whose distribution focuses on the south-western territories most of all.The distribution of plants and animals limited by not only the climatic but the edaphic parameters, as soil type also have a great importance. Thus it was important to examine whether the selected indicator species have wide tolerance to the soil type. In the distribution area of the studied species numerous different soil type can be observed, including leptosols, regosols, luvisols, cambisols, calcisols, fluvisols, vertisols, and umbrisols (FAO 1971). While almost all the soil types of Central and Western Europe is found within the current distribution area, the edaphic parameters will probably not limit the future expansion of these species.The latter is somewhat greater, primarily in Central Europe, Germany, and Poland. It should be noted that some distinct territories in Germany, South England and Poland are included the modelled potential distribution for the reference period, which is in accordance with the observation of Fischer et al. (2010). In the Carpathian Basin and Eastern Europe the modelled distribution shows significant similarities to that of the vectors. In the Carpathian Basin the northern border of the modelled distributions coincide with the northwestern-southeastern winter isotherms. The distance of the northern border of the indicator and vector species is 50-150 km; this difference is increasing towards the east. In Eastern Europe the distribution borders and the isotherms have a west-east direction. In Transylvania the presence of the indicators is not predicted for the studied periods. The climate in Northern Bosnia and Herzegovina is predicted to become suitable for the vectors by 2040, but for the indicators only by 2070.The Cluster Analysis of the studied climatic requirements of the 8 *Phlebotomus* species showed similar relationship patterns to the real phylogeny of genera *Phlebotomus* within the clad Brahycera (Yeates 2002, 1999, 1994). One of the most spectacular results the separation of *P. ariasi* from *P. perniciosus*.Hence, in the regions where young specimens of these species are able to survive without any (e.g. frost) protection the appearance of the vectors is expected. Therefore Hungary is highly endangered which is in accordance with the recent observation of sandflies in Southern Hungary (Farkas et al. 2011). While almost all the soil types of Central and Western Europe is found within the current distribution area, the edaphic parameters will probably not limit the future expansion of these species. Future predictions for the period of 2011-40 and 2041-70 show similarities in case of the indicators and vectors which is in accordance with the model observation of Fischer et al. (2010).

6. CONCLUSIONS

Using linear regression analysis the trend of LB incidence of each weekwas determined during the 13 years and an increasing trend was observed from the 15th to the 28th weeks. The onset of the LB season shifted significantly, to 3-4 weeks earlier, and the peak of the weekly LB incidence showed a shift to 2-3 weeks earlier in the calendar year. The decrease of the weekly LB incidence also started earlier by 2-3 weeks. The start of the onset of spring (the vegetation period) showed a similar magnitude and signified a significant trend and shifted by 3.5 weeks.

It seems that in general the ambient mean temperature determines the Lyme incidence in first half of the season. This observation can be explained by the relatively high soil moisture of spring and the relative early activity of the *Ixodes* tick's nymphs. From these facts it is plausible that in the increasing phase of the Lyme season temperature is sufficient to explain the observed change of the annual Lyme incidence values. The coincidence is good between the onset of the major LB disease season and that of a stable 10^{o}C or higher daily temperature.

A1.6°C difference was observed in the mean winter temperatures between the northeastern and southwestern regions. Ecologically it may be more important that the mean winter temperature of the NE counties was under 0°C, while it was above 1°C in the SW counties. In addition, spring warming started 2 weeks earlier in the SW counties, and there were only 3 weeks of the year in the SW counties, when the weekly mean ambient temperature dropped below 0°C by a few tenths of a degree. On the basis of the results I can conclude, that even a slight difference of 1.6°C in the mean winter temperatures and 1–2 weeks difference of the start of the vegetation season may influence significantly the features of the LB season. This period lasted for 8 weeks continuously (the main part of the winter) in the NE region. In the period of 1998–2010, LB showed a significant increasing trend in the analyzed NE and SW counties, in the latter region the trend was nearly steadily increasing during the entire period, while in the NE counties this trend was detectable only in the last 4 years. In the colder counties characterized by colder winters, the onset of spring can be detected 1–2 weeks earlier compared to the warmer counties.

The recent distribution of WNF suggests that climate, topographic run of the rivers, floods, the migrating routes of birds and the annual ontogeny of *Culex* mosquitoes together determine the occurrence of the disease. The annual features of the epidemics suggest brief exposures in multiple focuses. In contrast to e.g. the Lyme disease, an emerging vector-borne disease, occurrence of WNF in Hungary did not show a constant pattern in 2008 and 2010-2012. It may be explained by the fact, that in the case of Lyme disease the parasite persists permanently in the local tick and host animal populations, while it is plausible, that birds recurring from Africa and the Mediterranean wetlands re-introduce WNV into Hungary every year. It can also explain the very low incidence of WNF in Hungary. The major benefit of our model is that the observed temperature requirement of the WNF peak season in Hungary is similar to the modelled temperature needs (Tmean of the summer months and September more than 20°C). Climatically, the geographical occurrence of WNF is partly determined by the warm ambient temperature of July and August with wet summers. Our findings showed that floods have an important influence on the annual WNF case number. The water level of Tisza as a characteristic representative of the rivers of the Carpathian Basin and the annual WNF case number simultaneously changed between 2007 and 2011. The seasonality of the WNF is regular as far as can be judged from the low case number of the last decade: it starts in late July, has a peak from August to mid-September and decline, when the weekly mean ambient temperature drops below 13-14°C.

The main determinants of the European distribution of *Ae. albopictus* are climatic conditions, mainly the mean temperature in July, the minimum January temperatures and the low precipitation of the summer months (Mediterranean summers). In case of *Aedes* mosquito, wetlands and floodplains do not seem to be primary determinants of the distribution.

It was found that by the end of the 2060's the expansion of *P. ariasi* and *P. perniciosus* to Central Europe are the most likely among the studied species. In the Carpathian Basin and Eastern Europe the modelled distribution shows significant similarities to that of the vectors and projects the near future invasion of sandfly species to Hungary. In the Carpathian Basin the northern border of the modelled distributions coincide with the northwestern-southeastern winter isotherms.

7. SUMMARY

The results support the presumption thatthe earlier onset of spring and a longer vegetation period is favourable for the ticks and the anthropogenic climatic change will enhance the LB incidence. It is also likely that in Central Europe, due to the GCC, the seasonal activity as well as the modification of the annual biological activity of ticks will change significantly as in the short period of 1998-2010 the significant change of the spring start caused the significant shift of the start of the LB season.

This work indicates that when we develop a CEM for a vector-borne disease or a vector, the primary concern is to consider the ecology, the requirements and the behaviour of every elements of the vector chain. Climate can be the main determinant of the distribution, but in many cases climate itself is not sufficient to explain the observed change of the distribution or occurrence. Under the predicted warmer and dryer summers of the futurethe seasonal climate of the Carpathian Basin will allow the colonisation of *Ae. albopictus*in Hungaryand may modify the seasonality of the WNF, causing a shift in the WNF season by elongating the hottest period of summer and enhancing the warmer period of the autumn season.Among the eight studied, important vector *Phlebotomus* species aresix projected to be potentially present to the end of the 2060’s in theCarpathianBasin and leishmaniasis is likely to become endemic.

In summary it is adjustable that Global Climate Change will influence positively the 1) incidence and prevalence, the 2) diversity, and 3) the seasonality of the vector-borne diseases and it is also plausible that the mosquito-borne and sandfly-borne diseases will acquire a major importance among the infectious diseases in Hungary and also in many other temperate parts of Europe than the present’s.

We have to agree with Machiavelli who warned that even if the future outcomes are always doubtful we must prepare for the problemsbefore the problems completely manifest themselves. I hope that this dissertation could add some new information about the association between climate change and vector-borne diseases to prepare for the challenges of the future.

8. ÖSSZEFOGLALÁS

Eredményeim szerint az antropogén eredetűnek tartott modern kori klímaváltozás által egyre korábbra tolódó tavaszkezdet és a hosszabbá váló vegetációs periódus kedvez a kullancs vektoroknak és növeli a Lyme esetszámot. Feltehető, hogy a kullancsok éves biológiai aktivitását a klímaváltozás Európa-szerte meg fogja változtatni, ahogy az a viszonylag rövidnek számító 1998-2010-es periódus alatt a tavaszkezdetben beállt változás okozta emelkedő tavaszi-és összincidenciában már megmutatkozott Magyarországon. Mivel az erdősültség mértéke és a területi Lyme incidencia között erős összefüggést találtam elképzelhető, hogy a klímaváltozás hatására a jövőben szárazabbá és melegebbé váló klíma miatt az erdők visszaszorulása esetleg valamelyest lassíthatja a Lyme incidencia emelkedését.

A munkám során arra a következtetésre jutottam, hogy a Climate Envelope Modellek felépítésekor és eredményeinek értékelésekor körültekintően kell eljárni és minden esetben figyelembe kell venni a vektoriális lánc minden tagjának ökológiai igényeit, szezonális aktivitásukat. A klíma, habár az egyik legfontosabb meghatározója a fajok elterjedésének, sok esetben a klíma önmagában nem elegendő az térbeli előfordulás magyarázatára. A jövőben várható melegebb és szárazabb nyarak *hatására az* Ae. albopictus valószínűleg kolonizálni fogja a Kárpát-medence területét, valamint módosulni fog a humán Nyugat-nílusi láz szezonális előfordulása és esetszáma a hosszabbá váló nyári időjárás következtében. A tanulmányozott nyolc potenciális Leishmania vektor *Phlebotomus* faj közül hat esetében tartom valószínűnek, hogy a 2060-as évekig megjelenjen vagy elterjedjen Magyarország egyes területein, ami, egyben a humán leishmaniasis endémiássá válását is eredményezheti. *Összefoglalva* az eredményeimet valószínűnek tartom, hogy a klímaváltozás hatására 1) emelkedni fog a vektorok okozta megbetegedések száma, 2) a jelenleginél több vektorok okozta betegségre számíthatunk és 3) feltehetően emelkedni fog a szúnyogok és a lepkeszúnyogok terjesztette fertőzések arányszáma a vektorok okozta betegségek között.

9. REFERENCES

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10. LIST OF THE OWN PUBLICATIONS

Articles in the topic of the dissertation

Journal articles with IF

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. AAEM, 20: 245-251.
IF: 3.06

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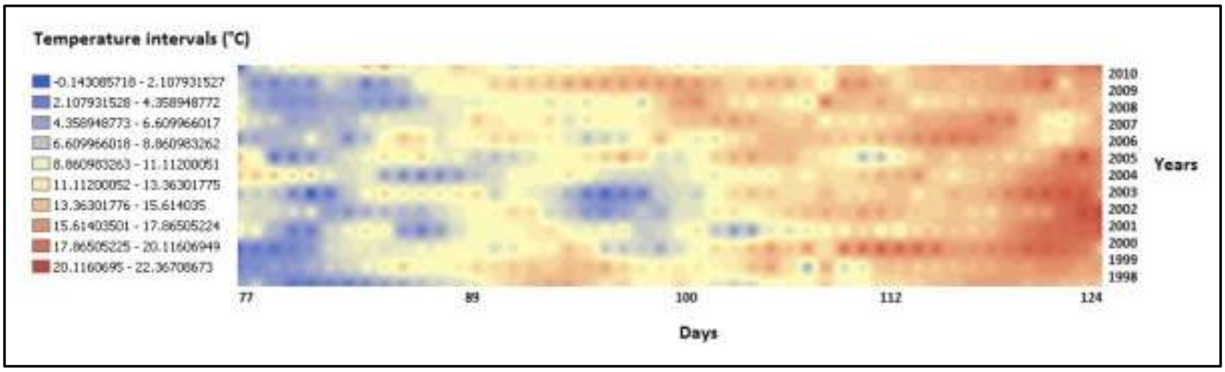
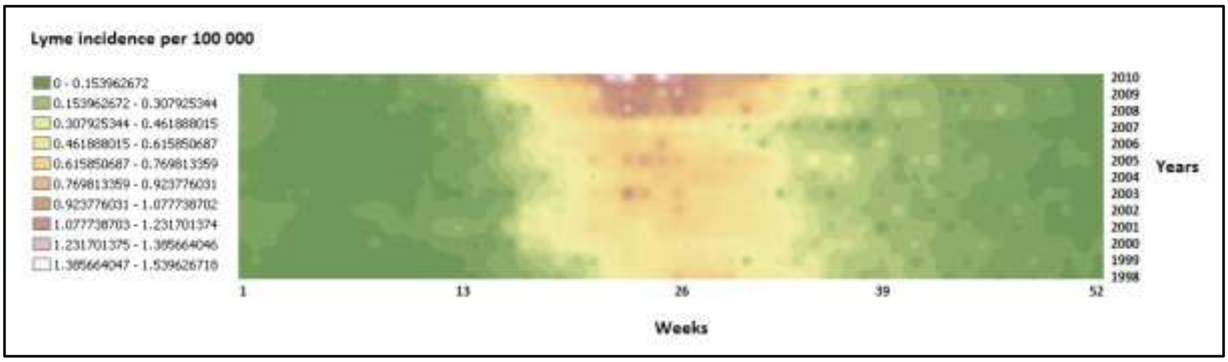
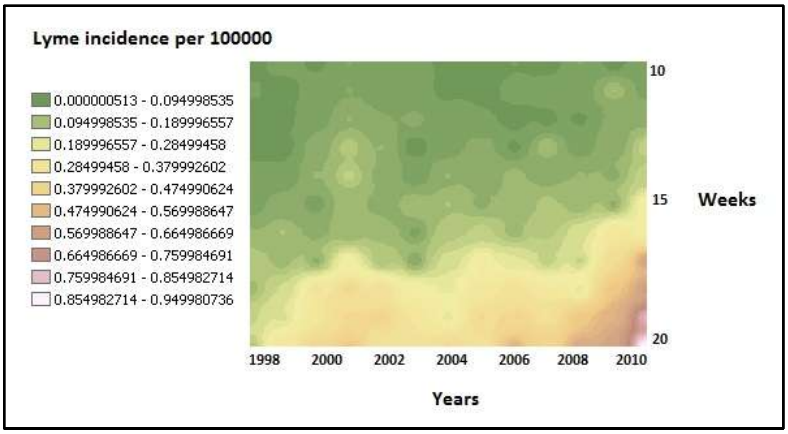
12. ANNEX



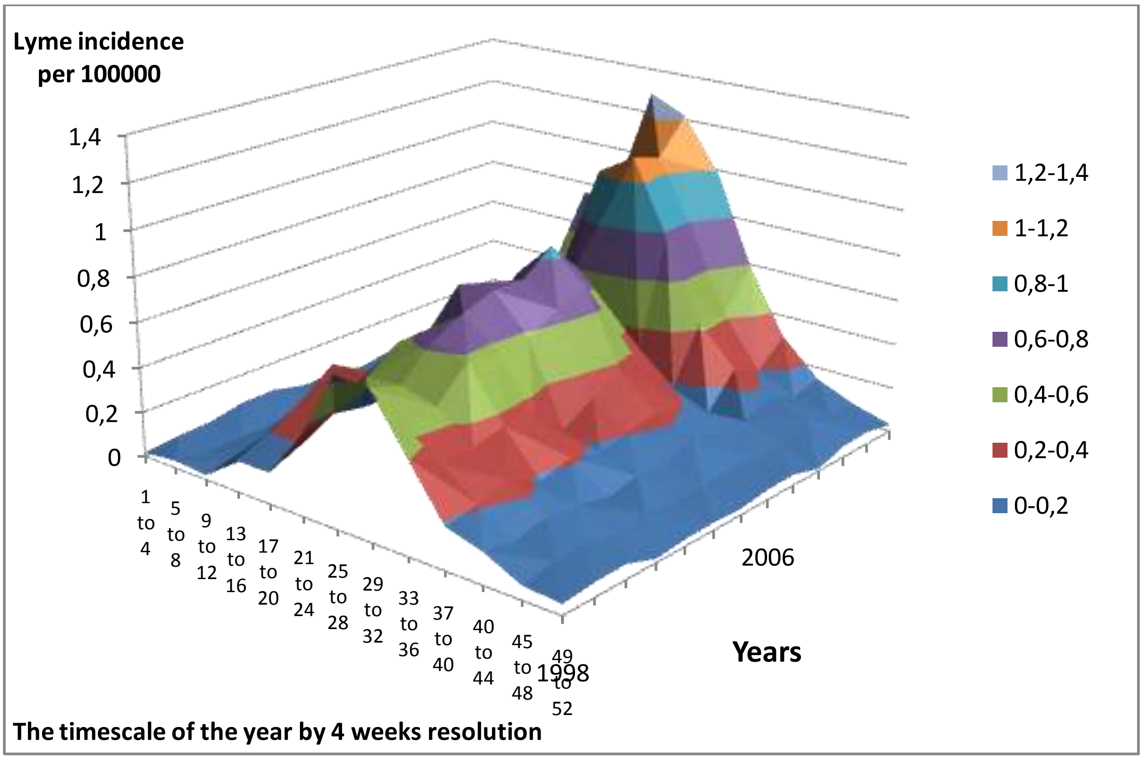
Annex Chart 1. The shift of the vegetation seasonsin the period of 1998-2010, Hungary.



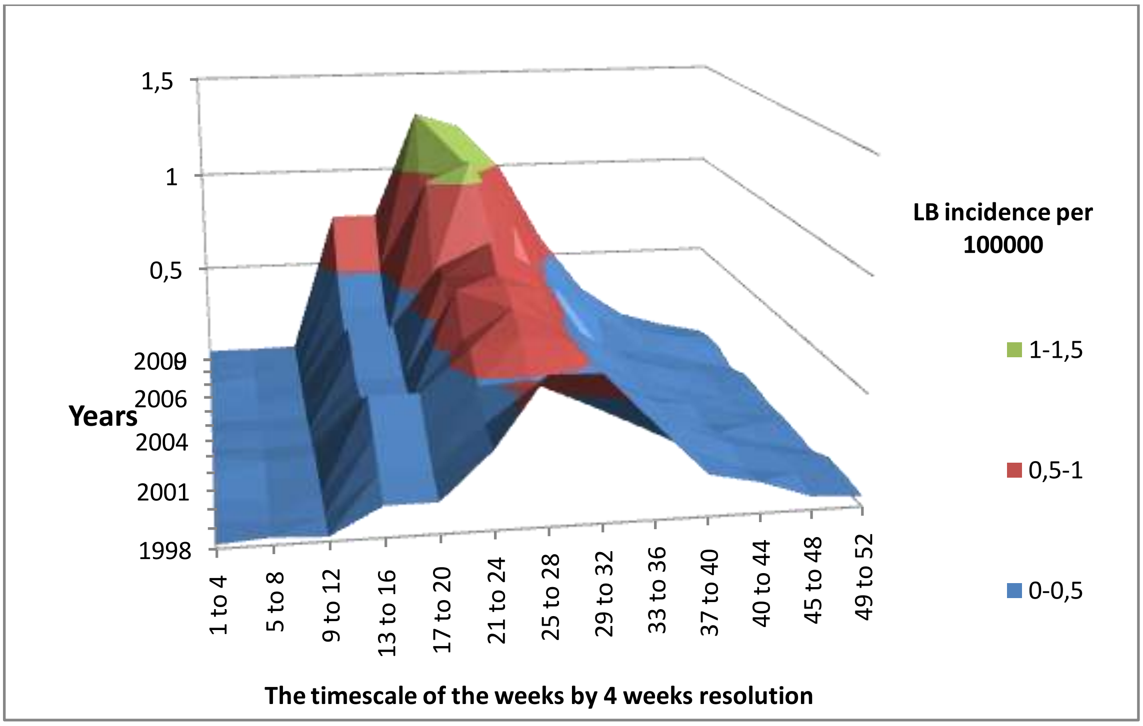
Annex Chart 2. The profile of the LB seasonsin 1998-2010 in Hungary.



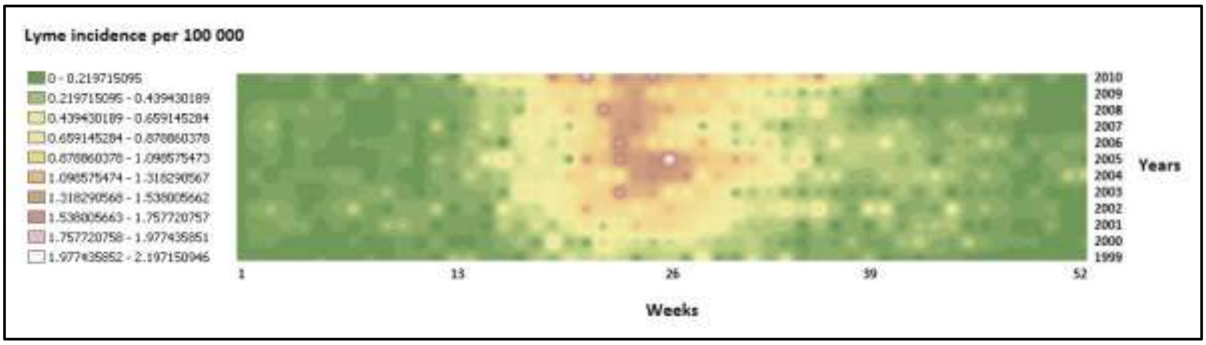
Annex Chart 3. The shift of the start of the LB seasonsin 1998-2010 in Hungary.



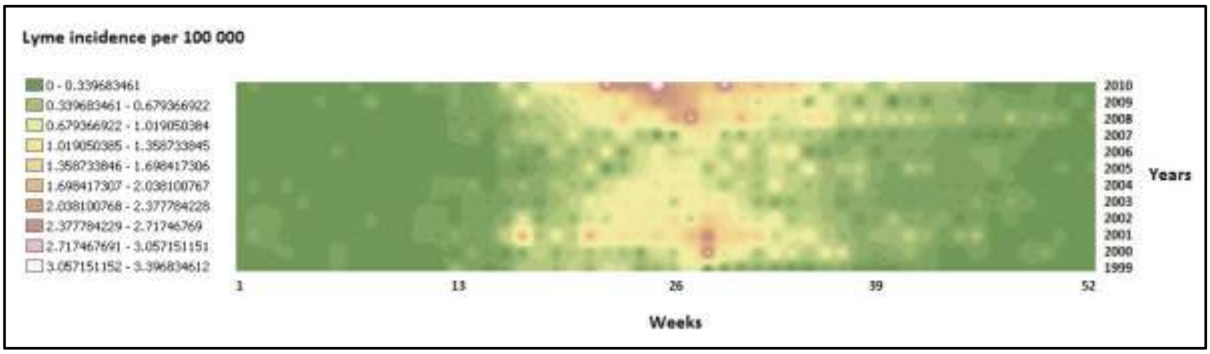
Annex Chart 4. The trend and profile of the LB seasons in 1998-2010 in Hungary.



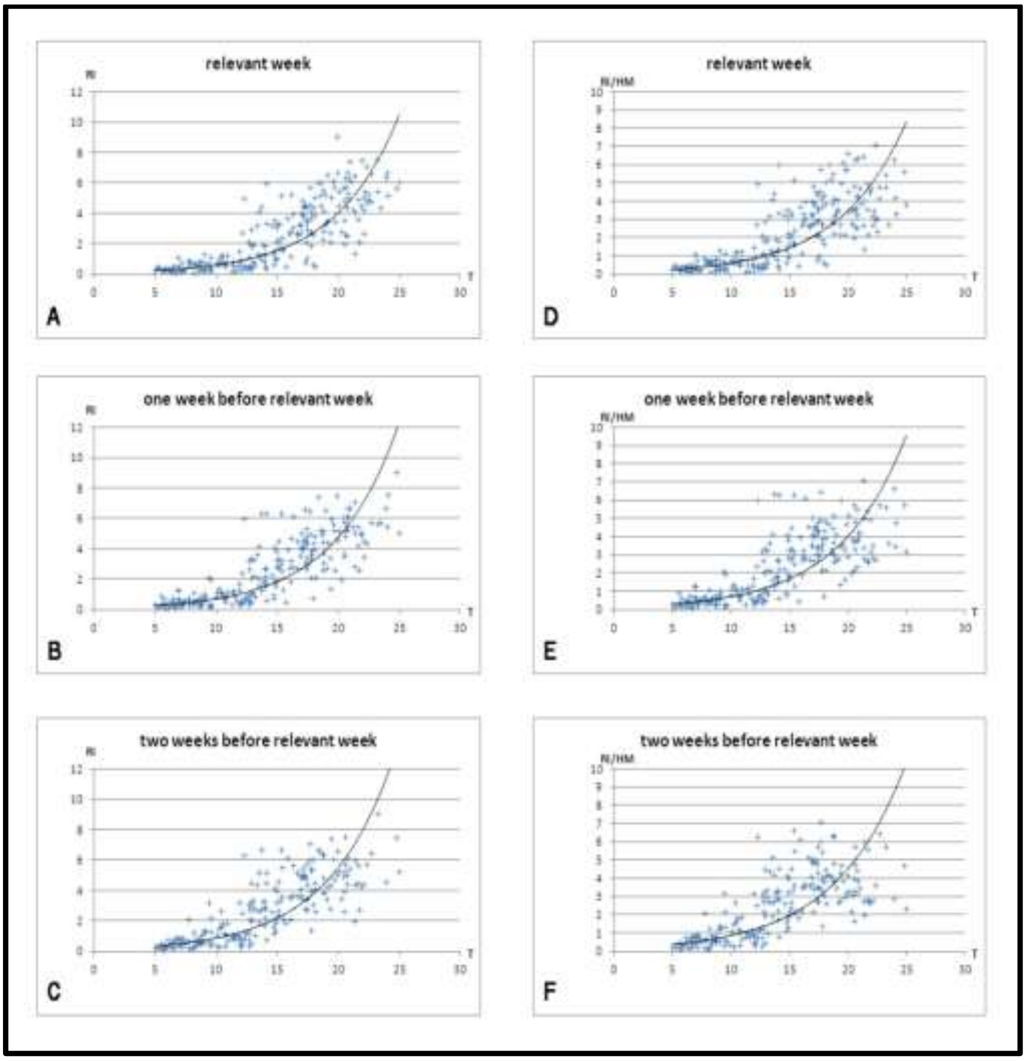
Annex Chart 5. The trend and the profiles of the LB season in 1998-2010 in Hungary.



Annex Chart 6. The profile of the LB seasons in the SW counties in 1999 to 2010.



Annex Chart 7. The profile of the LB seasonsin the NE counties in 1999 to 2010.



Annex Chart 8. The correlation between the mean ambient weekly temperature and the related weekly relative (percentage, according to he annual total LB numbers) Lyme cases

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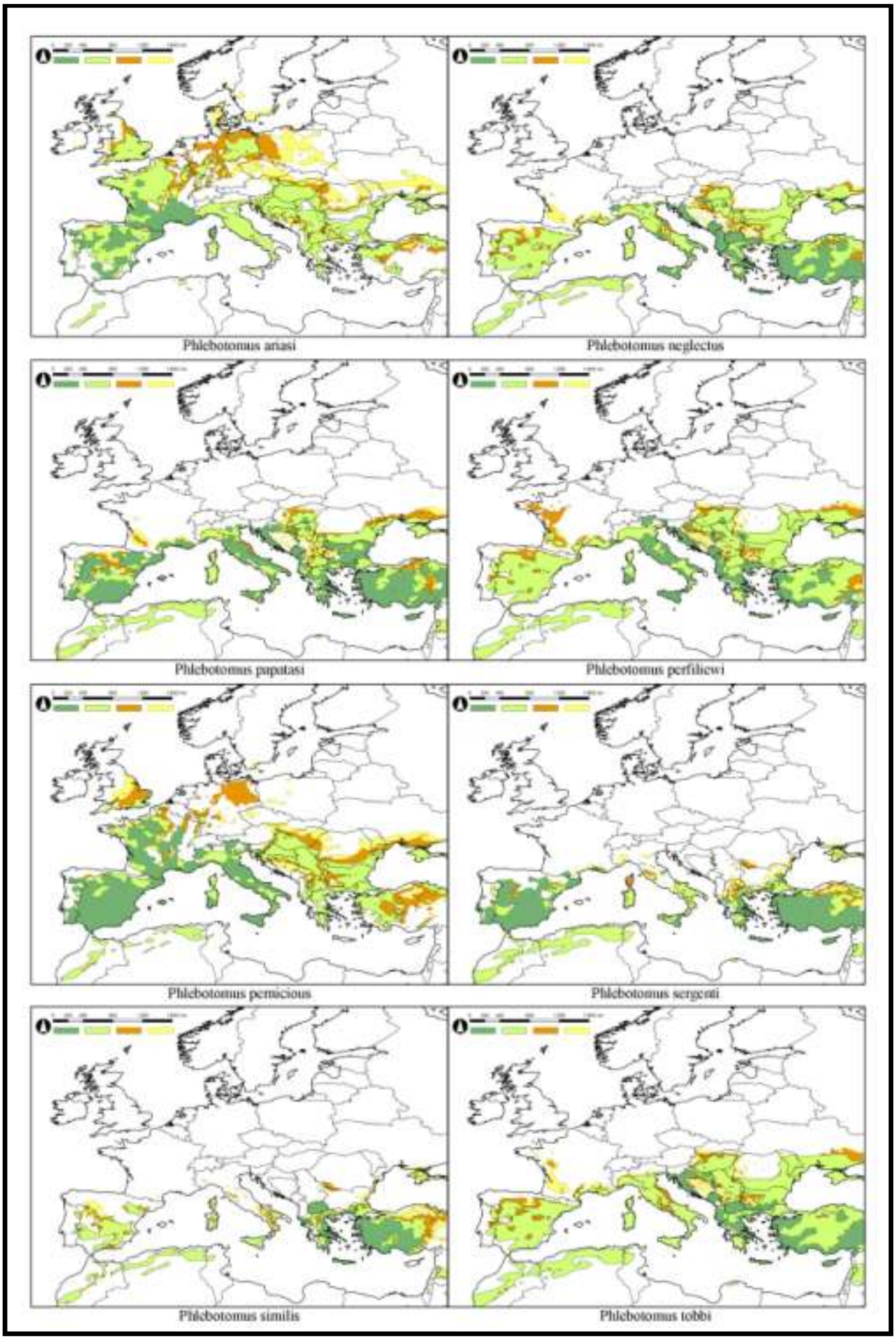

Annex Chart 9. Current distribution (dark green), modelled potential distribution in the reference period (light green), and predicted potential distribution in the period of 2011-2040 (orange) and 2041-2070 (yellow) of the eight studied *Phlebotomus* species

Annex Spreadsheet 1. The most important vector-borne viral infections. [1]: insect vector, [2]: tick vector.Sources: WHO 2013.Vector-borne viral haemorrhagic fevers (HF) (source: Suss J (2008) and WHO 2013)

Disease	Virus classification (family)	Magnitude of the annual cases	Vectors	Hosts
Congo-Crimean HF (CCHF)	Bunyaviridae	1000's	*Hyalomma sp.*[1]	Hares, Crows, Cows, Ostriches
Dengue DHF/DSS	Flaviviridae	250 000-500 000	*Aedes aegypti*[2], *Aedes albopictus*[2]	warm blooded
Kyasanur Forest Disease (KFD)	Flaviviridae	100's	*Haemaphysalis sp*[1].	Monkeys, Rodents, Birds
Omsk Haemorrhagic Fever	Flaviviridae	100's	*Dermacentor* sp[1].	Field Mouse
Rift Valley Fever	Bunyaviridae	10 000's	*Culex pipiens*[2], *Aedes africanus*[2], *Anopheles*[2]	Sheep, Cattle, Camels
Tick-borne encephalitis (TBE)	Flaviviridae	5000-7000 in Europe and Russia	*Ixodes ricinus*[1], *Ixodes persulcatus*[1], *Ixodes scapularis*[1]	Deers, cows and other forest mammals
Yellow Fever (YF)	Flaviviridae	200 000 before vaccine	*Aedes aegypti*[2]and other *mosquitoes*	Monkeys

		introduction		

Annex Spreadsheet 2. The main tick vectors and the transmitted potential VBDs in the northern hemisphere*=non vector-borne disease, **= vectors of the new world. Sources: CDC, Other Tick-borne Spotted Fever Rickettsial Infections and CDC, tick-borne diseases of the U.S. and WHO. (2013) Vector-borne viral haemorrhagic fevers (HF)

Tick genus	Parasite(s)	Disease
Dermacentor	*Rickettsia rickettsii*	Rocky Mountain spotted fever
	Francisella tularensis	tularemia
	Ehrlichia chaffeensis	human ehrichiosis
	Anaplasma phagocytophilum	anaplasmosis
	Rickettsia slovaca	Tick-borne lymphadenopathy
	tick neurotoxin*	Tick paralysis*
Hyalomma	CCHF virus	Crimean–Congo hemorrhagic fever
Ixodes	*Borrelia* afzeli, *Borrelia* burgdorferi, *Borrelia* garnii	Lyme borreliosis
	Babesia divergens,	babesisosis

	Babesiabovis	
	Coxiella burnetti	Q-fever
	tick-borne encephalitis	TBE virus
	Rickettsia conorii	Mediterranean spotted fever
	Ehrlichia chaffeensis	human ehrichiosis
	Anaplasma phagocytophilum	anaplasmosis
Rhipicephalus	*Rickettsia conorrii*	Mediterranean spotted fever
	Rickettsia rickettsi	Rocky Mountain spotted fever
Ornithodoros	*Borrelia* duttoni	Tick-borne relapsing fever
	Ehrlichia chaffeensis	human ehrichiosis
Amblyomma**	*Rickettsia rickettsii*	Rocky Mountain spotted fever
	Ehrlichia chaffeensis	human ehrichiosis
	Anaplasma phagocytophilum	anaplasmosis
	Rickettsia parkeri	*R. parkeri* rickettsiosis
	not known	Southern Tick – Associated

		Rash Illness
	Franciseella tularensis	tulearemia

AnnexSpreadsheet 3. The main potential and resident vector-borne diseases in Hungary. Bold: the notable endemic and primary vector-borne diseases. HME*: human monocytic erlichiosis, HGE**: human granulocytic erlichiosis

^{V}veterinary cases known in Hungary

^{I} recently only introduced cases known in Hungary

^{H} endemic human cases known in Hungary

$^{?}$ thehumaninvolvement is questionable in Hungary

^{Z}primary direct zoonoses

Parasite(s)	**Classification:** **family and the parasitological category**	**Diseases in humans**	**Potential vectors in Hungary**	**Status**
Babesia divergens	Babesiidae (protozoa)	Human babesiosis$^{?,V}$	*I. ricinus*	The infection of *Ixodes ricinus* ticks is well known^{1}**,** human involvement is suspected
Bartonella	Bartonellaceae	Cat scratch	*Ctenocephalides felis* and *Pulex*	**Endemic**, but the vector

henselae	(bacterium)	disease[H,Z,V]	*irritans*	way is questionable in Hungary[2]
B. garinii and *B. afzelii*	Spirochetaceae (bacterium)	**Lyme borreliosis**[H,V]	*Ixodes ricinus* is the main vector	**Endemic**, about **1000-2000cases** per year
Coxiella burnettii	Coxiellaceae (bacterium)	Q-fever[H,Z,V]	e.g. *Rhiphicephalus sanguineus*, *Dermacentor species*	**Endemic** and known from ard ticks in Hungary[3], but most of the cases Q-fever are direct zoonosis
Dirofilaria repens	Onchocercidae (helminth)	(mostly ocular) dirofilariasis[H,V]	*Aedes* and *Culexmosquitoes*	**Sporadic**[,4,5,6]
Dirofilaria immitis	Onchocercidae (helminth)	**dirofilariasis** (in humans mostly causes abortive cases)[V]	*Aedes* and *Culex* mosquitoes	No human cases, but endemic in dogs in southeastern and western Hungary[7].
Ehrlichia	Anaplasmataceae	Human	*I. ricinus*	Human

chaffensis, E. sennetsu, E. ewingii	(bacterium)	ehrichiosis forms (HME*, HGE**)[?]		involvement is suspected[8,9]
Francisella tularensis	Francisellaceae (bacterium)	tularaemia[*H,Z,V*]	*Dermacentor reticulatus, I. ricinus, Haemaphysalis concinna*	**Endemic**, but most of the cases are direct zoonosis.
Leishmania infantum	Trypanosomatidae (protozoa)	cutaneous or infantile visceral leishmaniasis[i,*V*]	Several *Phlebotomus* species; e.g. *Phlebotomus neglectus*is present in Hungary	Only imported caes[10], but endemic in dogs in southwestern Hungary[11, 12].
Plasmodium falciparum and other *Plasmodium* species	Plasmodiidae (protozoa)	malaria[i]	*Anopheles maculipennis* as potential resident vector in Hungary is present	No, only in the past[13, 14]. Recently introduced cases are observed.
e.g. *Rickettsia rickettsii*, (*R. conorii*), *R. slovaca*	Rickettsiaceae (bacterium)	Tick-borne spotted fevers, e.g. Mediterranean spotted fever[?]	Several tick genera, e.g. *Rhiphicephalus sanguineus* or *Dermacentor*species	Human involvemet is suspected [15]
European *TBE virus*	Flaviviridae	**Tick-borne encephalitis**	*Ixodes ricinus* (EU), but sometimes can	**Endemic**

complex	(virus)	(TBE)[H,V]	be transmitted by unboiled goat milk[16]	with **less than 100 reported cases** per year in the last 15 years[17]
Usutu virus	Flaviviridae (virus)	Usutu virus borne encephalitis[V]	*Culex* mosquitoes	Usutu virus is known from birds in Hungary[18]
WNF virus	Flaviviridae (virus)	**West Nile Fever**[H,V]	*Aedes* and *Culex* mosquitoes	**Endemic**, about **4-19 cases per year** but emerging disease in Hungary[19]

1: Kálman et al. (2003)
2: Sréter-Lancz et al. (2006)
3: Špitalská and Kocianova (2003)
4: Fok É. (2007)
5: Szénási et al. (2008)
6: Pónyaiet al. (2006)
7: Jacsó et al. (2009)
8: Sréter et al. (2004)
9: Blanco and Oteo (2002)
10: Péterfiet al. (2010)
11: Farkas et al. (2011)
12: Tánczos et al. (2012)
13: Szénási et al. (2003)
14: Melles and Jankó (2000)
15: Raoult et al. (2002)
16: Balogh et al. (2010)
17: Zöldi et al. (2013)
18: Bakonyi et al. (2007)
19: Krisztalovics K, et al. (2008)

ANNEX SPREADSHEET 4. THE OVERVIEW CHARACTERIZATION OF THE MAIN SRES SCENARIOS

SRES scenarios	**Total global cumulative CO_2 emissions (GtC) from 1990 to 2100**	**The worldwide population for 2050 (billion)**	**Atmospheric CO_2 content (*mean*;ppm)**	**Global mean temperature increment (*mean*; °C)**
B1	700-1400	**8.7** (8.6-8.7)	600	1.8
A1T	1000-1200	**8.7**	700-800	2.4
B2	1100-1700	**9.3** (9.3-9.8)	800	2.4
A2	1300-2000	**11.3** (9.7-11.3)	1250	3.4
A1B	1300-2100	**8.7** (8.3-8.7)	850	2.8
A1F1	2100-2700	**8.7**	1550	4.0

Annex Spreadsheet 5. The cladistical viewpoint most important vectors and examples for the transmitted diseases

Class or Suphylum*	**Subclass or class***	**Superorder**	**Order**	**Familiy**	**Genus(es)**	**Species (example)**	**a transmitted disease**	**parasite**
Crustacea*	Malacostraca*	-	Decapoda	Varunidae	*Eriocheir*	*E. sinensis*	westermaniasis	*Paragonimus westermani*

Arachnida	-	Parasitiformes	Ixodida	Ixodidae (hard ticks)	*Dermacentor*	*D. reticulatus*	tibola	*Rickettsia slovaca*
					Hyalomma	*H. marginatum*	Crimean-Congo hemorrhagic fever	*CCFH virus*
					Ixodes	*I. ricnius*	Lyme disease	*Borrelia burgdorferi, Borrelia garnii*
					Rhipicephalus	*R. sanguineus*	Rocky Mountain spotted fever	*Rickettsia rickettsii*
					Amblyomma	*A. americanum*	erlichiosis	*Erlichia chaffeensis*
				Argasidae (soft ticks)	*Ornithodoros*	*O. turicata*	relapsing fever	*Borrelia hermsii*

Insecta	Pterygota	-	Hemiptera	Reduviidae	*Panstrongylus, Rhodnius, Triatoma*	*T.brasiliensis*	Chagas-disease	*Trypanosoma cruzi.*
				Glossinidae	*Glossina*	*G. fusca fusca*	Human African trypanosomiasis	*Trypanosoma brucei, etc.*
		Neoptera	Diptera	Oestridae	*Dermatobia, Hypoderma*	*Dermatobia hominis and Hypoderma sp.*	myiasis	*larvae of Dermatobia hominis and Hypoderma sp.*
				Culicidae	*Aedes*	*Ae.aegypti*	Dengue fever	*Dengue virus*
					Simulium	*Simulium yahense*	onchocerciasis	*Oncocerca volvulus*
					Anopheles	*A. maculipennis*	malaria	*Plasmodium falciparum, etc.*

					Culex	*C.pipiens*	West Nile fever	*WNF virus*
				Psychodidae	*Phlebotomus*	*P. neglectus*	leishmaniasis	*Leishania infantum*
				Tabanidae	*Chrysops*	*C. dimidiata*	Loa loa	*Mansonella streptocerca or Onchocerca volvulus*
			Phthiraptera	Pediculidae	*Pediculus*	*P. humanus humanus*	Epidemic typhus	*Rickettsia prowazekii*
			Siphonaptera	Ceratophyliidae	*Nosopsyllus*	*N. fasciatus*	Plague	*Yersinia pestis*

Annex Spreadsheet 6. The overwiev of the transmitted parasites and the taxonomic classification of the studied sandfly species.

Species	**Subgenera**	**Auctor**	**Transmitted *Leishmania*species**	**Group**

Ph. ariasi	*Larroussius*	Tonn.	*L. infantum*	1.
Ph. neglectus	*Larroussius*	Tonn.	*L. infantum*	3.
Ph. papatasi	*Phlebotomus*	Scop.	*L. donovani, L. killicki, L. tropica, L. arabica, L. major*	3.
Ph. perfiliewi	*Larroussius*	Parrot	*L. infantum*	3.
Ph. perniciosus	*Larroussius*	Newst.	*L. infantum*	2.
Ph. sergenti	*Paraphlebotomus*	Parrot	*L. tropica, L. major*	not studied
Ph. similis	*Paraphlebotomus*	Perfiliev	*L. tropica*	not studied
Ph. tobbi	*Larroussius*	Adler, Theodor et Lourie	*L. infantum*	not studied

Annex Spreadsheet 7. The climatic extrema of the eight *Phlebotomus*species, their aggregation and the *L. infantum* used in the modeling. Abbreviations: LEI – *L. infantum*, PAR – *P. ariasi*, PNE –, PPA *P. neglectus* – *P. papatasi*, PPF – *P. perfiliewii*, PPN – *P. perniciosus*, PSE – *P. sergenti*, PSI – *P. similis*, PTO – *P. tobbi*, PUN – union distribution of *Phlebotomus*species

	month	1	2	3	4	5	6	7	8	9	10	11	12
PUnion	min(Tmean), °C	-1,2	-0,5	2,9	6,3	10,1	14,4	16,7	16,2	13,8	8,9	4,2	-0,3
	max(Tmean), °C	10,5	10,8	12,6	14,9	18,8	24,1	27,5	28,1	24,4	19,2	14,7	11,5
	min(Tmin), °C	-8,4	-7,8	-3,5	0,3	3,5	7	9,1	8,8	6,7	3	-0,6	-6,4
	max(Tmin), °C	9,3	9	10,4	12,1	15,1	19,4	23	23,8	21,3	17,1	13,3	10,3
	min(P), mm	18	18	15	12	6	0	0	0	0	6	12	18
	max(P), mm	180	126	141	132	111	78	75	72	78	123	171	138

PAria	min(Tmean), °C	-0,6	0,3	2,4	5,3	9	12,9	15,1	14,7	12,4	8,1	3,4	1,2
	max(Tmean), °C	9,5	10,1	11,6	13,8	17	22,4	25,6	26,1	22,6	17,6	13	10,4
	min(Tmin), °C	-8,8	-7,9	-6	-1,8	2,1	5,7	7,6	7,7	5,9	2,8	-2	-5
	max(Tmin), °C	8,1	8,3	9,5	10,8	13,6	18,2	20,9	21,7	19,3	15,3	11,3	9,2
	min(P), mm	21	21	27	21	15	6	0	3	15	27	30	21
	max(P), mm	183	141	159	156	138	96	87	84	93	150	186	156
PNegl	min(Tmean), °C	-2,4	-1,7	2,7	6,8	10,8	15,3	18,5	18,2	14,6	9	4,3	-1,5
	max(Tmean), °C	10	10,1	12,3	15,1	19,4	24,6	28,6	29,1	25	19,7	15,2	11,1
	min(Tmin), °C	-8	-8,2	-3	0,8	3,9	7,5	10,4	10,3	7,3	3,1	-0,1	-6,8
	max(Tmin), °C	8,7	8,3	9,8	12,1	15,5	19,9	23,8	24,6	21,9	17,3	13,3	9,8
	min(P), mm	24	24	21	15	6	0	0	0	3	9	15	24
	max(P), mm	207	144	138	120	78	54	45	45	72	114	189	171
PPap	min(Tmean), °C	-0,5	0,3	3,8	7,5	11,6	16	18,7	18,8	15,3	9,9	5,3	0,3
	max(Tmean), °C	10,7	11,1	13	15,5	19,3	24,6	28,6	29,1	25,3	20	15,3	11,7
	min(Tmin), °C	-6	-5,6	-1,5	1,7	4,7	8,6	11,3	11,3	8,2	4	1	-4,2
	max(Tmin), °C	9,6	9,4	10,8	12,9	15,9	20,2	23,8	24,6	21,9	17,8	14,2	10,8
	min(P), mm	18	18	15	12	6	0	0	0	0	6	12	18
	max(P), mm	177	120	129	114	81	57	45	42	66	108	162	138

PPerf	min(Tmean), °C	-2,3	-1,3	2	5,8	10	14,5	17,4	16,9	13,6	8,4	3,7	-0,9
	max(Tmean), °C	10,5	10,4	12,4	15,4	19,6	24,8	28,8	29,1	25,3	20,2	15,7	11,6
	min(Tmin), °C	-10	-8,1	-4,7	-0,5	3,1	6,7	8,7	8,2	6,2	2,7	-1,6	-6,4
	max(Tmin), °C	9,3	8,8	10,2	12,8	16	20,5	24	24,8	22,1	17,5	14,1	10,4
	min(P), mm	18	21	15	12	6	0	0	0	0	6	12	18
	max(P), mm	216	147	144	132	90	66	51	57	90	141	216	171
PPern	min(Tmean), °C	0,5	1,4	3,4	6,2	9,8	14,1	16,1	15,9	13,6	8,8	4,2	2,1
	max(Tmean), °C	10,7	11,2	12,9	14,8	18,4	23,6	26,9	27,4	24,2	19	14,4	11,6
	min(Tmin), °C	-9,4	-8	-4,7	-0,8	2,8	6,1	8,3	8	5,9	2,7	-1,9	-6,1
	max(Tmin), °C	9,4	9	10,4	11,7	14,4	18,7	22,3	23,1	20,8	16,4	12,7	10,3
	min(P), mm	18	18	24	18	12	3	0	3	9	18	24	21
	max(P), mm	171	117	144	135	117	84	78	81	81	129	171	126
PSerg	min(Tmean), °C	-0,7	0,1	3,9	7,7	11,4	16,3	19,2	19,4	15,7	10,1	5,3	-0,1
	max(Tmean), °C	10,8	11,3	13,2	15,7	19,4	24,9	28,8	29,4	25,9	20,2	15,3	11,7
	min(Tmin), °C	-7,2	-6,4	-1,8	1,7	4,5	8,6	11,4	11,4	8,7	4	0,8	-6,1
	max(Tmin), °C	9,4	9,2	10,5	12,8	15,8	20,2	23,9	23,9	21,9	17,5	13,4	10,5
	min(P), mm	18	18	15	12	6	0	0	0	0	6	12	18
	max(P), mm	183	123	144	114	75	42	27	24	45	93	135	135

PSim	min(Tmean), °C	-0,1	0,3	4	7,8	11,9	16,8	20,2	20,3	15,7	10,1	5,7	0,4
	max(Tmean), °C	10	9,8	11,7	14,7	19	24,4	28,3	28,9	24,3	19,1	14,9	11,2
	min(Tmin), °C	-4	-4,2	-0,8	2,2	5,3	9,4	12,7	12,8	9,1	4,5	1,3	-3
	max(Tmin), °C	8,5	8	9,6	11,8	14,8	19,3	23,1	23,6	20,8	16,3	12,9	9,6
	min(P), mm	24	27	21	15	6	0	0	0	3	9	15	24
	max(P), mm	180	120	114	93	60	36	27	24	36	69	129	150
PTob	min(Tmean), °C	-2,7	-1,8	2,5	6,5	10,6	15,1	18,3	18,1	14,3	8,9	4,2	-1,9
	max(Tmean), °C	10,2	10,2	12,8	16,2	20	25,3	29,2	29,7	26,3	20,9	15,9	11,3
	min(Tmin), °C	-8	-8	-2,8	0,8	4	7,6	10,6	10,5	7,4	3,2	0	-6,7
	max(Tmin), °C	9	8,5	10,2	13	16,5	20,8	24,3	25	22,3	17,8	14,1	10,3
	min(P), mm	18	21	15	12	6	0	0	0	0	6	12	18
	max(P), mm	216	150	141	120	78	66	51	51	69	114	192	174
LeiInf	min(Tmean), °C	1,9	2,7	4,8	7,5	11,8	16,5	19,4	19,6	16,1	11	6,1	3,3
	max(Tmean), °C	11,1	11,3	12,9	15	18,8	23,8	27	27,2	23,8	19,1	14,9	12,2
	min(Tmin), °C	-2	-1,6	0,2	2,1	4,9	9,1	11,6	12	9,4	5,3	2	-0,4
	max(Tmin), °C	9,5	9,2	10,5	12,1	14,8	19,1	22,3	23	20,3	16,9	13,6	10,7
	min(P), mm	18	18	21	15	6	0	0	0	3	9	18	21
	max(P), mm	183	111	147	120	84	48	39	36	72	120	171	123

ANNEX TEXT 1: ARACHNID VECTORS

Ticks are belonging to the class Arachnida. The distinctive characteristics of Arachnida that separate them from other arthropod classes is that all of them have eight legs and two appendages [the chelicerae (for feeding and defense)] and a pair of pedipalps which serve as the tools of feeding, locomotion, and/or have reproductive functions. Acarina is one of the most species-rich orders Arachnida, which contains mites and ticks. The superorder of Parasitiformes contains many important vector organisms, such as hard and soft ticks (the order Ixodida). The most ancient record of the parasitiform mites (ticks) is a 90-94 million years old (Cretaceous, Turonian in the ICS' geologic timescale (ICS homepage) larval Argasid tick fossil (Acari: Ixodida: Argasidae), which is preserved in amber in New Jersey (Klomplen and Grimaldi 2001). *Ixodes tertiarius* Scudder (1885) and *Ixodes succineus* Weidner (1964) were described from the upper Eocene (44-49 mya) stratas (Dunlop et al. 2003). *Amblyomma* Lane and Poinar (1986) and *Ornithodoros* Poinar (1995) ticks are also known from this period. Ticks have a special, complex sensory organ: the Haller's organ. This is an olfactory organ, with which ticks can perceive the presence of a host. They sense the temperature, the humidity and CO2 content of the air. It can be stated that the sensing function of Haller's organ has the strongest function with meteorological conditions (Kapiller and Szentgyörgyi 2001). The family Ixodidae ticks contains more than 700 species all over the World. Hard ticks as *Dermacentor*, *Haemaphysalis*, *Hyalomma*, *Ixodes* are the most important genera from a human viewpoint.

ANNEX TEXT 2: INSECT VECTORS

The most notable insect vectors, mosquitoes and sandflies, belong to the order of Diptera. They have 3 pairs of legs, a pair of wings, a pair of billers (a kind of body position sensor), a pair of very sensitive antennae (the organ for questing for food or for reproductive purposes), and some special piercing-sucking mouthparts. Diptera develop by holometabolism, which means that larvae undergo complete metamorphosis to develop into adult insects. In contrast, Arachnids and ancient insects (eg. cockroaches-Blattidae) are developing by the sequences of moults. Mosquitoes belong to the infraorder Culicomorpha. Generally, the female adults feed on warm-blooded animals and humans. The hairless humans, with their thin skin, are optimal blood-sources for mosquitoes. The most important family is Culicidae with such important genera as *Anopheles*, *Aedes* and *Culex*. The larvae can develop in small, open water bodies, even in jars or tins. They feed on microbial organisms (algae, bacteria). The larvae commonly have four stages (instars), after they metamorphose into pupae. While every part of the development's length varies among species, it is common that they are strongly influenced by the ambient temperature. The adults have good flying ability; therefore their expansion can be rapid. They are vectors of such important and serious viral infections as the West Nile Fever (hence: WNF), Yellow Fever, Eukaryote parasites-protozoans (eg. malaria) and parasitic diseases (eg. filiariasis).

ANNEX TEXT 3: FORESTS, DEGRADATION AND FRAGMENTATION OF NATURAL ECOSYSTEMS AND TICK-BORNE DISEASES DUE TO GCC

Climatic changes can cause the degradation and fragmentation of the natural ecosystems. Due to the GCC the phenological, physiological and genetic parameters, the distribution area of the plant species, and the stability of ecosystems seem to be changing (Hughes 2000, Kovács-Láng et al. 2008). The migration of species naturally could re-optimize the structure and composition of natural ecosystems, but in the last two thousand years human land using activity (eg. agriculture, river regulation, road building) has destroyed the natural connections between the remaining parts of the natural ecosystem. Furthermore, the dryer and warmer climate (through deforestation), the aggressive agricultural practises (plantations, monocultures, using high efficiency fertilizers) and the long distance trading allowed the chance of the invasion of extraneous plant and animal species. Areas, deprived from their natural communities become great open ecological windows for invasive organisms and the fragmentation increased the extent and the proportion of the borders between agricultural and natural habitats (Opdam and Wascher 2004). It is known, that fragmentation has a positive effect on LB risk, elevating the population density of host animals (eg. mice and deers, Allan et al. 2003). It was found in the United States, for example, that fragmentation can reduce the amount and diversity of other, eg. predator mammals, but enhance the population of white-footed mice (Peromyscus leucopus), which is the favoured host of *I. scapularis* (Li et al. 2012).