POTENTIAL EXPANSION OF TROPICAL VIRUSES IN SERBIA AND EUROPE

The current, hot topic is the risk of introducing new vector-borne diseases and harmful ectoparasites into Europe, or of the geographic extension of the existing ones. There are many doubts that global warming affects the transfer of a number of vector-borne diseases. Special emphasis was placed on spreading the Lyme disease, tick-borne encephalitis, West Nile fever and leishmaniasis, the recurrence of malaria and dengue fever. Climate models predict a 2-5ºC temperature increase and a significant increase in rainfall in Europe in the following years. However, non-environmental variables such as socio-economic situation and agriculture should be considered.

The main problem can be expected when new viruses emerge. As they change, their mutations can enter into the population and thus have “the greater potential” for the spread of the epidemic. The control network of the health system in our country and in Europe is very dense, and the outbreak of the virus can be always registered, giving the authorities enough time to take measures.

Although modeling studies indicate that climate change could increase the risk of transmission of vector-transmitted diseases in Serbia and Europe, historical analyses indicate that, at least for malaria, socio-economic conditions in combination with effective surveillance and early treatment are likely to prevent further spread, which is the main task of the Public Health Institutes. Tropical medicine experts said that the so-called supervirus causes mutations of the virus, and represents the greatest danger for human population. The circumstances that allow such a development already exist, an additional climate change is not necessary. The challenge for future research is the mechanism of tropical viruses and their persistence in endemic foci in temperate climate area in Europe. Acta Medica Medianae 2015;54(4):64-71.

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Introduction

The current hot topic is the risk of introducing new vector-borne diseases and harmful ectoparasites into Europe, or of the geographic extension of the existing ones. The recent out-breaks of bluetongue virus infection in north-western Europe and of chikungunya infection in Italy are real reminders of the vulnerability of this ill-prepared continent, where the idea prevails that these things cannot happen there but are merely problems that occur on other continents (1).

The role of the different factors that drive change in the epidemiology of diseases and pests are identified as a possible result of a complex interaction of factors such as climate change (whether or not it is anthropogenic), human-made environmental change (e.g. agricultural activities), increasing international trade and traffic (e.g. long-distance tourism), changes in human behavior (e.g. more outdoor activities), and the development of insecticide resistance (1).

Staying in nature carries with it certain risks, including the risk exposure to vector diseases. Vector infectious diseases are diseases whose causative agent (bacteria, virus, rickettsia, parasite) spends in the vector (mosquito, tick, and a variety of other insect species) some time before it enters into its host (human). After the so-called external incubation period (when it becomes a contagious vector), the vector transmits the infectious disease agents to susceptible host (humans, animals) by sting/bite. The infected vectors are usually the lifelong carriers of the causative agent (2).

Vectors are organisms that have no mechanism for maintaining body heat; they directly de-
Diseases transmitted by ticks

Ticks are arthropods whose sting can transmit certain infectious diseases such as Lyme disease, tick-borne encephalitis, Crimean-Congo hemorrhagic fever, ehrlichiosis, brucellosis, leptospirosis. Luckily, not all ticks are infected with microorganisms that are pathogenic to humans. Ticks live in wooded areas and untreated vegetation, but also in the fields, in gardens, hedges and the like. They are present from early spring to late autumn, and are mostly active in May and June. They feed on the blood of humans and many animals, and if they are infected, they transmit infective agent during feeding (2).

The tick must be present on the skin for at least 48 hours for inoculation of the agent. Ticks are usually found on low vegetation, to a height of one meter, and attach to animals and people passing there through. They suck blood 2 to 7 days before they return into the vegetation. The risk of infection is higher as the tick stays in the body longer. Insect bite is painless, and the puncture site is painless and does not itch (2).

Mosquito-borne diseases

Climate change in the form of an increase in the average values of temperature, and precipitation variability greatly affect the occurrence, distribution and seasonal variations of the vector of infectious diseases, in particular diseases that are transmitted by mosquitoes (West Nile fever, malaria, yellow fever, dengue, chikungunya fever). It is estimated that every increase in air temperature by 0.1 degree Celsius expands the habitat of mosquitoes and up to 150 kilometers in the direction of the northern latitudes of the globe (2).

Global warming effects

There are many speculations that global warming could affect the transmission of a range of vector-borne diseases in our country and in Europe. Special emphasis was placed on spreading the Lyme disease, tick-borne encephalitis, West Nile fever and leishmaniasis, the re-emergence of malaria and dengue fever. Climate models predict a 2-5ºC temperature increase in the next fifty years, and a significant increase in rainfall in Europe in the years to come (1, 4, 5).

Environmental changes are causing an increase in the number and spread of many vectors worldwide (3).

Results from biological and statistical models suggest that these changes could indeed increase the risk, particularly of malaria and Lyme disease. However, most predictions are based on model simulations which contain only a subset of the links between climate and vector-borne diseases and generally do not consider the effects of non-environmental variables such as socio-economy and agriculture (5).

Analyses have shown that the historical distribution of European malaria, and its later disappearance, was more strongly related to vector competence, land cover and socio-economic factors than to climate. Although climate change can improve the conditions for transmission, other settings that determine the appearance of endemism indicate that there is an extremely low probability of recurrence of malaria. Similar analyses of the past or present distribution of other vector-
borne diseases of interest for Europe can allow us to quantify the exact role of climate and make more valid predictions of the effect of future climatic changes (5).

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Transmission of arthropod-borne diseases

Five arthropod-borne diseases have been considered of importance to our country and Europe. These are either currently transmitted (leishmaniasis, Lyme disease, tick-borne encephalitis, West Nile virus), previously endemic (malaria) or have been highlighted as potential emerging diseases with respect to global warming (dengue fever) (5).

From around the 13th century, malaria transmission was endemic in nearly all European countries, causing severe morbidity and mortality in the Mediterranean and parts of western Europe (e.g. England and Holland) (6). In the early nineteenth century, the disease started disappearing from northern Europe due to various changes which reduced human-mosquito contact and cleared parasites from the human reservoir (7). However, the disease remained important in the Mediterranean and eastern Europe and prevalence was only reduced after the initiation of DDT spraying in the 1940s. This was followed by a string of country-wide eradication campaigns from Spain in 1964 to the last focus in the Greek republic of Macedonia in 1975. The resurgence of malaria transmission in the former Soviet Union and European Turkey soon after caused concern that the disease could yet again spread to the rest of Europe. Since then, there have been numerous speculations about whether the import of cases from endemic areas in combination with anthropo-genic climate changes can lead to the re-emergence of European malaria (8, 9, 10).

Leishmaniasis in Serbia and Slovenia was reported in the past, but the current endemic status has not been ascertained. In addition, other countries in Europe are still endemic: Albania (1.148 cases), Bosnia and Herzegovina (15), Bulgaria (61), Croatia (11), Greece (390), Italy (1.677) etc. This is the number of cases from 1996 through 2005 notified at CISID, WHO Regional Office from Europe (1).

Lyme borreliosis (Lyme disease) is currently the most commonly reported zoonotic tick-borne infection in Europe. It is widely distributed in Europe with focal patches of high intensity transmission in areas of Bulgaria, The Czech Republic, Slovenia and Sweden (11). This focality is thought to be caused by a combination of the specific vegetation and climate requirements of the tick vector Ixodes ricinus (12) and the availability of mammalian hosts (13). It has been debated whether recently observed increases in the incidence of Lyme disease are due to climatic changes (14) or a combination of changed human behavior and improved surveillance and diagnosis (15).

Tick-borne encephalitis (TBE) is a zoonotic viral infection distributed in coastal areas of Sweden, Poland, The Czech Republic, Central Europe and the former Soviet Republics. Disease is transmitted to humans by ticks through the involvement of wild mammal reservoirs such as deer, mice or voles. The distribution of TBE is obviously limited by its vector but also determined by both climatic factors, tick diversity and human behavior (16, 17). Like Lyme disease, the incidence of TBE in Europe has increased significantly during the past 20 years. Some studies report a strong correlation between this increase and observed temperature rises (14, 17).

The dengue virus is transmitted by culicine mosquitoes (Aedes aegypti and Aedes albopictus), and currently it is a major public health concern in parts of South America and Asia. Serologically confirmed dengue epidemics (transmitted by Aedes aegypti) were observed in Greece during the 1920s but the disease and vectors were eradicated in the 1940s as a result of the anti-malaria DDT campaigns. In the past twenty years, Ae. albopictus, the second most important vector, has been found in Albania and Italy, possibly imported in used car tyres from Asia (18, 19, 20). There has been a growing concern that climate changes could cause further spread of this mosquito in Europe as well as the return of Ae. aegypti (10). Dengue in particular is emerging as a serious public health concern. In 2012, it ranked as the most important mosquito-borne viral disease with epidemic potential in the world. There has been a 30-fold increase in cases during the past 50 years. The primary vector for dengue, the Aedes aegypti mosquito, is now found in more than 20 European countries (3).

West Nile virus (WNV) is transmitted by culicine mosquitoes (Culex pipiens, Culex molestus) through the involvement of bird reservoirs and was first isolated from a European population in 1958. The current incidence of human infections is largely unknown although it is believed to be very small. Recent human epidemics in the USA generated much media attention and speculation that similar episodes could occur in large cities of Europe, particularly in the more favorable climatic conditions caused by climate changes (5, 21).

During the 20th century alone, the average temperatures in Europe increased by 0.8ºC and models predict further average increases of 2-5ºC by the end of this century (4, 22). Additionally, it has been predicted that average precipitation at high latitudes will increase significantly (4, 9). As already outlined, there are good biological reasons to why these climate changes should affect vector-borne diseases but the very complicated life cycles and a great range of confounding variables (e.g. drug resistance and man-made environmental modifications) makes it difficult to assess both
whether climate change has already affected disease distributions, or to what extent it will do so in the future. In spite of this, there have been a number of assertions that global warming may have already affected some vector-borne diseases in Europe: TBE and ticks in Sweden (14, 17), Aedes albopictus in the Mediterranean (20, 23), and malaria in Italy and Germany (24-26).

For malaria, one of the most important determinants of disease risk is the presence of competent vectors. Recently Kuhn et al. (27) used a historical database of the presence and absence of five important malaria vectors in Europe to create climate-driven risk maps for the current distribution of these vectors throughout the continent. The Hadley Centre (HADCM3) climate change model for the A2 SRES scenarios have since been applied to these predictions to determine the change in Anopheles distribution with projected climate changes. Climate change simulations indicate that the distributional limits of An. messeae may not change much but that the probability of presence could have increased significantly by the 2080s. Risk maps like these can potentially serve as important entomological baselines for the prediction of future disease risk, though we must be aware that there are many other factors which also play an essential role in determining the intensity of disease transmission (5, 27).

A report recently published by the Chief Medical Officer in Britain claimed that "by 2050 the climate of the United Kingdom may be such that indigenous malaria could become re-established" (28). These statements are difficult to support without robust modeling and proper understanding of the quantitative relationships between climate and disease/vector distributions, along with the contributions of other determinants.

In general, the message is that we cannot predict the future unless we understand the past or the present. A good example of this is the case of British malaria. Recent analyses have shown that the disappearance of the disease from England was due to increasing cattle populations and decreasing acreages of marsh wetlands (7). Modeling scenarios suggested that projected (HADCM3) climate changes were likely to cause an increase in the risk of local malaria cases but that this was several orders of magnitude too small to lead to endemic transmission, given current socio-economic conditions, surveillance and treatment programmes. This will probably also be the case in the rest of Western Europe where socio-economic and agricultural factors were the main determinants of transmission intensity (10, 29). Even for those areas with current transmission (former Soviet Union and European Turkey), attribution of past changes to climate should be cautious as human migration, health system decays and cessation of control measures are considered to have made a greater contribution to the re-emergence of malaria (30, 31).

For the other diseases, the effect of climate on future transmission patterns is also likely to be outweighed by non-environmental factors. TBE and Lyme in humans are dependent on recreational habits (i.e. contact with tick-infested areas), host animal abundance and vegetation. Leishmaniasis is geographically limited by the distribution of the sandfly vector which is very habitat- and climate-specific, but stronger factors impacting on its prevalence is the existence of canine reservoirs and the prevalence of HIV-positive humans. However, the persistence of this disease in the Mediterranean in spite of the intensive historical DDT spraying here could suggest that climate may be more important in maintaining transmission than the case for malaria (5). With respect to West Nile virus, there is little evidence that its emergence in Europe was linked to climatic factors and the number of human cases is relatively small in comparison to other public concerns. This was not the case with the recent epidemics in the USA where climate changes were widely cited in connection with the increase in human cases (32). The epidemics were most likely caused by changed bird migratory patterns and increased monitoring for human cases (33).

The future of dengue virus transmission in Europe is also uncertain. Findings of Aedes albopictus in the Mediterranean could suggest that the climate is suitable for these mosquitoes, although the climate is more suitable for dengue vectors (as demonstrated by the historical epidemics in Greece) (5, 34). These factors may make it difficult for the reproduction rate to exceed in Europe, despite increased temperatures and precipitation. However, this requires further investigation as the ongoing transmission in Singapore and continuing outbreaks in Queensland show that it is possible for dengue to be maintained even in developed countries, given suitable climatic conditions and sufficient imported cases (5).

West Nile virus was discovered half a century ago and spread to the African continent, the Middle East, parts of Asia and Australia, Central and Eastern Europe and the Mediterranean. Man, as an accidental host becomes infected by an infected mosquito. In 80 percent, people pass the infection without symptoms, and less than 1 percent of patients have neuroinvasive, severe forms of the disease, with clinical signs of encephalitis and meningitis (inflammation of the brain and meninges) (21).

In Europe, the presence of West Nile virus was indicated in 1958, when two Albanians had specific West Nile virus antibodies. The first European isolations of the virus were recorded in 1963 from patients and mosquitoes in the Rhône Delta and from patients and Hyalomma marginatum ticks in the Volga Delta. West Nile virus was subsequently isolated in Portugal, Slovakia, Moldavia, Ukraine, Hungary, Romania, Czechland, and Italy (V. Deubel, G. Ferrari, pers. comm.). The incidence of West Nile fever in Europe is largely unknown. In the 1960s, cases were observed in southern
France, southern Russia, Spain, southwestern Romania, in the 1970s, 1980s, and 1990s in Belarus, western Ukraine, southeastern Romania, and Czechland. West Nile fever in Europe occurs during the period of maximum annual activity of mosquito vectors (July to September). West Nile virus can cause sporadic cases in humans, which is manifested by fever, even in areas with moderate climate in Europe. Environmental factors, including human activities that increase the density of population (irrigation, heavy rains accompanied by floods, higher than normal temperatures and the formation of ecological niches allow for mass production of mosquitoes) allow the occurrence of mosquito-borne tropical diseases. West Nile virus causes sporadic cases and out-breaks of human and equine disease in Europe (21).

In the period from June to November 2013, which is the transmission season, ECDC monitored the situation in EU Member States and the neighboring countries in order to inform blood safety authorities regarding WNF - affected areas and countries in order to inform blood safety the situation in EU Member States and the neighboring countries, which is the transmission season, ECDC monitored mosquito-borne tropical diseases. West Nile fever in Europe occurs during the period of maximum annual activity of mosquito vectors (July to September). West Nile virus can cause sporadic cases in humans, which is manifested by fever, even in areas with moderate climate in Europe. Environmental factors, including human activities that increase the density of population (irrigation, heavy rains accompanied by floods, higher than normal temperatures and the formation of ecological niches allow for mass production of mosquitoes) allow the occurrence of mosquito-borne tropical diseases. West Nile virus causes sporadic cases and out-breaks of human and equine disease in Europe (21).

In the period from June to November 2013, which is the transmission season, ECDC monitored the situation in EU Member States and the neighboring countries in order to inform blood safety authorities regarding WNF - affected areas and identify significant changes in the epidemiology of the disease. As of 17 October 2013, 221 human cases of West Nile fever have been reported in the EU and 511 cases in the neighboring countries since the beginning of the 2013 transmission season (Croa {216 cases, 86 cases in Greece, Italy - 68 cases, Hungary - 29 cases, Romania - 22 cases, Bosnia and Herzegovina - 3 cases, Montenegro - 4, Serbia has reported 260 cases of WN {2177 cases of WN}) (35).

As of 20 November 2014, 74 human cases of West Nile fever have been reported in the EU, and 136 cases have been reported in the neighboring countries since the beginning of the 2014 transmission season (Italy has reported 24 cases, Hungary has recorded 11 cases, Austria has reported one autochthonous case of West Nile fever, Greece - 15 human cases, 13 cases have been reported in Bosnia and Herzegovina, 13 cases in the Republic of Srpska, Serbia has reported 76 cases of West Nile fever, Russia - 29 cases, Israel - 17 cases and 1 confirmed case has been report {ed in Palestine) (36).

Environmental factors, including human activities that enhance population densities of vector mosquitoes (heavy rains followed by floods, irrigation, higher than usual temperature, or formation of ecologic niches that enable mass breeding of mosquitoes) could increase the incidence of West Nile fever (21).

**West Nile fever in Serbia**

West Nile fever is the arboviral infection transmitted by mosquitoes. The main vector is the mosquito of the genus Culex (i.e. House mosquito, which is prevalent in the territory of Serbia), and it is the primary reservoir of infected birds. The main route of transmission is the bite of infected mosquitoes. West Nile Virus (WNV) is a member of the flavivirus family, classified in two lines; Line 1 was isolated from the human population in the America {215, Europe, Israel, Africa, India, Russia and Australia, line 2 mainly in Sub-Saharan region of Africa and Madagascar (37).

It primarily occurs in rural areas, but since the end of the last century it has been registered in epidemic form of the disease in urban areas as well (Bucharest, 1996, Volgograd and New York 1999). In 2010 in the EU and EEA / EFTA countries, a total of 340 cases of illness from WNV was reported, with 41 dead persons (Greece - 262 ill subjects and 35 deaths, Romania - 52 ill subjects and 5 deaths, and 15 cases of illness in Hungary, and cases 3 in Spain). In 2011, a much smaller number of patients in the EU were registered; however, it is an obvious geographic spread of this disease, especially in Greece (38).

However, in 2010 in Greece and Russia, an epidemic in the human population with a significant number of patients, in whom neuroinvasive forms of the disease developed, was registered, and almost all isolated strains in both countries belonged to the 2nd line. WNV can be transmitted to humans and other mammals by mosquito bite, whose role in the transmission due to low viral load is not significant. Most of the infected animals have signs/symptoms of the disease, with the exception of the horse, in which it also leads to the development of encephalitis, without classic symptoms and signs. Most WNV infected people (80-90%) have no symptoms and signs of illness. In a small percentage of infected people (10 to 20%), the symptoms resemble the flu-like illness, with sudden onset of fever, headache, sore throat, back pain, muscle pain, joint pain, fatigue, mild transient rash and lymphadenopathy. However, some individuals develop aseptic meningitis or encephalitis (in 0.2% of patients younger than 65, and in 2% of patients over 65 years of age) (37).

In May 2012, Public Health Institute of Serbia, put out the district institutes’ Institute for Public Health professional methodological guide for establishing the control over the West Nile fever in the human population in the territory of the Republic of Serbia, whose main aim was to detect cases of illness in the human population. As of 14 November 2012, when the last laboratory - confirmed case of the West Nile Fever was registered, the Public Health Institute submitted copies of the results of laboratory testing of a total of 139 cases with suspected infection caused by the West Nile virus. Based on laboratory criteria for classifying cases of infection IM European Centre for Disease Control, 42 cases were classified as confirmed cases of infection with West Nile virus (specific IgM antibodies were isolated in the cerebrospinal fluid), 29 cases were classified as probable cases of infection (WNV - specific IgM antibodies present in serum), while in other cases there was no suspicion of West Nile Fever. Of the total number of registered cases (71), 60.6% of cases were male compared to 39.4% of female patients (ratio of male to female sex is 1.5:1). The total 81.7% of cases was in the age group above 50 years of
age, and among them 75.9% had a chronic disease. The highest incidence was in the City of Belgrade (53 patients, or 74.6%), South Banat District (8.5%) and Srem region (7%). Most cases of illness (86%) were registered in August and September 2012, which coincides with the peak mosquito activity. Among confirmed and probable cases of illness, there was a total of 9 deaths that may be linked to the IM infection in people older than 50 years (age range from 51 to 82, or 88.9% of the diseases were older than 60 years) with some chronic disease. Lethality was 12.7%, which is within the typical range of 4 to 14% for patients with neuroinvasive forms of the disease (37, 38).

In the framework of monitoring activities, 3,000 mosquitoes were collected at three different sites. A total of 150 females from 3000 mosquitoes Cx. piptiens were divided into three groups of 50 individuals and on the detection of West Nile virus genome. WNV line 2 was confirmed in 10 out of the 150 female mosquitoes Cx. piptiens using RT-PCR (West Nile). The distribution of cases in the human population in the territory of the City of Belgrade largely coincides with areas of the city where the population of mosquitoes proved the presence of WNV (37).

The world can no longer afford to be complacent. If we do not take action now, the implications are extremely serious for the entire globe. For many vector-borne diseases, there are no vaccines, and drug resistance is an increasing threat. Vector control plays a vital role and is often the only way to prevent disease outbreaks. Many existing interventions, such as insecticide treated bed nets and indoor spraying, are simple and proven. These vector-control tools can be particularly effective when used in combination with interventions such as mass drug administration involving large-scale treatment of affected communities. Vector management programmes can also combine interventions and resources to target more than one disease – a component of an approach called integrated vector management (3).

Conclusion

Although modeling studies suggest that climate change may increase the risk of transmission of vector-borne diseases in Serbia and Europe, historical analyses suggest that, for malaria at least, socioeconomic conditions coupled with efficient surveillance and treatment will probably prevent this being translated into a real public health problem. Similar quantitative modeling of climatic effects, in the context of other influences, should improve our ability to make predictions for other vector-borne diseases. Tropical medicine experts said that the so-called supervirus cause mutations of the virus and represents the greatest danger for human population. The circumstances that allow such a development already exist, and an additional climate change is not necessary. The challenge for future research is the mechanism of tropical viruses, and their persistence in endemic foci in the temperate climate area in Europe.

References


Aktuelna, goruća tema je rizik od nastajanja novih, vektorskih bolesti i štetnih ektoparazita u Evropu, ili geografsko širenje postojećih. Postoje mnoge sumnje da globalno zagrevanje utiče na prenos niza vektorskih bolesti. Poseban akcenat je stavljen na povećanje Lajmske bolesti, krpeljskog meningoeencefalitisa, groznice Zapadnog Nila i leishmanioze, ponovne pojave malarije, kao i denga groznice. Klimatski modeli predvidaju 2-5ºC povećanje temperature i značajno povećanje padavina u Evropi narednih godina. Međutim, u razmatranje treba uzeti i ne-ekološke varijable kao što su socioekonomsko stanje i poljoprivredu.

Glavni problem može se očekivati pojavom novih virusa jer oni promenama i mutacijama mogu ući u populaciju i tada poseduju "veći potencijal" za širenje epidemije. Mreža kontrole zdravstvenog sistema kod nas i u Evropi je vrlo gusta i u svakom slučaju može se ustanoviti izbijanje virusa, i može se i vrlo brzo reagovati.


**Ključne reči:** vektorske bolesti, tropski virusi, potencijal širenja

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