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# PREDICTING THE FUTURE ECOLOGICAL NICHE OF *CULEX PIPIENS* AND ASSOCIATED BIORISKS IN ARMENIA

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West Nile virus disease is an emerging infectious vector borne disease. Of registered invasive species of mosquitoes in Armenia, *Culex pipiens* is the most implicated one in the potential transmission of West Nile virus (WNV). In previous years (1985–1999), research on circulation of mosquito-borne arboviruses in Armenia was conducted by the research Institute of Epidemiology and WNV, *Batai*, *Sindbis*, *Tahyna* and *Gheta* were found in mosquitoes. The only mosquito-borne disease historically registered in Armenia was malaria, without autochtonous cases since 2006. However, per retrospective medical chart review study (2016–2019) in the Nork Infection Clinical Hospital, about 30% of febrile patients is diagnosed as "Fever of Unknown Origin". We hypothesize that these arboviruses are circulating in Armenia and largely mis-diagnosed and/or under reported. Based on the geographical locations of mosquitoes, the MaxEnt model with 19 bioclimatic variables was developed to predict future ecological niche of *C. pipiens* and potential high-risk areas for West Nile virus disease. It is the first step for the implementation of a statistically rigorous system for real-time alert of biorisk.

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***Keywords*:** *C. pipiens*, arboviruses, West Nile disease, ecological niche, MaxEnt, Armenia.

**Introduction.** Vector-borne diseases are a specific group of infections that present an emerging threat as new, invasive mosquito species spread from tropical areas to more temperate areas. Extensive trade has also increased the rate of exchange for goods that can result in the introduction and establishment of non-indiginous vector species. Historically, the only mosquito-borne disease registered in Armenia was malaria, which was without autochtonous cases since 2006. Mosquito-borne disease research on the circulation of arboviruses in Armenia was last conducted from 1985–1999, and the results published in 2006. In 2016, ten new species of mosquitoes, including *Aedes albopictus* were identified in Armenia for the first time. These, however were not probed for arboviruses or other pathogenic agents. *Aedes albopictus* (Asian tiger mosquito), an invasive species, which can transmit dengue, West Nile virus, Chikungunya and other arboviruses of public health significance have also been found in the Republic of Georgia, that borders Armenia, and where there have been registered dengue cases.

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West Nile fever is now spread all over the world, including the Mediterranean, causing high mortality. It is transmitted by the bites of *Culex*, a genus with species widely spread in Armenia. Dirofilariasis is the disease caused by the *Dirofilaria* worm and is present in the Black Sea region but has not been registered in Armenia yet. Several types of mosquitoes in Armenia are capable of transmitting *Dirofilaria* infection. During a 2003 to 2006 entomological investigation, West Nile Virus and other arboviruses, such as *Batai*, *Sindbis*, *Tahyna* and *Gheta* viruses were isolated from mosquitoes [1].

Geographical and climatic conditions of the territory of the Republic of Armenia are favorable for arthropod vectors of infectious diseases. The climate is highland continental with hot summers and cold winters. The territory is mostly mountainous, with fast flowing rivers and few forests. Though Armenia is mainly located in subtropical climatic zone, because of mountains in the small territory of the country are distributed almost the all-climatic zones: mountain-steppe, mountain forest, desert, semi-desert, alpine. The emergence of vector-borne diseases is related to environmental factors and conditions.

While climate change may lead to the increase and spread of existing vector-borne diseases, there are a number of infections whose importation may result in epidemic transmission in Armenia due to the presence of potential vectors. The fast-growing international travel and transport play an important role in the rapid spread of reservoirs, vectors and pathogens of vector-borne diseases all over the world. Armenia is a homeland for all Armenians residents of other countries in all over the world and they visit Armenia very frequently. This can cause import of mosquitoes and mosquito-borne infectious diseases and transmission in Armenia and also the diseases and mosquito-species can be exported to the other countries.

The proposed study is exploratory and addressed a growing threat to public health from the spread of vector-borne disease. Mosquitoes have high significance as vectors of infectious diseases such as aboviruses and understanding their prevalence and distribution together with the pathogens they might be currently harboring, is of great public health interest. The potential for this study to advance scientific knowledge is high. It is important to understand how vectors are distributed along temporal and spatial scales and to tie this in with the implications of climate change to predict the future trajectory of vectors and associated diseases.

As a result of this study, we have gained a better understanding of mosquito-borne disease prevalence risks, distribution in Armenia. The hypothesis is that there are disease agents circulating in mosquito vectors in Armenia, and that these cause/have caused cases of human disease and are underdiagnosed. The results of the retrospective medical chart review study (2016–2019) in the Nork Infection Clinical Hospital, about 30% of febrile patients is diagnosed as “Fever of Unknown Origin”. Our specific aims are designed to address our hypotheses by allowing us to identify the species and distribution of mosquito vectors and predict their associated pathogens.

The only mosquito-borne disease historically registered in Armenia was malaria, without autochtonous cases since 2006 [2, 3]. During the VectorNet field missions conducted in 2016 in Armenia, *Aedes albopictus* first time was found in Bagratashen (bordering to Georgia) and their distribution is expanding. *Aedes*

*aegypti* mosquitoes were found on the territory of Georgia, bordering to Armenia. *Aedes aegypti* and *Aedes albopictus* are the two mosquitoes that can carry Dengue and other arboviral vectors, such as Chikungunya and Zika virus. The first Dengue case was registered in bordering Georgia [4]. Dengue is the most rapidly spreading mosquito-borne disease, with a 30-fold increase in global incidence during the past 50 years, affecting more than 100 countries throughout tropical and subtropical regions of the world. According to current estimations by Bhatt et al. there are 390 million dengue infections per years, of which 96 million present clinical symptoms [5].

West Nile fever is recorded in tropical and temperate climatic zones until the 1990s was not a major threat to human health, but is now spread all over the world, including the Mediterranean, causing flares, high mortality. It is a viral illness, transmitted by the bites of *Culex*, the species widely spread in Armenia. Birds, also people and other mammals infected. About 80% of infected people do not develop any symptoms, 20% develop commonly occurring intoxication, only 1% of patients suffer from nervous system, may occur with encephalitis, meningitis, poliomyelitis and death [6, 7]. Among people, the prevention of West Nile fever is efficiently carried out by means of ecological control in the areas where the virus is detected.

There were no cases of West Nile fever in the Republic of Armenia, but during the 2003–2006 research carried out by the Institute of Epidemiology, Virology and Medical Parasitology of the Ministry of Health of the Republic of Armenia, the virus of the West Nile fever was also isolated from the mosquito samples. Other arboviruses, such as *Batai*, *Sindbis*, *Tahyna* and *Gheta* viruses have been isolated from the *A. maculipennis*, *C. pipiens*, *A. caspius*, and *A. claviger* mosquitoes [1].

**Materials and Methods.** Sampling of adult mosquitoes will be done using tubes, aspirators and traps (mouth aspirators, EVS + $CO_2$ traps, Mosquitoes will be collected across Armenia (10 Marzes and Yerevan) using classical entomological methods. Sampling of adult mosquitoes will be done from indoors in animal shelters (endophilic species) and outdoors (exophilic species). Sampling of adult mosquitoes was done also using tubes and aspirators. Larvae were collected from water pools using dippers and entomological nets. Microscopic identification method was used for mosquito species identification. Mosquitoes were identified and sorted by species by MosKeyTool, which is an interactive identification key for mosquito species (female adults and 4th stage larvae) of the whole Euro-Mediterranean area and comprehensively covers 7 genera and 128 mosquito species.

Based on the geographical locations of mosquitoes, the MaxEnt model with 19 bioclimatic variables from WorldClim (www.worldclim.org ) was developed to predict future ecological niche of *C. pipiens* and potential high-risk areas for vector-borne diseases. It is the first step for the implementation of a statistically rigorous system for real-time alert of biorisk.

**Results and Discussion.**

*The Current Composition of Mosquitoes in Armenia and the Proportion of Species of Culex Genera.* To clarify the species composition, patterns of vector distribution in various landscape and climatic zones of the republic in modern conditions and determine the role of mosquitoes in the transmission of malaria and other vector-borne diseases, we have conducted entomological surveys and field material collections in some Marzes of the Republic (Ararat, Armavir, Shirak,

Tavush, Lori, Syunik). Of total 4.236 larvae collected from five Marz (2014), the presence of all species (*Anoppheles*, *Culex* and *Aedes*) was observed, however, prevalence of *Aedes larvae* in Shirak (46.1%), Lori (38.0%) and Tavush (26.5%) Marzes was recorded, and *Culex* in Syunik (37.9%) and Ararat (42.1%), respectively. *Culiseta larvae* were observed in Shirak (6.4%) and Ararat (1.1%), Uranotaenia (5.8%) only in Shirak, respectively (Fig. 1).

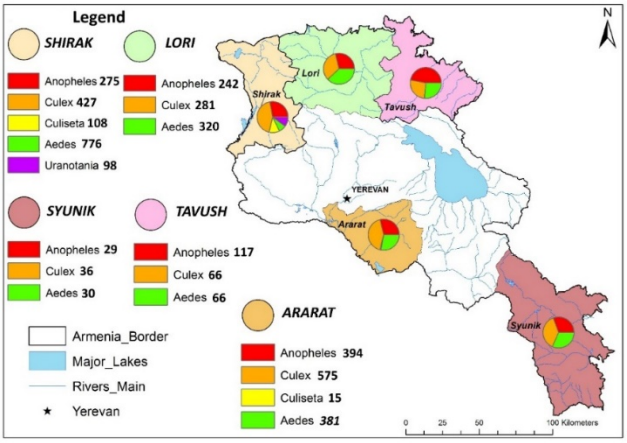


Fig. 1. Species composition of larvae according to surveys for 2014 (Shirak, Lori, Tavush, Syunik, Ararat Marzes).

During the continued entomological investigations in the autumn of 2014, in total 2.476 mosquitoes were identified (Fig. 1), including *Anopheles* (*n*=1195), *Culex* (*n*=787), *Aedes* (*n*=494). According to the study results, the species composition of non-malarial mosquitoes (Fig. 2) showed 5 species of genus *Culex*, of which *C. pipiens* 45.1% (24.0–55.1%), *C. theileri* 28.7% (25.8–32.0%) and *C. theileri* 28.7% (25.8–32.0%), *C. mimeticus* 2.7% (1.4–6.7%) and *C. hortensis* 18.7% (10.5–37.3%), respectively. *Culex* species were found in all marzas studied. Of all *Culex* species, *C. modestus* was found only in three Marzes and was 4.8% (3.3–11.0%) in total findings [8].

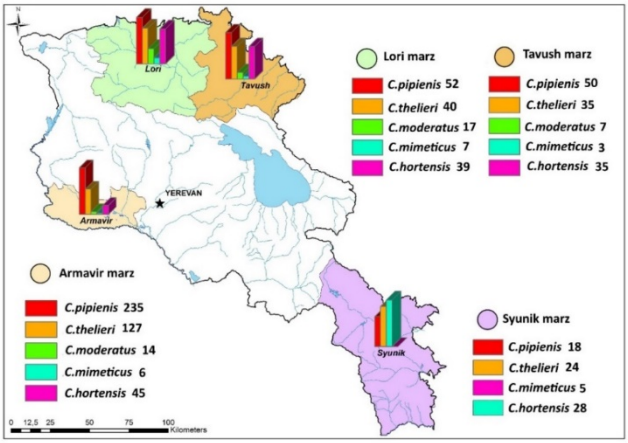


Fig. 2. Species composition of *Culex* mosquitoes (imago) according to entomological surveys in 2014.

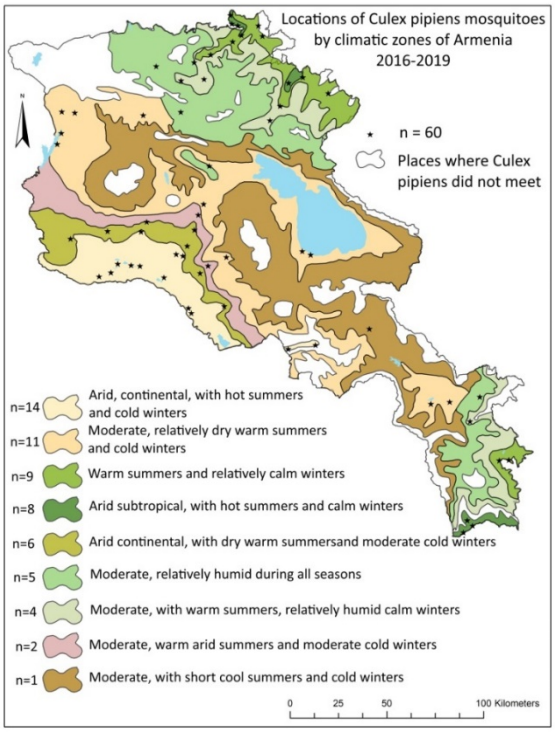


Fig 3. Geographic location of *C. pipiens* on the territory of Armenia using the Model MaxEnt (2016–2019).

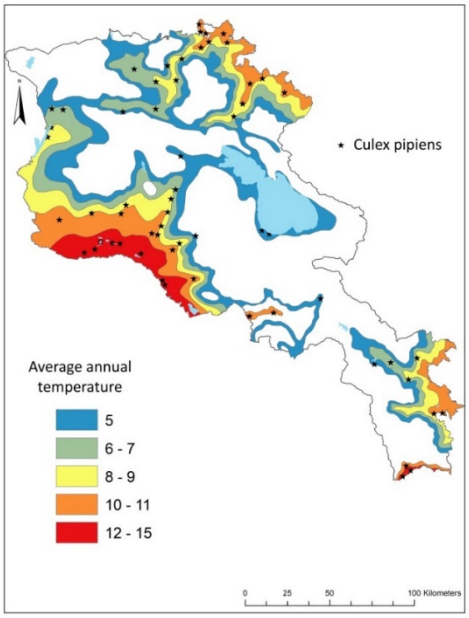


Fig. 4. Temperature impact on the prevalence of *C. pipiens.*

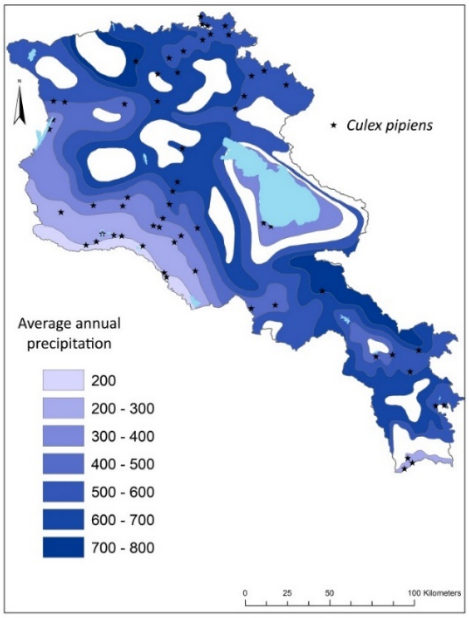


Fig. 5. Humidity impact of the prevalence of *C. pipiens.*

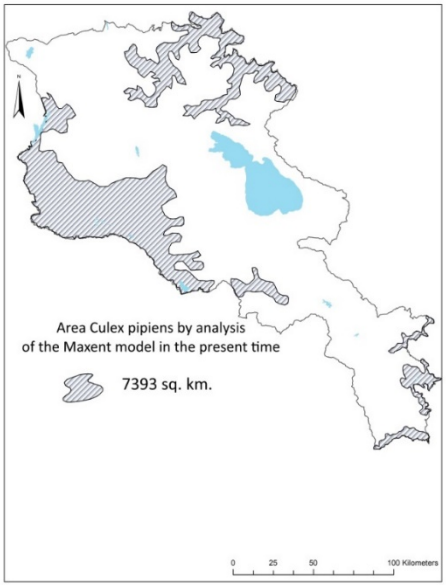


Fig. 6. Current niche of *C. pipiens* in Armenia (2016–2019).

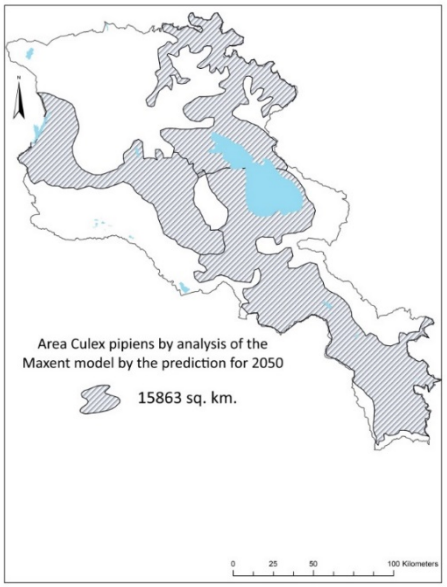


Fig. 7. The prognosed future niche of *C. pipiens* in Armenia (2050).

In April–November 2018–2019, in search of an invasive species of *Ae. aegypti* mosquito, we continued entomological investigations with the support of the NCDCP research team in the target regions. We have continuously monitored populations of vectors to determine their species composition and range. Of collected 20074 larva complied in the same period, the *C. pipiens* was 8.191 (40.8%), *An. maculipennis* 4110 (20.5%), *Ae. caspius* 2174 (10.8%), *Cs. longiareolata* 1178 (5.8%), and the rest in the overall collection was 22.1%, respectively. *Culex pipiens*, which becomes active since May, is widespread in the country in all regions studied (Fig. 3).

Figs. 4–5 show the impact of environmental conditions (temperature and humidity) on the further spread of *C. pipiens*' niche in Armenia, indicating the radius of the range change.

**Conclusion.** The key factors posing the threat are the predicted climate change, which, according to MaxEnt forecast, the niche of *C. pipiens* mosquitoes will be doubled (15863 $km^2$) by 2050, compared to the currently known niche of the latter (Figs. 6, 7). *C. pipiens* associated biological hazards include West Nile Fever, Japanese encephalitis, tularemia, lymphatic filariasis, meningitis.

So, along with the forecasted favorable ecological conditions for the future expanded mosquitoes' populations in terms of prevent the introduction of the virus in areas where competent vectors are abundant, will be really challenging. Mild febrile illnesses in travelers from endemic/epidemic areas are not easily detectable, and special effort is needed in terms of "risk-based surveillance". In the future modelling dynamics of the infection including also other risk factors for the introduction of the virus would be of further help (e.g., infected mosquitoes transported by aircrafts or ground transportation, transovarial transmission, the level of poverty, immune status of people, socio-economic and anthropogenic indicators

that affect virus transmission processes in complex interactions) for risk assessment and decision-making. Once a transmission cycle starts, it is very hard to face the problem through “control measures”, including of mosquitoes’ population control.

This research is significant because WNV, *Batai*, *Sindbis*, *Tahyna* and *Gheta* viruses had been previously isolated from the mosquitoes in Armenia, however no human cases have been diagnosed. While climate change may lead to the increase and spread of existing vector-borne diseases, there are a number of infections whose importation may result in epidemic transmission in Armenia due to the presence of potential vectors. The positive impact on public health is that based on the results from this study, public health risks for mosquito-borne diseases were estimated and recommendations made for preventive and proactive vector-control measures, including introduction of a broad range of laboratory diagnostics means.

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Լ. Գ. ՆԻԱԶՅԱՆ

## ՀԱՅԱՍՏԱՆՈՒՄ *CULEX PIPIENS* ՄՈԾԱԿԻ ԱՊԱԳԱ ԷԿՈԼՈԳԻԱԿԱՆ ԽՈՐՇԻ ԵՎ ԿԱՊՎԱԾ ԿԵՆՍԱՌԻՍԿԵՐԻ ԿԱՆԽՏԵՍՈՒՄԸ

Արևմտյան Նեղոսի տենդը (ԱՆՏ) հատուկ վտանգավոր վարակիչ հիվանդություն է: Հիմնական փոխանցող համարվում են *Culex* ցեղի,

մասնավորապես՝ *C. pipiens* մոծակները: Նախորդ տարիներին (1985–1999) Հայաստանում մոծակներով փոխանցվող արբավիրուսների շրջանառության վերաբերյալ հետազոտությունների արդյունքում հայտնաբերվել են ԱՆՏ, *Batai, Sindbis, Tahyna* և *Gheta* ախտածինները: Մոծակների միջոցով փոխանցվող միակ հիվանդությունը, որը պատմականորեն գրանցվել է Հայաստանում, մալարիան է՝ առանց տեղային դեպքերի 2006 թ.-ից ի վեր: Այնուամենայնիվ, ըստ «Նորք» ինֆեկցիոն կլինիկական հիվանդանոցում կատարված հետահայաց ուսումնասիրության (2016–2019), տենդով հիվանդների մոտավորապես 30%-ի մոտ վերջնական ախտորոշումներում նշվում է «անհայտ ծագման տենդ»: Մենք ենթադրում ենք, որ այս արբավիրուսները շրջանառվում են Հայաստանում և պատշաճ չեն հայտնաբերվում հիմնականում թերախտորոշման և (կամ) թերհաղորդման արդյունքում: Մոծակների աշխարհագրական տարածվածության հիման վրա՝ MaxEnt ծրագրային փաթեթեի կիրառմամբ՝ 19 կենսակլիմայական փոփոխականներով, մշակվել է մոդել՝ *C. Pipiens* մոծակների ապագա էկոլոգիական տարածագոտին և դրա հետ կապված ԱՆՏ-ի հավանական բարձր ռիսկային տարածքները կանխատեսելու համար: Դա իրական ժամանակի մեջ կենսաբանական ռիսկի ահազանգման վիճակագրորեն հավաստի համակարգի ներդրման առաջին քայլն է:

Л. Г. НИАЗЯН

## ПРОГНОЗ БУДУЩЕЙ ЭКОЛОГИЧЕСКОЙ НИШИ КОМАРА ОБЫКНОВЕННОГО И СВЯЗАННЫХ БИОРИСКОВ В АРМЕНИИ

Лихорадка Западного Нила (ЛЗН) является особо опасным инфекционным трансмиссивным заболеванием. Основным переносчиком вируса ЛЗН являются комары рода *Culex*, в частности, вид *Culex pipiens*. В предыдущие годы (1985–1999) в Армении проводились исследования по циркуляции арбовирусов, передающихся комарами, по результатам которых были обнаружены вирусы ЛЗН, *Batai, Sindbis, Tahyna* и *Gheta*. Единственным заболеванием, передающимся комарами, исторически зарегистрированным в Армении, была малярия без регистрации аутохтонных случаев с 2006 года. Тем не менее, согласно ретроспективному исследованию (2016–2019 гг.), проведенному в инфекционной клинической больнице “Норк”, у ~30% пациентов с лихорадкой окончательно диагностируется “лихорадка неясной этиологии”. Мы предполагаем, что эти арбовирусы циркулируют в Армении и в значительной степени не выявляются надзорной системой вследствие отсутствия обширного диагностического арсенала и активного надзора. Основываясь на известной географической распространенности комаров, с применением программы MaxEnt на основе 19 биоклиматических переменных, была разработана модель по прогнозированию будущей экологической ниши *C. pipiens* и определению потенциально высоких зон риска для ЛЗН. Это первый шаг к внедрению статистически достоверной системы оповещения о биориске в режиме реального времени.