

REVIEW



Emerging and threatening vector-borne zoonoses in the world and in Europe: a brief update

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ABSTRACT

Climatic changes, landscape management, massive human, animal and commodity transportation represent important factors which are contributing to the spread of zoonotic diseases. The environmental and socioeconomic factors affecting the incidence of vector-borne zoonoses and possibilities for the reduction of disease impacts are discussed in the article. The most important zoonoses with expanding area of incidence and/or increasing occurrence are summarized, with special emphasis on the European region. While some diseases and their respective pathogens are *indigenous* to Europe (e.g. Lyme disease), others have been introduced to Europe from tropical areas (e.g. chikungunya or dengue fever). These emerging diseases may represent a serious threat in near future and better understanding of their spreading mechanisms, pathogenesis and consequent treatment is very important.

KEYWORDS

Outbreak; climatic changes; pathogen; host; immunity; disease; zoonotic

Diseases transmitted and shared between animals and humans are as old as mankind itself as pathogens shared with animals cause more than 60% of infectious diseases in man [1]. The development and spreading of zoonoses are complex processes dependent on the evolution, variability, selection and interaction between pathogens and hosts. In addition, vector-borne zoonoses development and transmission are influenced by the ecology and distribution of vectors. Furthermore, vectors are often not dependent on the single host species, which means, that the vector-borne zoonoses have also often more host or reservoir species. It makes their dynamics less predictable and elimination more problematic [2]. Host, pathogen and vector characteristics are substantially influenced by environmental conditions. According to The One Health Triad, there is a close relationship and interaction between human, animal and environmental health [3].

Climatic changes and human activities lead to shifts in environmental conditions and indirectly influence zoonoses transmission and distribution. Arthropod vectors are usually considerably sensitive to environmental changes and often have the key influence on the disease distribution. Since vectors are ectotherms, they are strongly affected by changes in temperature patterns of environment [4,5]. Higher temperatures support the development, survival and increasing density and areal expansion of ticks and mosquitoes [6–9]. In addition, increased temperatures accelerate pathogen replication and support disease transmission [10]. These facts are in a correlation with

the increase of vector-borne zoonoses incidence that has been reported recently and which has also been predicted by some climatic models for the near future [6–8,11]. Moreover, other environmental factors, especially extreme weather events such as floods and storms, have often supporting effect on the vector density as well [9]. Intensive agriculture and industry, excessive grazing, drying of wetlands and deforestation lead to landscape transformations. Changes in the vegetation cover and water management may affect local precipitation and temperature conditions and lead to consequent changes in the ecosystem. This affects plant and animal communities and consequently vector and disease distribution [12,13].

Some human activities can directly influence transmission of pathogens on the local level. Contact rates between pathogens, vectors and humans are dependent on landscape utilization, human demography and a local lifestyle, and they are increasing due to global changes [8,14–16]. Global trade and affordable tourism enable the long-distance spread of infections by the transportation of infected animals or humans or by delivering of infected vectors together with agricultural commodities [17].

The distribution and epidemiology of vector-borne diseases are strongly influenced not only by environmental conditions but also by the socioeconomic situation in the region. The situation is alarming in many low-income countries with tropical or subtropical climate, as there are suitable conditions for some of the most life-threatening vector-borne diseases

such as malaria or dengue fever. The human population is steadily rising, people are living close to each other and often in the tight contact with wild and domestic animals. Weakened health reflecting poor living conditions may increase the chance of being infected [18,19]. Health care system is unsatisfactory and prevention and vaccination programs are not accessible for the considerable part of the population in these regions. Preventive programs for mosquitoes and sandflies density reduction have only negligible effects [20]. These factors support rapid and intensive spread of zoonotic infections and generally increasing number of outbreaks [21,22].

The geographical distribution of vector-borne zoonotic infections is closely related to the distribution and expansion of their vectors. Mosquitoes and sandflies are most common vectors in tropical areas, whereas in Europe, they act as zoonotic vectors only in a limited number in warmer areas [23]. However, due to the climate warming and consequent expansion of mosquitoes to the north, the diseases which are originally typically tropical have recently emerged in Europe as well [24]. Also excessive animal transport and human migration and consequent infection of existing vectors were responsible for sporadic outbreaks of non-autochthonous zoonoses – for example, a case of malaria outbreak in Greece in 2009–2012 [25,26].

In Europe, tick-borne zoonoses are the most important and their incidence has been increasing during the past decade [27,28]. The tick densities have risen due to changes in the climate, human activities and landscape management and ticks can now be found in higher latitudes and altitudes [27,29,30]. The regulation of the tick density is a difficult task; one option involves the control of invasive, pest and game species populations as their high densities promote tick populations and spreading of tick-borne diseases [27]. Cultural traditions (such as mushroom and berries picking and hunting) and a growing popularity of outdoor free-time activities in Europe leads to increased contact rate of humans and ticks and thus increase the probability of being infected [31].

The propagation of pathogens to new areas has often an extensive impact on host populations. If the host population has no common evolution history with the pathogen and its immunity system is naive and non-adapted, the infection can be highly challenging and may result into epidemic with serious impact on health of the host population [32,33], as was the case of West Nile fever outbreak at the US east coast in 1999 [34]. In case of viral infections, rapidly evolving viruses quickly acquire new mutations making them stronger and naive host populations even more vulnerable [35].

The most important and threatening vector-borne zoonotic diseases emerging and rapidly spreading in Europe and/or worldwide are summarized below

together with factors influencing their distribution and pathogenicity.

Viral diseases

There is a group of highly emerging viral diseases – dengue, chikungunya and Zika, transmitted by mosquitoes of the genus *Aedes* – *A. albopictus* and *A. aegypti*. Spreading of these zoonoses has similar patterns and is particularly linked to the expanding *Aedes* mosquito inhabited zone, which is related to the climate warming, and to their shipping introduction [36,37]. The distribution of *A. albopictus* in Europe is expanding to the north, as it was recently found not only in Southern Europe but also in Belgium, Netherlands and Great Britain [17,26,38,39]. Also, *A. aegypti* has been reoccurring recently in Europe [26,38]. Aside from the vector distribution, there are more factors affecting disease spreading, such as the outside temperature; the temperature threshold for viral replication is mostly relatively high [17].

Flavivirus Zika causes a fever illness, which is not dangerous for an infected individual, however in case of pregnant women, it may cause fetal microcephalia. It was first detected in Africa in 1947, later also in Asia. Recently, the majority of cases is reported from the Pacific Islands and South and central Americas [40]. There are reasonable concerns that Zika will emerge in Europe in close future as the virus can be easily introduced by human or animal transportation and consequent infection of highly competent and rapidly spreading *A. aegypti* or an adaptation to *A. albopictus* [17].

Dengue fever is globally the most important mosquito-borne viral infection affecting humans. This flavivirus infects almost 400 million people annually and has been reported in more than 125 mostly tropical or sub-tropical countries [41,42]. Even though dengue outbreaks had been occasionally reported for centuries; in recent decades, reports of dengue epidemics have risen worldwide as a result of changes in rainfall and humidity and due to an increase of urbanization and international travel [8,42,43]. In fact, recent studies have shown that dengue was a disease with the largest increase in number of cases among infectious diseases over the last 20 years [36,44]. Dengue is the second most commonly diagnosed cause of fever after malaria among travelers returning to Europe from low- and middle-income tropical countries [45]. First, autochthonous dengue cases were detected in France and Croatia in 2010 [46,47]. Dengue outbreak in Madeira in 2012–2013 led to 2000 number of cases [38,48]. According to models, current *Aedes* vectorial capacity in Southern Europe is sufficient for dengue outbreaks [17], and dengue epidemic potential will increase during the twenty-first century [36]. The unavailability of a vaccine and the

lack of sufficient vector control make dengue a serious worldwide public health concern [42,49,50].

Chikungunya virus, family *Togaviridae*, has similar patterns of spreading like the dengue virus as it is transmitted by the same *Aedes* mosquitoes. Chikungunya spread is related to temperature changes and to the transmission of vectors by commodity transportation [36]. In the past 15 years, chikungunya caused major epidemic outbreaks in Africa, Asia, the Indian Ocean and more recently also in the Caribbean and both North and South America [32,51,52]. In Europe, chikungunya was detected for the first time in a localized outbreak in Italy in 2007; since that time, epidemics have been repeatedly recorded in Italy and France [53] and the occurrence in Europe in general is steeply increasing [52]. Contrary to dengue, the new promising vaccine has been developed and is currently being tested [54,55].

Crimean-Congo hemorrhagic fever (CCHF) caused by the *navirus* of the same name causes globally the most widespread viral tick-borne infection of humans [56]. It is spread by ticks of the genus *Hyalomma*. While CCHF has only been endemic to Balkan and other east European countries for many years, the occurrence of CCHF in the rest of Europe is now increasing and the geographic distribution is expanding as it has been recently detected in Portugal, Spain, Netherlands and Germany [35,56]. Beyond endemic areas, the disease can also appear anywhere as an imported disease, as it was registered in France [57] and England [58]. CCHF spreading is related to the abandonment of arable land, growing of secondary vegetation, and also to the increase of mean temperature, rainfall and humidity which positively supports tick population growth [6,59,60]. The threat of CCHF lies in its strong epidemic potential and high transmissibility between close contact persons and health workers [35,56]. Since there is also a high mortality rate (10–40%) [35,56], CCHF is considered a real threat for Europe [35]. Despite the intensive process of vaccine development [61], no licensed vaccine is yet available.

West Nile Fever (WNF) is caused by a flavivirus transmitted by mosquitoes of the genus *Culex*. WNF is endemic in large areas of Africa, south Asia, the Middle East and in warmer parts of Europe, such as France, Greece, Romania and Italy [62,63]. The main reservoir hosts are wild migratory birds. Due to the avian transmission cycle, WNF can spread very fast on long distances [64]. For a long time, WNF was considered to be an infection typical for the Old World, but in 1999, due to its extremely high transmission potential, it appeared for the first time on the western hemisphere – at the northeast coast of the USA [65]. The extremely good spreading abilities were confirmed when WNF was detected 2 years later in Canada [66] and Mexico [67]. In Europe, an increasing

number of WNF outbreaks has been observed over the last 20 years [68] and the last one was recorded in 2018 in southern and central Europe [69]. It can be explained by hot summers and mild winters, which support both increased density and biting activity of temperature-sensitive *Culex* mosquitoes and high replication rate of flavivirus [10,70,71]. The strong influence of temperature on WNF transmission was clearly confirmed by WNF outbreaks and spreading to previously unaffected areas in years with abnormally high temperatures [10,72]. It was confirmed that the distribution of the main European WNF vector – *Culex molestus* has expanded to the north [73]. There are multiple vaccines potentially preventing WNF in humans, however, the sufficiently effective vaccine without any side effects is still lacking [49].

Bacterial diseases

Lyme disease (LD) caused by spirochetes of the genus *Borrelia* is the most common tick-borne disease in the temperate zone [27]. About 85,000 cases are reported in Europe annually [74] and approximately 35,000 in the USA [75]. However, this number is largely underestimated and most cases of LD infection remain undiagnosed [74]. Although the majority of cases have mild symptoms, if not properly treated, LD can cause serious health problems resulting in substantially reduced quality of life. The incidence of LD has been increasing during last decades in Europe, and LD zone has enlarged north and incidence has also been increasing in Fennoscandia and United Kingdom [27]. It is related to the expanding distribution and abundance changes of the tick genus *Ixodes*. It is influenced by climatic factors, type of agriculture management and changes in vegetation cover [76,77]. The increasing incidence of LD in Europe is also supported by increasing popularity of free-time outdoor activities [78]. There exist large differences in LD incidence between European regions, which are caused particularly by different levels of human exposition to ticks during traditional outdoor activities such as hunting or berries picking and working in forests [31]. No vaccine for human use is available at the moment. Currently, the most promising are OspA vaccines, yet their efficacy and side effects should be deeply verified [79,80].

Bacterial order *Rickettsiales* causes wide range of related diseases spread by ticks, fleas, chiggers and lice. Spreading abilities, morbidity and mortality rates of *Rickettsiales* are high. Typhus fever caused by *Rickettsia prowazekii* was classified as the category B on the list of bioterrorism agents [81]. The most common rickettsiosis in Europe is Mediterranean spotted fever caused by *Rickettsia conorii*. Even though the disease had been endemic to Southern Italy for many years [82], it has been spreading recently [83]. This infection may

represent a severe threat, as its mortality rate is about 32% [84]. Anaplasmosis caused by *Anaplasma phagophytrophila* has also a strongly increasing and widespread occurrence in Europe [85,86]. Recently, new human rickettsial infections have been recognized in Europe [82,87]. In general, rickettsioses occurrence increases in northern countries, which had been traditionally *Rickettsia* free [88]. It is supposed that this increasing occurrence is associated with the rise of temperature and decreasing number of frosty days [83,89,90]. Several rickettsial vaccines were developed; however, they were difficult, expensive and very hazardous to produce [91]. There is still no approved vaccine available yet [92].

Tularemia is caused by the gram-negative bacteria *Francisella tularensis*, which is one of the most virulent microorganisms currently known [93]. The lifecycle of *F. tularensis* takes place through terrestrial or aquatic environment. In terrestrial lifecycle, lagomorphs, rodents, and ticks are the main source of human infection and tularemia incidence is related to changes in rodent dynamics and to the expanding zone of ticks [94]. In aquatic lifecycle, the source is the water contaminated by carcasses and excrements of infected animals [94]. Tularemia outbreaks related to the aquatic lifecycle are more frequent [94]. Tularemia is highly infectious, can be easily transmitted by aerosol droplets, has a high mortality rate (up to 30%), remains in the environment for a long period of time and there is no vaccine available [93,95]. These alarming characteristics led to the consideration of tularemia as a potential bio-warfare weapon and it is currently classified as the most dangerous, category A infectious agent [81] *F. tularensis* was used for manufacturing of biological weapons during World War 2, although its use has never been reported [94]. Recently, tularemia has been detected in an increasing number of wild animal species, including lagomorphs, rodents, carnivores, fish and invertebrate arthropods [93]. The incidence of human tularemia is steeply increasing in Balkan countries and in Turkey [96]. In the rest of Europe, human incidence has declined, probably because of a more urban life style, decreasing number of people working outside in the countryside and a low exposition to infected wild animals [78]. However, it can represent a real threat to forest and field workers or to people living at the edge of society, such as homeless people; the transmission can be very fast and easy between them and they may comprise a center of infection outbreaks [78].

Protozoan diseases

The worldwide most common protozoan infection is *malaria*. It is a mosquito-borne disease caused by the genus *Plasmodium* and transmitted by *Anopheles* sp. mosquitoes. Human malaria is caused by five *Plasmodium* species. More than 75% of

human cases, together with the highest mortality rates, can be attributed to the infection by *P. falciparum*, and about 20% of cases are caused by *P. vivax* infection [97]. Approximately, 214 million cases of malaria arise and more than 400,000 people die from malaria every year [98]. Malaria with its high mortality and morbidity represents the greatest long-term selective pressure on human immunity-related genes in recent history, and the genetic resistance against malaria is the proven example of a long-term adaptation [99,100]. The introduction of malaria into areas where human population is not adapted and its immune system is naive may have dangerous consequences [101]. Malaria is a disease characteristic for many tropical and subtropical regions, however, vast majority of cases has been repeatedly reported in Africa over the years [98]. The predictions concerning malaria occurrence are debatable. As estimated in older climate models, a steep increase of cases in Africa can be expected [102]. On the other hand, according to the more recent WHO report [98], rates of the disease have decreased by 21% from 2010 to 2015, mainly due to the effective vector control [103]. In Europe, malaria has been endemic in Greece [25]. Due to the prevention programs, malaria was eliminated in the rest of Europe [16] and only sporadic cases of malaria without travel history to endemic areas were occasionally detected [25]. In the year 2015, the European region was malaria-free; all 53 countries in the region reported at least 1 year of zero locally acquired cases [98]. Nevertheless, the continuing transmission of *Plasmodium* by indigenous *Anopheles* vectors to areas with suitable environmental climatic conditions could cause malaria outbreaks [16]. There exists only one approved anti-malaric vaccine, but it has a low efficacy and its further improvements and consequent tests are recommended [104].

Leishmaniasis is an infection caused by the protozoan genus *Leishmania* and it is spread by the bite of sandflies from the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World [105]. There are differences in distribution patterns of sandfly vectors. Genus *Phlebotomus* prefers desert and semi-desert habitats and feeds on livestock and domestic animals in close surroundings of human settlements, whereas the genus *Lutzomyia* prefers forest habitats [105,106]. The incidence of leishmaniasis is about 1.3 million cases and mortality is about 30–50 thousands per year [107,108]. Leishmaniasis occurs in cutaneous, mucocutaneous and visceral form. Visceral form – kala-azar is worldwide the second most common lethal infection after malaria [109]. A combination of leishmaniasis and HIV infection may be especially dangerous for a human organism. This combination is quite frequent and the frequency is increasing in Southern Europe – up to 70% of local

cases of visceral leishmaniasis are associated with HIV infection [109]. Leishmaniasis is a climate-sensitive disease, strongly affected by changes in the rainfall, temperature, irrigation habits and deforestation, since these factors influence the ecology of sandfly vectors and reservoir hosts [105]. The increasing disease incidence is also strongly affected by socioeconomic risk factors, such as poverty, migration, urbanization and war, which lead to higher exposition of humans to vectors [105]. According to the WHO, leishmaniasis in Europe has been substantially underestimated. It is supposed that its increasing prevalence in Europe is largely caused by an increasing international traveling, the difficult elimination of leishmanial infection in HIV positive patients, development of drug resistance, the use of immunosuppressive medications [105,110]. As dogs are important reservoir hosts of leishmaniasis, their importation can spread the disease to new areas, contrary their vaccination may help to control the leishmaniasis outbreaks [105,110,111].

The spread reduction and the mitigation of the impact of zoonoses are complex problems and represent challenges for many scientific fields. Naturally, the best solution is the elimination of sources and advantageous conditions. However, this requires economic, social, political and behavioral changes, which are difficult or impossible to apply. We have only limited options to influence climate and landscape changes and thus sequentially stop disease spreading and vector range expansion. In fact, we are so far rather able to solve consequences than eliminate causes of zoonoses spreading. Such elimination would require, besides others, suitable landscape management or making a progress in the discovery of alternative ways of satisfying needs for food, water, space and energy.

Another specific problem is the control of vector density and spreading capacity. It is important to perform active surveillance of invasive vector species and to prevent their spreading into new areas. A feasible way is the formation of a warning system such as The European Environment and Epidemiology (E3) Network, which was successfully verified during recent malaria, dengue and WNF outbreaks [16]. The number of flies and mosquitoes can be reduced by chemical insecticide spraying, but it may disturb ecological relations in the landscape, as vectors are a part of complex food chain [112,113]. Recently, genetically modified vectors have been developed that carry gene modifications leading to the decrease of mating and biting activity or to the shift of sex ratio toward males. Genetically modified organisms (GMO) might introduce their modified genes into normal populations when released into the nature, which would lead to the reduction of transmission capacity of such populations [114,115].

On the individual level, main preventive intervention is a vaccination, which increases the survival of less resistant individuals and also decreases the number of potentially infected vectors. The development of treatment and medication for emerging diseases represents a challenge for medical and biochemical sciences. Recently, a treatment exists for a large number of zoonoses, however, due to economic reasons it is used mainly in well-developed countries. There is an urgent demand for developing cheap and accessible drugs affordable in low-income countries. Another and perhaps even more threatening problem is the increasing antibiotic resistance caused both by high mutation rate of infectious agents and by an excessive use of antibiotics. This makes the development of effective and alternative treatment considerably more difficult because more new pharmaceutical drugs have to be tested [116,117].

The zoonoses represent a problem of rising importance, as they are related not only to the environment but also to the human society and there is no simple solution for vector-borne zoonoses. They are hard or even impossible to be definitively eliminated, since spreading patterns of zoonoses are permanently changing and many natural reservoir hosts exist.

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