REVIEW ARTICLE

Climate change and its extensions in infectious diseases: South Eastern Europe under focus.

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Abstract

Climate change results from natural processes and human-made activities influencing the atmosphere. Many infectious diseases are climate-sensitive, and their nature and epidemiology are changing in parallel with the change in climatic conditions and global warming. Increased replication rates of pathogens at higher temperatures, extended transmission seasons, migration of vectors or human populations are some outcomes of the changing climate to trigger new concerns, including new epidemics with old or new pathogens. Climate change is presenting itself today as an urgent global health threat, and it requires immediate international action with high priority. Infectious diseases in relation to changing climatic conditions are reviewed with predominating current examples, focusing on Europe with particular emphasis on South Eastern European and Eurasian regions.

Keywords: Climate change, Communicable diseases, Disease reservoirs, Europe, Vector-borne diseases

Background

The United Nations Framework "Convention on Climate Change (UNFCCC)", signed in 1992, defines climate change as a change of climate which is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and which is in addition to natural climate variability observed over comparable time periods (1). In fact, the climate discussions had given way much earlier to gathering of the First World Climate Conference in Geneva in 1979, sponsored by the World Meteorological Organization (WMO) and attended by scientists from a wide range of disciplines. The first evidence of human interference in climate was presented and plans made to establish a World Climate Programme under the joint responsibility of the WMO and the United Nations Environment Programme (UNEP) at this same meeting to "prevent man-made changes in climate" that might harm the well-being of humanity (2, 3). In 1988, the UN decided to establish the Intergovernmental Panel on Climate Change (IPCC) in collaboration with WMO for providing the scientific basis of climate change and its environmental, economic and social impacts as well as its future risks, and for developing possible response strategies (3). Following, the before mentioned UNFCCC was established in 1992 as the first intergovernmental convention and 195 countries signed it but it remained as a goodwill act since it had no sanctions. The UNFCCC declared the dangerous effects of man-made environmental pollutions on climate and the aim to decrease the levels and sustain the negative effects of the atmospheric greenhouse gases. The Kyoto Protocol, which was constituted as an operational tool of the UNFCCC in 1997 but came into force not before 2005, recognized that the developed countries are largely responsible for the high levels of atmospheric greenhouse gas, and it obliged the parties to decrease their emissions. Addendum 1 – Annex B of the Kyoto Protocole stated the parties separately as "industrialized countries" such as the OECD members and EU countries and as "economies in transition", placing a heavier burden on the industrialized and developed countries according to their higher responsive capabilities and greater contributions to high emission levels (4). Being an OECD member, Turkey was included in the UNFCCC but did not immediately sign the Convention and had not yet become a party in UNFCC when the Kyoto Protocol was accepted in 1997, having, therefore, no listed responsibility to decrease its emission levels (4, 5). Later, Turkey became a UNFCCC party in 2004 and of the Kyoto Protocole in 2009.

As the strongest health agreement of this century, the Paris Agreement was launched at the United Nations Climate Change Conference (COP21) in 2015. The agreement came into force in 2016 after 196 countries adopted and signed it. It was a legally binding international treaty concerning climate change, with a specific goal to limit global warming to at least 1.5°C below the pre-industrial levels (6). Turkey signed the Paris Agreement in 2016 but did not approve it at its parliament till October 2021, which in fact was a "must". The coal-based energy policies of Turkey have to change now for decreasing emissions. COP25 was held in Madrid and was most talked about all over the World, due to the on-site performance of a group of young activists led by Greta Thunberg. Beyond all other warnings and complaints, Greta and the 15 activists aged between 8 and 17, complained about five countries to the UN-UNICEF for neglecting the struggle against climate change. These countries were France, Germany, Brazil, Argentina, and Turkey (7).

Greenhouse gases, global warming and extreme weather events

The greenhouse gases surround the globe like a blanket and inhibit energy escape from the surface and atmosphere, giving way to extreme warming. Sources of human-induced greenhouse gas increases are mainly the use of carbon-containing fossil fuels for energy and production, as well as deforestation, population increase and mobility, planless urbanization and unsuitable agriculture. Due to all of these, the arctic ice mass is melting by 2.7% per decade, the sea level is rising by 1.8 mm per year, and extreme weather events are getting more frequent. The IPCC predicted a global average temperature rise of 1.5–5.8°C for the 21st century, accompanied by increased abnormal weather events (8-10). Unless preventive measures are taken, the global temperature will continue to rise, rain patterns will change to cause floods in some regions and droughts in others, and the health effects of climate change are expected to be particularly adverse (11). El Niño Southern Oscillation (ENSO) is an extreme weather event defined as the hot water wave arising from the Pacific Ocean and a climate pattern resulting from the aquatic and atmospheric temperature differences. It has a hot phase called El Niño and a counter cold phase called La Niña. Since the Pacific Ocean is the greatest water mass in the World, every change in its temperature affects the weather and the climate. There are 33 El Niño events since 1900, and three of them in 1982, 1997 and 2015 are called Super El Niños when temperature peaks were recorded. During the 1997 El Niño, an area of oceanic water as large as the USA warmed up and pumped a large volume of heat into the atmosphere, changing the weather patterns all over the world. Hurricanes, regional floods and droughts resulted in many health problems and thousands of deaths. The 1997 El Niño was followed by La Niña in 1998-1999, having similar effects in different regions than El Niño. The 2015-16 El Niño was followed by La Niña in 2017-2018, as expected. The ENSO events always had influence on climate. Global warming is strengthening their influences, as well as increasing their frequency. All these occur as the inevitable results of the increase in atmospheric greenhouse gases, influencing in return the global weather events and climate (12, 13).

Climate change and infectious diseases

A pathogen, a host or a vector, and suitable transmission conditions are fundamental for infectious diseases. Nearly 75% of the emerging infections are zoonoses hosted by domestic or wild animals and 30% are caused by vector-borne pathogens. Zoonoses are sensitive to climate conditions and environment. Appropriate climate and weather conditions are necessary for survival, growth, distribution and transmission of pathogens, and geographic expansion of vectors and hosts. Most vector-borne and particularly insect-borne infections are linked directly or indirectly to the climate factors such as rainfall, moisture, wind and temperature. Global warming changes the habitats of the vectors, pushing them to northern and higher new locations where non-immune people live and get infected more readily. This means new epidemics with the old pathogens (14-16). Deforestation also causes animals and vectors to lose their habitats and pushes them to search for new ones, getting sometimes closer to humans and increasing the vector-borne human infections (17). Global warming favors the spread of infectious diseases, while extreme weather events enhance disease outbreaks at nontraditional places at unexpected times and intensities. Climate change has the potential to enhance development of epidemics and probable emergence of new pathogens and new threats. (14-18).

Climate-sensitive infections

Climate-sensitive infections are handled in three categories in general: Vector-borne, water-borne, and air-borne. The climate-sensitive vector-borne infections include viral infections such as Dengue, Zika and Hantavirus infections; or bacterial infections such as Lyme disease, plague and tularemia; or parasitic infections such as malaria and leishmaniasis. The climate-sensitive *water-borne* pathogens may also be viral such as Norwalk virus; or bacterial such as salmonella, Vibrio cholerae, non-cholera vibrios, legionella or campylobacter; or parasitic such as giardia and cryptosporidium. The major climate-sensitive *air-borne* infections are mainly viral such as influenza and respiratory syncytial virus, in addition to the meningococcic meningitis which is bacterial (17, 18).
When temperature increases and rainfall and moisture also increase, water-borne infections such as cholera, as well as leptospirosis and Weil's Disease or leishmania infections are more frequent in the relevant regions and mosquitos get more abundant to transmit infections such as malaria or Dengue fever. When temperature increases but rainfall and moisture decrease, meningococcal meningitis and West Nile virus infection can get more frequent. Two million deaths due to diarrheas, one million to malaria and thousands due to meningitis are recorded each year, and there are approximately 50 millions of Dengue patients globally. If, however temperature decreases but moisture increases, influenza infections and even epidemics are enhanced (17, 18).
La Niña had preceded the 1918, 1957, 1968 and 2009 influenza pandemics. The primary reservoirs of Influenza-A virus are birds. The migrating birds are affected by the weather and ecosystem changes induced by ENSO events. Not the epidemia-causing ones but the pandemia-causing viral strains are emerging as a result of viral reassortment processes. The ENSO events change the flight routes and stopover times of the migrating birds, thereby changing the pathogens they carry. Under these conditions, different influenza virus subtypes make simultaneous multi-agent infections and therefore reassortments in birds. Then, new viruses emerge, infecting animals and humans, making new pandemics from time to time (19). Particularly in Eastern and South-Eastern Asia, the population increase, agriculture types and changing routes of migrating birds induced by frequent extreme weather events have provoked the evolution of new influenza virus strains easily extending into far regions (11).

Vector-borne infections

a) Tick-borne infections

The *Ixodes ricinus* tick is the primary vector in Europe (Annex Fig.1a) for Lyme borreliosis and tick-borne viral encephalitis (TBE). Caused by the Ixodes-transmitted-bacterium *Borrelia burgdorferi*, Lyme borreliosis loades the EU with the largest disease burden with 65,000 cases per year and is linked to warm winters and high summer temperatures. TBE was detected to be more prevalent in Eastern and Northern Europe with 2,057 cases in 2014 (Annex 1b), indicating a four-fold increase of reported cases in European endemic areas during the last 30 years (20, 21). Since global warming pushes the tick-vectors to higher altitudes and northern parts, the TBE risk is expected to diminish in southern Europe while Lyme disease is being surveyed currently to predict its future spread (22).

Crimean-Congo hemorrhagic fever (CCHF) is caused by Nairovirus transmitted to humans by *Hyalomma* ticks. Difficult to prevent and treat with a case fatality ratio of up to 40%, CCHF is endemic in most of Africa, Asia, as well as the Balkans and the Middle East (Annex

Fig. 2a, 2b) (23). Bosnia and Herzegovina, Albania, Croatia, Serbia, Montenegro, Slovenia, Bulgaria, North Macedonia, Greece, Armenia, Georgia, Azerbaijan, and Russia are endemic for CCHF. Turkey was affected by CCHF outbreaks with more than 12,000 cases but with a case fatality ratio of only 5% in 2002-2019 (23-25).

b) Mosquito-borne infections

The vector-borne infections were endemic to tropical and subtropical regions until recently. Due to the long-term changes in temperature and rainfall patterns with global warming, the northern movement of the vectors will put the temperate countries into a greatest threat for emergence and re-emergence of the vector-borne diseases, and mosquito-borne diseases may become more epidemic (26). **Malaria** is transmitted to humans through the vector *Anopheles* mosquito. The causative parasite is *Plasmodium* and its most deadly species is *Plasmodium falciparum*. More than 200 million malaria cases and one million deaths per year worldwide were recorded in 2010 (18). Control efforts dropped malaria mortality to 409,000 in 2019. The *Anopheles* mosquito survives in environments above 16°C and global warming would support its survival. Even though malaria's current main location is Africa, it is projected by the European Environment Agency (EEA) that different countries including Turkey and some of South Eastern Europe will be affected due, among other factors, to the changing climate (18, 27, 28). **Dengue fever** is a vector-borne viral hemorrhagic fever transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitos. The pathogen carried by these vectors is the Dengue virus which is an RNA virus of the *Flaviviridae* family. Rainfall and moisture together with temperature increase enhance the vector survival and spread which may be very rapid. During epidemics, the infection easily spreads into cities and urban life. The infection was limited to tropical and subtropical areas until recently and was the cause of 50-100 millions of cases with 15,000 deaths per year in roughly 100 countries. The vector *Aedes albopictus* (the Asian tiger mosquito) which is the most invasive mosquito species in the world gained access to Europe by 2010 and cases in Croatia, southern France, Germany, Italy and much of the Mediterranean coastal region got acquainted with the Dengue Fever. *Aedes aegypti* exists more on the Black sea coast of Europe and in Portugal (Annex Fig. 3), and Dengue Fever mortality is increasing in the affected regions (18, 29). In 2012-2013, Madeira province of Portugal reported the first European outbreak with more than 2,000 cases, via *Aedes aegypti*. More than 390 million cases worldwide are estimated currently and it is known that many travelers from dengue-affected areas enter Europe (18, 20, 30, 31). The first case in Turkey was an imported one, detected in a traveler in 2013 (32). Dengue is currently the most widely spread mosquito-borne disease in WHO's Eastern Mediterranean Region and is actively surveyed for keeping the blood transfusion safety measures under control (31). **Chikungunya** is a viral disease transmitted by *Aedes* mosquitoes to humans. It is manifest with fever, arthralgia and rash, with a probability to end up with chronic arthritis. There is no antiviral treatment or licensed vaccine. Although all index cases were imported to Europe by travelers from endemic regions, the autochthonous transmission of the infection via local *Aedes albopictus* produced two large outbreaks of chikungunya with a total of 550 confirmed and probable cases in Italy in 2007 and 2017. More than 30 cases in France between 2010 and 2017 were also recorded. The risk of the chikungunya virus spread in EU is high due to importation through infected travelers, population susceptibility and presence of the specific vectors particularly around the Mediterranean coast (33).

West Nile virus (WNV) infection is transmitted to humans by the vector *Culex* mosquito. Human WNV infection had entered Europe in 1950. An increased number of outbreaks have been observed over the last twenty years. In 20% of infected cases, the virus develops the West Nile Fever (WNF), a febrile illness with symptoms similar to those of influenza or dengue. High temperatures in summer have been associated with a West Nile Fever epidemic in 2010 in Southeast Europe and following outbreaks have followed the same trend. The largest outbreak of human WNV infections in the European Union/European Economic Area (EU/EEA) was in 2018, with 11 countries reporting 1,548 locally acquired mosquito-borne infections. The most affected countries were Serbia (126 cases), Italy (123), Greece (75), Hungary (39) and Romania (31). The number of WNV cases dropped considerably in 2019, except in Greece (34, 35). During the 2020 transmission season from June 1st till mid-November, EU/EEA countries reported through the European Surveillance System a total of 315 human cases of WNV infection, including 22 deaths. The affected countries were again mostly in central and Southern Europe: Greece (143 cases), Spain (77), Italy (66), Germany (13), Romania (6), the Netherlands (6), Hungary (3) and Bulgaria (1) (35). In the 2021 transmission season and as of 21 October 2021, 135 human cases of WNV infection have been reported from EU/EEA countries including Greece (55), Italy (54), Hungary (7), Romania (7), Spain (6), Austria (3) and Germany (3), with 9 deaths in Greece (7), Spain (1) and Romania (1). EU-neighboring countries had 18 human cases of WNV infection and 3 deaths in Serbia (36). The past and present distribution of WNV infection cases in Europe are shown in Annex Fig. 4a and 2025 and 2050 projections for its future distribution are shown in Fig. 4b and 4c, respectively. WNV is transmitted also through blood transfusion or organ transplantation (16). **Hantavirus infection** is a rodent-borne, climate-sensitive zoonosis transmitted to humans by different Hantaviruses to cause three different clinical syndromes. Also referred to as epidemic nephropathy, hemorrhagic fever with renal syndrome by Puumala virus is the most prevalent (98%) type in Europe with 4,046 cases in 2019 (38, 39). ***Candida auris*** is an antifungal-resistant yeast preferring mainly the healthcare settings and making difficult-to-control outbreaks of invasive healthcare-associated infections. After its first identification in 2009, Centers for Disease Control and Prevention announced it as a catastrophic risk when its infections appeared in three continents simultaneously. Within a decade, it spread to 23 countries in five continents, also entering Greece and Turkey (40, 41). The explanation or hypothesis was its adaptation to global warming. More heat-resistant microbes are being selected while those heat-sensitive are being eliminated. Fungi are favored under these trends. The surviving more heat-resistant microbes will also resist endothermic regulations in humans and high fever, which is a defense mechanism for eliminating infectious agents, and serve for insistent infections (42).

Conclusions

Climate change brings up complicated health issues already. Infectious diseases, many of which are sensitive to the climatic and environmental conditions, may occupy a considerable place in the global agenda for a long time with probable new pathogens, new diseases, new epidemics and pandemics. Due to the nature of the climate-sensitive infections, the steps leading to solutions can only be within a One-Health frame, but legally binding intergovernmental precautions should be followed and monitored in the first place by Paris Agreement signatory parties, as well as all the remaining public who sincerely believe in "ensuring that the health of a child born today is not defined by a changing climate" (29, 43).

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Annex

Figure 1. Tick-borne encephalitis. (a) Distribution of *Ixodes ricinus* ticks in Europe, March 2021. Available from: https://www.ecdc.europa.eu/en/publications-data/ixodes-ricinus-current-known-distribution-march-2021 (Accessed: October 10, 2021). (b) Number of confirmed tick-borne encephalitis cases in EU/EEA, 2014. Available from: https://www.ecdc.europa.eu/en/publications-data/figure-1-number-confirmed-tbe-cases-eueea-2014 (Accessed: October 10, 2021).

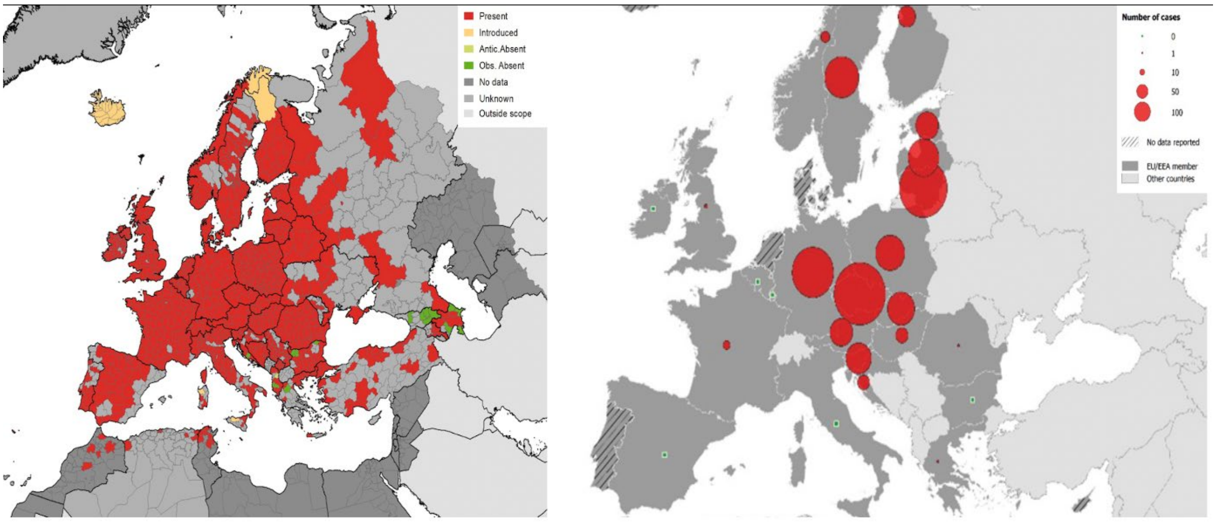

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Figure 2. Crimean-Congo Hemorrhagic Fever (CCHF). (a) Distribution of *Hyalomma marginatum* ticks as the major vector for CCHF, September 2021. Available from: https://www.ecdc.europa.eu/en/publications-data/hyalomma-marginatum-current-known-distribution-september-2021 (Accessed: October 10, 2021). (b) Endemic areas for CCHF. Available from: https://www.cdc.gov/vhf/crimean-congo/outbreaks/distribution-map.html (Accessed: October 10, 2021).

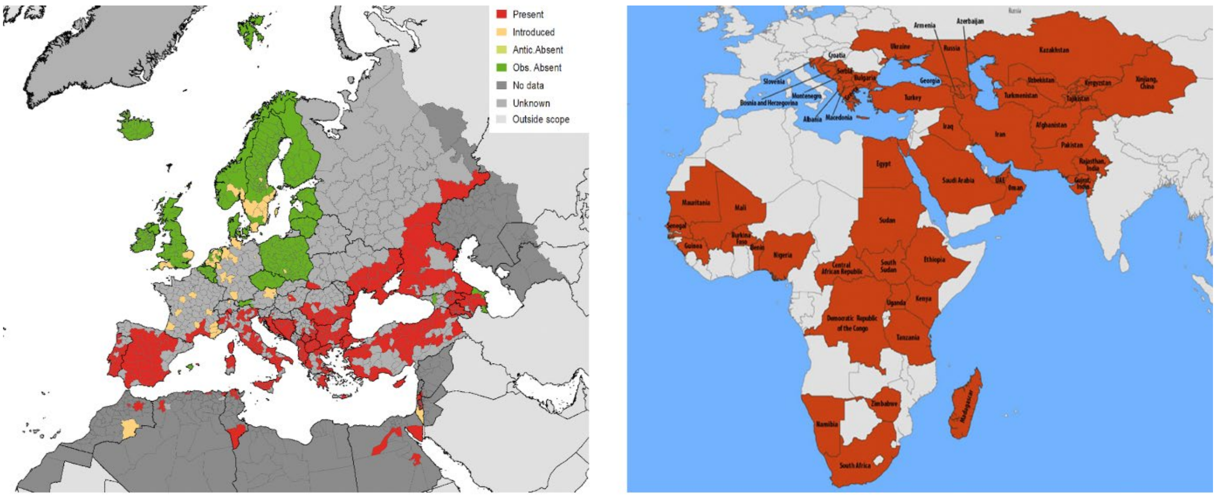

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Figure 3. Distribution of Aedes mosquitos in Europe. (a) *Aedes albopictus*, March 2021. Available from: https://www.ecdc.europa.eu/en/publications-data/aedes-albopictus-current-known-distribution-march-2021 (Accessed: October 10, 2021). (b) *Aedes aegypti*, January 2019. Available from: https://www.ecdc.europa.eu/en/publications-data/aedes-aegypti-current-known-distribution-january-2019 (Accessed: October 10, 2021).

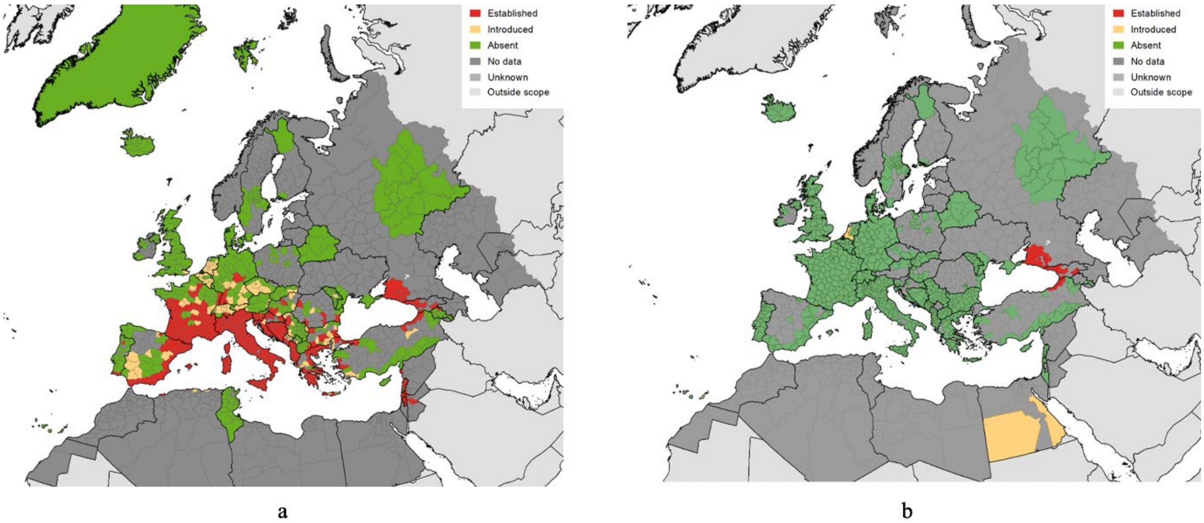

Figure 4. West Nile virus epidemiology. (a) WNV in Europe with human cases compared to previous seasons, updated 21 October 2021 (37) (Accessed: October 24, 2021). (b) 2025 prediction (16). (c) 2050 prediction (16).