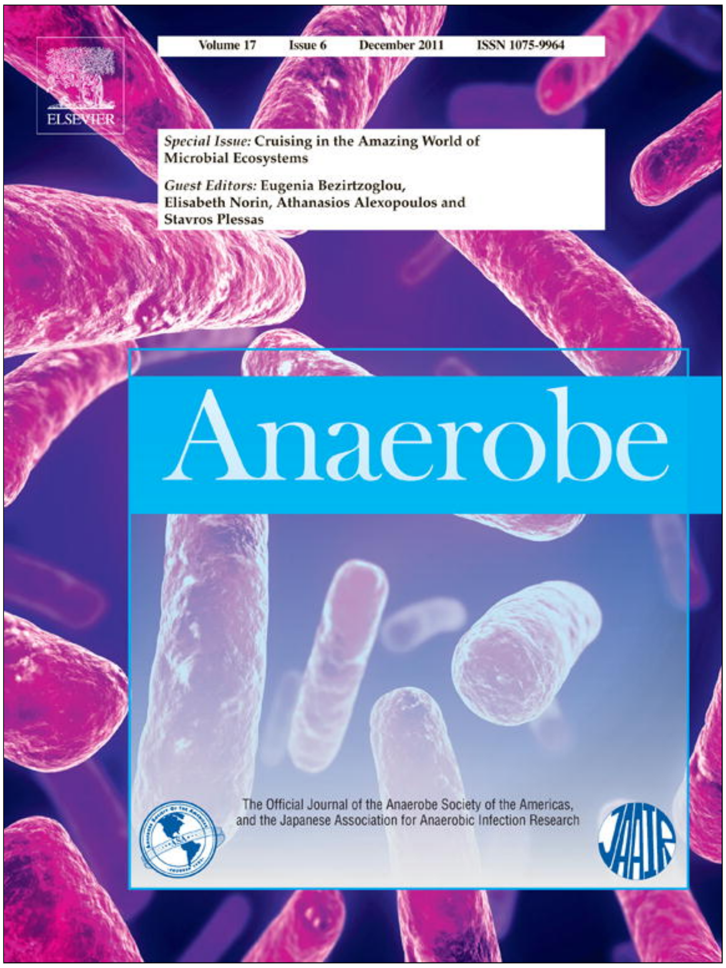
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Pathogenesis and Toxins

Climate changes, environment and infection: Facts, scenarios and growing awareness from the public health community within Europe

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ABSTRACT

Climate change is a current global concern and, despite continuing controversy about the extent and importance of causes and of its effects, it seems likely that it will affect the incidence and prevalence of both residual and imported infections in Europe. Climate affects mainly the range of infectious diseases, whereas weather affects the timing and intensity of outbreaks. Climate change scenarios include a change distribution of infectious diseases with warming and changes in outbreaks associated with weather extremes. The largest health impact from climate change for Europe doesn't come from vector borne infectious diseases. This does not mean that these types of health impacts will not arise in Europe. The ranges of several vector-borne diseases or their vectors are already changing in altitude due to warming. In addition, more intense weather events create conditions conductive to outbreaks of infectious diseases: Heavy rains leave insect breeding sites, drive rodents from burrows, and contaminate clean water systems. The incidence of mosquito-borne parasitic and viral diseases, are among those diseases most sensitive to climate. Climate change affect disease transmission by shifting the vector's geographic range and by shortening the pathogen incubation period. climate-related increases in temperature in sea surface and level would lead to higher incidence of waterborne infectious and toxin-related illnesses, such as cholera and seafood intoxication. Climate changes all around the world with impact in Europe are demonstrated by the fact that recent cases of cholera have been imported to Europe from Kenya, where spreading epidemic has been linked to the El Niño phenomenon, originated from the Pacific Ocean. Human migration and damage to health infrastructures from aberrant climate changes could indirectly contribute to disease transmission. Human susceptibility to infections might be further compounded by alterations in the human immune system caused by increased exposure to ultraviolet radiation and malnutrition due to alterations in agricultural products. Different kind of incidents in Europe with extreme weather events demonstrated effects on public health. The recent outbreak of the insect-borne Chikungunya virus in Italy in 2007 is an example of the kind of new health threat that the EU must be vigilant to confront. In addition, health effects of flooding, have been related to an excess cases of leptospirosis and campylobacter enteritis. Such examples have been demonstrated reported after flooding in the Czech Republic. Similarly, an increase of cryptosporidiosis in the United Kingdom has been related to flooding. Changing vector distributions associated with tickborne encephalitis and malaria have also been dempostrated in EU. A recently reported case of malaria in Italy in June 2008, suspected to be indigenously acquired, has shown how easily malaria could be reintroduced into several countries in the region. Another case of malaria in Greece in May 2010 affecting a young man living in a forestry region was claimed at KEELPNO-the Greek Center for disease control. Would this latest case be considered closely related to the one from Italy? If yes, then Public Health Services should elaborate plans to affront possible tickborne diseases. Heat waves are important causes of mortality on mortality are important. The deaths seen in France in 2003 from a heat wave are projected to be repeated, as heat waves become more severe. However, heat waves impacts on the transmission and severity of infectious diseases have not been elucidated. Finally scientific challenges include the elucudation of climate changes and extreme weather condition impact on infection transmission and outcome, human immune system changes and infection response, outbreak scenarios, animal and plant health and public health preparedness. European action plans to affront climate changes related health and infection problems are

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developed by the EU Commission at different levels and jointly by different DGs. In a few words within the EU the following points on human, animal and plant health are considered a priority: * Strengthening cooperation between the services of these three branches of health (human, animals, plants); * Developing action plans in the event of extreme weather conditions, in order to be better prepared and to react in the best way; * Gathering more reliable information on the risks of climate change whilst maintaining international cooperation, in particular with the WHO, as cooperation beyond that between Member States will be required to be more effective; * Providing additional effort to identify the most effective measures; * Improving the surveillance and the control of the animal diseases. The European Commission has decided to consider climate change, and the consequences it has on health, with greater importance whilst being aware that it is at the root of numerous diseases.

1. Climate changes

Climate change is a current global concern and, despite continuing controversy about its cause and the magnitude of its effects, it seems likely that climate change will affect the incidence and prevalence of both indigenous and imported infections in Europe. Climate restricts the range of infectious diseases, whereas weather affects the timing and intensity of outbreaks. Climate change scenarios predict a change distribution of infectious diseases with warming and changes in outbreaks associated with weather extremes, such as flooding and droughts. The largest health impacts from climate change worldwide seem to occur from vector borne infectious diseases. This does not represent the situation in Europe. It also does not mean that these types of health impacts will not arise in Europe. The ranges of several key diseases or their vectors are already changing in altitude due to warming. In addition, more intense and costly weather events create conditions conducive to outbreaks of infectious diseases, such as heavy rains leave insect breeding sites, drive rodents from burrows, and contaminate clean water systems.

The incidence of mosquito-borne diseases, including malaria, dengue, and viral encephalitides, are among those diseases most sensitive to climate [1]. Climate change would directly affect disease transmission by shifting the vector's geographic range and increasing reproductive and biting rates and by shortening the pathogen incubation period. Climate-related increases in sea surface temperature and sea level can lead to higher incidence of waterborne infectious and toxin-related illnesses, such as cholera and shellfish poisoning.

2. Endemic or imported infectious diseases in Europe?

Cases of cholera have been imported to Europe from Kenya [1], where the recent spreading epidemic has been linked to the El Niño phenomenon, which originates in the Pacific Ocean! Human migration and damage to health infrastructures from the projected increase in climate variability could indirectly contribute to disease transmission. Human susceptibility to infections might be further compounded by malnutrition due to climate stress on agriculture and potential alterations in the human immune system caused by increased flux of ultraviolet radiation.

2.1. Country cases

Many incidents in Europe with extreme weather events affect the public health [2]. The recent outbreak of chikungunya in Italy [3] is an example of the kind of new health threat that will increasingly confront the public health services across the EU. In addition, the health effects of flooding, the excess cases of leptospirosis and campylobacter enteritis reported after flooding in the Czech Republic [4] and of cryptosporidiosis in the United Kingdom [5], and changing vector distributions associated with tickborne encephalitis [3] and malaria. A recently reported case of malaria in Italy, suspected to be indigenously acquired, has shown how easily malaria could be reintroduced into several countries in the region, or to spread more rapidly in countries in the southern part of the former Soviet Union, where a resurgence of indigenous malaria has been reported.

In north-western Australia some locations have recorded a doubling of the annual rainfall over two decades, and cyclical rainfall variation has been observed. It is difficult to predict precisely how these complex changes are likely to impact on endemic infectious disease for which only limited environmental surveillance data are available. The addition of an insect vector to the equation adds another layer of ecological complexity. Ross River virus disease is the most common and widespread mosquito-borne infection in Australia. A recent investigation [5] found that rainfall, temperature and high tides were determinants of Ross River virus transmission, but that the nature and scale of the interrelationship between disease, mosquito density and climate variability varied with geographic location and socioeconomic conditions.

In some countries, contaminated water and foods, especially seafood, are common vehicles for transmission of *Vibrio cholerae*, as the following case reported in Germany [6]. A 36 year old German resident of Nigerian origin became acutely ill on 12 July 2001 with watery diarrhea and vomiting. He was admitted to hospital in Berlin on 14 July with continuing symptoms, aggravated by dehydration, electrolyte imbalance and acute kidney failure, but no fever. The patient was given fluids and electrolytes, but no antibiotic agents. He made a quick recovery, and his kidneys resumed their function. *V. cholerae* (serotype O1, biotype Inaba, phenotype El Tor) was isolated from a stool specimen taken on 17 July. No other gastrointestinal pathogens were found. He was discharged from hospital, free of symptoms, on 25 July. No further *V. cholerae* had been found. The patient had returned from a holiday in Nigeria on 30 June 2001. Four hours before the onset of symptoms he had eaten fish that had been brought into the country on a plane from Nigeria by friends on the preceding day. The patient had prepared the fish himself, boiled it in water, and was the only person to eat it. The incubation period for cholera is between a few hours and three days, and on this basis it can be concluded that the patient acquired his infection by eating the fish from Nigeria. As the cooking process would have killed the causative agent, it may be assumed infection was acquired during preparation or from kitchen equipment. No further cases are known among the patient's contacts in Berlin or among his friends and family in Nigeria [6].

West Nile virus (WNV) is transmitted by mosquitoes (mainly of the genus Culex) with wild birds as its natural amplifying hosts. Human cases have been reported from Romania since the 1960s, and sporadic outbreaks have occurred in several countries in eastern and southern Europe in the past 15 years [7]. The presence of the virus in birds suggests ongoing transmission and probable endemicity of WNV in Europe. Humans are mainly infected through mosquito bites, few infections through organ transplantation and blood transfusion have been documented in North America [8–11].

After the infectious bite, an incubation period of 2–14 days precedes symptoms which range from mild fever and malaise, moderately severe disease (high fever, red eyes, headache and muscle ache) to meningitis or encephalitis. The most severe manifestations are in the elderly and the debilitated [12]. However, 80% of the infected persons remain asymptomatic. No specific treatment or vaccines are currently available. Phylogenetically, WN viruses are assigned to at least two main lineages. Lineage 1 has been identified in the majority of outbreaks in Europe and the Americas in humans and horses. Lineage 2, in contrast, was identified outside of Africa only recently: in 2004 and 2005 in goshawks in Hungary, in 2007 in Volgograd, Russia, and in 2008, in wild hawks and a captive kea in Austria [13,14].

Following the large urban outbreak in Bucharest (Romania) in 1996–1997 [15], transmission of WN viruses to human and/or horses has been documented on several occasions in:

- Czech Republic (1997) [16];
- France (2000, 2003, 2004, 2006) [17–19];
- Italy (1998, 2008–2009) [20–24];
- Hungary (2000–2008) [25];
- Romania (1997–2001, 2008–2009) [26,27];
- Spain (2004) [27–29]; and
- Portugal (2004) [29–31].

More recently, in 2009, human cases of WNV infection were reported from Hungary (7 cases), Romania (2 cases) and Italy (16 cases). In July 2010, Portugal reported a probable case of WN virus infection, which was the first (probable) case of WN virus infection reported in 2010 in the EU.

In Greece, serological studies in the 1970s detected WNV antibodies in animals (horses, cattle, goats and rabbits) and humans [32]. Surveys conducted in the 1980s and in 2007 identified WNV antibodies in approximately 1% of selected populations in the region of Central Macedonia. Serum samples collected from 392 residents from northern Greece (Imathia) in 2007 revealed six positive samples for WNV, four of which (1%) were confirmed by micro-neutralisation assay [32,33]. In contrast, a survey of 9590 blood donations and 115 cerebrospinal fluid samples from patients with aseptic meningitis in Greece in June to October 2006 and 2007 revealed no positive results for WNV by NAT (Nucleic Acid Amplification Testing) [34].

The lowlands from which the majority of cases are reported are located between three major rivers. The three rivers converge into a common delta, which is a well-known resting ground for migratory birds. Mosquito vectors of WNV, including *Cx. modestus* and *Cx. pipiens* are known to be present throughout Central Macedonia. Following entomological surveillance activities in the affected region (August 16, 2010), preliminary laboratory analysis suggested the presence of WNV of lineage 2 in a pool of Culex mosquitoes. No virus has been isolated recently from human cases. Also, an initiative by the Veterinary Department of the University of Thessaloniki has provided evidence of recent clinical infection with WNV in horses near to the city of Thessaloniki; five cases of equine encephalitis were reported to the European ADNS System on 27 August.

After the recorded outbreak of WNV infection in humans in Bucharest, Romania, in 1996–1997 with 500 cases reported, this is the second largest outbreak of the disease in the EU. Even though the identification of the implicated virus or viruses infecting humans is pending, evidence of circulation of lineage 2 virus in the mosquito population would increase the number of EU countries where this lineage has now been identified. Whether this outbreak in Greece is due to climatic factors favoring unprecedented mosquito reproduction, an increased virulence in strains of WNV circulating in northern Greece (though unlikely) or some other factor, or a combination of them not accounted for, remains to be elucidated. Comparison of climatic conditions in other European countries where transmission has been documented would be interesting. In terms of geographic distribution, with the presence of birds (migrating and resident) and bridge vectors, the region of Central Macedonia presents all the ecological components for successful transmission of WNV to humans. The human cases currently reported from the city of Thessaloniki, however, suggest that there might be also an established urban cycle of transmission.

The precise reasons for the existence of the current outbreak of WNV infection in humans in the region remain unclear. However, meteorological data from 2010 for Central Macedonia suggest that there has been an unusual rainfall pattern and that temperatures were unusually high in July and August [32]. Such climatic factors are believed to have increased the abundance of mosquitoes and shortened the transmission cycle in the vectors, leading to increased human cases.

The current outbreak in Greece is the first large outbreak of WNV in humans in Europe since the Romanian outbreak in 1996–1997. The presence of West Nile virus is well-documented in several European countries. Climatic conditions (temperature and humidity) favor the presence and the multiplication of Culex spp. from May to October in the affected zones. At the same time, there has been an increase in the number of cases in the EU over the past decade [35,36]. The possibility that this reflects a changing epidemiology needs to be considered seriously by the local and regional authorities and at European level.

3. Climate changes, weather and heatweaves

Heat waves are important causes of mortality. The deaths seen in France in 2003 from a heat wave are projected to be repeated, as heat waves become more severe. However, heat waves impact on the transmission and severity of infectious diseases has not been elucidated.

Scientific challenges include the elucidation of climate changes and extreme weather conditions impact on infection transmission and outcome, human immune system changes and infection response, outbreak scenarios, animal and plant health and public health preparedness.

3.1. How to affront?

3.1.1. A successful management at regional level: Cryptosporidiosis is England declined after regulation

It is clearly demonstrated that infections worldwide as well as within EU are associated with climate changes, but body of knowledge remains fragmentary. In any case it is important to affront the problem, at regional as at European level be preventing, surveying and regulating. Special public authorities together with Europeans must be put together their efforts for this scope.

Promising are coming from the UK: results show that Cryptosporidiosis declined after regulation, in England and Wales 1989–2005 [37]. How? In the 1990s, several cryptosporidiosis outbreaks in England and Wales were associated with public drinking water supplies. Climatic variability and community spread from imported travel cases have been suggested as the main sources of inter-annual variability of cryptosporidiosis. An explanation may be that, precipitation may wash Cryptosporidium organisms from land into public water supplies, and warm, dry weather may increase the number of countryside visits. Both of these could result in exposure to Cryptosporidium organisms. A survey was accomplished by the University of East Anglia and the royal Institute of Hygiene and tropical Diseases. The results indicated that between mid-March and the end of June cryptosporidiosis cases were positively associated with river discharges that occurred 2 weeks previously. From July through early September, cryptosporidiosis was positively associated with warm, dry weather in the previous 2 months. No associations between cryptosporidiosis and weather existed at other times. Travel cases were not significant in any of the models. Following the survey, new drinking water regulation was implemented in England in 2000, to address the problem. Since new drinking water regulations were implemented in England and Wales in 2000, cryptosporidiosis has been significantly reduced in the first half of the year but not in the second. The estimated annual reduction in disease is of 905 reported cases and ≈6700 of total cases.

3.1.2. EU strategy for climate and environmental changes-borne infection and health

European action plans to affront health and infection related climate changes are developed by the EU Commission at different levels and jointly by different Directorate (s) General (s), (DGs). In a few words within the EU the following points on human, animal and plant health are considered a priority:

- Strengthening cooperation between the services of these three branches of health (human, animals, plants);
- Developing action plans in the event of extreme weather conditions, in order to be better prepared and to react in the best way;
- Gathering more reliable information on the risks of climate change whilst maintaining international cooperation, in particular with the WHO, as cooperation beyond that between Member States will be required to be more effective;
- Providing additional effort to identify the most effective measures;
- Improving the surveillance and the control of the animal diseases.

The European Commission has decided to consider climate change, and the consequences it has on health, with greater importance whilst being aware that it is at the root of numerous diseases. Moreover, the European Centre for Disease Control (ECDC) [38], prepares for climate and environmental changes with impact to human health by a strategy of surveillance and control. The ECDC has identified also the need to tackle the technical challenges by developing "a blueprint for an environmental and epidemiological network" that would link existing resources. Merging, integrating, and analysing such data will advance our understanding of the relationship between climate change and infectious diseases in Europe and inform public health action.

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