

WHAT'S NEW IN INTENSIVE CARE



Planet's population on the move, infections on the rise

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Introduction

In recent years we have been witnessing infections caused by emerging and re-emerging pathogens. Climate change extends the suitable environment for vectors previously confined to particular geographic areas; consequently, tropical diseases are no longer constricted in tropical areas. However, the most important parameter for “globalization” of infectious diseases is the restless mobility of humans. International travel has been steadily increasing beyond travel for business and tourism. Visiting friends and relatives, pilgrimage, medical tourism, and voluntary humanitarian and healthcare work may contribute to increasing risk for infectious diseases and cross-border spread [1]. On top of that, in the last 3 years, conflicts, poverty, and political instability in several countries produced a huge flow of migrants and refugees into Europe. Locally and internationally displaced people are temporarily settled in organized or random overcrowded camps. Until now, the most common infections reported in refugee populations have been skin infections, common viral respiratory syndromes, gastrointestinal syndromes, cases of inadequately treated tuberculosis, and outbreaks of vaccine-preventable diseases. However, concerns about emerging and re-emerging diseases in migrants and refugees include more severe diseases like viral hemorrhagic fevers, cholera, and severe respiratory syndromes. On the basis of the incubation periods, most infections concern transit and temporary settlement countries, whereas malaria, tuberculosis, HIV, and hepatitis B and C may also emerge in final destination countries. Migrants and refugees are prone to endemic

infections in the transit countries, including vector-borne diseases [2, 3].

Emerging and re-emerging diseases

There are a number of emerging vector-borne infections globally, which affect local populations but do not spare travelers (Table 1). Dengue fever is the cause of explosive outbreaks in tropical and subtropical regions, with an alarming peak in 2015. It is the second most commonly diagnosed cause of fever after malaria in the returned travelers from low- and middle-income countries. Its primary vector is *Aedes aegypti*, but its secondary vector *Aedes albopictus* has a considerable adaptability to temperate climates and constitutes a threat for European countries. Local transmission was reported in France and Croatia in 2010; an outbreak on Madeira in 2012 caused travel-related cases in mainland Portugal and other countries. The disease is generally non-fatal, but persons previously exposed to a different serotype of the virus who develop dengue hemorrhagic fever present with substantial mortality; severe dengue is a leading cause of death among children in some Asian and Latin American countries [4].

Zika virus (ZIKV), previously known to cause mild tropical disease, was declared a Public Health Emergency of International Concern on February 1, 2016. Starting from Polynesia in 2012, ZIKV is currently epidemic in most parts of the Caribbean, Central and South America. Vectors are the *Ae. aegypti* and *Ae. albopictus* mosquitoes. Eighteen European countries have reported travel-related cases whereas 13 countries (two European) have reported microcephaly and other congenital malformations associated with ZIKV infection during pregnancy [5]. Guillain-Barré syndrome (GBS) represents a severe and potentially lethal complication, with 15 countries having reported an increased incidence GBS with laboratory confirmation of a ZIKV infection as of July 2016. The

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Table 1 Basic characteristics of the most important globally emerging infections with potential for severe disease and ICU admission

Incubation (days)	Vector/transmission	Severe disease requiring ICU admission	Risk for Europe	People at risk ^a	Vaccine
Dengue fever 4–10	<i>Aedes aegypti</i> , <i>Aedes albopictus</i> mosquitoes	Severe dengue: plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment	Low probability of endemicity <i>Ae. albopictus</i> present	Residents, travelers and VFRs	Yes, licensed in 2016; Dengvaxia (CYD-TDV)
Zika virus 3–12	<i>Ae. aegypti</i> , <i>Ae. albopictus</i> mosquitoes Person-to-person sexual transmission documented Transmission to healthcare-provider under investigation	Guillain-Barré syndrome	Low probability of endemicity	Residents, travelers and VFRs, sexual partners, HCWs?	Ready to enter human trials
Yellow fever 3–6	<i>Ae. aegypti</i> (in urban areas)	15 % develop severe disease with jaundice, hemorrhagic manifestations, multi-organ failure	Low probability of endemicity <i>Ae. aegypti</i> only in Madeira	Residents, travelers and VFRs	Yes
West Nile virus 3–14	<i>Culex</i> mosquito	Neurologic disease, potentially fatal, particularly in immunocompromised persons	Present in Europe	Residents, travelers and VFRs, blood transfusion recipients	Vaccine in ongoing phase 1 in humans (NCT02337868)
Ebola virus 2–21	Natural reservoir unknown [probable spillover events: fruit bats or primates (apes and monkeys)] Exposure to infected bodily fluids of patients	Hemorrhagic complications, severe dehydration and capillary leakage, organ dysfunction, Gram-negative septicemia	Risk of imported cases and secondary transmission	Residents, family members, HCWs, travelers and VFRs, sexual partners	Vaccine in phase 2 and 3 study in humans in Sierra Leone (STRIVE)
MERS-CoV 2–14	Probable viral reservoir: Dromedary camels Person-to-person transmission (close contact needed, exposure to respiratory secretions)	Severe acute respiratory syndrome, acute kidney failure	Risk of imported cases and secondary transmission	Residents, HCWs, travelers and VFRs	Candidate for human trials

VFRs visiting friends and relatives in endemic areas, HCWs healthcare workers, MERS-CoV Middle East coronavirus

^a Residents refers to residents in endemic areas

US Centers for Disease Control and Prevention (CDC) has confirmed sexual transmission of ZIKV and is investigating a potential healthcare-associated transmission [5, 6]. Following confirmed, local, mosquito-borne spread of ZIKV, the Florida Department of Health has issued guidance for people who live in or traveled to the identified areas of Wynwood and Miami Beach any time after June 15 and July 14, respectively [7].

A yellow fever (YF) epidemic is ongoing in Angola, with 2954 cases and 328 fatalities as of June 2016. Travel-related cases were reported in China, Democratic Republic of Congo, and Kenya. Extensive vaccination is being implemented to terminate the epidemic. Europe is at low risk for an epidemic because of the absence of *Ae. aegypti* mosquitoes, the most competent YF vectors, except for Madeira [8].

Chikungunya, a virus spread by *Ae. aegypti*, has already been reported in European travelers returning from epidemic countries, but usually causes mild disease [1]. West Nile virus, transmitted by the widespread mosquito *Culex*, is found in Africa, Europe, the Middle East, North America, and West Asia. The majority of infected persons (80 %) develop a mild disease; 20 % of cases will develop more severe symptoms and a small minority neurological and potentially fatal disease [1].

Ebola and Marburg viruses belong to the *Filoviridae* family and cause severe disease with life-threatening hemorrhagic complications. The devastating 2014–2015 epidemic in West Africa caused a total of 28,616 Ebola virus disease (EVD) cases and 11,310 deaths. Extensive transmission is reported through infected bodily fluids from patients or dead corpses, affecting family members, social workers, healthcare providers, and missionaries [9]. Secondary cases have challenged many countries admitting repatriated patients, raising important concerns about healthcare providers' safety [10, 11]. Delayed transmission through sexual contact with survivors has been attributed to viral persistence in semen [9, 11].

Middle East respiratory syndrome coronavirus (MERS-CoV), first described in Saudi Arabia in 2012, is the cause of a severe respiratory syndrome with 36 % case-fatality rate. It is a zoonotic virus with camels serving as a reservoir and documented person-to-person transmission requiring close contact. Sporadic cases have been reported in many European countries linked to travel in the Arabian Peninsula where the epidemic is ongoing [12]. Although MERS-CoV posed important concerns during the hajj pilgrimage where thousands of pilgrims congregate in overcrowded conditions, mathematic modeling and real-life data showed a smaller-than-expected risk [13]. The vast majority of human-to-human transmission occurred in the healthcare setting, implying a serious public threat for admitted patients and healthcare

providers, particularly those exposed before diagnosis of the index patient [12].

People from the developed world travel to tropical areas mostly for leisure and recreation. Common diagnoses in the returned traveler requiring ICU admission include malaria, vector-borne infections, encephalitis, parasitoses, respiratory syndromes, and viral hemorrhagic fevers. HIV infection and sexually transmitted diseases should also be considered; HIV with co-infections can present with severe manifestations [2]. In addition to life-threatening disease, management of complicated malaria due to *Plasmodium falciparum* is further challenged by resistance to antimalarials and particularly artemisinin reported in North-East Asia, and the diagnostically challenging infection by *Plasmodium knowlesi* [1].

Medical travelers undergo medical procedures outside their country of origin seeking either shorter waiting times (i.e., solid organ transplant) or reduced costs. This practice has been associated with acquisition of multidrug-resistant (MDR) pathogens, depending on the visited country's epidemiology [i.e., KPC- or NDM-1-producing *Klebsiella pneumoniae*, extensively drug-resistant (XDR) *Acinetobacter baumannii*]. Persons who were urgently hospitalized in their vacation destinations share similar risks. Subsequent admissions in their country of origin with infections by these pathogens entail the risk of inadequate empiric treatment portending high mortality and spread of the resistant clones [14].

MDR and XDR tuberculosis remains an important public health issue; people displaced from endemic countries living in suboptimal conditions, malnourished, and without access to their medications are a significant reservoir for spread. It represents an equally important threat for healthcare providers and members of voluntary aid organizations [15].

Observe–report–get prepared is the survivor's triangle for intensivists and emergency care physicians. The initial investigation is usually triggered by the clinician's vigilance and diagnostic acumen combined with travel history, particularly in patients admitted to the emergency room with respiratory failure, shock with or without multiorgan failure, seizures, coma or paralysis of recent onset, persistent diarrhea and/or vomiting, jaundice, and febrile hemorrhagic rash [2]. Reporting and seeking proper advice are vital to confront a variety of life-threatening new challenges. However, effective preparedness ensuring timely and accurate diagnosis should include additional elements such as availability of up-to-date information on current outbreaks that present a public health threat and accessible laboratory testing and is a public health priority in a constantly changing global environment [3].

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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