Chapter 10
Risk of Globalization of the Disease in Europe

Abstract Risk of dissemination of ZIKV disease is based on multiple factors, including environmental (climate, socioeconomically, deforestation or industrialization) and travel/traveller factors. Both the disease (viremic travellers) and vector movement to mosquito-free area contributes to the introduction and establishment of autochthonous ZIKV transmission. Mass gathering events can contribute to magnify transmission due to close crowd life in a confined area. Also, multitudinary events can promote the introduction of an infectious disease to a previously naïve area when returning home. Although mathematical models estimate a low risk for introduction of ZIKV in Europe, specific European regions (mainly Portuguese Island of Madeira) account with suitable and efficient vector and opportune climate conditions to harbour the disease. Clinicians should be aware to enable early detection of autochthonous ZIKV cases. International and local guidelines can help clinicians on how to handle suspicious cases, how to confirm the infection and how to report suspected and confirmed cases. In case of autochthonous ZIKV detection, public authorities should perform surveillance and provide adequate resources to sustain enhanced mosquito control.

10.1 Factors Affecting the Risk of Spread of Vector-Borne Disease

It is known that ZIKV is primarily transmitted in tropical and subtropical regions by mosquitoes *Aedes aegypti* and *Ae. albopictus* bite, although other routes of infection have been also described (see Chap. 5). But, up to date epidemic/endemic transmission of ZIKV has been limited to tropical and subtropical regions, which suggests that ZIKV transmitted though alternatives routes to mosquito bites is not capable of maintaining on going transmission on their own in the absence of tropical/subtropical *Aedes* spp. vectors and/or a climate hot enough for ZIKV transmission by these species [1, 2].

To manage risks for endemic ZIKV infection in ZIKV-free countries some aspects should be considered.

10.1.1 Related to Environmental Factors

Climate patterns, specially temperature and rainfall trends, but probably also changing wind patterns, have important implications on vector-borne diseases transmission. But this influence may be significantly modified by confounding non-climatic factors, including epidemiological, environmental, social, economic and demographic factors implicated [3–7].

– **Climate facts**:

Temperature is known to modify directly vector-borne diseases in mosquito hosts. Variations of ambient temperature considerably modify insect internal temperature, as they are poikilotherms. Those variations greatly affect vector physiology and expose the pathogens they carry to ambient temperature [6, 8]. In laboratory, viral replication kinetics in mosquito-cultured cells has shown to depend on temperature, since higher temperatures lead to a more efficient viral attachment and cell infection [9, 10].

Several studies have also linked higher temperatures to shorter extrinsic incubation period, increase of female mosquito rate and faster dissemination rates [11–13].

Regarding precipitations and viral transmission dynamics, both increased and decreased rainfalls can promote the dispersal of ZIKV and other arboviriasis worldwide: although precipitations provide essential habitat for larval aquatic stage of *Aedes* lifecycle, drought can also contribute, as people increase water storage in household containers during the rainless periods, favouring larval hatcheries [14–16].

The atmospherical phenomenon known as El Niño has been linked to warm waves and drought in southern Africa and Southeast Asia, including Australia, while inundate the west coast of South America and to Central Africa [16, 17]. El Niño Southern Oscillation (ENSO) impacts on temperature conditions that caused the largest biting rates and the shortest extrinsic incubation period in 2015, which has favoured ZIKV outbreak in Latin America [18, 19]. The heather temperatures in North and Eastern South America, associated to an important drought throughout the second half of 2015 might be other of the multiple manifestations of ENSO and climate change that could have contributed to the rapid dispersal of ZIKV outside the native ecological niche [16, 20].

– **Socioeconomic factors**:

The human population is supposed to increase from 6 billion by the end of the 20th century to around 10 billion by 2050, half of them concentrated in urban and periurban areas [21, 22]. But the increase of human density is estimated to be disproportional, because of a higher proportion of those people will concentrate in cities compared with nowadays situation. Urban populations in Africa and Asia and those in Latin America and the Caribbean are expected to increase by almost 50% [23, 24]. This is of particular concern as rapid population growth is associated to

poverty due to concentrations of population without the necessary infrastructure for the safe storage and distribution of water and drainage of wastewater. In addition, as previously mentioned, the use of inappropriate household water containers favours an optimal habitat for larval development [25, 26].

– *Deforestation*:

Population increase implies the transformation of forestall areas in habitable areas. The consequent deforestation is expected to result in an increase in surface temperatures of up to 2 °C, with drier conditions where the land cover is reduced, which, again, favours the spread of vector-borne diseases as ZIKV [27, 28].

– *Industrialization*:

Industrial activity contributes to nearly 33% of atmospheric concentration of CO2 and 50% of methane. This cumulus of gases has been linked to an increase of ambient temperature. Also, CO_2 and methane emissions can increment plant foliage. These facts would impact in vector-born insects as the increase of temperatures and density biomass would provide more favourable microclimates for insect vectors [29, 30].

10.1.2   Related to the Travels and Travellers

The increasing numbers of people travelling worldwide is the result of a more economical mass transport and liberalization of international trade. International travellers (9.9 million in 2015) flying from Brazilian airports (ZIKV-affected area) to North America, Europe and Asia represents 65, 27 and 5%, respectively [31, 32]. These data exemplify the magnitude of the problem.

There are a number of different situations related to international movement of people and materials that directly impact on the distribution and incidence of vector-borne diseases. Travellers can either be a carrier of pathogens into new environments or accidentally translocate vectors in transport vehicles. People can also trigger further outbreaks if they become infected by vector-borne diseases during the travel and return to their non-endemic country while they are still viraemic, thereby increasing the risk of spreading to areas where suitable mosquito vectors already exist [32, 33].

However, it should not be forgotten that other routes of ZIKV infection than mosquito-bite have been reported (see Chap. 5), so the spread of ZIKV via viremic travellers to areas without the *Aedes* mosquitoes is equally of concern.

To asses the acquisition risk for the disease, it´s important to identify the type of stay of travellers in endemic areas for ZIKV, because it will also entail a different risk of transmission once the traveller returns to his/her country of origin: many travellers may go to holiday resorts or other locations where the risk of infection is dramatically lower compared to that of the resident population. In that sense,

immigrants returning home to visit their family (also known as VFR o "visiting friends and relatives") represent a high risk group for mosquito exposure [34, 35].

An increased risk of introduction and establishment of autochthonous ZIKV transmission has been linked with viremic travellers returning from a ZIKV endemic country traveling by air transportation and with the commercial transport of mosquito larvae by trucks, ships or aircraft. Although rapid identification of subclinical and/or viremic patients is nearly impossible, a special emphasis should be placed on fumigation at ports and border crossing points and use of larvicides and insecticides must be highlight [36–38].

10.1.3 Introduction of Mosquito Vector-Born in Naive Areas

A modification in the geographical distribution of mosquitos has an important impact on the exposure of naive hosts to that disease. The introduction of an exotic vector or pathogen in an area where it did not previously exist, requires the existence of certain factors that assess whether the pathogen or vector is able to persist in that new environment or not, and how susceptible the local population to the disease is [4, 39, 40].

When a vector moves to another location and changes the suitability of the environment, it can modify the development, survival, and reproductive rates of vectors and pathogens, affecting the intensity of disease transmission and exposure of the population to that disease.

On the other hand, sensitivity and susceptibility to vector-born diseases by population is influenced both by genetic or acquired immune developed in response to previous exposure. In the specific case of ZIKV, naive, non-immune population are especially susceptible to epidemics of acute disease, and that is one of the reasons why this disease has spread so rapidly [4, 41].

For more accurate information about mosquito dynamics, see Chap. 4.

10.2 Risk Due to Mass Gathering Events

The World Health Organization (WHO) defines a mass gathering as "an organized or unplanned event where the number of people attending is sufficient to strain the planning and response resources of the community, state or nation hosting the event" [1, 2]. Mass gathering events meets theoretical ideal conditions for the transmission of infections between people from remote and widespread geographical locations, with potentially different immune responses.

Pilgrimage, sports events, outdoor shows, musical festivals, political or cultural events and other celebrations that congregate crowds in a confined area increases the risk of a range of infectious diseases [3–7]. Travellers to these crowded events

cannot only introduce an infectious disease to a previously naïve area, but can also magnify transmission at the people meeting and further propagate transmission after their return home. This statement has been fulfilled on multiple occasions, as was the case of the transmission of 2009 H1N1 pandemic afterward a large Easter holiday gathering in Iztapalapa, Mexico [6, 8]. Similarly, crowded congregation of population has been associated to the spreading of the Great Pandemic in 1918 and the Asian Flu Pandemic in 1957, creating a global disease outbreak [9, 10].

The paradigm of mass gathering event at risk is the annual Islamic pilgrimage to Mecca and Medina in Saudi Arabia (Hajj), which congregates approximately three million Muslim pilgrims arriving from different parts of the world to Mecca. The outbreak of meningitis 2000–2001 after the Hajj demonstrates the importance of this type of mass events in the transmission of infectious diseases [11–13]. Other example that shows the possibility of dissemination of infectious diseases during a mass gathering event was the congregation in Taizé, Germany, for Christian pilgrimage in 2006, that was followed by primary measles cases identified among unvaccinated persons [14–16].

On the other hand, there are examples in which concentrations of people are not followed by an amplifying of a pre-existing disease: the outbreak of Middle East Respiratory Syndrome coronavirus (MERS-CoV) was at its peak in 2013 just when pilgrimage to Saudi Arabia was started. No cases of this respiratory infection disease were identified during Hajj and Umrah (a minor pilgrimage) during this year, even though some cases were identified during the following years [16, 17]. So probably other different factors must also be present to provide a favourable environment for the dissemination of infectious diseases.

Because of ZIKV outbreak in Brazil and its risk of dissemination, all the alarms were focused on the Olympic games of 2016, held in Rio. Previously, health authorities in Brazil were aware of other vector-borne risk and had already celebrated multiple mass gathering events with no evidence of significant international spread. As an example, during the 2014 FIFA Football World Cup in Brazil, mathematical models estimated 33 cases of DENV (range 3–59 cases) among foreign tourists, of nearly 600,000 of expected visitors [18, 19]. So far, only 3 cases of DENV were reported associated to this sport event [16, 20]. It's postulated that the low numbers of cases finally diagnosed of DENV were the result of a year with an unusually low incidence in Brazil, probably due to a severe drought in 2014, reducing the number of expected cases in visitors. Also, the typical lower temperatures of the months in which the event was held (June and July), contributed to this small amount of cases [21, 22].

Predictions of the risk of acquiring ZIKV during Olympic and Paralympic Games in Rio 2016 were initially difficult to asses. The lack of knowledge of real incidence of the disease, due mainly because of asymptomatic cases were not reported, made accurate estimations difficult to weigh. Based on forecast of between 500,000 and 1,500,000 ZIKV infections (both symptomatic and asymptomatic) [23, 24] the calculated risk during the period of the celebration (between August and September) ranged from 9×10^{-6} to 3×10^{-5}, which represents a risk 15 times lower than that of DENV for that period [25, 26].

Likewise, other mathematical models predicted travel-associated ZIKV risk in visitors to Olympic games in 2016, anticipating between 6 and 80 cases of both asymptomatic and symptomatic cases of total ZIKV infections among travellers attending the Olympics, with between 1 and 16 of them expected to be symptomatic [27, 28].

But by the end of Rio Olympic Games, no cases of ZIKV infection involving spectators, athletes or anyone associated with the Olympics were achieved [29, 30]. The lack of cases associated to this mass gathering event was probably because visitors' exposure level to mosquitos was lower than that of residents (i.e. adequate use of repellents, mosquito net). Also, tourist were likely to confine their stays to areas close to the Olympic Stadium and other mainly touristic, which were previously fumigated and free of mosquito and larvae, avoiding areas on the outskirts of the city, where mosquito density was higher [31, 32].

Other multitudinous event in Brazil is its annual Carnival. During the previous festivities of Carnival 2016 held in February, more than 1 million of visitors stayed at Rio de Janeiro, which represents twice the number expected for the Olympic Games. At that time, risk of ZIKV was highest, as cases reported were at their peak and most of activities were outdoors, increasing the exposure of visitors to mosquitoes. The resulting risk calculated for ZIKV infection for tourists was 36 per million tourists [32, 33]. But after Carnival celebration in 2016, there was no a significant increase of diagnosis over the following months [34, 35].

2017 carnival represents a new opportunity for ZIKV of spread. Although a decline in cases of Zika infection has been reported in Brazil, tourists and visitors are still posed to risk of ZIKV infection.

10.3   Specific Risk of Globalization in Europe

In Europe, multiple imported cases of ZIKV have been previously reported [36–38]. This is of particular concern, as *Aedes* vectors are known to be present, as previously described (Chap. 4). Therefore, returning ZIKV-viremic travellers to European countries may become a source of local transmission in the presence of this suitable vector. Previously, *Aedes* mosquito was implicated in local transmission of CHiKV and DENV in Mediterranean countries [4, 39, 40]. The species have also been responsible for outbreaks of yellow fever in Italy in 1804 [4, 41]. The existence of previous autochthonous arboviriasis transmitted by the same vector, make the infection by ZIKV also feasible in Western Europe at least seasonally, when competent vector species are present. The arrival of summer in North Hemisphere is linked to a peak in mosquito *Aedes* population and a most efficient viral replication, so from June to September climatic influence could also favour the establishment of ZIKV disease in Europe [42].

Different mathematical models have assessed the risk of ZIKV arrival, establishment, and autochthonous in Europe. Estimations of imported cases of ZIKV have been made based on published estimations of 500,000–1,500,000 infections in

Brazil (both asymptomatic and symptomatic) during 2015 [23]. Models predicts between 508 and 1.778 imported cases, particularly in France, Portugal, and Italy. Of these, approximately 20% would likely be symptomatic so it´s expected between 116 and 355 symptomatic ZIKV infections into all European countries in 2016 [38].

Once ZIKV arrives, a competent vector must be present to maintain the disease. The competence of European *Aedes* mosquitoes (both *Ae. aegypti* and *Ae. albopictus*) as an efficient vector for the currently circulating Asian genotype of ZIKV has also been assessed. Despite the fact that *Ae. albopictus* plays a central role in the transmission of other arboviruses in Europe, it's suggested that this mosquito is not good enough to maintain local transmission of ZIKV compared to CHIKV and maybe, DENV [43], concluding that there is low risk for ZIKV expansion in most parts of Europe, with the possible exception of the warmest regions bordering the Mediterranean coastline, and specially Madeira. In this specific autonomous region of Portugal two main factors are present: the presence of *Ae. Aegypti* (which is considered the most competent vector for ZIKV), introduced in 2005 [44] and the close contact with Brazil, with whom it maintains active commercial exchanges and people shares the same language [43].

Although the amount of travellers arriving from the Americas to Madeira is low compared to other cities in continental Europe, the presence of *Ae. Aegypty*, an extended season associated to high vectorial activity and the hazardous outbreak of DENV fever in 2012 [45], stress the potential for autochthonous transmission of ZIKV in that Portuguese location [42].

Other factor that must be considered is the numbers of travellers returning to Europe from areas in the Americas with known ZIKV activity during the period of higher vectorial capacity. It is estimated than between 475,000 and 715,000 travellers will arrive from endemic areas for ZIKV to the main central European capitals from May to October, of the total of population at risk of nearly 800 million central Europeans. In July and August, (when temperatures and vectorial capacity in Europe are peaking), 15,7% of this population might reside in areas with known occurrences of *Ae. albopictus* (i.e. 241 million of centre Europeans). European countries with a large percentage of their population living in areas where basic reproduction number (Ro) is over 1 in August include Albania (83% of population at risk), Italy (78%), Croatia (44%), France (20%), Greece (25%), Montenegro (39%), Slovenia (28%) and Spain (19%) [42], so health authorities of those specific locations should be aware of current risk.

Other mosquito species as *Culex*, which is present in central Europe that are able to transmit other arboviruses, has proved not to have vector competence for ZIKV [46].

Taking all these facts under consideration and adding that the average temperatures of s of most areas of Europe the possibility of large outbreaks of ZIKV in most areas of Europe, at least for the immediate future, seems to be irrelevant.

Imported cases of Zika virus have been documented in Europe and are expected to continue, not only because the high proportion of travellers arriving from the most affected regions to Europe. Sexual transmission of Zika has been also reported in European citizens without a previous travel to endemic region [47, 48].

There are documented precedents of containing an arbovirus disease outbreak in Europe. In 2014, after an outbreak of CHiKV in Montpellier, a successful integrated prevention and response programme was performed. Although the absence of immediate mosquito control treatment near the primary case's residence (because the vector was initially not identified) and a lack of awareness of this disease among health professionals facilitated the spread of the infection up to 12 cases. However, there was a quick response following the alert. Subsequently after the detection of the cases, French authorities focused on epidemiological and Entomological investigations and stressed vector control treatments, which played a part in prompt containing the outbreak [49].

EU countries must be prepared for this new threat. This requires capability to detect and diagnose cases early, perform systematic and regular surveillance, and adapt resources to sustain enhanced mosquito control. Clinicians should be aware to enable early detection of ZIKV cases and there must be sufficient and validated laboratory capacity for virus detection, virus identification and serological testing. International and local guidelines can help clinicians on how to handle suspicious cases, how to confirm the infection and how to report suspected and confirmed cases. In case of autochthonous ZIKV detection, public authorities should perform surveillance and provide adequate resources to sustain enhanced mosquito control. Also, information should be promptly circulated to all health professionals, public health services and other sectors. Failure to do so could lead to the possibility of spreading more extensively, resulting in greater costs for vector control and health care for infected people [50].

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