Editorial

Zika virus – the 21st century traveller

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Zika virus (ZIKV) has emerged from the shadows to become one of the hottest topics of public discussion amongst health practitioners and lay people alike, surpassing most of its viral relatives in notoriety. At first, ZIKV infection was a geographically distant problem but has this issue, now, migrated much closer to home?

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ZIKV is an arbovirus of the genus Flavivirus, along with other notable viruses such as dengue, chikungunya, West Nile, Japanese encephalitis and yellow fever viruses. Although only surfacing in the media recently, ZIKV was actually first described in April 1947 in the Zika Forest near Entebbe, Uganda. It was here that during the Rockefeller Foundation's research studies on its relative, the yellow fever virus, ZIKV was isolated from a febrile sentinel Rhesus monkey (*Macaca mulatta*). Like other flaviviruses, ZIKV is mainly transmitted by mosquitoes. Among the various mosquito species, Aedes mosquitoes appear to be the most important vector for ZIKV transmission, with the main vectors in humans being *Ae. aegypti* and *Ae. albopictus*. Aedes species present special difficulty to vector control agencies, mainly because they can reproduce in extremely small amounts of water and their eggs are extremely hardy. Furthermore, both these species are known to thrive in proximity to people and are thus considered to be important vectors in the urban transmission cycle of ZIKV of the recent large-scale epidemics. Moreover, from places with established autochthonous transmission, viraemic travellers have the capacity to introduce ZIKV into new countries, where Aedes mosquitoes may become infected and perpetuate local transmission cycles. Therefore, the potential for autochthonous transmission in countries where Aedes vectors are present is real and is causing major concern given the speed at which the disease has recently spread. Non-vector-borne transmission routes of ZIKV have also been confirmed, including via blood transfusion as well as through sexual contact.

The first human cases of ZIKV were first described in 1952 in Uganda and Tanzania. Subsequently, only isolated cases in Africa and Asia were reported, with a total of less than 20 cases reported in humans in the first 60 years after discovery. This could have been partly because most patients with ZIKV infection are asymptomatic and unnoticeable. The exact ratio of symptomatic to asymptomatic infection is unknown, but about an estimated 20-25% of people infected with ZIKV develop symptoms of "Zika Fever". These symptoms include a low-grade fever; an erythematous, maculopapular down-spreading rash; retro-orbital headache; bilateral non-purulent conjunctivitis; myalgia and arthritis/arthralgia with periarticular oedema of the small joints of hands and feet.

It was only in 2007, in Yap Island, Federated States of Micronesia, that the first major outbreak of ZIKV outside Africa occurred. This resulted in an estimated 73% of the population above 3 years being infected within 4 months. Several explanations have since been suggested for the outbreak. The lack of population immunity could have precipitated the outbreak and the absence of outbreaks in Africa and Asia could have been a result of pre-existent immunity from regular exposure to the endemic ZIKV. Another possibility may be due to under-reporting, as clinical presentation is similar to a mild illness associated with Zika, dengue, and chikungunya viruses, the three of which co-circulate through their common vector. Subsequently a 2013 outbreak in French Polynesia affected more than 11.5% of the inhabitants – an estimated 30,000 persons. Subsequently, more outbreaks of ZIKV infection occurred in New Caledonia, Easter Island and the Cook Islands, indicating rapid spread of the virus in the Pacific area.

By February 2015, north-eastern Brazil was next to report increased outbreaks of exanthematic disease affecting thousands of patients. The Pan American Health Organisation (PAHO) issued an alert in May 2015 confirming the presence of ZIKV. In fact, the country has since become the epi-centre of the current ZIKV epidemic which rapidly spread across the Americas.

As at the 10th March 2017, vector-borne ZIKV transmission was reported in 84 countries, 59 of which reported their first transmission since 2015 and with some also being included in the 13 countries with evidence of person-to-person transmission. Moreover, Australia, Japan and several European countries, have confirmed cases of Zika virus in travellers returning from countries with ongoing ZIKV transmission.

Association with Microcephaly and other Neurological Complications

Initially, ZIKV infection was considered a benign illness, even less severe than dengue or chikungunya. However, following a systematic review of the scientific literature up to 30th May 2016, on 7th September 2016, WHO concluded that ZIKV infection is a trigger of Guillain-Barré syndrome (GBS) and is a cause of congenital brain abnormalities, manifesting as microcephaly, in the unborn foetus.

In the French Polynesia outbreak between October 2013 and April 2014, 42 patients were admitted to hospital with GBS. This represented a 20-fold increase in GBS incidence, suggesting that ZIKV was the cause of this syndrome. As of 10th March 2017, 23 countries and territories worldwide have reported an increased incidence of GBS and/or laboratory confirmation of ZIKV among GBS cases.

In Brazil, by the second half of 2015 alone, more than >2700 cases of microcephaly were reported, which were suggested to be linked to ZIKV infection, marking a dramatic increase over the 150 microcephaly cases recorded in 2014. Moreover, in October 2015, Brazilian authorities declared a national public emergency due to this significant 20 fold increase of reported microcephaly in ZIKV-affected areas, including three foetal deaths. As of 10th March 2017, microcephaly and/or central nervous system malformations potentially associated with ZIKV infection or suggestive of congenital infection had been reported in 31 countries.

Zika in Europe

In May 2016, the WHO European Region released an interim risk assessment which assessed each European country's risk for a ZIKV outbreak. The likelihood of local ZIKV transmission was based on the presence and climatic suitability for *Ae. aegypti* and *Ae. albopictus*, and factors related to the introduction and onward transmission of ZIKV, such as a history of previous arboviral outbreaks, shipping and air connectivity, population density and urbanisation. A country capacity score was then derived by evaluating integrated vector management, clinical surveillance, laboratory capacity and emergency risk communication.

The most important factor in the assessment was ultimately the presence of the vectors. *Ae. albopictus* is considered to have lower vector capacity than *Ae. aegypti* for transmitting arboviruses, including ZIKV; however, *Ae. albopictus* is established in many countries in the

European Region and has been implicated in recent arboviral outbreaks in continental Europe.

Three localized geographical areas with established *Ae. aegypti* populations were categorized as having a high likelihood for transmission: Madeira Island, the Black Sea coastal area of Georgia and the Black Sea coastal area of the Russian Federation. Eighteen countries, mainly concentrated in Southern Europe, were classified as having a moderate likelihood, due to established populations of *Ae. albopictus*. Malta was classified as moderate likelihood, along with France and Italy. Consequently, it is predicted that future climate trends will increase the risk of establishment of *Ae. albopictus* in northern Europe, due to wetter and warmer conditions.

Another factor assessed was the history, if any, of past arboviral outbreaks. ZIKV has essentially the same epidemiology and mosquito vectors in urban areas as dengue virus and chikungunya virus. For example, from 2012 to January 2013, the autonomous island province of Madeira, Portugal, reported its first dengue outbreak with 2168 dengue cases. In fact, Madeira is now classified as the geographical area at highest risk. Furthermore, a potential for arbovirus outbreaks in Italy was demonstrated by chikungunya virus outbreak in the province of Ravenna, region of Emilia Romagna, in August 2007.

Currently, imported cases are being reported in several European countries. The European Centre for Disease Prevention and Control (ECDC) is collecting data on cases imported into the European Union and the European Economic Area from the media and official government communications. As of 1st March 2017, ECDC recorded 2141 cases in 21 countries, including 108 in pregnant women. These data are important, as returning travellers who are infected with Zika virus could initiate local transmission if there are established competent vectors. As of 1st March 2017, no autochthonous case of Zika virus transmission had been reported in the WHO European Region but 7 European countries have reported person-to-person ZIKV transmission mainly through sexual contact.

Zika in Malta

Until the 27th March 2017, Malta had two confirmed cases of imported ZIKV infection from residents travelling to countries with active transmission. Even though, no direct air connections currently exist with any countries with active Zika transmission, Malta does have direct air routes to several major hubs throughout Europe and the Middle East from where onward travel to Zika affected countries is possible. Furthermore, the multiple global shipping connections could be additional introductory routes. If ZIKV reaches our island, the locally established vector *Ae. albopictus* living amongst our highly dense population, places Malta at moderate risk for further ZIKV transmission. In view of the potential serious complications of ZIKV infection, especially during pregnancy, it is imperative that we invest major efforts to prevent the establishment of ZIKV in Malta.

The currently introduced measures include entomological surveillance and vector management plans. In addition, clinical surveillance for rash and fever in people returning from high risk areas exists and ELISA and PCR laboratory confirmatory testing is available.

However, being a small island, we should be even better able to prevent this serious public health threat from becoming a reality. In fact, major efforts are necessary for Malta to strengthen its vector control activities, with improved entomological surveillance and source reduction strategies through public education and awareness campaigns. Moreover, local options to decrease vector numbers include diminishing the habitats of *Ae. albopictus*. Notably, in Brazil, vector reduction strategies have involved the release of genetically modified mosquitoes, such as Wolbachia-infected and Oxitec mosquitoes which eliminates their ability of transmitting viruses. It has yet to be proven if these interventions can result in a reduction of the associated vector-borne diseases in humans.

Lastly, it should be of utmost importance to increase awareness amongst Maltese individuals, especially those who are pregnant, to avoid travelling to endemic areas. Returning travellers from the 2016 Summer Olympics held in Rio de Janeiro, Brazil created a potential for ZIKV introduction in Malta. In circumstances where travel cannot be avoided, more up-to-date advice on protection against ZIKV should be more readily available, including methods of avoiding mosquito bites and preventing ZIKV acquisition during sexual activity. Barrier methods during sex as well as avoiding blood donation for at least 1 month from return have to be emphasised. Additionally, pregnant women whose sexual partners live in or travel to endemic areas need to ensure appropriate barrier methods during sexual intercourse or the abstention from sex during the pregnancy. Screening of persons returning to Malta from Zika affected areas is a pragmatic approach in preventing the introduction of the virus in the local *Ae. albopictus* population through appropriate isolation measures.

On 18th November 2016, at the fifth meeting of the Emergency Committee (EC), the Director-General of the WHO declared the end of the Public Health Emergency of International Concern (PHEIC). However, ZIKV and its associated consequences remain a significant enduring public health challenge. The potential of the ZIKV to spread geographically to areas where competent vectors are present remains a concern and appropriate vigilance needs to remain in place to prevent introduction of this virus to Malta.

Cover Picture:
'Old Farm house'
Ink
By Daren J Caruana

Daren J. Caruana has an interdisciplinary background, having read Biochemistry at the University of Warwick, PhD in Electrochemistry at the University of Southampton, then after a spell at the Department of Biomedical Sciences in Malta he spent a postdoctoral fellowship at the Chemical Engineering department at the university of Texas at Austin working with Prof. Adam Heller. He was awarded the Marlow Medal and prize (2004) for the development of gas phase electrochemistry and is now a Reader in Physical Chemistry at the Department of Chemistry at UCL. His research interests are focused towards understanding the electrochemical properties of plasmas and extending electrochemical science to the gas phase through new applications, including developing new analytical methodology for bioaerosols.