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ZIKA – AN EMERGING INFECTIOUS DISEASE. THE RISK ASSESSMENT FROM POLISH PERSPECTIVE

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ABSTRACT

In the last years, attention has been paid to Zika virus (ZIKV) infection, the emerging vector-borne disease. It is responsible for major outbreaks in Africa, Asia and, more recently, in previously infection-naïve territories of the Pacific area, South America and Caribbean. The etiology, epidemiology, transmission, and clinical manifestations of ZIKV disease are discussed, along with the diagnostic possibilities in the aim to assessing the risk of its introduction to Poland. ZIKV is spread by *Aedes* mosquitoes which are not found throughout Poland. The prevention strategies adopted by national public health authorities should be based on a surveillance of imported cases and on increasing awareness among healthcare professionals and travelers. Due to a large number of asymptomatic ZIKV infections and limitations in the availability of diagnostic tests, monitoring based on laboratory results is likely to be unreliable in Poland. There are no requirements to report ZIKV infections to the European Centre for Disease Prevention and Control. Nevertheless, the global epidemic continues to spread, and despite travels of Poles to countries in which *Aedes* mosquitoes are active, Polish sportsmen will be travelling to Brazil in August 2016 to participate in the Olympic Games, the will also be true of the many fans who will follow them; therefore imported cases of ZIKV infection are possible. As the awareness of the infection risk will increase among medical staff and travelers, the number of suspected cases of travel-related ZIKV infections may rise in Poland. Medical staff should be informed where and how to report such cases. Thorough surveillance, adequate assessment of possible threats, action plans, rapid and effective intervention development, spread of up to date information of ZIKV, as well as other emerging or re-emerging infectious pathogens can play a key role in guaranteeing population health.

Key words*: Zika virus, infection, introduction of Zika virus to Poland, risk assessment, prevention*

INTRODUCTION

Despite optimistic prognoses made in the late 1970s, that "the time has come to close the book on infectious diseases" (1), we are witnessing an aggressive march of the new infections - almost 90 new pathogens have been identified since then; more than two thirds of them are zoonoses (2).

Recently, particular attention has been focused on mosquito-borne diseases caused by emerging viruses (arboviruses), such as dengue, West Nile, and chikungunya (2,3). The latest in this list is the Zika virus (ZIKV), first identified in the Zika Forest near Lake Victoria, Uganda, in 1947 (4) in rhesus monkeys through a monitoring network of sylvatic yellow fever. It was subsequently found in the *Aedes Africanus* mosquito captured in the same forest (5). The first cases in humans were identified in 1952 in Uganda and the United Republic of Tanzania, followed by Nigeria in 1954 (6). Up until 1981, serologic evidence of human ZIKV infection was reported from other African countries such as Egypt, Central African Republic, Sierra Leone, and Gabon, as well as parts of Asia (India, Malaysia, the Philippines, Thailand, Vietnam, Indonesia) (7). However, for decades ZIKAV remained a rather lesser known pathogen, limited to a narrow equatorial belt crossing Africa, reaching across to Asia which points to two ZIKV lineages: African and Asian (3,8-9). Serological surveys in Africa and Asia indicate a most likely silent ZIKV circulation with the detection of specific antibodies in various animal species (rodents and large mammals such as elephants, hippos, lions, water buffaloes, wildebeest, zebra, impala, goats, sheep, orang-utans) (8,9).

In 2007 an outbreak caused by this pathogen was reported in a new geographical area - the south-western Pacific Ocean (Yap Island, Micronesia), marking the first detection of ZIKV beyond Africa and Asia (9). More recently, between 2013 and 2015, several significant outbreaks were notified on islands and archipelagos from the Pacific region including a major outbreak in French Polynesia (7). In 2015, several countries in Central and South America (with widespread outbreaks reported in Brazil and Columbia), the Caribbean, as well as in North American Mexico and African Capo Verde, have confirmed autochthonous virus transmission, indicating rapid geographic expansion of ZIKV. Cases have also been reported in Europe (Germany, France, Italy, the UK, Ireland, Denmark, the Netherlands, Spain, Austria, Finland), in Israel, the US, Canada, Japan and Australia, although isolated; all were imported from endemic areas, Fig. 1 (10-12).

On February 1st 2016 WHO declared Zika virus (ZIKV) infection as a *Public Health Emergency of International Concern* due to the rapid increase in the number of new cases, the broad geographical distribution of infections, the lack of specific commercial serological tests, specific treatment or preventive vaccines and the absence of population immunity in newly affected countries, as well as the possible linkage of microcephaly in babies exposed to ZIKV *in utero* (13-15). Since February 2016 local transmission has been confirmed in more than 30 countries (16, Fig.1). According to WHO estimates, ZIKV has infected 1.5 million people in the last few years; next 3-4 million could become infected in the next year (13,14).

To date, there has not been a single case of ZKV identified in Poland. However recent expand of ZIKV infection in various regions of the world underscore the potential for the virus to spread further beyond the Americas, not only in those territories where the vector is present. Given the worldwide spread of malaria, chikungunya or dengue, associated with globalization and universal access to transportation - there is now the potential risk of the importation of ZIKV cases to any part of the world.

The aim of this article is to discuss currently available information on ZIKV in the context of a risk assessment from the perspective of Poland, regarding the possibilities of importing this infection, as well as the role epidemiological surveillance should play in a rapid case detection and response.

Analysis of medical literature regarding ZIKV infection was performed, based on articles published between 1947-2016, accessible in MEDLINE and Google Scholar, as well as on dedicated World Health Organization, Centers for Disease Control and Prevention (CDC) and European Centre for Disease Prevention and Control (ECDC) websites.

ETIOLOGY AND TRANSMISSION

ZIKV is an enveloped arbovirus of the Flaviviridae family, *Flavivirus* genus. It is a single-stranded RNA virus, containing 10,794 nucleotides encoding 3,419 amino acids, with a positive-polarity RNA genome of approximately 11 kb in length. The genome includes its complete open reading frame (ORF) sequence. The ORF encodes a polyprotein that is cleaved into three structural proteins and seven non-structural proteins (17,18).

ZIKV is transmitted to people through the bite of an infected mosquito from the *Aedes* genus (3,7-9,12). These species bite during the day (especially in mid-

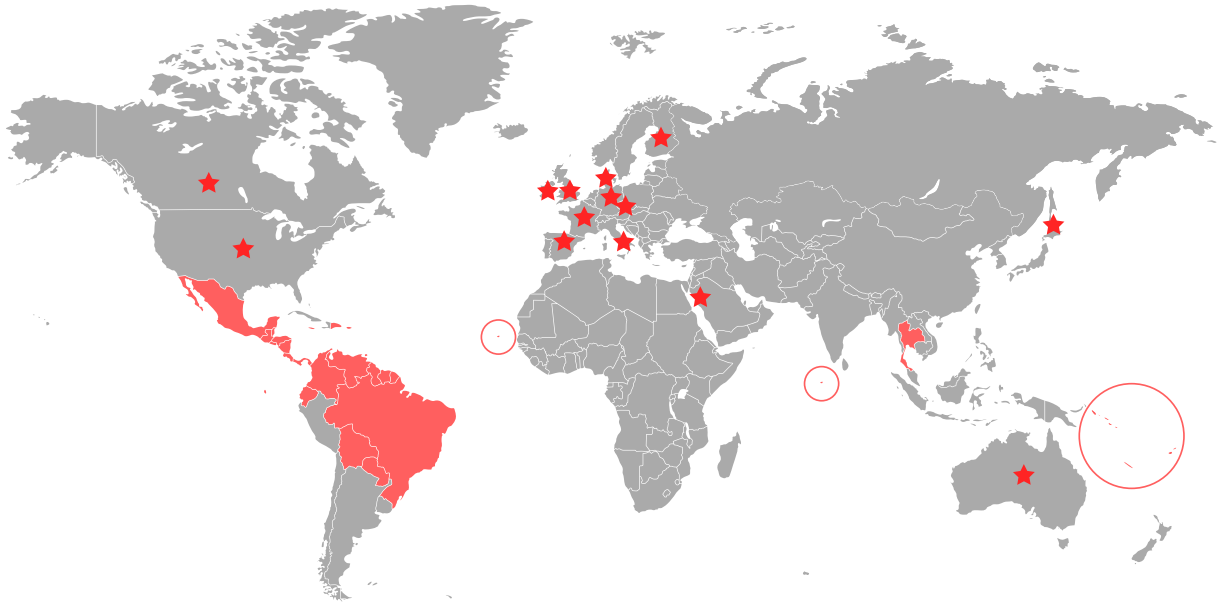

Fig. 1. Countries or territories with reported confirmed autochthonous cases of Zika virus infection in the past 9 months and countries with imported cases (marked with stars); b*ased on data reported by 5 February 2016, ECDC (13)*

morning and between late afternoon and twilight). Since the first report of *Aedes albopictus* as a potential vector of ZIKV (2007), other *Aedes* species *(Ae. aegypti, Ae. Africanus, Ae. polynesiensis, Ae. dalzieli*, *Ae. unilineatus, Ae. vittatus* and *Ae. hensilli*) have been reported as vectors of ZIKV, which may point to a molecular evolution of the pathogen (3,7,19). This implies that the increasing presence of this vector world-wide could influence the appearance of new ZIKV epidemics, with a growing risk for urban areas (16,17).

Additional modes of transmission have been identified. There is a potential risk of ZIKV transfusion-derived transmission (7-9,11,12). Perinatal transmission can occur most probably by trans-placental transmission or during delivery when the mother is infected; ZIKV has been found in placenta, amniotic fluid and brain tissues of foetuses and newborns (9,11,12,20). A high ZIKV RNA load and replicative ZIKV found in semen more than two weeks after recovery which support the hypothesis that it can be transmitted by sexual intercourse. Possible cases of sexual trans-mission of ZIKV have been reported (21,22).

In 1964 the first well-documented report of human ZIKV infection was described by Simpson (23) (of note, it was his own occupationally acquired ZIKV illness). The incubation period ranges between approximately 3-12 days (9,12,23). Disease is usually a mild or asymptomatic (60-80%) dengue-like disease characterized by a short-lasting self-limiting febrile illness of 4–7 days duration without severe complications, with no associated fatalities and a low hospitalization rate (3,7,9,12). Most frequently patients present mild fever, arthralgia (small joints of hands and feet), muscle aches, headache, abdominal pain, retro-orbital pain, prostration, oedema, lymphadenopathy, non-purulent conjunctivitis/conjunctival hyperaemia, and cutaneous maculopapular or papular rash which starts on the face and then spreads throughout the body; less frequently, gastro-intestinal signs can be present (3,7,9,11,14,23). Therefore, ZIKA can be misdiagnosed in the acute phase due to non-specific influenza-like symptoms. In almost 70 years of observation, ZIKV has not been noted to cause hemorrhagic fever or death (3).

Auto-immune or neurological complications, such as Guillain-Barré syndrome (GBS), have been observed (9,12,14,24). Microcephaly in foetuses and newborns from mothers exposed to ZIKV in the two first trimesters of the pregnancy were observed during Zika disease outbreaks raises concerns (12,14). However, further research is needed to establish a causal link (3,12,14).

The viraemic period of ZIKV infection appears to be short, allowing for direct virus detection during the first 3-5 days after the onset of symptoms (25). The diagnosis is based on the detection of viral RNA genome from clinical specimens in acutely ill patients with the use of RT-PCR (reverse transcription polymerase chain reaction) and virus isolation or the detection of specific ZIKV IgM/IgG antibodies from blood samples through serological tests (enzyme-linked immuno-sorbent assay [ELISA] or immunofluorescence) (11,12,25,26). The latter may be difficult as the virus can cross-react with other flaviviruses (dengue, West Nile, yellow fever) (11). It is recommended to analyse paired serum specimens, collected at different stages of disease. Of note, there are only a few laboratories able to perform an ELISA for ZIKAV; no licensed commercial test for ZIKV diagnosis is currently available (11,12,26). Serological results should be interpreted according to the vaccination status and previous exposure to other flaviviral infections (9). Urine samples are also suitable for diagnosing ZIKV infection, as viral RNA is detectable in urine up to 10 days after the onset of the disease at a higher load than in serum (26). Differential clinical diagnostic should be considered as well as co-infection with other mosquito-borne diseases such as dengue fever, chikungunya and malaria.

TREATMENT AND PREVENTION

Currently there is no vaccine or preventive drug (3,9,12). The management is based on frequent monitoring, bed rest and symptomatic care, such as fluid intake, pain relief, fever reduction and anti-histamines for pruritic rash (3,9,12). Treatment with acetylsalicylic acid and no-steroidal anti-inflammatory drugs was discouraged because of a potential increased risk of haemorrhagic syndrome reported with other flaviviruses as well as the risk of Reye's syndrome after viral infection in children and teenagers (27).

Mosquitoes and their breeding sites pose a significant risk factor for ZIKV infection. Prevention and control relies on reducing mosquitoes through source reduction (removal of yard and household debris and containers that provide breeding sites, such as buckets, flower pots or tiers) and reducing contact between mosquitoes and humans with the help of physical barriers such as screens, closed doors and windows, or mosquito nets when air conditioning is not available (3,9,12,27). Safeguards include also wearing long-sleeve shirts and long pants (preferably light-coloured), especially during the hours of highest mosquito activity and using insect repellents. Special attention should be given to those who may not be able to protect themselves adequately, such as young children or the elderly (9,12,27).

ZIKV is spread by *Aedes* mosquitoes which are not found throughout Poland where it is too cold for them to survive (28, Fig.2). Therefore, as a ZIKV-vectors free country, there is no need for monitoring of vector species and humans to identify cases of indigenous ZIKV

Fig. 2. Current known distribution of invasive *Aedes albopticus* mosquito in Europe at regional administrative level; adapted from (27).

infection in order to take measures aimed at reducing the risk of transmission by the vector. At the moment, the prevention strategies adopted by national health authorities and institutions should be based on a surveillance of imported cases and on increasing awareness among health care professionals and travelers. Due to limitations in the diagnostic capacity, a large number of ZIKV infections would remain unrecognized; monitoring based on laboratory results is likely to be unreliable in Poland, as well as in the other EU countries. There are no requirements to report ZIKV infections to ECDC (12). Nevertheless, according to the forecast made by prominent epidemiologists, as the epidemic continues to spread, and the awareness of the risk of infection would increase among medical staff and travelers, we might expect an increase in the number of suspected cases of travel-related ZIKV infections in Poland. Medical staff should be thoroughly informed where and how to report such cases.

Imported cases of ZIKV infection in Poland are possible due to constant international travel. According to the Ministry of Sport and Tourism estimates, 4.5 million Poles over 15 years of age travelled abroad in the first six months of 2015, including those countries in which *Aedes* mosquitoes were active; this is an increasing trend (29). This refers to countries around the Mediterranean, and the Black Sea, but also Turkey, the Azores, the Canary Islands and Madera, which are popular destinations regarding Polish travelers (9,12,29). Madeira is of a special concern because of the close relationship with Brazil and Venezuela where ZIKV is currently present, and the dengue epidemic, four years ago, which demonstrated the conditions for mosquito-borne outbreaks (30). Of note, despite typical touristic travels of Poles to various destinations, a relatively large group of Polish sportsmen will be travelling to Brazil in August this year to participate in the Olympic Games, the will also be true of the many fans who will follow them.

To actively detect possible cases of ZIKV infection medical stuff, especially in GP and travel health clinics, should be supported by recent information on actual epidemiological situation regarding ZIKV infection, as well as symptoms and diagnostic possibilities to increase their awareness so that they can include it in their differential diagnosis in the cases of travelers returning from epidemic areas and presenting fever and/or maculo-papular rash (3,12). It should be also stressed that, for a Polish doctor, current epidemiological situation and clinical manifestation should be the main criteria to suggest ZIKV infection. The initial diagnosis

may be difficult and pose problems as the symptoms are similar to other arbovirus infections, such as dengue or chikungunya (2,3). It is recommended to refer suspected ZIKV cases to infectious disease specialists, which are most experienced at dealing with patients infected with other arboviruses, described above. Awareness of possible ZIKV health threats should be also increased among obstetricians who should be advised to inquire about recent travel when caring for pregnant women and to thoroughly monitor female patients returning from *Aedes* affected areas. Pediatricians should be informed they should investigate for babies presenting with congenital central nervous system malformations, and microcephaly. Neurologists and other health care professionals should inquire about recent travel patients presenting with GBS (12).

Although laboratory testing for people who have recently travelled abroad and have a clinical history of ZIKV infection should be recommended, Zika-specific tests are not yet available in Poland (11,12,26). However, blood samples of suspected cases could be further investigated to differentiate ZIKV infection from other arboviral infections (i.e. dengue) for which tests are available (31). Strengthen laboratory capacity to confirm suspected ZIKV infections in the EU is an urgent need (9,12,14).

The recognition of newly described infectious disease agents poses problems for specialists in transfusion medicine who have an obligation to ensure the safety of blood products (11). Blood donated by viraemic travelers returning from affected areas could be the source of the ZIKV (11,12,32). Therefore, according to the ECDC, in Poland, like in the other European countries, blood authorities need to be vigilant regarding the epidemiological situation and should consider deferral of donors with travel history to the outbreak areas, in line with measures defined for dengue virus (12).

ZIKV was detected in semen more than two weeks after recovery from an illness (22). Therefore, a need to defer potential semen donors for 28 days after returning from *Aedes* affected areas should be foreseen in every case of a tissue establishment for assisted reproduction (12).

Standard WHO recommendations regarding disinsection of aircraft and airports should be implemented (13,14).

Since people travel to warmer climates and countries where ZIKV is found, Polish residents should be urged to take preventive measures when traveling in affected areas. Broad information campaigns in the media could be a useful education platform for the whole population. Travellers, especially children, and those with immune disorders or severe chronic illnesses, should be asked to consult their doctor to receive recommendations on protection from mosquito bites before travelling. Adequate institutions, such as the National Sanitary Inspectorate, the Ministry of Health, the Ministry of Foreign Affairs, the National Institute of Health, and Polish Tourism Office following ECDC, American CDC and WHO recommendations (12,14,15,33), should announce (e.g. through their updated websites) that travelers showing symptoms compatible with ZIKV disease (as well as dengue or chikungunya) within three weeks after returning from an affected area should contact their healthcare provider. In addition, pregnant women who have travelled to areas with ZIKV transmission should mention their travel during antenatal visits to be monitored appropriately.

Pregnant women in any trimester should be informed to consider postponing travel to territories where ZIKV transmission is possible; women who are considering pregnancy should consult with their physician before traveling to these areas, and if they do, they should strictly follow precautions to prevent mosquito bites (wear appropriate clothing – as described above, use insect repellents with at least 20% DEET, and permethrin-treated clothing, remain in air-conditioned areas, use a bed net when sleeping in an area exposed to the outdoors) (12,14,15,33).

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