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Review scientific paper

VECTOR ZOONOSES THAT MAY THREAT THE REGION OF SOUTHEAST EUROPE

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Summary

The first Faculty of Veterinary Medicine was founded in France (Lyon) in 1762, in order to prevent the cyclical waves of rinderpest at the beginning of the 18th century in Europe. Three centuries later, infectious diseases, including zoonoses, cannot be eradicated in the regions where they appear enzootically, and also thair spread is a real threat to distant regions of the world. A special segment of the infectious diseases studies is focused to the group of zoonoses that are transmitted by vectors. There are numerous infectious diseases of animals and humans, whith the causative agents that are transmitted by insects and arthropods, and in some cases, vectors appear as real hosts and reservoirs of zoonotic agents. Until two decades ago, the appearance of West Nile fever in regions of the world where this zoonosis was enzootic and endemic (for example, the African continent), did not attract the attention of epizootiologists and epidemiologists. However, this infectious disease has caused a disease in a numerous people in our region over the past twenty years, and in some cases the outcome was fatal. Analogous to the example of West Nile fever, it can be assumed that a greater number of vector-borne zoonoses are practically "knocking on the door" of the Southeastern Europe region. That region can be considered a buffer zone, where there are more or less distant regions to the south and east, where until nowadays "exotic" zoonoses appear enzootically, and from which direction we can expect the penetration of vectors, and the infectious diseases they transmit. The potential for the transmission of vector-borne zoonoses primarily refers to diseases transmitted by insects and arthropods. In the case of insects, a sudden outbreak could be expected, for example, of Rift Valley fever, *Chikungunya* virus infection, Japanese encephalitis or Yellow fever. The fight against such zoonoses should primarily be based on vector control. For some

of these zoonoses, vaccines have already been developed for use in human (e.g. Japanese encephalitis) and veterinary (e.g. West Nile fever) medicine. In the case of zoonoses transmitted by arthropods (Crimean-Congo hemorrhagic fever, tick-borne encephalitis), it is expected that the infection will spread slowly but steadily, whereby diagnostic tests and the application of methods of monitoring the presence in animal species that can be indicators of the disease are of more importance. The paper presents the basic mechanisms in the transmission of vector-borne zoonoses as well as certain infectious diseases transmitted by insects and arthropods, which have a significant potential to threaten the region of Southern and Eastern Europe.

Key words: Epizootiology, vector infections, arboviruses.

INTRODUCTION

Vectors, in the broader sense of the term, mean living carriers of infectious diseases in populations of susceptible vertebrate species. That is the epizootiological (epidemiological) interpretation of the term. However, of greater importance is the definition of vector in the narrower sense that refers to insects and arthropods as carriers of viruses, bacteria and protozoa. They are most often insects of the *Diptera* order, which includes mosquitoes (*Culicidae*), sand flies (*Psychodidae*) and hematophagous flies (*Ceratopogonidae*). In some cases, black flies (*Simuliidae)* can also serve as carriers of diseases. In addition to insects, as vectors in the epizootic and epidemiological sense, acarinae, subclass *Acari*, class *Arachnida*, i.e. ticks are of great importance. The vast majority of infectious diseases that are transmitted by vectors (vector infections) are caused by viruses that, due to the fact that they are transmitted by arthropods, are classified in the so-called Arbovirus group (Arboviruses: Arthropod-borne viruses) (Tsai and Chandler, 2007). These viruses can be transmitted vertically, in vector populations. However, in most cases their maintenance in nature depends on horizontal transmission between vertebrates, via vectors. Hence, it can be said that arboviruses are significantly different from other viruses whose maintenance in nature depends only on direct transmission in the population of a susceptible species.

Arboviruses consists of over 500 viruses, of which over 100 can infect humans, and over 40 types of viruses cause infection in animals, but the list is not final (Karabastos, 1985). The most important arboviruses that infect humans and animals belong to the RNA viruses in the families: *Togaviridae*, *Flaviviridae*, *Bunyaviridar*, *Reoviridae* and *Rhabdoviridae*. Only one DNA virus belongs to arboviruses, and it is the causative agent of African swine fever (*Asfarviridae*). The high prevalence of

RNA viruses in the group of arboviruses is explained by the characteristics of the genetic material. Namely, the RNA genome varies significantly and is able to adapt to different replicative conditions and mechanisms that prevail in hosts that are phylogenetically and oncogenetically very distant, such as vertebrates and vectors (Beaty et al., 1988).

Human arboviruses are classified according to disease characteristics: systemic febrile diseases, encephalitis, and hemorrhagic fevers. In veterinary medicine, arboviruses cause diseases with multiple symptoms and forms, but even in this case encephalitis and hemorrhagic syndromes are the most common (Bres, 1988).

In relation to the type of vector, it can be said that most arboviruses transmitted by ticks cause encephalitis. The most important viruses of this category that cause epidemics and epizootics are togaviruses, alphaviruses, flaviviruses and bunjaviruses. The first virus for which vector transmission was proven in the 17th century was the cause of Yellow fever. It is a disease that still appears today (South America and Africa) in the form of sporadic and seasonal epidemics despite the existence of effective vector control measures (mosquitoes) and an effective attenuated vaccine (Ludwig and Iacono-Connors, 1993). Dengue, a vector-borne zoonosis that was first mentioned in 1907, still causes illness in hundreds of thousands of people in tropical regions (Monk, 1994). Venezuelan equine encephalitis has caused mass encephalitis in horses and humans from the 1920s to the present day (Rico-Hesse et al., 1995), despite the existence of an effective vaccine for horses. Ross River virus causes epidemics of arthritis infecting up to 68% of the human population on some islands of the Pacific region (Walton and Grayson, 1988). Compared to alphaviruses and flaviviruses, most bunyaviruses cause mild infectious diseases in humans. However, the virus that causes Rift Valley fever causes severe disease in animals and humans with a high mortality rate. Historical data indicate that this virus appeared in Africa after 12 years of "rest" causing epizootics and epidemics (Arthur et al., 1993). The above data indicate that arboviruses will continue to appear in the future as the cause of vector-borne zoonoses, which certainly emphasizes the need for further research into the characteristics of the disease "*per se*" as well as the mechanisms of these infectious diseases in general.

Cycles of infections caused by arboviruses

These are the cycles thanks to which arboviruses are maintained in nature, infecting vertebrates (hosts) and vectors (hematophagous insects and arthropods). Mostly, vectors are from the group of mosquitoes. Less common vectors are ticks (*Argas*)

and sandflies (*Phlebotomus spp*), where there is a close connection between the causative agent (virus) and the vector. Moreover, in some cases it is thought that vectors are actually the hosts of viruses. At the same time, different vectors (mosquitoes) can serve as vectors of the same virus to different vertebrates depending on individual geographical and ecological situations. Most often, vertebrates, especially humans, appear as a "dead end", in the role of intermediate hosts (Tsai and Chandler, 2007). The epizootiology (and epidemiology) of arbovirus infections is influenced by numerous and often mutually independent factors such as the number and immune status of the species, i.e. vertebrate (host) that serves as a reservoir of a given arbovirus in nature, climatic conditions on which vector reproduction depends. In the complex cycle of maintenance of arboviruses in nature, different species of mosquitoes participate with variable affinity towards different species of vertebrates on which they feed, with frequent host changes. The seasonal increase in the incidence of infections depends on the conditions of vector reproduction and their survival. In the case when a new arbovirus is introduced into a uninfected region of the world with a continental climate, the question arises of the vector's survival during the winter, but also the possibility of overwintering new local vector species to which the given virus can adapt.

Of key importance for understanding arboviral infections is knowing whether the vector, in which the virus maintenance cycle, also appears as a reservoir, i.e. whether the virus is transmitted trans-stage and transovarially within the vector population. *Bunyavirus*, for example, directly depends on viral gene expression and host metabolic activities. The vector's meals in the form of a drop of blood activate cellular genes in the ovary of the vector (female mosquito), which simultaneously stimulates virus replication. At the same time, during the period of diapause (egg hibernation) of the vector, it is possible to demonstrate the expression of viral genes whereby almost the entire mechanism of replication is used for the viral mRNA. At the end of diapause, the replication mechanisms of the cells are fully utilized for viral mRNA (Dobie et al., 1997). This unique way of virus expression and recombination at the inter and intramolecular level is particularly significant if the eggs of the vector are infected with two different buna viruses. In that case, the mechanisms of recombination and reassortment create new variants of the virus.

In the event that the causative agent of an infectious disease is transmitted by ticks, we have to remember that the period of time for development into an adult form (from egg to larva and nymph) is over two years (in continental climate conditions). At each of these stages, the vector needs a meal in the form of a drop of blood, with arbovirus transmission occurring at each feeding. Tick population density depends not only on climatic factors during a given season but also during previous years.

Sometimes, completely different viruses use the same maintenance cycles in nature that are common to vertebrates i.e. reservoirs of viruses and vectors. In that case, as a result, a close epizootiological relationship can appear, so for example, the causative agent of western equine encephalitis (alphavirus) and the causative agent of *St. Louis* encephalitis (flavivirus), spread by the same epizootic cycle in which wild birds and mosquitoes (*Culex tarsalis*) are participants. In nature, both diseases occur simultaneously. A similar association exists in Africa and Asia between Sindbis virus (alphavirus) and West Nile virus (flavivirus), both viruses using an epizootic cycle in which birds are reservoirs and insects (*Culex univittatus*) are vectors. The urban cycle of Yellow fever, dengue and *Chikungunya* fever depends on the mosquito vector *Aedes* (*Stegomya*) *aegypti*. Likewise, the *Ixodes ricinus* tick transmits the virus that causes tick-borne encephalitis, but also the causative agent of Lyme disease (*Borrelia burgdorferi*). The tick *Dermacentor marginatus* transmits Q fever (*Coxiella burnetii*) as well as viruses causing eastern and western encephalitis (Porterfield, 1995). The simultaneous presence of bacteria and viruses in the same vector can be harmful to the virus, but at the same time it can be one of the methods of vector control. It was established that the mosquito *Aedes aegypti*, if infected with an intracellular bacterium (strain *wMel* isolated from *Drosophila melanogaster*), loses its ability to transmit the causative agent of dengue fever.

Numerous studies are being conducted worldwide, with the aim to clarify the epizootiological cycles of the maintenance of certain vector-borne zoonoses (Tsai and Chandler, 2007). For example, it has recently been established that there are sylvatic cycles in the case of arbovirus infections (dengue fever, dengue hemorrhagic fever and sandfly fever) which involve the multiplication of the virus in wild rainforest rodents, transmission by vectors (mosquitoes) on the one hand, and the "urban" cycle (man-mosquito-man). Apparently the "urban" cycle is not related to the "sylvatic" one because in humans there is a viremia of sufficient intensity and duration to maintain the virus in the vector and human population. However, there is certainly also the possibility that the "sylvatic" cycle is necessary as a reservoir of viruses in nature.

In the case of Rift Valley fever, there is no "sylvatic" cycle. Several species of mosquitoes (*Aedes*) transmit the virus both vertically and trans-stage. Mosquitoes lay infected eggs in flooded areas, so the virus survives for a long period of time (during drought for years). Upon reflooding, new generations of vectors hatch and a new cycle of epizootics occurs, whereby the virus multiplies in susceptible vertebrates (sheep, goats, cattle and humans) (Anyamba et al., 2009).

The global spread of arbovirus infections, most of which are zoonoses, has surprised epizootiologists and epidemiologists in the past few decades. Examples of this are

the spread of West Nile fever in Europe and North America (Nash et al., 2001) as well as Rift Valley fever in the Middle East region (Saudi Arabia). The persistence of an imported West Nile fever epizootic in the US is not conditioned by the presence of *St. Louis* encephalitis (an endemic zoonosis in North America). In contrast, the spread of Japanese encephalitis in Australia was probably prevented or at least slowed because wild pigs on that continent possess neutralizing antibodies specific for the causative agent of *Murray Valley* fever, a virus that is antigenically similar to the virus that causes Japanese encephalitis as well as *Kunjin* virus (Mackenzie, 1999).

Crimean-Congo Hemorrhagic Fever

The disease, which was first described in 1944 in Crimea, is of viral etiology. The causative agent is a virus from the Bunjavirus family, genus Nairovirus, which is transmitted by ticks. It also appears in Serbia, the surrounding countries, Russia, Turkey, China and in most countries of the Near and Far East (Leblebicioglu, 2010). It is also registered in Australia and South Africa. In endemic and enzootic regions, humans and domestic animals (cattle, sheep, goats and camels) are infected. Reservoirs of the virus are horses, hedgehogs and rodents, and the virus has been isolated from more than 30 species of ticks (Hyalomma, Ixodes) in which transovarial and trans-stage transmission has been demonstrated (Flick and Whitehouse, 2005). However, the tick-vertebrate cycle is necessary to maintain the virus in nature. The spatial distribution of the disease largely coincides with the distribution of the *Hyalomma* tick. The disease can be spread by infected animals (cattle, camels). The sources of infection are diseased animals that infect ticks, and human can be infected by the consumption of contaminated meat (ostriches). Transmission of Crimean-Congo fever is through vectors (ticks) or contact with infected animals. Manipulation with animals and their meat is also a risk, and the possibility of an aerogenous way of infecting workers in laboratories is not excluded.

After about a week of incubation, the first symptom in humans is an increase in body temperature, weakness, shivering, pain in the head, limbs and back. A common symptom is vomiting. The skin on the face and neck is red and swollen. After 4 - 5 days, hemorrhages are observed in the form of petechiae on the skin of the whole body, mucous membranes and blood in feces and urine appears. The lethality is from 30 to 50% and is higher in the case of severe bleeding (Tsai and Chandler, 2003). The diagnosis is based on the epidemiological anamnesis, in which case attention should be paid to the presence of ticks as well as on the work with animals. The antigen of the virus can be proven by the method of polymerase chain reaction (PCR) or indirectly, by proving seroconversion (IgM). Differential

diagnosis includes septic conditions, leptospirosis, borreliosis, malaria, dengue or rickettsiosis (typhoid).
Sick persons are treated in intensive care units and with strict isolation measures, and in addition to non-specific therapy which aim is to increase the general resistance of the organism, antiviral therapy is also applied (Soares-Weiser et al., 2010). In Russia, an inactivated vaccine is used, and from non-specific prophylaxis measures, it is necessary to pay attention to the possibility of transmission of infection during contact with sick people or animals (cattle, sheep, goats and camels). Special care must be taken during the processing of tissue samples in the laboratory.

Central and Eastern European Tick-borne Encephalitis

Flaviviruses which cause encephalitis are transmitted by ticks and have been known for a long time. Their prevalence often affects the naming of the causative agents themselves. Namely, in the region of Europe, it has long been known that there are viruses causing the so-called Central and Eastern European tick-borne encephalitis (Heyman et al., 2010).
The most important reservoirs of the virus causing Central and Eastern European tick-borne encephalitis are wild rodents (shrews, moles), and viremia of sufficient intensity can develop in wild (deer, hedgehog) and domestic animals (sheep, goats, cattle and dogs). Viremia in natural reservoir species is a necessary condition for the distribution of European encephalitis in a region (Kaiser, 2008). Recently, it has been proven that viruses can also multiply in bats and waterfowl.
Both viruses are transmitted by ticks, namely *Ixodes Ricinus*, *Ixodes persulcatus*, *Dermacentor marginatus*, *D. silvarum* as well as some species of *Haemaphysalis*. Most often, ticks in the nymph stage are infected by feeding on viremic hosts, vertebrates. Once infected, ticks transmit the infection to the next generation, whereby each developmental form of the parasite is infectious, i.e. when feed on the host (vertebrate) it may transmit the causative agents of Central and Eastern European tick-borne encephalitis. Transmission between an infected individual (and person) and a susceptible one is not possible. Ticks are not only vectors of the virus but also serve as its reservoirs. Viruses are transmitted in ticks transovarially and trans-stage. In Europe, cases of tick-borne encephalitis appear during the period of May and June (Central European tick-borne encephalitis) and in spring and autumn (Eastern European tick-borne encephalitis). Central European tick-borne encephalitis can also be transmitted to humans through milk and unpasteurized milk products, and infections of laboratory workers have also been reported (Lasala and Holbrook, 2010).

The clinical signs in humans are dominated by symptoms of the central nervous system demage, and as with other flavivirus infections, the rise in body temperature is biphasic. People who spend time outside (livestock farmers, forest workers) are especially at risk. Up to 30% of infected people have severe symptoms in the form of a biphasic increase in body temperature. Symptoms are less common in children. After the first increase in body temperature, there is a period without symptoms. Meningoencephalitis is followed by a second phase of body temperature increase during which there are non-specific symptoms that resemble those of the flu (joint pain, headache, gastrointestinal disturbances). In more severe cases, there are meningitis, encephalitis, severe headaches, paresis and paralysis. The degree of lethality is lower in Central European encephalitis (1-5%) compared to the Eastern European type (up to 20%), and in general it is lower in children (Logar et al., 2000).

The diagnosis of tick-borne encephalitis is complex and primarily refers to monitoring the occurrence in susceptible animal species as well as knowledge of the epizootic situation in terms of the season of vector activity or the consumption of uncooked milk. Finding dead wild animals, which could serve as virus reservoirs, can be of importance. Direct confirmation of the virus is difficult, given that the virus is in circulation for a relatively short period of time and when there are no symptoms. On the other hand, the virus can be confirmed in brain tissue, which certainly complicates diagnostic procedures. Confirmation of the European tick-borne encephalitis virus is performed by cell culture isolation methods (neutralization test) and confirmation of the virus genome by polymerase chain reaction. Seroconversion (IgM) is confirmed by immunoenzymatic methods (Martin et al., 2001). Differential diagnosis includes influenza, mumps, enteroviruses, as well as encephalitis of other etiologies.

Treatment of European tick-borne encephalitis is reduced to maintaining the homeostasis of patients. Specific immunoprophylaxis exists, inactivated vaccines are applied. However, vaccines must not be given after exposure to the virus. The same applies to the use of hyperimmune serums in humans. Vaccination is used in persons who are at higher risk (forest workers, livestock farmers) who live in regions where tick-borne encephalitis is endemic (Rendi-Wagner, 2008). The antigen in the vaccine is inactivated, and after the first immunization, which involves the application of three doses (0, 7 and 21 days), a booster is performed 1 to 3 years later (Rendi-Wagner, 2006). Vaccination after exposure is contraindicated (Bröker and Kollaritsch, 2008). Non-specific prophylaxis refers to preventing the consumption of uncooked (and unpasteurized) milk, especially from sheep and goats, as well as preventing contact with ticks by wearing adequate clothing and footwear.

In the Republic of Serbia, the diagnosis of tick-borne encephalitis was initially

based on the results of serological tests of human serum, collected in the period from 1962 to 1969. Out of a total of 1726 sera, positive were from 1.1% (Srem) to 52.6% (Sandžak) (Petrović et al., 2018). Using PCR in 2014 and 2015, the virus was detected in ticks (*Ixodes ricinus*) that were collected on the territory of Fruška Gora and Belgrade (Potkonjak et al., 2017). Tests performed on animals indicate the presence of specific antibodies in the sera of dogs, horses, wild boars, cattle and deer, and in 2017, the presence of the virus in horses in the vicinity of Požarevac was confirmed (Živojinović et al., 2017).

Rift Valley Fever

The Rift Valley stretches across great part of East Africa, encompassing an area almost the size of Europe. Enzootic and endemic, a viral, vector-borne zoonosis appears in this region, accompanying epizootics in sheep, goat and cattle populations. The causative agent belongs to the Bunjavirus family, genus Phlebovirus despite the fact that it is not transmitted by sandflies but by mosquitoes. The disease has been registered in more than 30 countries, and the incidence is associated with rainy periods in regions south of the Sahara. The virus is constantly present in Kenya, Uganda, Namibia, Angola and Nigeria, and recently epizootics were recorded in Egypt (1993) and Madagascar (Jost et al., 2010). The last epizootic outside the endemic region was recorded in Saudi Arabia and Yemen in 2000 (Gerdes, 2004). Reservoirs of the virus and species for its reproduction in nature are sheep, goats, cattle, buffaloes and camels. The virus can be transmitted by over 40 species of mosquitoes, and based on this fact, it is considered that there is a high risk of global distribution of Rift Valley fever. Pandemics are also possible due to the fact that the virus that causes Rift Valley fever is not specific to only one type of vector (mosquito). In previously "free" regions, the virus is most often introduced by infected animals, mostly sheep (Anyamba et al., 2009). In populations of susceptible species, the virus is transmitted by vectors (Stegomia and Culex species). People can be infected in the same way, however, people who are in contact with contaminated meat (slaughterhouse workers) and veterinarians are more often at risk. The virus is transmitted transovarially in vectors, and *Stegomia* mosquitoes also serve as reservoirs of the causative agent in nature. Infected female mosquitoes lay infected eggs which, when dried, can survive for a long period of time (years). The epizootic begins after the next rainy season, when new generations of mosquitoes hatch from the eggs. In addition to this biological way of transmitting the virus, the possibility of mechanical transmission through flies, mosquitoes and other hematophagous insects has also been proven.

Pregnant sheep and goats are particularly susceptible to infection. In addition to abortions, hepatitis and encephalitis are observed, and mortality is higher in younger animals. Clinically, the disease in humans begins with an increase in body temperature, weakness, stiffness, muscle and back pain, skin rash (maculopapular rash), and these symptoms are accompanied with gastrointestinal disturbances. Most often, a person recovers within 2 to 7 days. However, in 1-3% of patients, there are hemorrhages and kidney failure, in which case the mortality is up to 50%. About a month after the first acute symptoms, encephalitis, headache, spasms, symptoms of damage to the central nervous system and coma are found in these patients (Kahlon et al., 2010). The most common side effect is blindness as a result of retinal damage (Al-Hazmi et al., 2005). Out of a total of 140 cases of the disease in Saudi Arabia and Yemen (in 2000), the fatality rate was 19%, and it is believed that a significant number of milder cases were not reported. In most cases, people were infected through contact with animals, in addition to the fact that they were all in contact with mosquitoes (*Stegomia* and *Culex*). Complications were in the form of retinitis, hepatitis, kidney failure, hemorrhages and encephalitis.

The diagnosis of Rift Valley fever is based on epizootiological and epidemiological history. Rift Valley fever should be suspected if there are frequent abortions in sheep and cattle, the death of lambs and calves, and the death of pregnant sheep and cattle. During the acute phase of the disease, the virus can be isolated from the circulation, in the laboratory using the cell culture method or by confirming the viral genome, using the polymerase chain reaction (Sall et al., 2001). During the convalescence phase, serological reactions can prove seroconversion. In the case of encephalitis, IgM antibodies can also be demonstrated in the cerebrospinal fluid. Hemorrhagic diseases, encephalitis and, in animals, abortions come into consideration in the differential diagnosis.

In terms of therapy, interferon and specific anti-viral serum can be applied to sick people (Bouloy and Flick, 2009). Success has also been observed with the use of antiviral drugs (ribavirin).

There is a specific prophylaxis for sheep. Both an inactivated (cattle) and a vaccine in which the immunogen is a live, attenuated (sheep) virus are used. Both vaccines can be used in humans, but their application is currently limited (LaBeud et al., 2010). The best way to control Rift Valley fever is immunization of susceptible species of animals (sheep and cattle), vector control and application of animal hygiene measures in slaughterhouses and during the manipulation of potentially infected animals (slaughterhouses, animal marking, assistance with birth, etc.).

Chikungunya

It is a vector-borne zoonosis that occurs in Africa and Asia (south and southeast). The main symptoms are pain in the joints and a macopapular rash on the skin. In birds (reservoirs), symptoms are absent. The causative agent is Togavirus (alpha), and the disease is endemic (and enzootic) in all regions south of the Sahara, as well as in South and Southeast Asia. Recently, the disease was also registered in South America, and in 2007, the disease also appeared in Italy (Liumbruno et al., 2008). The risk of transmission of *Chikungunya* infections in Europe exists, especially as a result of global changes in climate conditions on the one hand and intensive and rapid transport of potential carriers on the other (Gould and Higgs, 2009; Pistone et al., 2009).

Reservoirs in nature are wild primates, bats and birds, and in addition to the urban cycle (man-vector-man) there is also a rural or sylvatic one. Transmission of the *Chikungunya* virus is carried out by vectors, mosquitoes (*Aedes*, or according to the new nomenclature *Stegomyia*), where there is no vertical transmission of the virus in mosquitoes. The main reservoir of the virus are humans who infect mosquitoes. Direct human-to-human transmission has not been recorded. In Italy, the most important virus vector is *Stegomyia albopicta*; earlier name *Aedes albopictus* (Talbalaghi et al., 2010).

Clinically, there is a sudden rise in body temperature and immediately after that severe pain in the joints, so the patient cannot move. There are also myalgias, nausea, headache, nasal discharge and conjunctivitis, photophobia (Borgherini et al., 2007). A macopapular rash on the skin follows 2 to 5 days later, and hemorrhages on the skin can also be observed. The average lethality is 0.4%, and in children 2.8% (Economopoulou et al., 2009). The pain and swelling of the joints can last for weeks, but thereafter the recovery is complete.

In endemic regions of the world, the diagnosis is based on history and viral antigen detection (PCR), and serological diagnosis is not reliable due to the existence of cross-immunity with other alphaviruses. However, confirmation by seroconversion is important given that cross-reactive viruses appear in different regions of the world in relation to *Chikungunya* virus (Grivard et al., 2007).

The therapy is symptomatic, and in cases of severe pain in the joints, it is necessary to use strong analgesics. The use of steroid preparations should be avoided. There is currently no specific prophylaxis in commercial use. Non-specific prophylaxis refers to the prevention of contact with mosquitoes (nets and repellents), and in regions where the *Chikungunya* virus does not appear, it is necessary to exclude the contact of mosquito and viremic persons, since it is necessary to avoid biggening

of the urban cycle through *Stegomyia albopicta* mosquitoes. Particular attention should be paid to the risk of virus introduction through viremic individuals who have been in endemic regions of the world (Chen and Wilson, 2010). In enzootic and endemic regions, vector control in the vicinity of cities is of great importance.

Yellow Fever

Yellow fever is a vector-borne zoonosis of viral etiology (*Flaviviridae*, genus *Flavivirus*), which is characterized by icterus and an increase in body temperature in primates (and humans). In enzootic and endemic regions of the world, there are parallel urban and sylvatic (jungles of Africa and South America) cycles that overlap each other (Barnett, 2007). Namely, the reservoirs of the virus are monkeys, and within the urban cycle, the virus is transmitted between humans by mosquitoes (Vasilakis and Weaver, 2008).

The disease is endemic in a large part of Africa where over 450 million people live, primarily in large cities. In those regions, there are also several species of reservoirs (monkeys). In South America, the epizootiological and epidemiological characteristics are the same, so there is a great possibility of this zoonosis spreading to other regions of the world (Gardner and Ryman, 2010). Yellow fever is endemic in rural regions, and eradication is thought to be achievable in urban areas through vector control (CDC, 1999). The lethality can be high, even over 55%, and the population of people who live in vicinity of large cities and who live in unhygienic neighborhoods are particularly at risk. Official data (WHO, 2009) indicate that the number of cases is several thousand annually. However, the number of Yellow fever cases worldwide is thought to be a hundred times higher. A significant number of cases, for example in Brazil and Bolivia, could not be linked to the travel of those persons to enzootic and endemic regions, so it can be concluded that there is a potential for foci to appear outside the region where this disease is present. The same applies to regions in Africa, which indicates the possibility of epidemics in urban areas (Mutebi and Barrett, 2002).

Yellow fever does not appear in Asia, which can be explained by the cross-reactivity of the causative agent with the virus that causes Dengue fever, as well as the weaker competence of the vector (*Stegomyia aegypti*). In Africa and South America, Yellow fever and Dengue fever coexist in the same regions (Gubler, 2004). Compared to Northern Hemisphere residents, travelers returning from regions where Yellow fever is endemic are particularly at risk (CDC, 2000; Muñoz et al., 2008).

The vectors of Yellow fever are mosquitoes (*Stegomia albopicta* and *S. aegypti*).

Clinically, the disease in humans can progress inapparently to severe forms with

a fatal outcome (CDC, 1999). In the case of a mild form, the symptoms resemble the flu. The rise in body temperature is sudden, there is bradycardia, headache, nausea, nosebleeds, muscle pains and pronounced blood vessels of the conjunctiva. Symptoms last relatively short, up to a few days. In severe cases, remissions are observed with the appearance of icterus, vomiting of bloody contents, melena, urogenital bleeding and kidney failure (oliguria and anuria). Fatal outcomes are preceded by delirium and coma. Lethality is from 10 to 50%. The diagnosis of Yellow fever is based on the epidemiological history, symptoms and laboratory findings (albuminuria and prolonged prothrombin time). The virus can be isolated from blood or cerebrospinal fluid during the first febrile phase. The method of cell culture isolation and detection of the viral genome (PCR) is applied. Evidence of seroconversion using an ELISA test is also used, and specific antiviral IgM antibodies can be demonstrated up to two years after recovery. In terms of differential diagnosis, malaria, hemorrhagic form of dengue fever, hemorrhagic fevers (Marburg, Ebola, Crimean-Congo fever), meningitis, leptospirosis, hepatitis and hantavirus infection come into consideration. Treatment of Yellow fever is symptomatic, and especially hemodialysis is used in case of kidney and liver failure.

Specific Yellow fever prophylaxis exists. In particular, vaccines are intended for people who need to travel to endemic regions of the world, as well as for those who travel from those regions to "free" countries. Basically, there are two types of legal regulations. The first type refers to countries in endemic and enzootic affected regions where a certificate of vaccination of persons is required. The second type of regulation involves countries that are "free" from Yellow fever but where there are potential vectors of the virus. In that case, a vaccination certificate is required for those persons who are citizens of countries located in endemically affected regions (countries) or for persons who have previously been in such countries. Two types of live vaccines are used in which the virus is attenuated. Vaccinated persons are protected for a longer period of time. Adverse effects were observed (Oyelami et al., 1994) after vaccination of persons with a damaged immune system (Receveur et al., 2000) as well as persons over 60 years.

Dengue Hemorrhagic Fever

It is the most serious and common zoonosis transmitted by vectors, but the infection is benign. It is believed that over 2 billion people worldwide in over 100 countries are at risk of getting a disease (WHO, 2009), and that annually up to 50 million people are infected (Kyle and Harris, 2008). About 1% of infected people become ill with severe clinical symptoms in the form of dengue hemorrhagic fever and

dengue shock syndrome. It should be noted that the risk of a more severe form of the disease is higher after the second contact with the virus. Namely, during the first contact, severe forms occur in 0.2% of cases. This percentage is 20% with the second infection. Children are especially sensitive. Dengue hemorrhagic fever is the most common vector-borne zoonosis found in tourists who have stayed in endemic regions of the world and who bring the infection into the country, i.e. a region where the virus has not appeared before. The virus that causes dengue fever belongs to flaviviruses.

Dengue fever does not appear (for now) only on the territory of Europe and Antarctica. It is believed that up to 50 million people are ill annually, and the prevalence is particularly high in Brazil (about a million cases in 2010). It is of particular epizootiological and epidemiological importance that vectors (*Stegomyia aegypti* and *S. albopicta*), which are competent vectors of the causative agent of Dengue fever, are found in previously "free" regions and countries (Jansen and Beebe, 2010). Until 2014, cases of the disease in Japan only occurred in people who had previously traveled to endemic regions. However, that year, 20 people were infected by the vector in a park in the central part of Tokyo.

In endemically affected regions (Central and South America, equatorial Africa and northern Australia), the disease in humans is inapparent (CDC, 1999). However, there are regions where a higher percentage of severe forms of the disease occur in the form of hemorrhagic fever and septic syndrome (India, Indonesia, Philippines). In animals (chimpanzees, gibbons and macaque monkeys), viremia is of sufficient intensity and duration to lead to vector infection. The prevalence of monkey infection is particularly high in Africa and Indonesia. Other monkey species are not as good reservoirs (short-term and low-level viremia).

The virus, the causative agent of Dengue fever is transmitted by vectors, mosquitoes (*Stegomyia aegypti*, *S. albopict* and *S. africana*) (Jansen and Beebe, 2010). These are biological vectors and reservoirs in nature, since the virus is transmitted transovarially to subsequent generations of vectors. The link between the urban and sylvatic cycles of Dengue fever is maintained by *Stegomyia nivea*, a mosquito that feeds on both primates (monkeys) and humans. It is a zoonosis which is limited to the human population within the urban cycle but which can become an epidemic in regions close to the rainforest. The virus, the causative agent of Dengue fever, can also be transmitted by transfusion.

Clinically, after incubation for about a week, there is a sudden increase in body temperature, headache and myalgias, retroorbital and epigastrium pains. In addition, there is nausea, vomiting, inappetence, insomnia and weakness. Sometimes, bleeding is also present (melena, hematuria, epistaxis). It is the first stage of the

disease that lasts for several days. The second stage is characterized by milder symptoms. In more severe cases, hemorrhagic syndrome and septic shock are found when high body temperature, bleeding, liver enlargement and shock are present. It is considered that the more severe form of the disease is a consequence of immunopathogenetic mechanisms, that is, the presence of immune complexes composed of non-neutralizing antibodies and viral antigens (Halstead et al., 2010). This is especially the case when a person is infected with two types of dengue virus (Martina et al., 2009). Antibodies present as a result of the first infection do not neutralize the second type of virus, but form immune complexes with it and initiate productive infection of macrophages via Fc receptors (Rodenhuis-Zybert et al., 2010). Today, it is known that there are six factors that determine the more severe forms of Dengue fever (hemorrhagic fever and septic shock):

1. infection in the presence of non-neutralizing antibodies,
2. if the second virus is of Southeast Asian origin,
3. women more often get sick in a more severe form,
4. the inhabitants of Asia and the Caucasian type of people get sick more often in a more severe form; blacks are less likely to get the disease,
5. children under 15 years of age are most often affected in a more severe form (Jain and Chaturvedi, 2010) and
6. newborns with maternal antibodies to different types of viruses

The diagnosis of Dengue fever is made on the basis of epidemiological history (travel to an endemic region) and clinical symptoms. The virus can be isolated from the circulation, and the finding of blood hypovoluminemia (increased hematocrit) and blood coagulation disorders is also important. The virus can be isolated in cell culture (Teles et al., 2005). Liver, lung, kidney, spleen and lymph node tissue, taken by biopsy, can be used to confirm viral antigen (TFA) or viral genes by polymerase chain reaction (Conceição et al., 2010).

Seroconversion implies the finding of IgM anti-viral antibodies (Schwartz et al., 2000). Flu, hepatitis, leptospirosis, malaria, hemorrhagic fevers (Ebola, Marburg, hantaviruses), rickettsiosis, as well as other vector-borne zoonoses (Chikungunya, Rift) come into consideration in the differential diagnosis. There is no specific therapy for Dengue fever.

Specific prophylaxis consists of the application of a quadrivalent vaccine in which all four types of viruses are attenuated, however, the safety of this preparation has not yet been confirmed (Swaminathan et al., 2010). The same applies to the recombinant vaccine in which the *Theiler 17D* strain of yellow fever virus is found as an immunogen (Miller, 2010; Van Der Most et al., 2000).

The main way to fight Dengue fever is the control of the vector (*S. aegypti*), where

success refers to the prevention of not only Dengue but also *Chikungunya* fever (Chen and Wilson, 2010). Persons traveling to endemic regions of the world (Venezuela, Southeast Asia) are advised to wear appropriate clothing, window screens, and repellents (CDC, 2012). People who have already been infected with dengue virus are especially at risk (WHO, 2009).

Ross River Fever

In Australia and Oceania, the disease is also known as epidemic polyarthritis. The causative agent is Togavirus (Alpha). The incidence of Ross River fever can be predicted on the basis of meteorological data (precipitation and temperature), and in the endemic region, the disease most often appears in the period from January to May (Woodruff, 2006). The seroprevalence in humans was established in those regions where no clinically manifested infections were reported. If it would appears in Europe, epizootics and epidemics would be expected during the period of activity of the vectors, mosquitoes (*Aedes* and *Culex*). In addition to humans, many types of domestic (cattle, sheep, goats, horses, pigs, dogs) and wild (rodents, birds) animals are susceptible (Jacups et al., 2008). The mechanism by which the virus survives the period of mosquito inactivity is still unknown (Kelly-Hope et al., 2004).

In vectors (mosquitoes), the virus is transmitted vertically from one generation of insects to the next, and an urban epidemiological cycle (human-vector-human) is also considered possible.

Of the infected people, 20-30% show symptoms in the form of a slight increase in body temperature, after which there are pains in the joints (hands and feet in particular) which can also swell. Many patients have a maculopapular rash on the body and extremities, and some have petechiae. The disease is a benign, and joint pain disappears within 3 months, however, it can last for years. Ross River fever is a disease in the pathogenesis of which the relationship between macrophages and viruses plays a significant role (Rulli, 2007). Namely, the virus prevents the expression of genes in macrophages, which are responsible for antiviral defense (Linn et al., 1996). The diagnosis is based on the confirmation of virus antigen (PCR) in samples (blood and synovial fluid) as well as on the basis of seroconversion (ELISA). In regions where Ross River fever is an endemic disease, the diagnosis is most often made on the basis of epidemiological data (vector season) and clinical manifestations. Rubella, Lyme Disease, *Chikungunya* virus infection and Rheumatic Fever are considered in differential diagnoses. In most cases, therapy is not required, and if antirheumatic drugs are administered, the use of steroid preparations should be excluded. There is no specific prophylaxis (vaccine).

Usutu viral infection

Although the first isolation of this flavivirus was in the middle of the 20th century (in 1959), the importance of this virus was noticed only when it was isolated from dead red-winged blackbird (Weissenböck et al., 2002), in Austria (in 2001). The disease is transmitted by mosquitoes, and wild birds are reservoirs of the virus in nature. In the wild, the Usutu virus causes severe infections with a high degree of lethality. In Europe, the vectors are *Culex mosquitoes*. In humans, the virus does not cause any symptoms, however, people with other health problems (Cavrini et al., 2009) or those receiving immunosuppressive therapy are at risk. In horses and humans, viremia is not of sufficient intensity for these species to be considered reservoirs.
Specific anti-Usutu virus antibodies have been demonstrated in birds in Serbia (Petrović et al., 2013).

Wesselsbron Fever

A flavivirus that is limited to the region of southern and central Africa, causes this fever, which is transmitted to humans by mosquitoes, and the reservoirs are still unknown wild animal species. In addition to Africa, the virus is also present in Asia (Thailand).
The vectors of Wesselsbron fever are mosquitoes *(Aedes* or *Stegomyia species*). Sheep and cattle, within domestic animal species, are susceptible to infection. The virus can reproduce in canids (coyote) and birds (ducks). Mosquitoes, the vectors, become infected by feeding on domestic animals (sheep and cattle). People (veterinarians, livestock farmers) can become infected by contact with contaminated meat and organs of infected animals as well as during work with samples in the laboratory (Diallo et al., 2005).
It is a benign disease that is acute. Symptoms, if they occur, are an increase of body temperature, headache, muscle and joint pain, and rash. A common symptom is swelling of the liver and spleen. In more severe cases, encephalitis (impaired consciousness), visual disturbances and photophobia are found. In sheep, symptoms are similar to those in Rift Valley fever. Pregnant animals miscarry, and in newborn lambs, Wesselsbron fever is a fatal disease. The diagnosis is based on the epidemiological anamnesis, and contact with diseased animals and their organs is important (aborted fetus in sheep). During the febrile phase, the virus can be isolated from blood and throat swabs. Confirmation of the viral genome is performed by the PCR method, and serological analyzes can confirm seroconversion (Johnson et al., 2000). In the differential diagnosis, influenza should be excluded, and in the region where it appears, if there was contact with sheep, also Rift Valley fever should be

excluded. Wesselsbron fever therapy is symptomatic, and prophylaxis is limited to vector control. There is no specific prophylaxis (vaccine).

Murray Valley Encephalitis

Infections with flavivirus, the causative agent of *Murray* Valley encephalitis, are limited (so far) to Australia and New Guinea (Huppatz et al., 2009). By antigen characteristics, this virus is similar to the one that causes West Nile Fever, and antibodies against Japanese Encephalitis neutralize this virus as well.

In the period from 1917 to 1974, eight outbreaks of *Murray* Valley encephalitis were registered in Australia. The outbreaks were during the active season of the vector (mosquito, *Culex annulirostris*), a species that lays its eggs in ponds and small lakes (Broom et al., 2003). As for other regions of the world, there is a possibility of introduction of the virus causing *Murray* Valley encephalitis (Stich et al., 2003). Clinically, it is a serious disease despite the fact that only 0.2% of infected people develop symptoms. The disease begins suddenly with headache, photophobia, anorexia, severe weakness, vomiting, fever and meningitis. In severe cases, after about 2 weeks of severe symptoms, coma and death follow. Paralysis of the motor nerves can lead to difficult swallowing and breathing. During the first epidemics, the mortality was high (60%), and later it was reduced to 20%. In people who have recovered from the disease, permanent consequences often remain in the form of psychological and neurological disorders. Despite the reduced mortality rate, an increase in the percentage of people who have recovered from the disease and who remain with permanent neurological disorders has recently been observed. The diagnosis is made on the basis of epidemiological data, clinical symptoms and laboratory findings. The virus can only be isolated from brain tissue, i.e. post mortem, by polymerase chain reaction (Studdert et al., 2003). Seroconversion (IgM can be confirmed by enzyme-linked immunosorbent assays-ELISA). Encephalitis of other etiologies is considered in the differential diagnosis, especially in people who have traveled to regions of the world where other flaviviruses occur endemically and enzootically. Therapy is symptomatic, and intensive patient care is important. No specific therapy exists. In regions where *Murray* Valley encephalitis is endemic, mosquito control (larvicides and treatment against adult forms of the vector) is carried out.

CONCLUSION

We have witnessed the "overflow" of the coronavirus from the currently insufficiently defined reservoir populations of SARS-CoV-2 to humans over the past three years. Similar epizootiological and epidemiological scenarios, when an infectious disease spreads like wildfire from some region, can also be expected in the case of over 100 arboviruses that circulate in different regions of the world in more or less known natural cycles. Especially, flaviviruses stand out, which are very dynamic in terms of epizootiology and epidemiology. For example, Dengue hemorrhagic fever was almost eradicated in Central America in the 60s and 70s of the 20th century. However, from 1,000 reported cases in 1958 in Africa and Southeast Asia, there were 500,000 cases in 1998, with the disease beginning to reappear in all regions of South and Central America.

All arboviruses (with the exception of African swine fever) have an RNA molecule as genetic material. It is a highly adaptable molecule that not only has the ability to mutate in relation to virulence, but also in relation to the possibility of replication in species that were previously unsusceptible. These are vector species (mosquitoes and arthropods) as well as wild and domestic animals. This simply means that some of the arboviruses, by entering previously "free" regions and continents, can acquire an affinity both for the local vector population and find a new type of reservoir (animal) in nature. In this way, a new epizootiological and epidemiological cycle would be formed in a new location and with new "players".

It is believed that the spread of a large number of arbovirus infections is a consequence of the change in climatic conditions, meaning global warming and, as a consequence, the conquest of new territories by vectors. Likewise, in large regions of the world, until three decades ago, the pesticide DDT (*dichlordiphenyltrichlorethane*) was used to effectively control vector populations, primarily mosquitoes (*Stegomyia*, *Anopheles*, etc.). As a consequence of the banning of this pesticide, there is a significant increase in the number of vectors globally, which, together with warming, i.e., a higher degree of vector survival, significantly increases the risk of the spread of vector-borne zoonoses.

Veterinary service both in Republic of Serbia and the region, has contributed to the control of coronavirus infections in the past three years, primarily in the diagnostic term. At the same time, specialists in epizootiology significantly influenced the clarification of the principles of spread, control, suppression and eradication of the SARS-CoV-2 pandemic. With their expert knowledge of infectious animal diseases and the lateral approach provided by epizootiology, veterinarians certainly make a significant contribution to the "one health" system, so it can be concluded that there

is a high probability that veterinarians will be the first to notice the appearance of new vector-borne zoonoses in their field.

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