

# Emerging and neglected zoonoses in transplant population

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Mrzljak, Anna; Novak, Rafaela; Pandak, Nenad; Tabain, Irena; Franušić, Lucija; Barbić, Ljubo; Bogdanić, Maja; Savić, Vladimir; Mikulić, Danko; Pavičić-Šarić, Jadranka; ...

Source / Izvornik: **World Journal of Transplantation, 2020, 10, 47 - 63**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.5500/wjt.v10.i3.47>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:047362>

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Download date / Datum preuzimanja: **2025-01-11**



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# World Journal of *Transplantation*

*World J Transplant* 2020 March 31; 10(3): 47-78



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**INDEXING/ABSTRACTING**

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Lu-Lu Qi*  
 Proofing Production Department Director: *Yun-Xiaojuan Wu*

**NAME OF JOURNAL**

*World Journal of Transplantation*

**ISSN**

ISSN 2220-3230 (online)

**LAUNCH DATE**

December 24, 2011

**FREQUENCY**

Irregular

**EDITORS-IN-CHIEF**

Sami Akbulut, Vassilios Papalois, Maurizio Salvadori

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2220-3230/editorialboard.htm>

**EDITORIAL OFFICE**

Jia-Ping Yan, Director

**PUBLICATION DATE**

March 31, 2020

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**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Emerging and neglected zoonoses in transplant population

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**Author contributions:** Mrzljak A and Vilibic-Cavlek T made contributions to conception and design of the study, involved in drafting and revising the manuscript critically; Novak R, Pandak N, Tabain I, Franusic L, Bogdanic M, Barbic L, Savic V, Mikulic D, Pavicic-Saric J and Stevanovic V were involved in collecting data and drafting the manuscript; all authors read and approved the final manuscript.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

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### Abstract

Zoonoses represent a problem of rising importance in the transplant population. A close relationship and changes between human, animal and environmental health ("One Health" concept) significantly influence the transmission and distribution of zoonotic diseases. The aim of this manuscript is to perform a narrative review of the published literature on emerging and neglected zoonoses in the transplant population. Many reports on donor-derived or naturally acquired (re-)emerging arboviral infections such as dengue, chikungunya, West Nile, tick-borne encephalitis and Zika virus infection have demonstrated atypical or more complicated clinical course in immunocompromised hosts. Hepatitis E virus has emerged as a serious problem after solid organ transplantation (SOT), leading to diverse extrahepatic manifestations and chronic hepatitis with unfavorable outcomes. Some neglected pathogens such as lymphocytic choriomeningitis virus can cause severe infection with multi-organ failure and



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**Manuscript source:** Invited manuscript

**Received:** December 22, 2019

**Peer-review started:** December 22, 2019

**First decision:** February 20, 2020

**Revised:** March 15, 2020

**Accepted:** March 22, 2020

**Article in press:** March 22, 2020

**Published online:** March 31, 2020

**P-Reviewer:** Hibberd AD, Maggi F

**S-Editor:** Wang YQ

**L-Editor:** A

**E-Editor:** Qi LL



high mortality. In addition, ehrlichiosis may be more severe with higher case-fatality rates in SOT recipients. Some unusual or severe presentations of borreliosis, anaplasmosis and rickettsioses were also reported among transplant patients. Moreover, toxoplasmosis as infectious complication is a well-recognized zoonosis in this population. Although rabies transmission through SOT transplantation has rarely been reported, it has become a notable problem in some countries. Since the spreading trends of zoonoses are likely to continue, the awareness, recognition and treatment of zoonotic infections among transplant professionals should be imperative.

**Key words:** Zoonoses; Solid-organ transplant; Vector-borne diseases; Non-vector borne diseases; Viruses; Bacteria; Parasites

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**Core tip:** The importance of zoonotic diseases in the transplant population is rising. Given the current diversity and extent of zoonotic pathogens, modes of transmission and clinical presentation in immunocompromised hosts, this manuscript aims to summarize the published literature on emerging and neglected zoonoses in the transplant population.

**Citation:** Mrzljak A, Novak R, Pandak N, Tabain I, Franusic L, Barbic L, Bogdanic M, Savic V, Mikulic D, Pavicic-Saric J, Stevanovic V, Vilibic-Cavlek T. Emerging and neglected zoonoses in transplant population. *World J Transplant* 2020; 10(3): 47-63

**URL:** <https://www.wjgnet.com/2220-3230/full/v10/i3/47.htm>

**DOI:** <https://dx.doi.org/10.5500/wjt.v10.i3.47>

## INTRODUCTION

Zoonotic diseases - transmitted and shared between animals and humans, are nowadays receiving increased recognition. WHO estimates that more than 60% of all human pathogens are zoonotic, and that they represent 75% of all emerging pathogens during the past decade<sup>[1]</sup>. They encompass a wide range of pathogens (viruses, bacteria, parasites) and modes of transmission: *via* direct contact with infected animals or their secretions, the bite of arthropod vectors or indirect contact *via* the environment<sup>[2]</sup>. Given a close relationship between human, animal and environmental health (the "One Health" concept), human activities, climate and landscape changes influence significantly transmission and distribution of zoonoses<sup>[3,4]</sup>. The number of zoonotic diseases has been increasing in the last two decades and the spreading trends are likely to continue in future years. For example, West Nile virus (WNV), one of the most widely distributed arboviruses has expanded its area of circulation in many European countries<sup>[5]</sup>. In 2018, a large outbreak occurred across Southern and Central Europe with the number of confirmed human cases increasing up to 7.2-fold from the previous transmission season<sup>[6]</sup>. A total of 2083 human cases and 285 outbreaks among equids were reported, including previously virus-free regions<sup>[7]</sup>. In addition, geographical distribution of Zika virus (ZIKV) has steadily expanded. In 2015 and 2016, large outbreaks of ZIKA occurred in the Americas. In the USA and US Territories, 5168 and 36512 symptomatic ZIKV disease cases were reported in 2016<sup>[8]</sup>. Hepatitis E virus (HEV) is an important cause of acute viral hepatitis worldwide, with an increasing incidence in Europe since 2010. The reported incidence over 10 years has grown by ten times: From 514 cases in 2005 to 5617 cases in 2015<sup>[9]</sup>. On the other hand, solid-organ transplant (SOT) population is expanding as a result of increasing transplant rates, improved post-transplant management and survival<sup>[10,11]</sup>. In comparison to immunocompetent hosts, immunocompromised state of SOT recipients is an inevitable additional risk for the infection and unfavorable outcomes due to atypical presentation, possible delay in diagnostic tests (serology), more frequent presence of disseminated/advanced disease and prolonged treatment. Although majority of zoonotic infections develop in the post-transplant period, donor or transfusion transmitted zoonotic infections have been increasingly acknowledged as well. Therefore, the increasing trend of reports on zoonotic diseases in the transplant population over the past decade substantiates a need for a comprehensive review. This narrative review will cover two main groups

of zoonotic infections; vector and non-vector borne infections and focus on major pathogens and their clinical manifestations in the transplant population (Table 1).

## VECTOR-BORNE ZOOSESES

### ***Tick-borne encephalitis virus***

Tick-borne encephalitis virus (TBEV) is a tick-borne flavivirus widely distributed from Europe through far-eastern Russia to Japan. The virus is maintained in cycles involving *Ixodid* ticks (*Ixodes ricinus* and *Ixodes persulcatus*) and wild vertebrate hosts (mainly rodents)<sup>[12]</sup>. Transmission to humans occurs most commonly through a bite of an infected tick, however approximately 1% of all TBE cases are thought to be caused by food-borne TBEV (consumption of raw goat milk)<sup>[13,14]</sup>. TBEV can cause a wide spectrum of the disease, ranging from asymptomatic infection to severe encephalitis and even death<sup>[14]</sup>. Diagnosis is usually confirmed by the detection of TBEV IgM and IgG antibodies in serum and cerebrospinal fluid (CSF) samples. Determination of IgG avidity may be helpful in cases of atypical antibody response<sup>[15]</sup>. There are very few data on the transplant-transmitted TBEV infection. In 2012, a cluster of fatal TBEV infection was reported in Poland. Transmission of TBEV occurred through the transplanted organs (liver, kidneys) from a single donor to three recipients. The donor lived in an endemic area and the presence of TBEV was confirmed by the same viral strain detected in all recipients and in the donor<sup>[16]</sup>. Although transmission of TBEV through organ transplantation is rare, clinicians should consider screening donors who live or have recently visited endemic areas for TBEV, particularly during the arbovirus transmission season.

### ***Borrelia burgdorferi (Lyme disease)***

*Borrelia burgdorferi* is a tick-borne zoonosis widely distributed in North America and Europe. All three pathogenic species, *B. burgdorferi*, *B. afzelii* and *B. garinii* occur in Europe, and the latter two have been identified in Asia. *Borrelia burgdorferi* circulates between *Ixodes* ticks and vertebrate hosts in an enzootic cycle. Ticks can transmit borrelia to humans, but humans are dead-end hosts, unlikely to continue the life cycle of the spirochete<sup>[17]</sup>. Lyme disease (LD) has a broad spectrum of clinical manifestations. Primary infection presents as erythema migrans (EM). Late stages occur weeks to years following infection and include arthritis, peripheral neuropathy, and skin findings such as acrodermatitis chronica atrophicans<sup>[18]</sup>. Neuroborreliosis is one of the manifestations of LD involving the central nervous system (CNS)<sup>[19]</sup>. The role of immunosuppression in the development and progression of LD is not well understood. An analysis of SOT recipients on immunosuppressive treatment who presented with solitary EM did not reveal any significant differences in the clinical course of infection as compared with the general population<sup>[20]</sup>. The first case of LD in a transplanted patient was described in 1993 in a kidney transplant recipient in whom the disease progressed into the disseminated stage with severe neurological signs<sup>[21]</sup>. A study from Slovenia presented a case series of six SOT recipients with EM. All six patients had solitary skin lesions with clinical characteristics comparable to those of the skin lesions in immunocompetent patients. No clinical signs or symptoms suggesting borrelia dissemination were present or were reported either during the initial course of the illness or during the one-year follow-up period after antibiotic treatment and persistence of borrelia organisms in the skin after treatment was not established<sup>[20]</sup>. A case report of Lyme carditis after liver transplant that progressed to disseminated illness with a concomitant heart block and deterioration of mental status has also been described<sup>[22]</sup>.

### ***Anaplasma phagocytophilum (Human granulocytic anaplasmosis)***

Human granulocytic anaplasmosis (HGA) is a tick-borne infection caused by *Anaplasma phagocytophilum*, an intracellular bacterium, which commonly infects neutrophils<sup>[23]</sup>. The infection is mostly spread through a bite of *Ixodes* ticks in Europe (*Ixodes ricinus* and *Ix. persulcatus*) and in North America (*Ix. scapularis* and *Ix. pacificus*) after feeding on infected animals such as domestic (dog, horse) and wild ruminants, hedgehogs and wild boars<sup>[24,25]</sup>. However, there are reports of transmission through infected blood as well as of perinatal transmission<sup>[25]</sup>. Immunocompetent individuals with HGA develop high-grade fever, malaise, nausea, headache, myalgia, arthralgia, CNS and gastrointestinal symptoms. Rarely individuals present with an erythematous rash<sup>[26]</sup>. Whereas anaplasmosis is mostly a self-limiting disease, predictors of a more severe course include advanced age, immunosuppression, and comorbidities such as diabetes<sup>[26]</sup>. Severe course includes the development of acute respiratory distress syndrome, peripheral neuropathies, DIC-like coagulopathies,

**Table 1 Clinical manifestations of emerging and neglected zoonoses in non-transplant and transplant population**

Pathogen	Clinical presentation		Laboratory diagnosis	Ref.
	Immunocompetent patients	Immunocompromised patients		
Vector-borne zoonoses				
Tick-borne encephalitis virus	Asymptomatic infection to severe encephalitis	Few data: One cluster of fatal TBE	ELISA (IgM, IgG), Avidity; VNT; RT-PCR	[4,14-16]
<i>Borrelia burgdorferi</i>	Erythema migrans, arthritis, peripheral neuropathy, acrodermatitis chronica atrophicans, neuroborreliosis	Possible dissemination with severe neurological and cardiac symptoms	ELISA (IgM, IgG); IFA (IgM, IgG); Immunoblot (IgM, IgG); PCR	[4,18-20]
<i>Anaplasma phagocytophilum</i>	Mostly self-limiting disease, non-specific symptoms, rash, gastrointestinal and CNS involvement	Unusual presentations: Acute respiratory distress syndrome, haemorrhagic manifestations, pancreatitis, acute renal failure, orchitis	Microscopy of peripheral blood (morulae); IFA (seroconversion of 4-fold increase in IgG titer); PCR	[4,26,32,33,43]
<i>Ehrlichia</i> spp.	Self-limiting febrile illness to fatal multi-organ failure	More frequently severe manifestations: Fatal multiorgan failure, acute respiratory distress syndrome meningoencephalitis, toxic and septic-like syndromes	Microscopy of peripheral blood (morulae); IFA (seroconversion of 4-fold increase in IgG titer); PCR	[4,25,36,37,42]
<i>Rickettsia</i> spp.	Self-limiting disease, flu-like symptoms, with or without eschar and rash; vasculitis-mediated organ failure	Few data: More frequently severe manifestations, splenic rupture	IFA (IgM, IgG); PCR	[4,49,51]
<i>Orientia tsutsugamushi</i>	Nonspecific febrile illness to fatal multiorgan failure, eschar, CNS involvement	Few data: Only one case with eschar and renal graft dysfunction	IFA (IgM, IgG); PCR	[4,53,54]
Rift Valley Fever virus	Subclinical to severe febrile illness, fatal haemorrhagic fever	Few data: Only one case with meningoencephalitis	ELISA (IgM, IgG); VNT; RT-PCR	[4,59,61]
St. Louis encephalitis virus	Majority asymptomatic, febrile illness, aseptic meningitis and encephalitis	Few data: Meningoencephalitis	ELISA (IgM, IgG); VNT; RT-PCR	[4,63,65]
Zika virus	Asymptomatic infection to severe neurological disorders	Infectious complications and graft rejection	ELISA (IgM, IgG); VNT; RT-PCR	[4,69-71]
Chikungunya virus	Mild febrile illness and polyarthralgia, rarely meningoencephalitis, myocarditis	No impact on graft function	ELISA (IgM, IgG); VNT; RT-PCR	[4,74,75,77,79,80]
Dengue virus	Asymptomatic infection to severe fatal illness	More commonly prolonged course with complications and graft rejection	ELISA (IgM, IgG); VNT; NS1 antigen; RT-PCR	[4,82,84-86]
West Nile virus	Asymptomatic infection, mild febrile disease, neuroinvasive disease (elderly)	Fatal neuroinvasive disease more frequent	ELISA (IgM, IgG); VNT; Avidity; VNT; RT-PCR	[4,87,96,97,108,109]
Usutu virus	Asymptomatic infection, neuroinvasive disease (elderly)	Fatal neuroinvasive disease more frequent	ELISA (IgM, IgG); VNT; RT-PCR	[4,114-119]
Eastern equine encephalitis virus	Asymptomatic, neuroinvasive disease (meningitis, encephalitis)	Few data: Neuroinvasive disease	ELISA (IgM, IgG); VNT; RT-PCR	[4,123,124]
<i>Leishmania</i> spp.	Cutaneous, mucocutaneous and visceral leishmaniasis	The same as in immunocompetent; organomegaly may be less frequent in visceral leishmaniasis	Microscopy; Culture; PCR; IFA (IgM, IgG)	[4,129,130]
Non-vector-borne zoonoses				
Hepatitis E virus	Asymptomatic infection, fulminant hepatitis, acute-on-chronic liver failure, extrahepatic manifestations	Chronic hepatitis, cirrhosis, extrahepatic manifestations	ELISA (IgM, IgG); Immunoblot (IgM, IgG); RT-PCR	[4,131-133,135,136]
Rabies virus	Fatal encephalitis	Fatal encephalitis	Microscopy (Negri bodies); DFA (antigen detection); IHC (antigen detection); RT-PCR, RFFIT, FAVN	[4,143-146]



Lymphocytic choriomeningitis virus	Asymptomatic infection, nonspecific febrile illness, aseptic meningitis	More severe clinical presentation, hepatitis, meningoencephalitis, multiorgan failure	ELISA (IgM, IgG); IFA (IgM, IgG); RT-PCR	[4,99,151,152]
<i>Toxoplasma gondii</i>	Asymptomatic, mononucleosis-like symptoms	More severe clinical presentation, cerebral toxoplasmosis, fatal disseminated disease	ELISA (IgM, IgG); IFA (IgM, IgG); Avidity, Immunoblot (IgM, IgG); PCR	[4,156-158]

CNS: Central nervous system; DFA: Direct immunofluorescence assay; ELISA: Enzyme-linked immunosorbent assay; FAVN: Fluorescent antibody virus neutralization test; IFA: Indirect immunofluorescence assay; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IHC: Immunohistochemistry; NSI: Non-structural protein 1; PCR: Polymerase chain reaction; RT-PCR: Reverse-transcriptase polymerase chain reaction; TBE: Tick-borne encephalitis; RFFIT: Rapid fluorescent focus inhibition test; VNT: Virus neutralization test.

hemorrhagic manifestations, rhabdomyolysis, pancreatitis and acute renal failure<sup>[26]</sup>. The diagnosis can be confirmed by microscopic identification of morulae in neutrophils on peripheral blood smear or in buffy coat, PCR or serology<sup>[27]</sup>. Based on the few case reports of anaplasmosis in recipients of kidney, pancreas or liver<sup>[28-32]</sup> the incidence of anaplasmosis in transplant recipients does not appear to be high and manifestations of the disease seem to be similar to non-transplant patients. In transplant patients, the clinical presentation commonly involved non-specific systemic symptoms. However, there was also a rather unusual presentation in a kidney recipient in the form of orchitis<sup>[33]</sup>. It was observed that immunosuppressive therapy does not seem to alter acute or convalescent antibody titers<sup>[34]</sup>. Solid organ transplant (SOT) recipients with anaplasmosis usually also have a good initial response to treatment with doxycycline<sup>[33]</sup>.

#### ***Ehrlichia* spp. (Human monocytic ehrlichiosis)**

Human monocytic ehrlichiosis (HME) is a tick-borne zoonosis caused by *Ehrlichia chaffeensis* and less commonly, *E. ewingii*. HME occurs across the south-central, south-eastern, and mid-Atlantic states, corresponding to areas where their reservoirs (white-tailed deer) and vectors (*Amblyomma americanum* ticks) both exist<sup>[35]</sup>. The clinical manifestations of HME vary from a self-limited febrile illness to fatal multi-organ failure<sup>[25]</sup>. Severe manifestations such as acute respiratory distress syndrome, pulmonary hemorrhages, meningoencephalitis, toxic shock-like, and septic shock-like syndromes have also been described<sup>[25,36,37]</sup>. The diagnosis can be confirmed by PCR or serology<sup>[25,38]</sup>. In some cases, morulae may be observed in leukocytes on Wright stained peripheral blood smear, particularly in immunocompromised hosts<sup>[25,39]</sup>. There have been reports of HME transmission through SOT<sup>[37]</sup>, as well as through blood product transfusions<sup>[25]</sup>. Ehrlichiosis was described in kidney<sup>[37,40-44]</sup>, liver<sup>[36,43,45]</sup>, lung<sup>[38,42,43,46]</sup> and heart transplant recipients<sup>[42,43]</sup>. Immunocompromised persons, particularly SOT recipients, more frequently develop severe and prolonged manifestations of ehrlichiosis with higher case-fatality rates<sup>[25,37,42]</sup>. Furthermore, SOT recipients showed having a higher risk to develop acute lung injury and acute respiratory distress syndrome<sup>[42]</sup>. However, one report showed that 15 transplant patients with ehrlichiosis had similar and favorable outcomes compared with immunocompetent patients<sup>[43]</sup>. Among SOT recipients, infected lung recipients showed more severe and progressive clinical course<sup>[42]</sup>. Some reports, have also described re-infections in liver transplant recipients, suggesting that initial infection may not provide long-lasting immunity in patients on immunosuppressive therapy<sup>[45]</sup>.

#### ***Rickettsia* spp.**

Rickettsioses are bacterial infectious diseases that occur in endemic areas across the world. They are classified into two main groups: The spotted fever group with the main representatives; *Rickettsia rickettsii* (Rocky Mountain spotted fever; RMSF) transmitted by the ticks in the USA, Mexico and South America<sup>[47]</sup>; *R. conorii* (Mediterranean spotted fever; MSF) transmitted by dog ticks in Southern and Eastern Europe, Africa, India, Russia<sup>[47,48]</sup> and the typhus group which includes *R. prowazekii* (epidemic typhus) and *R. typhi* (murine typhus)<sup>[48]</sup>. Following a tick exposure, clinically significant rickettsial infections present with flu-like symptoms with or without eschar at the site of the tick bite, accompanied by rash. The clinical course is highly variable and ranges from self-limited to vasculitis-mediated organ failure and death<sup>[49]</sup>. The diagnosis of rickettsioses is most often established by serology. Indirect immunofluorescence assay (IFA) has been considered the gold standard. The test has limited utility in species determination within a serogroup due to extensive cross-reactivity and as any immunoglobulin-based assay in the context immunocompromised patient should be interpreted with caution<sup>[49]</sup>. Rickettsioses have been rarely reported in the transplant population. The scarcity of the data implies that even in

immunocompromised hosts majority of the infections are mild and rarely result in a malignant vasculitis-associated form. A case of RMSF in a cardiac transplant recipient from southern Utah demonstrated a prompt clinical response after empirical treatment with doxycycline and delayed development of rickettsia antibodies (5 mo after the infection)<sup>[50]</sup>. Only one case demonstrated the development of complications. Severe MSF infection has been reported in a kidney transplant recipient from Southern France, who developed flu-like symptoms, maculopapular rash and splenic rupture requiring splenectomy. Doxycycline therapy resulted in rapid improvement and favorable outcome<sup>[51]</sup>. Rickettsial infections are probably underrecognized and underreported in the transplant population.

### ***Orientia tsutsugamushi* (Scrub typhus)**

Scrub typhus is a zoonosis caused by *Orientia tsutsugamushi*, an obligate intracellular bacterium. It is a common re-emerging rickettsial infection in India and many other countries in Southeast Asia, the Pacific Islands, and Northern Australia (the "tsutsugamushi triangle")<sup>[52]</sup>. *Orientia tsutsugamushi* is transmitted to humans by the bites of the larval life stage of infected *Leptotrombidium* mites (*Leptotrombidium deliense* and *Leptotrombidium akamushi*) while field rodents serve as reservoirs. The clinical presentation of scrub typhus ranges from nonspecific febrile illness to potentially fatal multi-organ involvement such as liver, kidney, or lung<sup>[53]</sup>. In some patients, an eschar may develop at the site of mite feeding. CNS involvement (meningitis, encephalitis) has also been observed<sup>[54]</sup>. The diagnosis of scrub typhus is usually made by a single IFA titer against *O. tsutsugamushi* of 400, a seroconversion or a 4-fold increase in IgG titer using paired serum samples<sup>[55]</sup>. So far, only one study described scrub typhus in a renal transplant recipient in India. The patient presented with fever, headache, meningeal signs, graft dysfunction, and eschar and responded well to intravenous azithromycin and became afebrile within 24 h<sup>[53]</sup>. Since many cases of scrub typhus are underdiagnosed, clinicians should consider in differential diagnosis this potentially fatal zoonosis in regions of endemicity.

### **Rift Valley fever virus**

Rift Valley fever virus (RVFV) is a mosquito-borne phlebovirus. RVFV outbreaks in humans have been reported in Africa, the Indian Ocean islands, and the Arabian Peninsula<sup>[56]</sup>. Cattle, sheep, goats, and camels are particularly susceptible to RVF and serve as amplifying hosts for the virus<sup>[57]</sup>. RVFV transmission to humans occurs by direct contact with infected animals or their body fluids, consumption of raw milk or meat or by mosquito bites (*Culex*, *Aedes*)<sup>[58]</sup>. Human infections are usually subclinical or presenting as moderate to severe febrile illness while 1-2% of RVFV infections result in fatal haemorrhagic fever<sup>[59]</sup>. RVFV can be diagnosed by RNA detection, antigen detection or serology<sup>[60]</sup>. In 2015, an imported case of RVF in a kidney transplant recipient was reported in France. The initial clinical presentation was characteristic for acute hepatitis and four weeks later, the patient presented with a meningoencephalitis. IgM and IgG antibodies were detected in CSF and blood up to 2 mo after symptoms onset, whereas in urine and semen, RVFV RNA was detected by RT-PCR up to three and four mo, respectively. The severity of clinical presentation may have been related to immunosuppression, which might also have slowed down the clearance of the virus<sup>[61]</sup>.

### **St. Louis encephalitis virus**

St. Louis encephalitis virus (SLEV) is a mosquito-borne flavivirus. The virus can be found in the Western Hemisphere, but epidemics typically occur in the Ohio River-Mississippi River basin. Humans are dead-end hosts of a mosquito-bird-mosquito cycle<sup>[62]</sup>. While mostly asymptomatic, less than 1% of all SLEV infections lead to symptomatic disease ranging from febrile illness to aseptic meningitis or encephalitis<sup>[63]</sup>. Diagnosis is based on serology<sup>[64]</sup>. The prevalence of SLEV infections in transplant recipients is largely unknown. During the 2015 outbreak, three SOT recipients were hospitalized with confirmed neuroinvasive SLEV infection (meningoencephalitis) in Phoenix, Arizona. One patient died, whereas two other patients survived but required prolonged hospitalization. One patient recovered fully; the other patient had residual dysarthria<sup>[65]</sup>.

### **ZIKV**

ZIKV is an emerging mosquito-borne flavivirus. Before the large outbreak of ZIKV infection on Yap Island (Federated States of Micronesia), only sporadic cases were reported in Africa and Asia, but in 2007 ZIKV emerged as an important human pathogen<sup>[66,67]</sup>. Human infections mainly occur through the bite of *Aedes* mosquitoes (*Ae. aegypti* and *Ae. albopictus*), however, non-vector borne transmission of ZIKV such as sexual and transplacental transmission was also reported<sup>[68]</sup>. Although symptoms

associated with ZIKV infection are generally mild and the majority of infected persons do not develop any symptoms, ZIKV is also associated with severe neurological disorders, mainly Guillain-Barré syndrome. Diagnostic testing for ZIKV infection can be accomplished using molecular and serologic methods<sup>[69,70]</sup>. Case reports describing ZIKV infection in transplant patients are limited. In 2015 and 2016, ZIKV infection was confirmed among 129 kidney transplants and 58 liver transplants tested in Brazil. All ZIKV-infected SOT recipients presented with complications, notably bacterial infections, and required hospitalization. Based on this small case series, it was not possible to assess the potential impact of ZIKV in the immunosuppressed SOT recipients, including infectious complications and graft rejection<sup>[71]</sup>. Therefore, further studies are needed to evaluate the impact of ZIKV infection in this population group.

### **Chikungunya virus**

Chikungunya virus (CHIKV) is an emerging mosquito-borne alphavirus. Since 2004, CHIKV caused several large outbreaks in Africa, the Indian Ocean islands, Asia, Europe, and the Americas<sup>[72]</sup>. In an urban transmission cycle, humans are the major hosts and mosquitoes of the genus *Aedes* are vectors<sup>[73]</sup>. Although chikungunya fever is usually benign, prolonged polyarthralgia may lead to considerable disability in a significant proportion of patients<sup>[72]</sup>. Atypical manifestations include meningoencephalitis, myocarditis, respiratory, renal and hepatic failure<sup>[74,75]</sup>. Laboratory diagnosis is accomplished by detection of CHIKV RNA and/or detection of IgM and IgG antibodies<sup>[72]</sup>. Few data exist regarding the clinical characteristics of CHIKV infections in the transplant population<sup>[76-79]</sup>. In one case series of SOT recipients from Colombia with confirmed CHIKV infection, most patients had a benign clinical course with no severe complications<sup>[78]</sup>. A study from Brazil analyzed clinical symptoms of chikungunya in four kidney transplant recipients. The clinical picture was typical, none of patients developed any severe manifestations and all recovered fully with no complications<sup>[77]</sup>. Another Brazilian study showed similar results. SOT recipients with CHIKV infection seem to have a clinical presentation and course similar to those seen in the general population, with no apparent damage to the graft. Among liver transplant recipients, elevation of liver enzymes was not observed, and there was no clinical impact on graft function. Among kidney transplant recipients, only a few had a slight increase of serum creatinine levels, without acute kidney failure or dialytic support<sup>[80]</sup>. Although reports on the chikungunya in the transplant population are rare, the transplant community must be reminded that the risk of CHIKV infection should be considered in deceased organ donor candidates recently returned from travel to endemic areas<sup>[76]</sup>.

### **Dengue virus**

Dengue virus (DENV) is a mosquito-borne flavivirus widely distributed in the tropics and subtropics. In an urban cycle, the virus is transmitted from human to human by the bite of *Ae. aegypti* and *Ae. albopictus* mosquitoes. Non-vectorial DENV transmission through SOT can also occur<sup>[81]</sup>. The clinical presentations of DENV infection range from asymptomatic to severe illness with fatal outcome. The symptomatic cases are categorized as undifferentiated febrile illness, dengue fever, dengue hemorrhagic fever and dengue shock syndrome<sup>[82]</sup>. Etiologic diagnosis can be obtained by virus isolation, detection of NS1 antigen, DENV RNA or specific IgM and IgG antibodies<sup>[83]</sup>. SOT recipients showed a spectrum of clinical manifestations similar to the non-transplant population. However, the course of the illness can be prolonged with complications such as graft dysfunction. Fatal cases were also reported<sup>[84-86]</sup>. A Thai study analyzed outcomes of DENV infection in a large cohort of kidney transplant recipients. Although a transient decline in allograft function occurs in some patients, the overall clinical and allograft outcomes seemed to be favorable<sup>[87]</sup>. A Colombian study on retrospective case series of SOT recipients with DENV infection showed that regarding the clinical course, 75% of patients had at least one warning sign, 45% were managed in the intensive care unit, and 30% had severe dengue. However, all patients had a full recovery after the infection<sup>[88]</sup>. In contrast, a study from India showed that early post-transplant DENV infection appears to be severe and associated with more complications in kidney transplant recipients<sup>[89]</sup>. There have been limited descriptions of possible DENV transmission through SOT, of which the majority are classified as possible transmission due to the lack of DENV RNA confirmation in the donor<sup>[81,90,91]</sup>. A case of DENV transmission from donor to the recipient after liver transplantation was described in India. The recipient developed dengue fever without showing any features of severe graft dysfunction and recovered fully<sup>[81]</sup>. Several studies in SOT recipients who developed dengue through organ transplantation showed that the liver was the main target organ in all patients, even in subjects that received heart and kidney transplantation. Transplant patients were more likely to present with elevated liver transaminases and hyperbilirubinemia, suggesting that the liver could be more

susceptible to DENV or is generally more compromised in transplant recipients<sup>[81,91,92]</sup>. A recently published study from India presented the first report on the detection of DENV in the donor cornea indicating the risk of iatrogenic DENV transmission through corneal transplantation<sup>[93]</sup>. To avoid DENV transmission by organ or tissue transplantation, the donors should be screened in endemic areas.

### **WNV**

WNV is one of the most widely distributed emerging mosquito-borne flaviviruses. In a natural cycle, the virus is maintained in a bird-mosquito-bird cycle. Transmission to humans occurs through the bite of *Culex* mosquitoes<sup>[94]</sup>. Approximately 80% of immunocompetent individuals infected with WNV remain asymptomatic while 20% develop mild febrile disease (WNV fever). Less than 1% of infected individuals, mainly immunocompromised and elderly develop neuroinvasive disease (meningitis, encephalitis, myelitis)<sup>[95]</sup>. Diagnosis is confirmed by the detection of WNV IgM and IgG antibodies in serum/CSF with confirmation by virus neutralization test in samples with cross-reactive antibodies<sup>[96]</sup>. Since WNV IgM antibodies may persist up to 500 d in some patients, IgG avidity differentiates current/recent WNV infection from persistent IgM seropositivity from the previous WNV transmission season<sup>[97]</sup>. WNV RNA can be detected in blood, CSF and urine samples using RT-PCR, but molecular methods are less sensitive than serology<sup>[98]</sup>. WNV has been identified as a cause of both donor-derived and post-transplant infection<sup>[99]</sup>. WNV transmission by organ transplantation was first reported in 2002<sup>[100]</sup>. Thereafter, there are many reports on donor-derived or naturally acquired WNV infection in the adult transplant population<sup>[101-108]</sup>. Although WNV infection is associated with higher mortality in the transplant patients<sup>[105,108,109]</sup> there are some reports on WNV in SOT recipients with a complete recovery as well as asymptomatic infections<sup>[108,110]</sup>. Few reports describing post-transplant WNV neuroinvasive disease in pediatric patients showed a complete recovery in all patients<sup>[104,111,112]</sup>. In the light of the WNV (re-) emergence, clinicians should be aware that SOT recipients could be exposed to WNV *via* multiple sources. Therefore, WNV should be included in the differential diagnosis in all patients presenting with fever and neurological symptoms after transplantation during the arbovirus transmission season.

### **Usutu virus**

Usutu virus (USUV) is a mosquito-borne flavivirus that emerged in Europe in 1996<sup>[113]</sup>. The natural cycle, geographic distribution and clinical symptoms of USUV overlap with WNV. Although human clinical cases of USUV infection are rarely reported, several recently published reports highlight its role in the etiology of neuroinvasive diseases<sup>[114-117]</sup>. Like WNV, the majority of USUV infections are asymptomatic or present as a non-specific febrile disease (USUV fever)<sup>[117]</sup>. Neuroinvasive disease was reported in both immunocompetent and immunocompromised patients in Italy, Croatia, and Hungary<sup>[114,116,118,119]</sup>. In addition, some atypical presentations such as facial paresis have also been described<sup>[120]</sup>. However, there is only one published report on USUV infection in a transplanted patient in Italy. The patient who underwent an orthotopic liver transplant developed neuroinvasive disease in the post-transplant period<sup>[121]</sup>. Since many of USUV cases remain underdiagnosed or misdiagnosed as WNV due to similar clinical symptoms and serological cross-reactivity, clinicians should keep in mind this viral zoonosis, especially during the arbovirus transmission season.

### **Eastern equine encephalitis virus**

Eastern equine encephalitis virus (EEEV) is a mosquito-borne alphavirus endemic to eastern North America. In nature, the virus spreads between *Culiseta melanura* mosquitoes found in forested wetlands. Mosquitoes of *Aedes* and *Culex* genera may transmit EEEV to humans<sup>[122]</sup>. Most persons infected with EEEV are asymptomatic or they present with a non-specific febrile illness, while less than < 5% develop neuroinvasive disease (meningitis, encephalitis). The case fatality rate is around 50% and many survivors suffer residual neurological sequelae<sup>[123]</sup>. There is only one report of organ-derived EEEV. In autumn 2017, three SOT recipients (lung, heart, liver) from a common donor developed encephalitis one week after transplantation. Lung and liver recipients died, while the heart recipient survived but had residual tremor. The donor and all organ recipients showed laboratory evidence of EEEV. The fact that all SOT recipients developed encephalitis suggests that the risk of neuroinvasive disease may be increased with this route of transmission. EEEV should be considered in SOT recipients who develop encephalitis after transplantation, particularly if donors and recipients reside in endemic areas of the USA<sup>[124]</sup>.

### **Leishmania spp.**

Leishmaniasis is a cosmopolitan zoonosis caused by the protozoan parasite of the



genus *Leishmania*. It is transmitted by the bite of phlebotomine sandflies of the genus *Phlebotomus* (in the Old World) or *Lutzomyia* (in the New World). So far, at least 20 different *Leishmania* species have been associated with human infection. Clinical presentation of leishmaniasis includes cutaneous (CL), mucocutaneous (MCL), or visceral leishmaniasis (VL)<sup>[125]</sup>. CL occur in three different forms: Localized, diffuse and disseminated. CL is characterized by single or multiple skin ulcers, satellite lesions, or nodular lymphangitis. MCL present with mucosal tissue metastasis in the mouth and upper respiratory tract *via* lymphatic or hematogenous dissemination. VL is the most severe form of leishmaniasis and if untreated it is fatal in 95% of patients<sup>[125,126]</sup>. VL is usually caused by *Leishmania donovani* or *L. infantum* although other *Leishmania* species that usually cause CL have been described causing VL too<sup>[125]</sup>. Clinical presentation of VL is nonspecific with prolonged fever, anorexia, weight loss and overall poor health status. Typically the patients have hepatosplenomegaly and lymphadenopathy and in laboratory examination pancytopenia is frequently found<sup>[127]</sup>. The worldwide number of VL cases in SOT recipients has steadily increased since the 1990s, although VL is still a rare disease among transplant recipients<sup>[128]</sup>. VL is the most frequently observed clinical presentation in this population, followed by MCL and more rarely CL. Fever is the most common symptom of VL in SOT recipients, whereas organomegaly may be less frequent in SOT recipients than in immunocompetent individuals. Immunosuppression seems to predispose to development of MCL caused by viscerotropic strains<sup>[128-130]</sup>. Clinical presentation in these patients is almost the same as in immunocompetent persons although sometimes it can be atypical making it much more difficult for the diagnosis, therefore it is frequently overlooked or delayed in transplant patients. The combination of conventional and molecular diagnostic methods may serve as the best approach<sup>[130]</sup>.

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## NON-VECTOR-BORNE ZOOSES

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### **Hepatitis E virus**

HEV is a non-enveloped RNA virus that belongs to the family *Hepeviridae*. Genotypes 1 and 2 are restricted to humans only, while 3 to 8 are zoonotic genotypes. In fragile sanitary infrastructure (*e.g.* Asia, Africa, Mexico) genotypes 1 and 2 usually cause human diseases, whereas genotypes 3 and 4 are nowadays found to be the most common genotypes in high-income countries<sup>[131]</sup>. Waterborne, zoonotic and foodborne transmissions are the most common routes of infection, with the primary reservoirs (Europe) being domestic pigs, wild boars, and deer<sup>[131]</sup>. Parenteral transmission, transmission *via* solid organs and blood components has been increasingly recognized<sup>[131,132]</sup>. HEV is diagnosed through serology and nucleic acid amplification test, although, only HEV RNA testing is recommended for the immunocompromised population<sup>[131]</sup>. Hepatitis E virus infection typically manifests as an acute self-limiting hepatitis, but may also present as fulminant hepatitis (pregnant women) or acute-on-chronic liver failure in patients with pre-existing liver diseases or extra-hepatic manifestations<sup>[131,132]</sup>. After solid-organ transplantation, genotype 3 and 4 HEV can be responsible for chronic hepatitis (positive HEV RNA > 6 mo) where the majority of cases are asymptomatic accompanied by mild liver test abnormalities. Chronic infections may rapidly progress to liver fibrosis and cirrhosis<sup>[133]</sup>. Thus far, there have been numerous reports of chronic hepatitis E in the liver, kidney, heart, lungs, liver-kidney, kidney-pancreas, islet cell recipients<sup>[133,134]</sup>. Furthermore, extrahepatic manifestations are also common in SOT recipients, including neurological (neuralgic amyotrophy, Guillain-Barré syndrome, encephalitis, myelitis)<sup>[135]</sup>, renal manifestations (membranoproliferative and membranous glomerulonephritis)<sup>[136]</sup>, as well as thrombocytopenia<sup>[135]</sup> and cryoglobulinemia<sup>[136]</sup>. After an acute infection, one third of the patients will clear the virus after the reduction of immunosuppression<sup>[131]</sup>. In other patients (about 60%), the infection will typically progress to chronic forms and lead to the need for additional treatments<sup>[131,133]</sup>. A recent multi-center study which included 255 solid organ transplant recipients, confirmed that ribavirin is highly efficient for treating chronic HEV infection and that HEV RNA polymerase mutations do not play a role in HEV clearance<sup>[137]</sup>.

### **Rabies virus**

Rabies virus (RABV) is a neurotropic lyssavirus that belongs to the family *Rhabdoviridae*. With some exceptions (particularly islands), the RABV is found worldwide, however almost all human deaths caused by RABV occur in Asia and Africa. Typical reservoirs of RABV are domestic dog (Africa and Asia), jackal (Africa), mongoose (Africa), fox (Europe, Asia, America), raccoon (America), skunk, coyote (America) and bats (Europe, Australia, America). Humans become infected by the bite



of infected animals or by contact with infectious saliva through mucous membranes or breaks in the skin<sup>[138]</sup>. Human-to-human RABV transmission may occur through tissue or organ transplantation. The first case of RABV transmitted through corneal transplantation was reported in 1978 in the USA<sup>[139]</sup>, followed by several other reports<sup>[140-142]</sup>. However, rabies transmission through SOT transplantation has rarely been reported. In 2004 (USA), four recipients of a liver, kidneys and an arterial segment from a common organ donor with unrecognized rabies developed encephalitis within 30 d after transplantation. The patients presented with fever and altered mental status (confusion, agitation, tremors, and delirium). All patients died within 50 d after transplantation<sup>[143]</sup>. In 2013, a patient died of rabies 18 mo after receiving a deceased-donor kidney transplant in the USA. Three other recipients (kidney, heart, and liver) did not show symptoms consistent with rabies or encephalitis. All received post-exposure prophylaxis with rabies immune globulin and vaccine and remain asymptomatic<sup>[144]</sup>. The transmission of RABV through SOT has become a notable problem in China. In 2015, two patients who received kidney transplants from the same donor presented with typical symptoms of rabies and eventually died. In 2016, infected donor organs were transplanted to three patients. Two recipients that were diagnosed with rabies died<sup>[145]</sup>. In 2016, another two cases of RABV transmission through SOT were reported in China. Two kidney transplant recipients died, whereas a liver recipient did not show any signs or symptoms of rabies or encephalitis<sup>[146]</sup>. A case of RABV transmission through a kidney transplant was also reported in a child in Kuwait<sup>[147]</sup>. Since the mortality rate of rabies is extremely high, rabies should be considered in patients with acute progressive encephalitis of unexplained etiology, especially for potential organ donors<sup>[144]</sup>.

### **Lymphocytic choriomeningitis virus**

Lymphocytic choriomeningitis virus (LCMV) is an Old World arenavirus distributed in Europe and Americas. The main reservoir of LCMV is a house mouse (*Mus musculus*, *Mus domesticus*), but some other rodents including pet animals may also transmit the virus<sup>[148]</sup>. LCMV transmission to humans occurs by inhalation of aerosolized excreta/secretions of infected rodents (urine and saliva), bites and contact with rodent blood<sup>[149]</sup>. LCMV infection in immunocompetent individuals is typically asymptomatic or it presents as nonspecific febrile illness or aseptic meningitis<sup>[99]</sup>. In contrast, immunocompromised hosts such as transplant recipients develop severe infection with multisystem organ failure and high mortality rate. Several clusters of organ-transplant-associated LCMV infections have been reported in the USA from 2003 to 2013. Signs and symptoms suggestive of LCMV infection occurred in clusters of SOT recipients, in 2003 and 2005. Laboratory testing revealed the LCMV in all the recipients, however, the virus could not be detected in donors. Seven of eight recipients died, 9-76 d after transplantation. In the 2005 cluster, the donor reported contact with a hamster pet, infected with an LCMV strain identical to that detected in the organ recipients. No source of infection was found in the 2003 cluster<sup>[150]</sup>. In 2010-2011, four clusters of organ-transplant-associated LCMV transmissions have been reported; 11 of 14 recipients died<sup>[151]</sup>. The majority of patients with fatal donor-derived LCMV infection showed hepatitis as a prominent feature<sup>[99]</sup>. In a recently published study, a case of LCMV infection in a renal transplant recipient that was non-organ donor-derived was described. The patient presented with meningoencephalitis acquired by the exposure to mice excreta. The clinical course was complicated by the development of hydrocephalus, requiring a ventriculoperitoneal shunt<sup>[152]</sup>. Although the risk of LCMV among organ recipients is low, clinicians should be aware of the possibility of transplant-transmitted LCMV infection.

### **Toxoplasma gondii (Toxoplasmosis)**

Toxoplasmosis is a zoonotic disease caused by a protozoan *Toxoplasma gondii*. It is an obligate intracellular parasite that is widely spread all over the world. Warm-blooded vertebrates are the intermediate hosts where asexual reproduction takes place. This results in the formation of tachyzoites and bradyzoites. Tachyzoites can invade various tissues *e.g.* lungs, CNS and heart but also, they can cause intrauterine infection with possible transplacental transmission to the fetus. Bradyzoites form the tissue cysts in the intermediate host. Felids are the only definite hosts where sexual reproduction occurs resulting in excretion of oocysts into the environment *via* feces. Transmission to humans occurs through the ingestion of water, vegetables, or soil contaminated with oocysts or raw or undercooked meat containing tissue cysts with bradyzoites<sup>[153]</sup>. The worldwide prevalence of toxoplasmosis in the human population varies from 10 to 80%<sup>[154,155]</sup>. The course of infection is generally benign and most infected individuals remain asymptomatic or mildly symptomatic. The disease may have an acute or chronic form. The presence of bradyzoites in tissue cysts represents the latent infection which can reactivate at any age. Prenatal transplacental infection

can result in intrauterine fetal growth retardation, hepatosplenomegaly, eye and/or brain damage, fetal death or premature birth. If symptomatic, postnatal toxoplasmosis can present as fever with lymphadenopathy. Chorioretinitis as a manifestation of acquired toxoplasmosis is seen less frequently. Rarely, a potentially fatal disseminated disease, myocarditis, pneumonitis, hepatitis, myositis or encephalitis can be seen in an immunocompetent patients<sup>[156]</sup>. Toxoplasmosis as an infectious complication is a well-recognized entity in SOT recipients. If it presents in the first three post-transplant mo, the graft transmission is most likely, but if it presents after this early period, most often it is the result of the latent infection reactivation or the primary infection. Clinical presentation in SOT patients is more severe as cerebral, disseminated and pulmonary toxoplasmosis is seen more often than mild forms (fever and ocular toxoplasmosis). Even more severe forms with higher mortality are seen in graft transmission<sup>[157,158]</sup>. As toxoplasmosis in SOT patients might be a fatal disease and as at the same time it is a preventable infection, clinicians have to follow the screening and chemoprophylaxis guidelines to optimize the patient's outcome.

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## CONCLUSION

This article summarizes the most important emerging and neglected zoonotic pathogens and their clinical presentations in the transplant population. In recent decades, human activities along with climatic changes have led to the shifts in environmental conditions influencing among others, the transmission and distribution of zoonotic pathogens. As the number of zoonotic diseases is increasing, the spreading trends are likely to continue in the future. In parallel, the expanding transplant population worldwide imposes additional challenges for diagnostics and treatment of zoonotic infections. Immunosuppressed state may influence the serologic response and delay diagnosis, modify and aggravate clinical presentation and prolong treatment and recovery. Keeping that in mind is of particular importance in the context of emerging and neglected pathogens which may not be familiar to the wider community of transplant professionals in different geographical locations. The increasing trend of the pathogens transmitted and shared between animals and humans in global and especially transplant population, emphasizes the need for the multidisciplinary approach ("One Health") in the surveillance and control of zoonotic infections around the world.

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## ACKNOWLEDGEMENTS

This study was supported in part by the Croatian Science Foundation, project No. IP 2016-06-7456: Prevalence and molecular epidemiology of emerging and re-emerging neuroinvasive arboviral infections in Croatia; CRONEUROARBO (to TVC).

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