

USUTU VIRUS IN ROMANIA CURRENT KNOWLEDGE AND FUTURE PERSPECTIVES

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Abstract: Usutu virus (USUV) is a mosquito-borne flavivirus that has been emerging across southern and Central Europe since 2001. USUV is maintained by cycling through birds and mosquitoes and is accidentally transmitted to mammals. It shares many features with West Nile virus including a close phylogenetic relatedness and a co-circulation frequently observed in nature. The virus caused large outbreaks of severe neurological disease in birds, especially in blackbirds and, symptomatic neurological human cases. Continuous USUV activity confirmed by the detection or serologic evidence of USUV in birds, humans, horses, mosquitoes, and bats since 2001 indicates the endemization in many Southern and Central European countries. However, due to a limited number of human USUV infections, the zoonotic potential and clinical relevance of USUV need to be further investigated. It is considered that, since the virus activity in birds has increased, also human infection might become more frequent. Eastern Europe and Romania have reported little data concerning USUV. The present paper is aiming to discuss/describe the current state and future perspectives of USUV research in our country.

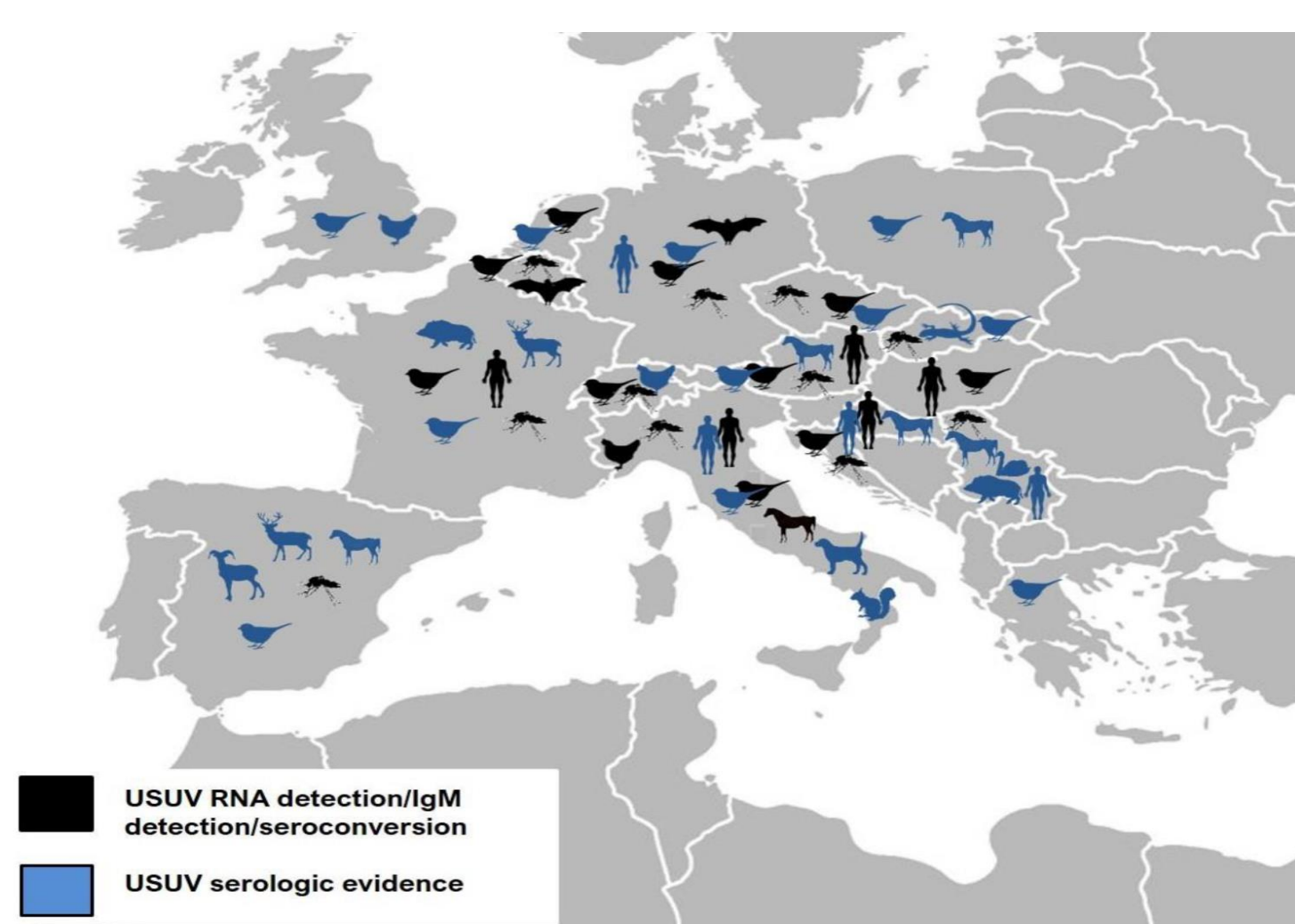
Key words: mosquito-borne flavivirus, Usutu virus, opinion, Romania

•Introduction

USUV is a mosquito-borne flavivirus that has been emerging across southern and Central Europe since 2001. Originally non-pathogenic, USUV was first recognized and isolated in 1959 from *Culex neavei* mosquitoes collected near the Usutu River, in South Africa. Subsequently, USUV dispersed on the African continent and in recent decades, was found to circulate in European countries. Usutu shares genetic and antigenic similarities with WNV, alongside belonging to the family *Flaviviridae*. In addition, they share the same vector species and avian reservoirs involved in the transmission cycle.

•Introduction in Europe and genetic diversity of Usutu virus

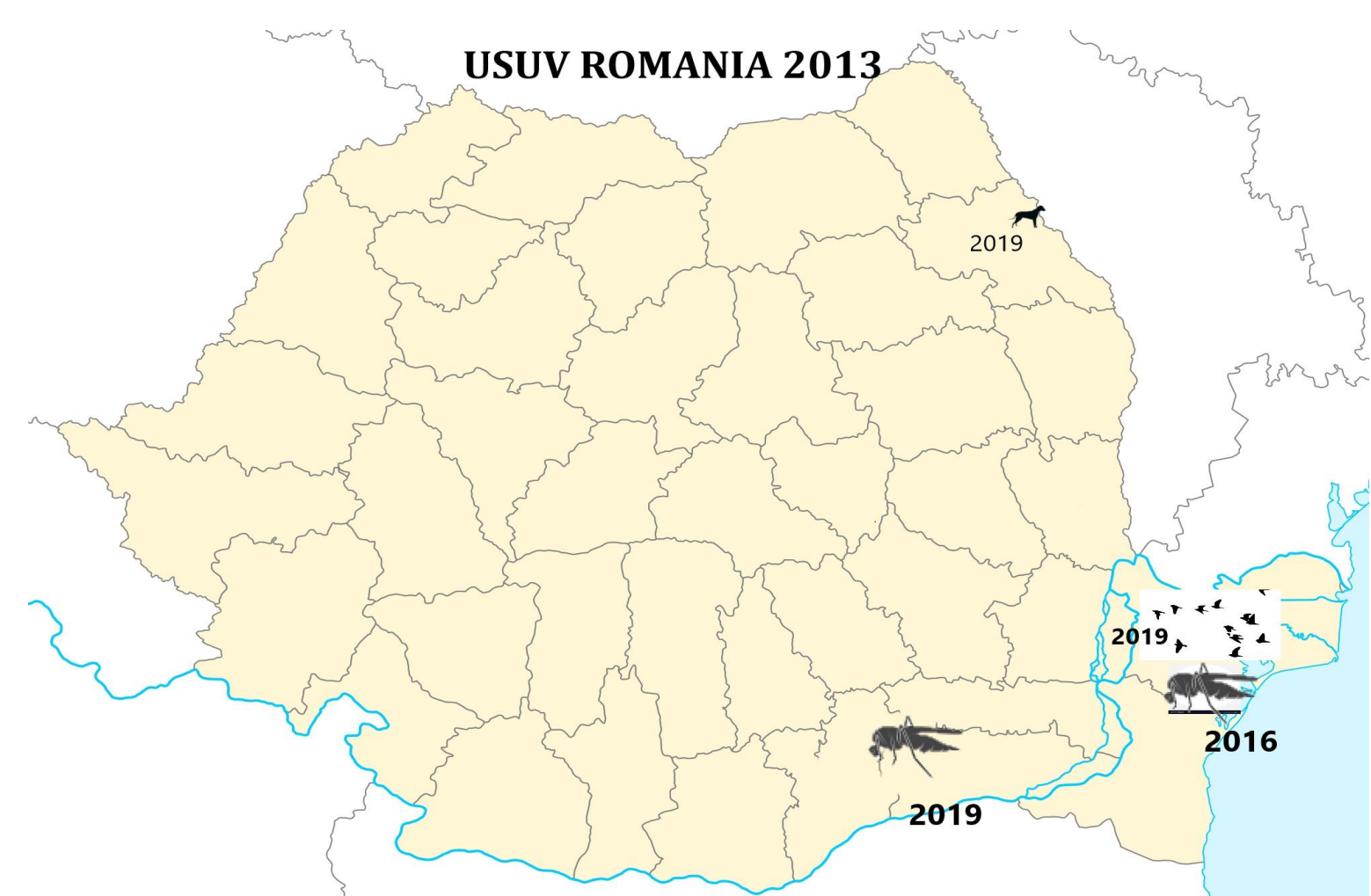
The first demonstration of USUV circulation was reported in Austria in 2001, with a silent viral circulation retrospectively recognized in 1996–2001. In 2018, the virus spread rapidly in Western Europe, associated with a large epidemic of WNV, suggesting both the continued expansion of the virus and the colonization of new ecological niches. In the subsequent years, USUV had an extensive spread in Europe. Based on the origin of the isolates, USUV can be divided into eight genetic lineages clustered into two groups: African and European. Strain from Africa belong to three lineages (Africa 1 to 3) and the European group comprises five distinct lineages (Europe 1 to 5).



Geographic distribution of Usutu virus in Europe (Vilibic-Cavlek et al., 2020)

•Zoonotic potential of USUV

Clinical manifestations in USUV infections are similar to WNV, leading to misdiagnosis and suboptimal case management. With both viruses being circulated by the same vector species for over two decades, their co-circulation represents a concern for public health. The zoonotic potential of the virus has been highlighted by seroprevalence studies suggesting that USUV can be, in most cases, asymptomatic or associated with mild forms. The symptomatic phase of the infection is usually characterized by moderate fever, sometimes associated with skin rashes and febrile jaundice. In rare cases, in patients with other comorbidities, the infection has been described with neurological manifestations, meningitis and meningoencephalitis. It is considered that significant circulation of USUV in both reservoirs and vectors, at a given time and place, increases the relevance and probability of human cases.



• Research in Romania

While WNV is endemic in certain areas of Romania, few data regarding USUV infections have been documented.

In animals, USUV antibodies were documented for the first time in 2020, in a domestic dog sampled in 2019. **In avian hosts** a retrospective study on migratory and resident birds from the South-Eastern region of Romania sampled in 2018-2019, showed a 2.71% seroprevalence for USUV and 8.72% for WNV. Even so, seroprevalence data are still very scarce for assessing the incidence of USUV.

In humans a study on healthy blood donors from north-western Romania sampled between 2019-2020 showed a 0% seroconversion for USUV.

In mosquitoes collected between 2014 and 2016 in rural/urban areas (Letea, Sulina) in the DDBR one mosquito (*Anopheles hyrcanus*) that fed on a dog in Sulina, was positive for USUV specific antibodies. The study published in 2019 by Tomazatos et al., is the first indication of USUV in Romania in vector species.

Recently, a retrospective molecular study published by Prioteasa et al., showed that USUV was detected by real-time RT-PCR in *C. pipiens s.l.* collected from Bucharest in 2019 and that the virus belongs to the Europe 2 lineage (EU2) (2023).

•Recommendations and conclusion

Considering that USUV spreading is likely to continue, multidisciplinary interventions in the frame of the "One Health" concept, should be conducted to increase public awareness and implement appropriate monitoring and prevention methods for this emerging arboviral infection. The true prevalence, regional range, and seasonality of USUV infection still needs to be determined. An integrated veterinary and human surveillance system, is needed to estimate USUV risk and spatial dynamics.

The recent findings in Romania confirm the virus presence and raise a concern. We consider that similar to other European areas, in our country, due to its co-circulation, antigenic relatedness and similar clinical outcome with WNV the detection of USUV is suboptimal.

The first signals in Romania were registered starting with 2016 but more data showed a higher percent of positivity in animals and vectors in 2019. This can be considered as a starting point for the virus introduction in the country.