44 | USUTU VIRUS

44.1 | Disease agent

- Usutu virus (USUV)

44.2 | Disease agent characteristics

- Family: *Flaviviridae*; Genus: *Flavivirus*; closely related to West Nile virus (WNV) and belonging to Japanese encephalitis virus serogroup.
- Virion morphology and size: Enveloped, icosahedral nucleocapsid symmetry, spherical particles, 40–60 nm in diameter.
- Nucleic acid: Linear, positive-sense, single-stranded RNA genome, ~11.0 kb in length
- Physicochemical properties: Inactivated by heating for 10 min at >56°C; half-life of 7 h at 37°C; sensitive to treatment with lipid solvents, detergents, ether, trypsin, chloroform, formaldehyde, and β-propiolactone; infectivity reduced after exposure to irradiation and inactivated at pH 1–3.

44.3 | Disease names

- Usutu fever

44.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Theoretical: transfusion transmission of USUV is a theoretical risk as viral RNA has been detected in donated blood products. However, no cases of USUV transfusion transmission have been documented to date.
- Public perception and/or regulatory concern regarding blood safety: Absent in non-endemic areas. Low to moderate in endemic areas.
- Public concern regarding disease agent: Absent in nonendemic areas. Low to moderate in endemic areas and during epidemics.

44.5 | Background

- USUV was first identified in mosquitoes in 1959 in South Africa. USUV has also been detected in birds, mosquitoes, and, rarely, humans in several other African countries. According to phylogenetic studies, USUV has been introduced at least 3 times in Europe along migratory bird routes from Africa. USUV has spread throughout Europe over the last 2 decades and has been detected serologically and/or molecularly in birds and mosquitoes in at least 15 European countries (including the UK), and Israel. Some countries have identified USUV in mammals (horse, dogs, bats), though these are thought to be incidental hosts.
- USUV co-circulates in endemic areas with the closely related WNV from late spring into the fall in temperate climates. It demonstrates high cross-reactivity on WNV serologic and nucleic acid tests, leading to an underestimation of USUV prevalence in areas where both viruses are endemic.
  - USUV was implicated in neuroinvasive disease in two immunosuppressed patients in northern Italy (one an orthotopic liver transplant patient who was viremic immediately prior to the transplant and one following chemotherapy). USUV RNA was detected by RT-PCR in the plasma of both patients and virus was isolated from the blood in one patient and CSF in the other; in both cases, sequencing revealed 98% identity with known USUV isolates. Infection in both cases occurred while USUV was circulating in the area; prior to these two cases, USUV had not been associated with neurological disease in humans. In one of the cases, the patient was identified due to low-level NAT reactivity.
- Surveillance studies in the European Union have detected USUV RNA in donated blood products.

44.6 | Common human exposure routes

- Vector-borne (primarily *Culex* spp.)

44.7 | Likelihood of secondary transmission

- Undocumented, although it can infect human placental explants and in mice can cause occasional fetal demise and congenital defects, raising the question of vertical transmission and its potential morbidity.

44.8 | At-risk populations

- The primary geographic distribution of USUV is in Africa and Europe.
- Specific at-risk populations are unknown, but case reports suggest that immunocompromised persons and those with underlying chronic illness may be at higher risk for clinical disease.

44.9 | Vector and reservoir involved

- USUV is maintained through an enzootic cycle in birds, mainly passerines (over half of all bird species) and Strigiformes (owls) acting as amplifying hosts, and ornithophilic mosquitoes, such as *Culex* spp., as vector. Retrospective studies have shown it to be responsible for blackbird die-off in Italy.
- Humans and other mammals (e.g., horses, dogs, rodents, and wild boars) are dead-end hosts because they do not develop adequate viral concentrations to infect mosquitoes.

44.10 | Blood phase

- Asymptomatic viremia is recognized for USUV but has not been well characterized for duration and magnitude.

44.11 | Survival/persistence in blood products

- Surveillance studies in the European Union have detected USUV RNA in donated blood products from asymptomatic donors.

44.12 | Transmission by blood transfusion

- As of 2022, there are no published cases of transfusion-transmitted USUV.

44.13 | Cases/frequency in population

- Found in sub-Saharan Africa and detected in at least 15 European countries (including the UK), and in Israel.
- Documented cases of acute USUV infection (USUV RNA-positive) are rare, most of which were detected in donated blood products from asymptomatic donors.
- Seroprevalence studies conducted in Italy, Serbia, and Germany reported USUV-antibody prevalence in blood donors to be 0.02%–1.1%. Serological cross-reactivity among the Japanese encephalitis virus serogroup is relatively common.

44.14 | Incubation period

- Unknown

44.15 | Likelihood of clinical disease

- Considered to be very low

44.16 | Primary disease symptoms

- Most infections are asymptomatic; however, clinical illness has been described in several case reports. Symptoms have included fever, rash, jaundice, facial paralysis, encephalitis, and meningoencephalitis.

44.17 | Severity of clinical disease

- Severe USUV infection is very rare. Cases of neuroinvasive disease have mostly been limited to patients who are immunocompromised or have underlying chronic illnesses.
- Two cases of symptomatic infection have been described in Africa with fever and skin rash but no neurologic symptoms; To date, 112 infections have been described in Europe, most without symptoms but with 30 having some neurologic complications.

44.18 | Mortality

- No USUV associated fatalities have been reported to date.

44.19 | Chronic carriage

- Not documented following Usutu infections although identified uncommonly in Japanese encephalitis virus infections.

44.20 | Treatment available/efficacious

- Supportive; no specific anti-viral treatment is available.

44.21 | Agent-specific screening question(s)

- No specific question is in use.
- No sensitive or specific question is feasible.

44.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening tests exist for USUV.

- USUV demonstrates high cross-reactivity and direct detection with WNV serologic and NAT assays respectively.
  - On sequencing and virus-specific testing, 6 of 7 donors testing reactive with the cobas WNV RT-PCR test (Roche) among 12,047 Austrian donors were infected with USUV. No assay has regulatory clearances for the detection of USUV RNA in blood donors.
- Serology on paired serum samples showing four-fold rise in titer by neutralization, CF or HI is diagnostic.
- NAT and viral sequencing

44.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- In the European Union, where USUV NAT-reactive donors have been identified, a minimum 28-day deferral is applied, as is done for WNV, with some jurisdictions using longer intervals up to 120 days.
- In the United States, the FDA required donor deferral for WNV NAT reactivity is 120 days. It may be prudent to apply this deferral for USUV in the United States should it be detected in the future.

44.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

44.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

44.26 | Leukoreduction efficacy

- Unknown

44.27 | Pathogen reduction efficacy for plasma derivatives

- Multiple pathogen reduction steps used in the fractionation process have been shown to be robust in removal of enveloped viruses.

44.28 | Other prevention measures

- Mosquito control and avoidance.
- Flaviviruses are inactivated by multiple pathogen reduction processes that are available or in development for labile components.

SUGGESTED READING

1. Bakonyi T, Jungbauer C, Aberle SW, Kolodziejek J, Dimmel K, Stiasny K, et al. Usutu virus infections among blood donors, Austria, July and August 2017—raising awareness for diagnostic challenges. Euro Surveill. 2017;22(41): https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2017.22.41.17-00644. Accessed 12 Dec 2022
2. Cadar D, Simonin Y. Human usutu virus infections in Europe: a new risk on horizon? Viruses. 2023; https://www.mdpi.com/1999-4915/15/1/77. Accessed 19 Jan 2023
3. Clé M, Beck C, Salinas S, Lecollinet S, Gutierrez S, Van de Perre P, et al. Usutu virus: a new threat? Epidemiol Infect. 2019;147:e232. https://doi.org/10.1017/S0950268819001213 Accessed 12 Dec 2022.
4. Domanovic D, Grossner CM, Leishout-Krikke R, Mayr W, Baroti-Togh K, Dobrota AM, et al. West Nile and Usutu virus infections and challenges to blood safety in the European Union. Emerg Infect Dis. 2019;25:1050–7.
5. European Centers for Disease Control. Widespread activity of multiple lineages of Usutu virus, western Europe, 2016. Eurosurveillance. 2016. https://doi.org/10.2807/1560-7917.ES.2017.22.4.30452 Accessed 19 Jan 2023.
6. Gaibani P, Pierro AM, Cavrini F, Rossini G, Landini MP, Sambri V. False-positive transcription-mediated amplification assay detection of West Nile virus in blood from a patient with viremia caused by an Usutu virus infection. J Clin Microbiol. 2010;48:3338–9.
7. Martin H, Barthelmy J, Chin Y, Bergamelli M, Moinard N, Cartron G, et al. Usutu Virus infects human placental explants and induces congenital defects in mice. Viruses. 2022;14:1619–35.
8. Percivalle E, Cassaniti I, Sarasini A, Rovida F, Adzasehoun KMG, Colombini I, et al. West Nile or Usutu virus? A three-year follow-up of humoral and cellular response in a group of asymptomatic blood donors. Viruses. 2020;12. https://doi.org/10.3390/v12020157 Accessed 12 Dec 2022.
9. Pecorari M, Longo G, Gennai W, Grottola A, Sabbatini A, Tagliazucchi S, et al. First human case of Usutu virus neuroinvasive infection, Italy, August-September 2009. Euro Surveill. 2009;14. https://doi.org/10.2807/ese.14.50.19446-en Accessed 12 Dec 2022.
10. Roesch F, Fajardo A, Moratorio G, Vignuzzi M. Usutu virus: an arbovirus on the rise. Viruses. 2019;11. https://doi.org/10.3390/v11070640
11. Vilibic-Cavlek T, Petrovic T, Savic V, Barbic L, Tabain I, Stevanovic V, et al. Epidemiology of Usutu virus: the European scenario. Pathogens. 2020;9. https://doi.org/10.3390/pathogens9090699 Accessed 12 Dec 2022.