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MINI-REVIEW

# Usutu virus disease: a potential problem for North America?

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## Abstract

Usutu virus is an emerging mosquito-borne flavivirus initially identified in South Africa in 1959 that is now circulating throughout parts of Africa, Europe, and the Middle East. It is closely related to West Nile virus, and has similar vectors, amplifying bird hosts, and epidemiology. Usutu virus infection can occur in humans and may be asymptomatic or cause systemic (e.g., fever, rash, and hepatitis) or neuroinvasive (e.g., meningitis and encephalitis) disease. Given few reported cases, the full clinical spectrum is not known. No anti-viral treatment is available, but it can be largely prevented by avoiding mosquito bites. Because of similar mosquitoes, birds, and climate to Europe, the potential for introduction to North America is possible.

**Keywords** Usutu · Usutu virus · Flavivirus · Flaviviridae · Arbovirus · Arboviral disease

## Virology and vectors

Usutu virus is an emerging mosquito-borne flavivirus in family *Flaviviridae* (CDC 2018a Arbovirus Catalog). Similar to other flaviviruses, it is a small (40–60 nm), spherical, enveloped, positive-sense ribonucleic acid (RNA) virus (Bakonyi et al. 2004). Classified within the Japanese encephalitis virus serogroup, Usutu virus is closely related to Murray Valley encephalitis, Japanese encephalitis, West Nile, and St. Louis encephalitis viruses (Bakonyi et al. 2004; Poidinger et al. 1996).

*Culex pipiens* appears to be the primary vector for Usutu virus transmission, at least in Europe (Calzolari et al. 2012; Engler et al. 2013; Fros et al. 2015). However, Usutu virus has also been found in other *Culex* and certain *Aedes*, *Anopheles*, *Coquillettidia*, *Culiseta*, *Mansonia*, and *Ochlerotatus* mosquito species (Ashraf et al. 2015; Camp et al. 2019, Engler et al. 2013; Mannasse et al. 2017; Nikolay et al. 2011), though these species' potential roles in transmission is not known. Interestingly, experimental data suggest *Culex pipiens* and *Culex quinquefasciatus* (but not *Aedes albopictus*) may be competent vectors for potential future Usutu virus transmission in North America (Cook et al. 2018).

A wide variety of birds throughout Europe (e.g., blackbirds, doves, jays, magpies, partridges, owls, and sparrows) have been found to carry Usutu virus and may serve as the primary amplifying hosts for mosquito vectors (Ashraf et al. 2015; Calzolari et al. 2012; Chvala et al. 2007; Nikolay 2015). Many of the same or related bird species that likely serve as Usutu virus amplifying hosts in Europe are also found in North America.

Usutu virus has also been found to infect bats, rodents, and other mammals (Cadar et al. 2014; Diagne et al. 2019), but these may be primarily dead-end hosts (i.e., not capable of amplifying the virus and transmitting it other vectors) rather than amplifying hosts. Humans, when infected with Usutu virus (or similarly with West Nile virus), are also are thought to be incidentally infected dead-end hosts.

Usutu virus has been found to co-circulate with West Nile virus in parts of Europe (Cabanova et al. 2019; Nikolay 2015), and one asymptomatic blood donor in Austria was found to be potentially co-infected acutely with both viruses (Aberle et al. 2018). This co-circulation is not surprising given the two closely related viruses share common amplifying hosts

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(various bird species) and vectors (primarily *Culex* spp. of mosquitoes). Similar co-circulation between West Nile virus and the closely related St. Louis encephalitis virus has been described in North America (Venkat et al. 2015).

## Epidemiology and geographic distribution

Usutu virus was first isolated from *Culex neavei* mosquitoes near the Usutu river in Natal, South Africa, in 1959 (McIntosh 1985; Williams et al. 1964), although it is suspected that Usutu virus emerged in Africa approximately 500 years ago and gradually spread throughout parts of the continent (Engel et al. 2016; Nikolay et al. 2011). The first report of Usutu virus emergence in Europe occurred in 2001 during a widespread bird die-off in Austria (Weissenbock et al. 2002). Analysis of dead bird tissue (from blackbirds, owls, and a swallow) revealed the presence of Usutu virus, and it was initially thought that this represented the first emergence of Usutu virus in Europe. A later retrospective investigation found that Usutu virus was present in tissue samples from Eurasian blackbirds who died during a similar bird die-off in 1996 in Tuscany, Italy, suggesting that Usutu virus was circulating in parts of Europe by 1996 or earlier (Weissenbock et al. 2013).

Usutu virus (or nucleic acid) has since been detected in mosquitoes, birds, or bats in several other European countries including Belgium (Garigliany et al. 2014), France (Lecollinet et al. 2016), Germany (Cadar et al. 2014; Engler et al. 2013; Michel et al. 2019), Hungary (Bakonyi et al. 2007), Slovakia (Cabanova et al. 2019), Spain (Busquets et al. 2008; Engler et al. 2013; Vazquez et al. 2011), and Switzerland (Engler et al. 2013; Steinmetz et al. 2011). Usutu virus has also been detected in mosquitoes in Israel (Mannasse et al. 2017), as well as in mosquitoes or animals in the African countries of Central African Republic, Cote d'Ivoire, Senegal, Nigeria, and Uganda (Diagne et al. 2019; Nikolay et al. 2011). Usutu virus neutralizing antibodies have been found in various animals in other European and African countries (Ashraf et al. 2015; Nikolay et al. 2011; Nikolay 2015), but it is not clear in all cases whether the antibodies produced were against a different infecting flavivirus or, if from Usutu virus infection, where the virus was actually acquired. Regardless, all of this data provides evidence for current or prior Usutu virus circulation throughout parts of Africa, the Middle East, and Europe.

Humans in parts of African and Europe have also been infected with Usutu virus. Usutu virus or nucleic acid has been isolated from symptomatic residents of Burkina Faso (Nikolay et al. 2011), Central African Republic (Nikolay et al. 2011), and more recently France (Simonin et al. 2018) and Italy (Cavrini et al. 2009; Grottola et al. 2017; Pecorari et al. 2009). Usutu virus nucleic acid has also been recently isolated from asymptomatic blood donors in Austria (Aberle et al. 2018; Bakonyi et al. 2017), Germany (Cadar et al. 2017), and the Netherlands (Zaaijer et al. 2019). Additionally, Usutu virus neutralizing antibodies have recently been found in symptomatic residents of Croatia (Santini et al. 2015) and asymptomatic residents (including blood donors) of Germany (Allering et al. 2012) and Italy (Gaibani et al. 2012; Grottola et al. 2017; Percivalle et al. 2017; Pierro et al. 2013).

As Usutu virus infection is likely under-recognized, the full incidence, geographic distribution, and seasonality is yet to be determined (though one might expect more cases occurring in warmer months when other mosquito-borne arboviral diseases tend to occur). Given so few Usutu virus disease cases have been reported in the literature, it is currently difficult to determine any potential age, gender, or other demographic predilections (though most age groups and both sexes have been affected). This may change with future reports of infections.

## Clinical presentation and disease

The asymptomatic rate of Usutu virus infection in humans is not yet known, but asymptomatic infections do occur as evidenced by reports of acutely viremic asymptomatic blood donors (Aberle et al. 2018; Bakonyi et al. 2017; Zaaijer et al. 2019). Based on limited case reports or case series, for those infected who develop symptoms, Usutu virus disease appears to manifest with a systemic or neuroinvasive syndrome.

Systemically, acute infection with Usutu virus has been reported to cause a fever with rash and a fever with jaundice (Nikolay et al. 2011). A transient rash was also described in a blood donor positive for Usutu virus nucleic acid (Aberle et al. 2018). One complicated systemic case involved a woman in her 40s who developed thrombotic thrombocytopenic purpura requiring multiple plasma exchanges followed by fever, rash, and fulminant hepatitis with coma eventually requiring liver transplantation. While she regained consciousness after transplantation, her final outcome was not reported. Her pre-transplant serum sample was later found to be positive for Usutu virus nucleic acid. It is not known when or how she acquired Usutu virus infection, or how it may have contributed to her complex disease course (Cavrini et al. 2009).

Usutu virus infection also appears capable of causing neurologic disease. In laboratory experiments, Usutu virus has been shown to infect mature neurons, human neuronal precursors, microglia and primary human astrocytes (Salinas et al. 2017). It has also been shown to cause neuronal death and demyelination in mice (Weissenbock et al. 2004).

One of the first reported cases of Usutu virus neuroinvasive disease was in an older woman with diffuse large B cell lymphoma on chemotherapy who presented with fever, resting tremor, and anemia requiring blood transfusion (Pecorari et al. 2009). MRI of the brain showed lesions in her substantia nigra and subcortex. Cerebrospinal fluid (CSF) analysis was reportedly unremarkable, but both the serum and CSF were

positive for Usutu virus nucleic acid. She was treated with a course of steroids. Her fever resolved, but her resting tremor remained.

A retrospective analysis on banked CSF samples in Italy from between 2008 and 2011 identified 8 acute Usutu virus neuroinvasive infections among those with various chronic diseases; four had limited clinical descriptions (two cases of meningoencephalitis, one of encephalitis, and one of encephalitis and polyneuritis) (Grottola et al. 2017).

In 2013, three cases of meningoencephalitis (with headache, fever, nuchal rigidity, hand tremor, and/or hyperreflexia) diagnosed as Usutu virus infection on the basis of serologic testing were reported from Croatia (Santini et al. 2015). All had a CSF pleocytosis with elevated protein and normal glucose. Recovery was partial in one and complete in two.

Additional case reports of Usutu virus neuroinvasive disease among healthy adults include an uncomplicated meningitis case that presented with fever, headache, and nuchal rigidity (Nagy et al. 2019) and an acute facial palsy with ptosis, dysgeusia, and unilateral paresthesias (Simonin et al. 2018). Both recovered fully after a few weeks.

Given the limited number of case reports, the possible clinical syndromes, morbidity, and potential mortality of Usutu virus disease are not yet known. More studies are needed to better define its full clinical spectrum.

## Diagnosis and testing

Similar to other arboviral infections, the diagnosis of Usutu virus infection can be confirmed by viral isolation in culture or detection of viral nucleic acid in serum and/or CSF by reverse transcription-polymerase chain reaction (CDC 2015 Arboviral Diseases). Viremia, however, may not be sufficiently high and persistent enough for detection by culture or molecular methods. Serologic testing of serum and/or CSF for antibodies, despite being fraught with potential cross-reactivity and IgM persistence problems, may instead be required for diagnosis. A positive viral-specific immunoglobulin (Ig) M test followed by a confirmatory neutralizing antibody test (e.g., plaque reduction neutralization tests or PRNTs) or a four-fold or greater change in neutralizing antibody titers between acute and convalescent samples are both considered confirmatory for recent arboviral infection (CDC 2015 Arboviral Diseases). Serologic testing results must be interpreted carefully, however, given significant potential cross-reactivity between the Usutu and West Nile virus IgM and even neutralizing antibody tests (CDC 2015 Arboviral Diseases; Llorente et al. 2019).

No commercial Usutu virus tests exist at this time, though some public health reference laboratories may be able to perform testing. Health care providers should contact their local or state health department for assistance with Usutu virus testing.

## Treatment and prevention

Similar to West Nile virus disease (CDC 2018a, b West Nile virus), there are no proven human anti-viral treatments for Usutu virus disease at this time, though favipiravir (a viral RNA polymerase inhibitor) has shown some efficacy in mice (Segura Guerrero et al. 2018). Current management is largely supportive and may include intravenous fluids, anti-pyretic medications, anti-nausea medications, pain control, and/or clinical observation. Patients who develop meningoencephalitis may need to be monitored for elevated intracranial pressure and/or seizures. Consultation with infectious disease and/or neurology specialists may be needed.

Usutu virus is likely primarily transmitted by mosquitoes; therefore, preventing mosquito bites is the best way to prevent Usutu virus disease. People should consider using insect repellent on exposed skin, wearing long-sleeved shirts and pants when feasible, and/or applying permethrin on clothing when spending time outdoors when mosquitoes are active (CDC 2018a, b West Nile virus). Using air conditioning or window screens while indoors will help keep mosquitoes outside. Standing water should be periodically dumped from containers around homes and businesses as well.

There is also a potential risk of Usutu virus transmission through blood transfusion (and possibly organ transplantation by extension) given reports of viremic blood donors (Aberle et al. 2018; Bakonyi et al. 2017; Cadar et al. 2017; Domanovic et al. 2019; Zaaijer et al. 2019), though the exact risk is not known. Blood donors in endemic areas who have been recently sick with a clinical illness compatible with an arboviral disease may want to delay blood donation. Blood donation agencies and regulators may want to assess the risk for transmission in endemic areas and consider updating their testing protocols accordingly. Of note, there have been reports of blood donors with Usutu virus infections testing positive for screening West Nile virus nucleic acid tests (NAT), suggesting potential screening NAT cross-reactivity between these related viruses (Domanovic et al. 2019).

No human vaccine against Usutu virus is currently available, though an experimental DNA vaccine appeared to be protective in mice (Martín-Acebes et al. 2016). It is not known whether previous infection with a closely related flavivirus (e.g., West Nile virus) may protect humans against later infection with Usutu virus, though there is some evidence of partial post-flavivirus infection cross-protection in mice (Blazquez et al. 2015).

## Summary and recommendations

Usutu virus is a mosquito-borne flavivirus currently circulating in parts of Africa, Europe, and the Middle East. It has been reported to co-circulate with West Nile virus at times, and bears many similarities to West Nile virus in terms of virology, transmission, epidemiology, and clinical presentation. Several cases of Usutu virus disease, including neuroinvasive disease, have been reported from Europe and Africa. People in endemic areas should practice mosquito bite prevention, and physicians in endemic areas should consider Usutu virus infection on their differential of patients presenting with a potential arboviral disease.

Although Usutu virus has not been detected in North America, there is a risk of introduction and circulation given similar vectors, amplifying bird hosts, and climates to Europe. Public health surveillance authorities throughout North America should be aware of this possibility.

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### Compliance with ethical standards

**Conflict of interest** Drs. Gill, Kapadia, Beckham, Tyler, and Pastula have no conflicts of interest.

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