



Usutu virus avian and human infection after more than 25 years of circulation

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Usutu virus (USUV), is a mosquito-borne epornitic and zoonotic virus, belonging to the Flaviviridae family and genus *Flavivirus* [1]. USUV was first identified in South Africa, near the Usutu River in 1959 [1]. Its circulation cycle involves a mosquito-bird sylvatic interaction, with mosquitoes acting as biological vectors and birds as amplifying hosts [1].

In birds, episodes of mortality have been linked to severe systemic and neuroinvasive disease with variable susceptibility to the infection and disease development. The highest infection and disease susceptibility are suspected for the Eurasian blackbird (*Turdus merula*) and the great grey owl (*Strix nebulosa*) [2], the two most represented species in published reports. On the contrary, susceptible to the infection but resistant to the development of the disease are domestic chickens [3]. Clinically, only few studies describe general (non-specific) to neurologic (specific) signs in diseased blackbirds (Fig. 1; detailed data on clinical signs are in Table 1 in supplementary materials) [4, 5]. A list of USUV-susceptible species to USUV-associated disease development and USUV-associated lesions has been recently reviewed by Agliani et al. [6]. The impact of this virus on the wild bird population can have cascading consequences on the ecosystem since birds play crucial roles in ecology, such as controlling insect populations and dispersing seeds [7]. Furthermore, mass mortality in susceptible birds can have

negative effects on ecosystem balance and species diversity when considering threatened or endangered species.

Humans are USUV dead-end hosts; the first USUV-associated disease was described in 1959. After this, cases of infections have been commonly reported as asymptomatic [8], but occasional reports of USUV-associated disease in humans have been reported as flu-like syndrome characterized by fever, myalgia, and skin rash, highlighting the importance on the infection and disease surveillance and placing a high concern on organ and blood donors. An increasing trend in the report of human cases of infection has been reported recently by Lupia et al. [9]. In total, up to now, of the total reports of USUV infection, 110 cases of human USUV-associated clinical disease have been reported in Europe, of which 30 were recorded as neuroinvasive diseases as reviewed by Cadar and Simonin [8]. Additionally, only recently, Gaibani et al. [10] reported a fatal case of USUV infection in an old and immunocompromised Italian patient. This suggests that, although humans are only occasionally affected by this virus, cases of infection can have serious consequences, especially for immunocompromised individuals. A graphical summary of the most common reported USUV-associated clinical findings in the literature cases is shown in Fig. 1; data of clinical disease cases is available in Table 2 in the supplementary materials.

Similar to birds, human monitoring is critical to protect public health. Collecting accurate data on human cases, including symptoms, modes of transmission, and incidence, allows to assess the risk to the general population and implement effective preventive measures. Furthermore, currently knowledge is still lacking on the USUV-associated lesions in humans; targeted research can help develop specific treatments for neuroinvasive fatal forms of the disease.

In conclusion, after more than 25 years from its first identification in Europe, USUV still circulates in many European countries with outbreaks of avian and human infections and disease. From the avian perspective, a variable susceptibility

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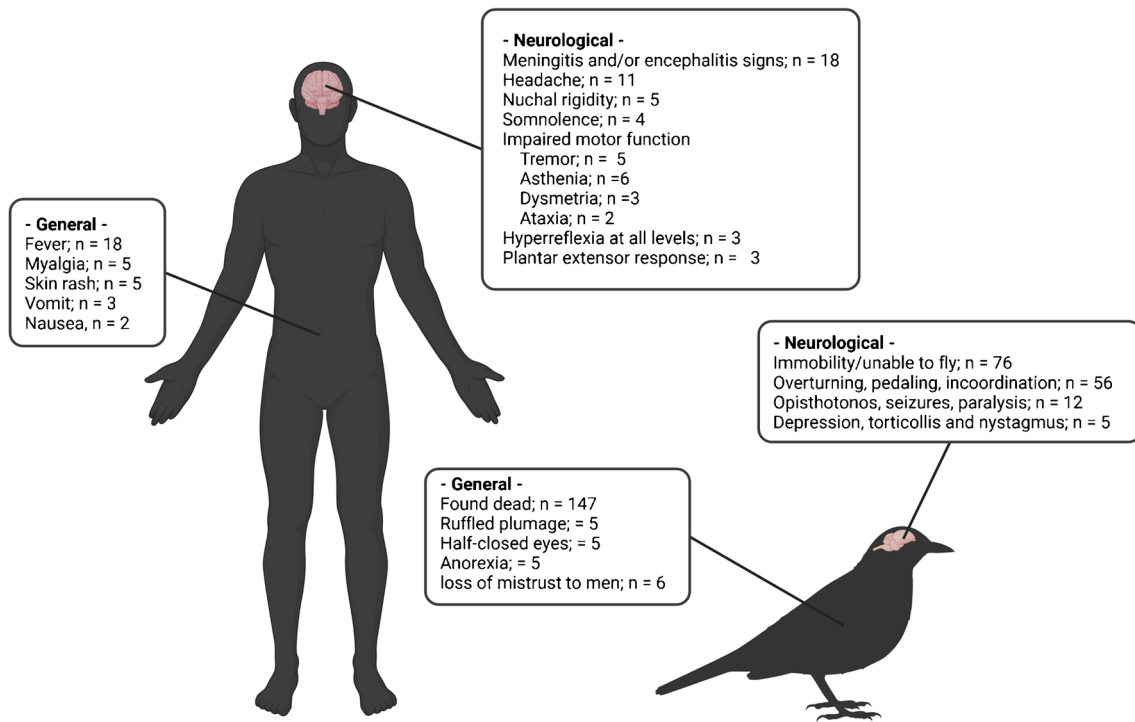


Fig. 1 Summary of common symptoms and signs in human and blackbird cases of USUV-associated clinical disease reported (more than once) in literature. Created with BioRender.com. Detailed data are reported in the supplementary material

to the infection and disease development has been reported in various species, some of them being dramatically affected, and others not showing signs of disease, acting as potential reservoirs. Additional susceptibility and pathogenesis studies are needed to gain new insights and clarify the steps involved in the disease development and progression. From the human perspective, the continuous circulation is reported in blood donors and in sporadic cases of USUV-associated disease. For these reasons, surveillance on both, live and dead birds, as well as mosquito pool testing and blood and organ donor screenings, are necessary keystones in the evaluation of the impact of USUV on animals and human health.

Usutu virus still poses a significant threat to biodiversity and public health, requiring a thorough understanding of its spread, effects, and preventive measures needed to mitigate

its impacts. A call of action should be addressed with collaboration between governments, health care organizations, research institutes, and local communities which is essential to monitor the circulation and evaluate its genetic evolution, pathogenicity, and ability to adapt to new vectors, hosts, or new environmental conditions, aiming to develop effective strategies for prevention and control the impact of USUV on public health.

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Declarations

Competing interests The authors declare no competing interests.

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