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Commentary OMICS International

West Nile Virus Infections in (European) Birds

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Commentary

West Nile virus (WNV), a member of the *Flaviviridae* family is an important emerging pathogen transmitted by mosquitoes of the *Culex sp.* wild-and (peri) domesticated birds act as the natural hosts of WNV. Birds are not only susceptible to WNV, but also participate in maintaining the transmission cycle. WNV emerged in North America in 1999 and its emergence was associated with high numbers of neuroinvasive disease in humans and horses. In general, WNV outbreaks were preceded by mass mortality in birds, especially birds belonging to the family *Corvidae* proved to be particularly susceptible [1]. Today, crows serve as an important early warning system in the USA to monitor WNV activity [2]. WNV outbreaks have been reported in Europe since 1950s. These outbreaks were small and remained focal. In contrast to the USA, bird mortality has not been reported in Europe. The emergence of a lineage 2 WNV coincided with increased reports of neuroinvasive disease in Europe. The WNV strains that have been characterized in Europe are very heterogeneous (Figure 1). This heterogeneity of WNV, at lineage level, together with the appearance of point mutations potentially affecting virulence and/or transmissibility, and the co-circulation of other flaviviruses infecting birds and humans, have important consequences for understanding their ecology and pathogenicity.

A couple of hypotheses have been proposed and investigated to explain these observations: (1) European birds are not susceptible to natural WNV infection, (2) WNV strains in Europe are less virulent compared to the American viruses, (3) Culex mosquitoes in Europe are not competent to transmit WNV to birds, (4) The feeding behavior of WNV infected Culex mosquitoes is different. These hypotheses have been addressed by our laboratory and others providing valuable answers, which allows for more tailored surveillance programs. Specifically, it has been shown that carrion crows are susceptible to experimental infection with certain WNV strains and therefore carrion crows could act as potential amplifying hosts in Europe [3,4]. In our laboratory, we have also shown that jackdaws can be productively infected and succumb to WNV infection. Although approximately 50% of this bird species is susceptible to lethal infection, jackdaws could function as sentinel to follow WNV activity in Europe [5]. Nevertheless, these experiments clearly showed that not all WNV strains that circulate in Europe can cause lethal infection in these birds [4,5]. Characterization of European WNV strains in mice has revealed little differences in virulence between the different strains [6]. However, clear differences in virulence were reported in birds, which do not correlate with virulence in mice and humans. Due to these differences in virulence, we propose a surveillance system in birds, which is based on identifying antibodies to WNV, and when possible the genotype, since active surveillance may only reveal circulation of WNV strains that are virulent to birds.

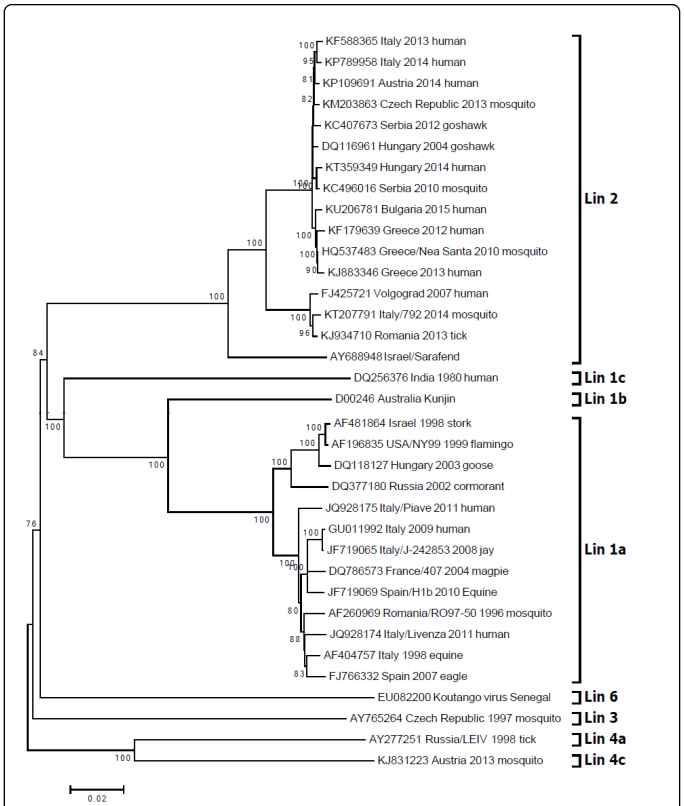

Figure 1: Phylogenetic tree of (European) WNV isolates depicting the different lineages of WNV as well as the phylogenetic differences of virulent and avirulent European strains.

Mosquitoes from the *Culex* biotype *pipiens pipiens* are competent to transmit WNV in Europe and once infected by WNV their feeding behavior for birds do not change [7]. For an arthropod-borne virus like WNV, vector competence is strongly linked to transmissibility of the virus. Surprisingly, it was shown that European mosquitoes are somewhat better in transmitting WNV, making these *Culex* species competent vectors for WNV. Therefore, lack of bird mortality in Europe cannot be explained by any of the hypotheses mentioned above. An alternative explanation to the lack of bird mortality in Europe is that bird mortality is so low and does not exceed the threshold of detection with current surveillance programs.

To date there is no specific treatment of WNV neuroinvasive disease. Our limited knowledge of the pathogenesis at the cellular and molecular level still hampers the development of intervention strategies to reduce mortality and long-term functional deficits in survivors of WNV encephalitis. Understanding the correlates of virulence and pathogenesis of WNV neuroinvasive disease using state-of-the art technology could allow the identification of biomarkers and leads for novel treatment protocols. We have used the mouse model to study determinants of virulence [6,8] and to identify potential biomarkers [9]. Some of these markers have been validated using samples of human clinical cases [10]. At least two potential biomarkers were identified. Further studies are needed to elucidate the importance of these biomarkers for diagnostics or therapeutic purposes.

Taken together, it is clear that European birds are as susceptible to WNV infection as their North American counterparts. Therefore, intrinsic resistance of European birds cannot explain why mass mortality among birds has not been reported in Europe. Since WNV specific antibodies were not detected in any of the collected birds, the hypothesis of herd immunity is unlikely and therefore not sufficient to explain lack of bird mortality in Europe during WNV outbreaks. Avirulent strains circulates in Europe, but their low-frequency cannot explain the lack of mass mortality amongst birds. In addition, no other species have been reported to act as reservoir species for WNV transmission. It is therefore important to continue our efforts to understand the factors that drive ecology, transmission and pathogenesis of WNV disease.

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