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The A(H5N1) Avian Influenza Virus at the Domestic Animal-Wildlife-Human Interface

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Abstract: *A brief overview of the past and present trajectories made by the A(H5N1) avian influenza virus among domestic birds, avian and mammalian wildlife species and humans is presented here, thereby taking into special account the 2.3.4.4b clade of the virus recently emerged in several geographic areas of the globe.*

Keywords: A(H5N1) avian influenza virus; Influenza viruses; Virus host range; Zoonotic risk, Human exposure risk; Viral infection; Epidemiology.

While the SARS-CoV-2 betacoronavirus keeps undergoing mutations in its genetic make-up, thereby increasing its fitness towards our target cells and tissues and evading the immunity conferred by previous infection and/or vaccination - as remarkably shown by the XBB.1.5, or "Kraken" omicron subvariant -, the highly pathogenic avian influenza (HPAI) virus A(H5N1) has alarmingly emerged, once again, in the global eco-epidemiological scenario. Indeed, following its first appearance over 25 years ago among domestic birds (ducks and chickens) in South-Eastern Asia, alongside a number of fatal and non-lethal cases of infection in people as well as in domestic and wild mammalian species, thousands of additional episodes have recently occurred across the globe in poultry farms as well as in wild terrestrial and marine birds (e.g. seagulls, pelicans and cormorants) and, most notably, among aquatic mammals including sea lions, seals, porpoises, and bottlenose dolphins.

Within this framework, the mass involvement of seabirds, sea lions and, to a lesser extent, of bottlenose dolphins along the coast of Peru (as well as of other South American Countries) is a matter of concern, in view of the "clade 2.3.4.4b" as the "common denominator" behind all these cases of HPAI A(H5N1) infection, often leading to a fatal outcome due to the marked neurotropism and neuropathogenicity displayed by the virus in pinnipeds and in cetaceans (1). Still noteworthy, an outbreak of HPAI A(H5N1) virus infection has been recently detected in intensively farmed minks from the Galicia region of Spain (2). As previously reported in intensive mink herds from The Netherlands and Denmark, where the "cluster 5" variant of concern

(VOC) developed following SARS-CoV-2 acquirement from infected people (viral spillover), with subsequent transmission of the mutated virus to humans (viral spillback) (3), also in this case the viral pathogen - which could have been transferred by infected seagulls - underwent a number of mutational events in mink, followed by sustained intraspecies transmission of the mutated virus (2). In this respect, although the high susceptibility of mink to circulating human and avian influenza viruses is not new to the scientific community (4), it should be additionally emphasized that the alanine (A) mutation found at position 271 of PB2 (T271A) from all mink viruses is a well-known pathogenicity determinant increasing the polymerase gene activity of influenza A viruses in mammalian host cells and mice (5).

Notwithstanding the above, no cases of human infection associated with the newly emerged 2.3.4.4b clade have been hitherto identified, while a lethal disease case has been recently diagnosed in an 11 years-old girl from Cambodia, with this fatality having been caused by the HPAI A(H5N1) 2.3.2.1c clade, widely circulating in poultry farms from that geographic area (6).

From 2003 until the end of 2022, almost 900 cases of human infection caused by the HPAI A(H5N1) virus have been officially reported, with more than the half of them having been characterized by a fatal outcome. Of course, the "human exposure risk" does not equally involve all of us, provided that some professional categories - i.e. people working in poultry farms as well as in avian slaughterhouses, alongside veterinarians working in the aforementioned facilities and/or performing necropsies on domestic and wild birds - tend to be more exposed than others. Within such a context,

although this zoonotic, multi-segmented RNA viral pathogen has hitherto shown a low human-to-human transmission efficiency, its high propensity to undergo genetic recombination and reassortment events undoubtedly represents a great concern issue. Besides, the recent finding of a mutated A(H5N1) strain in intensely reared mink from the Galicia region of Spain, among which the virus spread rapidly and diffusely (2), raises further concern in this direction.

Once again, as the SARS-CoV-2 pandemic has clearly taught us, the One Health principle should be the "polar star" around which the eco-epidemiological surveillance of HPAI A(H5N1) and, more in general, of all animal and human influenza viruses should be developed worldwide, within a global multidisciplinary and intersectorial collaboration effort, a key element of which resides in the continuous uploading into public repositories as well as in the mutual exchange of viral genomic sequences among all laboratories involved in the aforementioned surveillance activities.

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