The highly pathogenic avian influenza (HPAI) virus AH5N1 has alarmingly emerged, once again, in the global eco-epidemiological scenario. From 2003 until the end of 2022, almost 900 cases of human infection caused by the HPAI AH5N1 virus have been officially reported, with more than the half of them having been characterized by a fatal outcome. 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. 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 AH5N1 2.3.2.1c clade, widely circulating in poultry farms from that geographic area. 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 AH5N1 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 surveillance activities. (F: G. Di Guardo, letter to the editor of British Medica Journal - BMJ 2023;380:p401-17.02.23). La lettera integrale > https://tinyurl.com/cntkrtye