

Mammalian-Transmissible Highly Pathogenic H5N1 Influenza: Epidemiological Context

There are many uncertainties regarding the potential applicability of epidemiological data from ferrets infected with laboratory-created highly pathogenic H5N1 viruses to human public health. These concerns can be better understood and articulated when discussed in the context of observational and clinical data from infections of mammals and humans by unmodified “wild-type” H5N1 highly pathogenic avian influenza (H5N1 HPAI) viruses, factors which have been largely overlooked or ignored in most of the ongoing public and scientific debate over this issue.

Key factors most relevant to the debate include the following:

- Natural or laboratory-induced infections from unmodified H5N1 HPAI virus strains have been reported for more than 20 species of mammals, with fatal consequences reported for humans and least 12 other mammal species, including ferrets (1).
- Human-to-human transmission of H5N1 HPAI virus has been documented in at least 5 countries (China, Indonesia, Pakistan, Thailand, and Vietnam), including documented person-to-person-to-person transmission within family clusters in Indonesia and Pakistan (2, 3).
- Horizontal transmission of H5N1 HPAI virus between mammals of the same species has been experimentally demonstrated in domestic cats, and probable instances of transmission between tigers in captive breeding facilities have been reported (4, 5).

Natural or laboratory infections with H5N1 HPAI virus have been reported for an extremely broad range of other mammal taxa (carnivores, ungulates, primates, rodents, and lagomorphs), including numerous wild as well as domesticated species. The available data indicate that ferrets and other mustelids may have a higher level of susceptibility to H5N1 HPAI virus infection than many other mammal taxa, as fatal or severe infections by unmodified H5N1 viruses have been documented in domesticated ferret, mink, and stone marten. Felines are also particularly susceptible to H5N1 HPAI virus infection, as shown by reports of fatal or nonfatal infections of the domestic cat, tiger, lion, leopard, clouded leopard, and Asiatic golden cat (5). Other mammal species susceptible to potentially fatal H5N1 HPAI virus infections include domestic dog, hamster, rhesus macaque, cynomolgus macaque, palm civet, red fox, and raccoon. Mammal species that can exhibit asymptomatic or nonfatal infections by H5N1 HPAI virus include pikas, raccoon, domesticated swine, cattle, donkey, rats, and rabbits (1).

The exceptionally high fatality rate associated with H5N1 HPAI virus infection among documented human H5N1 HPAI virus cases is a key driver in the current debate, particularly when coupled to the known potential for limited human-to-human transmission of unmodified H5N1 HPAI virus strains acquired through exposure to diseased poultry. We are handicapped, however, by significant gaps in our knowledge of the epidemiology of H5N1 HPAI virus in humans. Despite more than a decade of clinical experience with human H5N1 “bird flu” outbreaks in 15

countries on three continents, there are only limited data available on the community-level prevalence of mild and asymptomatic cases of H5N1 HPAI virus (6) infection, and we do not yet understand to what degree differences in age-specific morbidity and mortality rates in different countries may be artifacts of surveillance intensity, socioeconomic factors, or genetic differences in the H5N1 strains in circulation (7). Case fatality rates among WHO-confirmed human cases reported to date range from approximately 35% in Egypt ($n = 163$) to 50% in Vietnam ($n = 122$) and 83% in Indonesia ($n = 186$). The fatality rate among children <10 years old in Egypt is approximately 5%, while the average fatality rate for this age group in countries in Asia has been as high as 59% (8, 9).

The potential for increased efficiency of respiratory transmission of the modified H5N1 viruses in humans is another central focus of the current debate. Although the normal route of transmission for avian influenza in nature is gastrointestinal via oral-fecal infection cycles in water, H5N1 HPAI viruses circulating in Asia have exhibited changes consistent with a shift in the modality of H5N1 virus transmission in poultry from shedding via the gastrointestinal-oral-fecal mode to respiratory-aerosol modes, i.e., increased rates of virus shedding from the respiratory tract and reduced survival times in water (10). Most H5N1 HPAI virus cases in mammalian carnivores have been linked to the ingestion of infected poultry or wild birds (5). Although respiratory tract infection is typically cited as a probable primary route of infection for humans with H5N1 HPAI virus infections, circumstantial evidence from human cases in Asia suggests that gastrointestinal infection is a potential route of infection for at least some human H5N1 HPAI virus cases (11, 12).

The observed broad range of virulence and transmissibility of unmodified H5N1 HPAI viruses in humans and other mammals clearly demonstrates the need for further in-depth field and laboratory epidemiological investigations to increase our understanding of genetic and environmental factors that modulate the transmissibility and virulence of H5N1 HPAI viruses in humans and other mammals.

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