CDC Influenza Division Key Points
July 31, 2015

Study: Pathogenesis and transmission of novel HPAI H5N2 and H5N8 avian influenza viruses in ferrets and mice

- On July 29, 2015, the *Journal of Virology* published a study entitled "Pathogenesis and transmission of novel HPAI H5N2 and H5N8 avian influenza viruses in ferrets and mice." The article is available at: http://jvi.asm.org/content/early/2015/07/24/JVI.01438-15.abstract.
- The study is authored by CDC's Drs. Joanna Pulit-Penaloza, Terrence Tumpey and colleagues.
- Highly pathogenic avian influenza (HPAI) H5 viruses have caused several outbreaks in domestic poultry in multiple U.S. states, raising concerns in the poultry industry and general public due to the potential risk of human infection.
- In this study, researchers investigated the transmissibility and disease severity of novel highly pathogenic H5 avian influenza viruses in ferrets and mice using H5N2 and H5N8 viruses isolated from birds in Washington State.
- Understanding how disease caused by H5 viruses develops (i.e., pathogenesis) and the capacity of these viruses to cause human-to-human transmission is a key component of public health risk assessment.
- Mice provide a reliable mammalian model for the study of HPAI H5 disease pathogenesis. Ferrets are an excellent model for studying influenza virus transmission and also exhibit clinical signs of disease that are similar to those seen during human influenza infection.
- When public health researchers use animal models to assess the pathogenicity of a virus to determine the virus' implications for human health, they consider several factors such as:
    - Does the virus replicate (i.e., make copies of itself) efficiently in the respiratory tract?
    - Where does the virus replicate and does infection spread to the lungs?
    - Does infection cause severe illness?
    - Does infection spread systemically (i.e., to multiple organs throughout the body)?
- The novel H5N2 and H5N8 viruses analyzed in this study exhibited "moderate pathogenicity" in mice. Researchers termed these viruses as having moderate pathogenicity because these viruses were less infectious and lethal in mice and ferrets compared to more virulent Asian-lineage H5N1 viruses (such as

A/Thailand/16/2014), although they were still capable of causing severe disease in mice at high inoculation doses. In addition, although the virus replicated (i.e., was able to make copies of itself) efficiently in both the upper and lower respiratory tracts of ferrets, symptoms were generally mild and the virus did not spread systemically to multiple organs.

- The results are consistent with previous pathogenicity studies with H5N8 viruses isolated from South Korea, which also exhibited low to moderate virulence in mammalian models.
- Influenza virus replication in lung tissue is thought to be a pathogenic trait that may contribute to the severity of H5 infection, if humans became infected by close contact with H5 infected poultry.
- Importantly, the novel H5N2 virus and H5N8 viruses lacked the ability to transmit between ferrets in a direct contact setting.
- Researchers further assessed the ability of these novel H5 viruses to replicate in human lung cells (specifically, Calu-3, which is a human bronchial epithelium cell line, Calu-3). The results showed that both H5 viruses replicated to a level comparable to a human seasonal H1N1 virus, but significantly lower than a virulent Asian-lineage H5N1 (A/Thailand/16/2004) virus.
- Overall, despite being highly pathogenic in chicken and turkeys, the novel H5 viruses exhibited low to moderate virulence in mammals.
- The authors conclude that the H5 viruses have not yet acquired all the features required for mammalian host adaptation.
- When a virus obtains adaptations to infecting a mammalian host, it makes the virus more likely to pose a threat to human health.
- As these and other H5 viruses continue to circulate in wild birds and cause widespread outbreaks in commercial poultry operations and backyard flocks, the likelihood of human exposure increases.
- Their ability to rapidly spread among birds, mix and swap genetic material (reassortment) when exposed to other flu viruses, and generate novel strains underscores the need for continued risk assessment in mammals.