Competent intermediate hosts and genetic re-assortment: what does the ferret and raccoon model tell us about influenza pandemic risk?

Letter to the editor

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Avian influenza (AI) is caused by avian (bird) influenza viruses, found naturally among wild birds. Domestic birds are more prone to illness from the highly pathogenic (HP) forms.[1] AI can also infect humans. Concern is mounting that AI may develop the adaptations[2] necessary for efficient transmission among humans. Some cases of H5N1 AI bird flu virus have been documented in people.[1] Person-to-person spread of H5N1 remains inefficient which is a requirement for a pandemic virus.[3]

Swine and pigs are regarded as the competent and intermediate hosts between AI species and humans, infected more frequently by both AI and human influenza (HI) viruses.[4] Swine presently function as the main re-assortment genetic 'mixer' of subtypes of AI. However, other re-assortment and intermediate non-avian hosts may be emerging and a cause for concern. While there has been inefficient transmission of H5N1 avian-human re-assortment influenza viruses in the ferret model,[3,5] H9N2's AI pandemic candidature has increased given recent ferret model findings.[6] H9N2 was shown to replicate within the respiratory tract of ferrets, following a Leu to Gln mutation of a single amino acid 226 in the HA receptor-binding-site. Efficient spread to direct ferret contacts emerged. Moreover, an H9N2 avian-human re-assortment virus revealed heightened virulence, replication and transmissibility.[6]

Findings in raccoons[7] also raise pandemic concerns in the generation of novel AI subtypes, where 2.4% of 730 screened wild U.S. raccoons had antibodies for AI (H10N7, H4N6, H4N2, H3, and H1).[7] Multiple AI exposures and subtypes were detected and the raccoons were competent hosts that could become infected and then shed virus capable of infecting other previously virus-free naïve animals (secondary transmission). Raccoons experimentally infected with HI virus shed levels of virus at higher levels than AI shed virus.[7] Levels and distribution of AI and HI receptors in tissue were similar to those in human respiratory tract tissue. The raccoon model[7] alike the ferret model[6] suggests intermediate and competent hosts besides the swine[4] that are capable of becoming infected, re-assorting, generating novel virulent strains, harboring, and spreading AI and HI virus. The leap from avian wild birds and domestic land-based poultry to competent hosts such as swine,[4] ferret,[6] and raccoon,[7] indicates an expanding host range. Minor genetic adaptations and the risk of pandemic influenza strains is becoming increasingly distinct. The recent non-avian host findings[6,7] indicate that there is a steady progression via genetic evolution and adaptation in intermediate hosts, and the potential, for AI virus to eventually acquire the ability to transmit more efficiently to humans and then readily among humans.

The potential for an influenza pandemic is growing especially given the re-assortment roles of intermediate species. AI virus such as H9N2 are evolving and could further evolve and undergo genetic adaptation and re-assortment that could confer heightened virulence, pathogenicity, and efficient spread among humans. A single amino-acid residue change was sufficient to allow efficient spread and increased virulence among ferrets.[6] Similar is now seen in the raccoon model[7] and thus the pandemic threat to humans is real. Further research on the ferret and raccoon models of infection and efficient transmissibility is needed, with a focus on the molecular basis of interspecies transmission and aerosolized spread. Improved avian and non-avian surveillance is needed with an acute focus among humans, swine and pigs, and birds/poultry. There must be stronger collaboration between public health, veterinarians, and veterinarian/avian epidemiologists. Genetic re-assortment and adaptation as well as surveillance in other peri-domestic species must be a focus. Influenza/pandemic clinical trial research is critical and given the emerging evidence especially as to human virus-like specificity,[6,7] pandemic preparedness and vaccine research and manufacture focus should not be limited to the HP H5N1 strain.

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