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Pandemic influenza virus: tracking a three-headed monster

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Pandemic influenza poses one of the largest threats to human health. The past one hundred years has witnessed 4 influenza pandemics that caused significant morbidity and mortality: 1918 Spanish flu (H1N1), 1957 Asian flu (H2N2), 1968 Hong Kong flu (H3N2), and 2009 (H1N1) flu.¹ Featured in issue 6(1) of *Virulence*, Abdelwhab and Abdel-Moniem document the avian-origin influenza A viruses currently circulating in reservoir hosts in Egypt,² wherein highly pathogenic avian influenza (HPAI) H5N1 is endemic and poses a significant pandemic risk.³ This provides a useful paradigm for understanding the molecular basis of how new pathogenic subtypes arise, how they overcome host range barriers and infect new species, and what precautions can be implemented to slow the inevitable emergence of new influenza strains with pandemic potential.

Influenza A virus (IAV) is a single-stranded, enveloped RNA virus capable of infecting a wide range of animal hosts in addition to humans.⁴ The viral genome is comprised of 8 gene segments (chromosomes) encoding several products, including 2 surface proteins with reciprocal functions that contribute to infectivity, host range, and virulence.⁵ Hemagglutinin (HA) confers viral adherence to sialic acid receptors located on respiratory epithelium, whereas neuraminidase (NA) encodes a sialidase activity that releases progeny virus from infected cells. New influenza strains arise by 'antigenic drift', associated with minor changes in either HA or NA commonly observed in

'seasonal' influenza strains; and those that arise via 'antigenic shift', associated with marked changes in these 2 proteins (and others) that occur when 2 different viral subtypes recombine or reassort chromosomes. Such reassortment can engender the emergence of new pandemic influenza strains for which little or no pre-existing immunity exists in the human population.

Avian-origin (HPAI) H5N1 virus is endemic to Egypt and is largely a bird-restricted subtype that is prevalent and asymptomatic within wild birds, and is highly infectious and lethal in domestic poultry. Although H5N1 is associated with poor transmission to humans and between infected individuals, it is highly fatal. Of particular concern is the potential evolution of this subtype toward efficient human transmission via co-circulation with other viral subtypes in reservoir hosts. Insights into the genesis of new influenza strains with pandemic potential have come from molecular analyses of a novel avian-origin H7N9 recently reported in China (2013).⁶ The H7N9 virus was derived from avian-origin H9N2 strains that have circulated in poultry for 20 years with subsequent reassortment upon co-circulation with H7, and N9 viruses.⁷ Thus, the surveillance of host reservoirs for (HPAI) H5N1 and co-circulating subtypes that may contribute to the origin of lethal subtypes with efficient human transmission is a top priority. Avian influenza A viruses have been isolated from dozens of different species of wild birds, including waterfowl that carry the virus asymptotically in their gut,⁸ with

frequent transmission to poultry and possible subsequent transmission to other livestock.⁹ Avian-origin influenza viruses are also found to a lesser extent in animals that have close contact with humans (horses, camels, cats, dogs).^{10–12} Along with Asia, Egypt may be 'ground zero' as it lies geographically on 2 of the main flyways of migratory birds linking Africa to Europe and Asia.² Thus, increased surveillance of avian-origin influenza A viruses as well as other co-circulating subtypes in wild and domestic animals is warranted to identify reservoir hosts and co-circulating subtypes of highest pandemic potential.¹³ Once pathogenic subtypes are identified, culling of infected animals is warranted; this is also a necessary precaution for infected vaccinated animals since they can shed the virus in absence of disease.¹⁴

Important lessons have been learned from the emergence of avian-origin viruses with pandemic potential from circulation and/or co-circulation with other subtypes in reservoir hosts, necessitating a thorough review of surveillance, identification and eradication practices that have led to the following recommendations: 1) improved surveillance in reservoir hosts;¹³ 2) banning live markets to avoid contamination and interspecies transmission;¹⁴ 3) restricting backyard animal and free range poultry practices to mitigate exposure to infected waterfowl;² and 4) culling of infected animals.¹⁴ Implementation of these recommendations will require a global effort to make them feasible from a cost, accessibility, and educational standpoint, due to

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impacts on cultural, social, and economic aspects of long-standing animal husbandry practices. Moving forward, implementation of these recommendations will likely

play a vital role in the success of any comprehensive influenza safety plan to avoid the genesis of lethal viral subtypes with efficient human transmission.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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