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The Novel H7N9 Influenza A Virus: Its Present Impact and Indeterminate Future

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Influenza A viruses are unpredictable in their emergence, ability to mutate or reassort, and especially their capacity to cross species. Each of these three aspects of unpredictability are evident in a puzzling new virus which began in China earlier this year and has become a significant public health hazard, but not (at least thus far) a harbinger of a pandemic. It appears that this virus is a newly emerging reassorted bird flu virus with the significant characteristic of travelling among numerous avian and mammalian species as a low pathogenic avian influenza virus which surprisingly is a highly pathogenic virus for the human species. The good news is that there is no evidence of sustained human-to-human transmission, but the bad news is that this newly minted H7N9 avian virus can kill human beings who come in contact with birds or poultry that appear healthy but are in fact carrying a lethal zoonotic agent. The world is being given a crash course in the importance of "One Health," because it is primarily through research at the human–animal–environmental interface that this virus can be better understood and hopefully controlled. There are no existing vaccines for the H7N9 virus for any species, including humans.

Despite on-going laboratory investigation of the new viral pathogen in hundreds of laboratories, both in China and globally, the source and significance of H7N9 is not yet clear. The virus has been found in chickens, pigeons, and ducks, but the prevalence of the virus in other species (especially wild and domestic birds, geese, turkeys quail, and pigs) remains unknown. Among 108 detected human infections (as of April 22, 2013) in many cities in Eastern China (including the 23 million people in Shanghai) and one case already in the capital Beijing (with its 22 million people) – far away from the epicentre in Shanghai –only approximately 40%, but not all, of the 22 people who have died (approximately 20% case fatality rate) or are at present severely ill had contact with poultry. A critical key goal will be the identification of all virus reservoirs through expanded agricultural and wildlife testing. Right now, live poultry markets can explain some, but not all, of the reported human cases. Underlying health conditions may have been a significant contributory factor to the demise and severe illnesses of infected people, but the tracing of hundreds of human contacts has not found a single person who has definitely contracted H7N9 from those who have died or been sickened by the virus. It is still puzzling that the 4-year-old boy in Beijing who tested positive for H7N9 never had symptoms of infection. If human-to-human transmission with this virus proves possible, then subclinical infected people could be important reservoirs and carriers spreading the virus unknowingly. The current situation has been succinctly summarized by Moderator CP in ProMed Digest 164 of April 11, 2013: "Overall the pattern remains unchanged; the victims are mainly elderly males. Infection in children is rare and mild. Despite the speculation there is no evidence so far of evolution of human-to-human transmissible virus. The case numbers are rising dramatically but this may in part be a consequence of greater availability of diagnostic agents." (see: www.promedmail.org/ April 11, 2013: Avian Influenza, human [34] [6-Mod CP]). In public health parlance, the basic reproduction rate in humans is zero at this time. For an epidemic or a pandemic to take place, each person with the infectious agent must pass it on to more than one other person. The question we could ask now is: What are we worried about?

We are worried about the ubiquity of cross-species transmission of avian influenza viruses. We are worried about the incredible mixing of species in Chinese live markets and their potential contribution to a H7N9 spreading from the unknown original host species, just as it was with SARS (Severe Acute Respiratory Syndrome). In the U.S, and other Western countries, 'poultry' means basically chickens, ducks, and geese. In China, besides those three species, practically every live market also includes pigeons, quail, pheasants, guinea fowl, and sometimes peafowl, and right next door you'll have open-air pet markets selling captive songbirds, many of them illegally caught from the wild, as well as pigs, and maybe dogs. In brief, the environment of a South Asia wet market is an ideal breeding ground for influenza and other promiscuous viruses, both new and old, which is why the Chinese Government decided to close some of these markets. While such closures are an important, sensible and necessary mitigation strategy, it is doubtful if this alone will be sufficient to stop the transmission of this new virus entirely.

Zeng Guang, Chief Epidemiologist at the Chinese Centre for Disease Control and Prevention, has recognized that

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"banning the [live poultry] trade and culling [i.e. killing] birds is only an expedient. Research into vaccines and effective medication are essential" he says (ProMed Digest 166 of April 12, 2013). However, Helen Branswell of the Canadian Press, has set out significant problems in both the development and utilization of such a vaccine for human use: "Making vaccines for new flu H7N9 flu virus could be a challenge, experts say" (Branswell 2013). Furthermore, even if an H7N9 vaccine becomes available and is shown to be safe and efficacious, it will be difficult, if not impossible, to convince poor farmers in Southeast Asia to vaccinate their flocks against a virus which does not cause losses or obvious clinical disease"

Despite the significance of wet markets in the spread of H5N1 and SARS, H7N9 is a very different phenomenon than H5N1 and SARS, the former one which emerged in Hong Kong in 1997 and re-emerged in Southeast Asia and Europe since 2003 killing more than 50% of infected humans; the latter one emerged in China in 2002 and killed about 10 per cent of the 8,000 people it infected worldwide. The fact that there appear to be no human transmission of H7N9 to other human beings — similar to H5N1— is reassuring, but not conclusive in assessing the significance of H7N9. We have to accept that humans and microbes are not 'at war,' but rather, both parties are engaged in amoral, self-interested, co-evolutionary struggles. As human beings we tend to search for culprits as to which species or place is responsible for the emergence and spread of a dangerous pathogen. However, the reality is that both microbes and people are striving to live at the animal-human-environmental interface. The precise identification of a new zoonotic pathogen requires animal, human, and environmental scientist to carefully work together in the field and laboratory to ensure (1) the identification of the original host species, (2) its mode of transmission into intermediate host species including humans, and (3) its ecology and survival in the environment.

Avian influenza viruses tend to bind to the *lower* parts of the human lung, which are not easily reached. Therefore, these influenza viruses are not easily transmissible between humans. However, mutations in the avian influenza genome can allow an avian influenza virus to bind to the human influenza receptor. Such mutations would then render these avian viruses transmissible between humans, as it is feared to happen with the H5N1 avian flu virus. It must be emphasized that in the case of the new H7N9 virus this has already partially happened. The amoral reality is that influenza viruses are so unpredictable because they use sophisticated and efficient methods of molecular evolution, adaptation and cross-species transmission. One method is called "reassortment" or "genetic shift," which is the mixing of the gene segments from different influenza viruses. Another method is called "genetic drift," which is the constant introduction of mutations into the influenza genome with an unpredictable impact on the phenotype of the newly mutated influenza virus. In the case of H7N9, In the case of H7N9, reassortment of several influenza viruses appears to be the basis of this new strain; and several adaptive mutations have already occurred, leading to a partial adaptation to the human environment. This is a very disturbing reality, as this new avian virus seeks not only to survive in avian species but it is looking for new opportunities in mammalian and human populations. The outcome of this cross-species interaction with this new H7N9 virus is at present indeterminate. What is determinate—what is conclusively settled—is that an increased commitment to the objectives and implementation of the "One Health" approach to medicine in general is now more urgent than ever.

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