Benefits and Risks of Influenza Research: Lessons Learned

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Given the yearly challenge of seasonal influenza and the potential catastrophic consequences of future pandemics, the need for intensive basic and clinical influenza research is unquestionable. Although the fruits of decades of research have enabled dramatic improvements in our ability to prevent and treat influenza, many fundamental questions remain, including those related to the complex factors associated with host switching and transmission of influenza viruses. Recent public concern over two H5N1 influenza manuscripts that studied the transmissibility of influenza viruses has triggered intense discussion on dual-use research and the way forward.

Influenza A virus is an ancient and persistent threat to individual and global health (Fig. 1). Seasonal influenza (which occurs annually, usually in winter) kills ~500,000 people globally and up to 50,000 people in the United States each year. Influenza viruses have animal reservoirs, especially in birds and pigs. They can undergo extensive genetic changes and even jump species, sometimes resulting in a virus to which humans may be highly vulnerable. Such an event can lead to a global health disaster; global influenza pandemics have occurred only three times in this past century. A prime example is the 1918 influenza pandemic, which killed between 50 and 100 million people worldwide and caused enormous social and economic disruption. Influenza A viruses circulate widely and are constantly evolving toward pandemic capability, as seen again in 1957, 1968, and 2009 (1). There is thus a clear danger of future pandemics.

Over the last decade, a highly pathogenic avian influenza virus (genus A; subtype H5N1) has emerged among chickens (2). Rarely, the virus has spread to humans, usually individuals with heavy exposure to infected birds. Since 2003, ~600 confirmed cases have occurred in humans in more than a dozen countries. Nearly 60% of these reported cases have resulted in death (3). Because it has been impossible thus far to completely eliminate the virus from chicken flocks or from wild birds or to prevent transmission to mammals, there is a persistent danger that H5N1 viruses [which have continually mutated and evolved (2)] will eventually become more easily transmissible to and among humans. Because humans are not specifically immune to H5N1 influenza, this scenario would have the makings of a potentially devastating pandemic.

One of the goals of pandemic influenza research is to recognize and anticipate how viruses are evolving in the wild toward a phenotype that is dangerous to humans, thereby staying one step ahead of potential pandemics. In this regard, compelling research questions relevant to global health and pandemic preparedness include determining whether highly pathogenic viruses, such as H5N1, have the ability to mutate and/or reassort with another influenza virus to become readily transmissible by the airborne route among humans. If so, (i) what is the likelihood that such mutations or reassortments will happen in nature? (ii) Is there a genetic signature of such a virus that might be helpful in surveillance? (iii) Would such a virus be highly pathogenic for humans? And (iv), would such a virus be sensitive to currently available antiviral drugs and vaccines, or would new ones be necessary? In response to these and related questions, the National Institutes of Health (NIH) has intensified the research we conduct and support on pandemic influenza. Much of this research is specifically focused on developing improved countermeasures, including a "universal" influenza vaccine that would protect people from multiple influenza subtypes. In complementary research, NIH-supported scientists study the factors involved in the pathogenesis and transmissibility of H5N1 and other influenza viruses to nonhuman mammals (mice, guinea pigs, ferrets, and nonhuman primates) to identify potential clues to the determinants of the same properties in humans.

Within this context, global attention has been paid recently to two NIH-funded studies of H5N1 transmissibility and pathogenesis in ferrets. In those studies, H5N1 viruses were made transmissible via respiratory droplets among ferrets by engineering the virus; well-described and published protocols including reverse genetics, re-assortment, and passaging of viruses in mammals were used. Manuscripts describing the studies (4, 5) have generated an unprecedented degree of discussion, concern, and disagreement among scientists, as well as the public, regarding whether the experiments should have been performed in the first place and whether they should be published in their entirety. Major sources of concern have been that the results might be used by bioterrorists to harm the public or that the virus might accidentally escape and cause a pandemic.

Research on H5N1 viruses, including the experiments reported in these two papers (4, 5), is comparable to that which has been conducted over decades with other seasonal and pandemic influenza viruses in ferrets and other animal models. The use of the ferret as an animal model for influenza transmissibility dates back to the 1930s, as ferrets are easily infected with influenza and sneeze when infected, which is useful for studying the airborne route needed for sustained human-to-human transmission. Understanding the virus characteristics associated with enhanced transmissibility—even in an imperfect animal model, such as the ferret—can benefit surveillance for naturally evolving wild viruses if they continually mutate toward a “genomic signature” that could be recognized as potentially predictive of a certain phenotype. Given the complexities of viral transmission, a virus’s ability to adapt to a host species, pathogenesis (a virus’s ability to cause disease), and the interrelation among these factors, which are likely to be unique to each influenza virus, any particular genomic signature will not necessarily predict how a given virus will act. Nonetheless, studies such as these provide incremental knowledge that the scientific community can build upon. A more in-depth

Fig. 1. H5N1 avian influenza virus particles, colored transmission electron micrograph. Magnification: ×670,000 when printed 10 cm wide.
A new U.S. policy for dual-use life science research defines what is permissible by scientists and the government. However, further negotiations will be needed as governments realize the consequences of such boundaries for research and society.