Sciencexpress Policy Forum

H5N1 Debates: Hung Up on the Wrong Questions

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Information related to influenza transmissibility should be published in its entirety.

Over the past few months, there has been an ever-increasing debate, echoed by the media, about the wisdom of publishing the details of two studies that have looked at the respiratory transmission potential of the so-called "bird flu" (H5N1 highly pathogenic avian influenza viruses, or H5N1 HPAIV). Some voices have gone as far as asking for stopping or restricting this type of research. In the next paragraphs, I would like to argue against such calls and argue that it is important for this research to be continued under the current conditions. It is also important that the information gathered from these studies finds the necessary channels to benefit public health worldwide. The attention on this issue should be redirected to the larger problem of how to eradicate a bird flu that has the capacity to affect us on a global scale.

The H5N1 bird flu emerged in Southeast Asia in the late 1990's. In 1997, it crossed to humans in Hong Kong, where 18 people were diagnosed with the virus and the infection resulted in 6 fatalities (*1*). Live bird markets were associated with the source of the virus. Culling of birds from these markets prevented new human cases. Until this incident, the prevailing dogma was that HPAIVs—bird flu H5N1 being just one of the them—were viruses restricted to poultry, with no direct consequences to humans. Far from being eradicated, H5N1 viruses have had an unprecedented geographic spread, not typical of HPAIVs, spreading from Southeast Asia into the Middle East, Europe, and Africa. A combination of factors has contributed to this spread, including live poultry trade and transport, other agricultural activities, the failure of poultry vaccination campaigns, and introduction of these viruses into the wild bird population. From 2003 onward, the list of countries reporting human cases of H5N1 have been associated with outbreaks of the disease in domestic poultry. So far, 576 human cases have been reported, resulting in 339 deaths. Countries that eradicated the disease from domestic poultry have had no additional reports of human cases (*1*).

The H5N1 situation, however, is far from over. These viruses have continued to evolve genetically and antigenically at a pace that resembles the evolution of human influenza viruses. In two countries, Indonesia and Egypt, H5N1 is endemic in poultry and, not surprisingly, these two countries continue to report human cases (*2*). The cumulative case-fatality rate of H5N1 is 35% in Egypt and 82% in Indonesia. It is not clear whether the differences in fatality rate between these two countries are related to either differences in molecular attributes of the prevalent H5N1 strains in each country or environmental conditions and/or timing of the diagnosis and/or treatment options and regimes. The uncontrolled spread of H5N1 viruses in poultry continues to pose a major pandemic threat. If we do not "take the bull by the horns" and make a worldwide concerted effort to help countries eradicate H5N1 viruses from domestic poultry, we will continue to face a potential H5N1 influenza pandemic.

An influenza virus is only capable of causing a pandemic if it acquires the ability to maintain sustained human-to-human transmission (*3*). The prevailing thought is that pandemic influenza strains must transmit efficiently by respiratory droplets, particularly by droplet nuclei or aerosols. A distinctive feature of avian influenza viruses in general, and H5N1 viruses in particular, is that they are incapable of being transmitted among humans by aerosol. Because pandemic influenza strains originated in avian influenza viruses, it can be argued that past pandemic influenza viruses were once avian influenza viruses that "learned" how to jump to and transmit by aerosol in humans. Understanding the molecular attributes that make influenza viruses transmissible by aerosol is the key to predict and/or prevent the emergence of pandemic strains. Receptor specificity plays a major role in the ability of influenza viruses to perpetuate in the human population. Pandemic influenza strains ultimately evolve in the human population with a preference for α2,6 sialic acid receptors (α2,6SA)—sialic acids bound to the adjacent galactose residue in an α2,6 conformation (*4*). In contrast, most avian influenza viruses recognize α2,3SA receptors (*4*). However, this rather simplistic observation does not explain the fact that the highly prevalent H9N2 strains in Eurasia and the Middle East have α2,6SA human-like receptor specificity (*5*) but have yet to cause a pandemic, despite serological evidence showing considerable human exposure to these viruses. Likewise, this narrow view does not help understand why H5N1 viruses with typical α2,3SA avian-like receptor specificity can jump from birds to humans and replicate efficiently in the human host but fail to be transmitted among

humans (*6*). We are certainly only making our first steps into understanding influenza transmission; we are at the infancy stage when it comes to predicting the transmission potential of influenza strains. In this regard, the independent work by Fouchier and Kawaoka's groups showing that H5N1 can be transmitted by respiratory droplets in the ferret model is of great importance. Ferrets are considered the best animal model for predicting the transmission of influenza in humans. If there ever was a sense of complacency about H5N1 viruses, these studies are a wake up call. More importantly, the molecular changes associated with this phenotype are surprisingly few, and although the combination of these changes has yet to be found in a field isolate, the mutations themselves are not unique or exclusive to the viruses produced in these two laboratories. Make no mistake, it is likely that these viruses can emerge in the field. Nature has an uncontrolled environment, thousands of susceptible subjects at its disposal, versus the handful available to scientists in the laboratory, and therefore it is just a matter of chance for these or viruses with a similar phenotype to emerge naturally. Just as researchers use new findings to learn how to predict earthquakes and tsunamis, the key elements that have made these viruses transmissible by respiratory droplets in the laboratory must be properly communicated to help public health officials make informed decisions if they are faced with similar field viruses.

The National Science Advisory Board for Biosecurity (NSABB)—an independent expert committee that advises the U.S. Department of Health and Human Services (HHS) and other federal departments and agencies on matters of biosecurity—has recommended that "the general conclusions highlighting the novel outcome be published, but that the manuscripts not include the methodological and other details that could enable replication of the experiments by those who would seek to do harm" (*7*). Althugh I greatly respect the views of the NSABB, the fact that the these two and other research groups have already published similar studies in the past makes it almost impossible to prevent access to details on the methodology (*8*–*14*). Preventing access to crucial pieces of information will hamper our ability to develop better vaccines and antivirals against these viruses. There is an intricate relationship between receptor binding, transmissibility, and antigenic make up of the virus. Therefore, it is possible that changes that affect transmissibility can affect antigenicity and, thus, vaccine efficacy. Access to the virus sequence information could be used to increase eradication efforts if a similar field isolate is identified. The question is now not whether H5N1 viruses can be transmitted by aerosol but when it will happen in nature. In this regard, the World Health Organization highlights the importance of this research and "notes that studies conducted under appropriate conditions must continue to take place so that critical scientific knowledge needed to reduce the risks posed by the H5N1 virus continues to increase" (*15*).

The worst mistake that we could make is to stop this type of research out of fear for the potential misuse of it. We should avoid the temptation to increase the containment levels for handling these viruses under laboratory conditions. Currently, these viruses are handled under BSL3-Ag conditions, which include biological safety cabinets, controlled access to the laboratory, protective equipment for investigators, filtration of supply and exhaust air, sewage decontamination, exit personnel showers, and facility integrity testing (*16*). This is historically the type of containment that many countries around the world use for these viruses. No containment condition is fail-proof, but it must be emphasized that there have been no human H5N1 cases reported from laboratory contamination and no accidental release into the environment from any laboratory. At present, far more people are at risk of infection with H5N1 in countries where the virus remains endemic. In these countries, backyard poultry owners and their families, from where most human cases have been reported, use no protection whatsoever. Smallpox was not defeated out of fear. Smallpox was defeated because Edward Jenner, among others, was fearless in his pursuit of controlling an infectious disease and in the process conferred a scientific status to the process of vaccination (*17*). We are much better prepared to confront infectious diseases than in Jenner's time. We know a great deal more about influenza than during the 1918 Spanish influenza. We were ill prepared to cope with the logistics of mass vaccine production during the 1957 and 1968 pandemics. In 2009, we dealt with an H1N1 pandemic virus that was not growing properly in eggs, the primary substrate for preparation of influenza vaccines, causing a major delay in vaccine availability. However, through technology and the tireless efforts of dedicated virologists, an optimal vaccine against the H1N1 virus was produced. This initial roadblock triggered many countries to build their own capacity for making vaccines (*18*). The H5N1 grows well in eggs, and the United States has been committed since 1997 to making vaccine seed stocks for viruses with pandemic potential. If the laboratory variants are cross-reactive with the seed stock, then we have a vaccine candidate. If it is not, then the question becomes whether we wait or begin stockpiling now vaccines against these variants.

Yet, there are still fundamental questions about influenza viruses that we must discover in order to prevent the next influenza pandemic. We failed at containing the 2009 pandemic influenza simply because, among other factors, we do not have a comprehensive understanding of what makes an influenza strain transmissible in humans. We still do not know whether an H5N1 virus that gained the capacity to transmit by respiratory droplets in ferrets can effectively

transmit by the same route in humans. We now do know that the potential is there, but it is not through fear that we will stop H5N1 from becoming pandemic. The pursuit of knowledge is what has made humans resilient, a species capable of overcoming our worst fears.

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Published online 19 January 2012; 10.1126/science.1219066
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published online January 19, 2012