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H5N1 Debates: Hung Up on the Wrong Questions

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

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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 1990s. In 1997, it crossed to humans in Hong Kong, where 18 people were diagnosed with the virus, and the infection resulted in six 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 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 reported human cases of H5N1 in several countries have been associated with outbreaks of the disease in domestic poultry. So far, 576 human cases and 339 resulting deaths have been reported. Countries that eradicated the disease from domestic poultry have had no additional reports of human cases (*1*).

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The importance of information. A duck farmer in Thailand installs a net to keep ducks and wild birds apart, a measure against spread of the avian flu virus to other birds. In places where the infrastructure for molecular analyses is not available, it is important to build the infrastructure, not deny people the information.

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 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 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 (see the photo).

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 predicting and/or preventing the emergence of pandemic strains.

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Published by AAAS

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 receptors with α2,6-linked sialic acid (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 simplistic observation does not explain the fact that the highly prevalent H9N2 strains in Eurasia and the Middle East have α2,6SA humanlike receptor specificity (*5*) but have yet to cause a pandemic, despite serological evidence showing considerable human exposure to these viruses. Likewise, this narrow approach does not explain 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*).

Preventing access to crucial information will hamper our ability to develop better vaccines and antivirals against these viruses.

We are certainly only making our first steps into understanding influenza transmission; we are in the infancy stage when it comes to predicting the transmission potential of influenza strains. In this regard, the independent work by Fouchier's 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 important, 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 and 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*). Although I greatly respect the views of the NSABB, the fact that 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.

The relations between receptor binding, transmissibility, and antigenic make up of the virus are intricate. 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 now is 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 uncontrolled spread of H5N1 viruses in poultry continues to pose a major pandemic threat.

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 Biosafety Level-3 (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 now than in Jenner's time. We know a great deal more about influenza than was known 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, which caused 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 they are not, then the question becomes whether we wait or begin now stockpiling vaccines against these variants.

Yet there are still fundamental questions about influenza viruses that we must dis-

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cover 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 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.

References

1. Y. Watanabe *et al.*, *Trends Microbiol.* **20**, 11 (2012).
2. M. D. Van Kerkhove *et al.*, *PLoS ONE* **6**, e14582 (2011).
3. J. K. Taubenberger, J. C. Kash, *Cell Host Microbe* **7**, 440 (2010).
4. M. Matrosovich, J. Stech, H. D. Klenk, *Rev. Sci. Tech.* **28**, 203 (2009).
5. M. N. Matrosovich *et al.*,*Virology* **281**, 156 (2001).
6. J. Stevens *et al.*, *Science* **312**, 404 (2006).
7. PBS NewsHour, Fearing bioterrorism, government panel asks: What research should be secret? 22 December 2011; www.pbs.org/newshour/bb/health/july-dec11/bird-flu_12-22.html.
8. E. M. Sorrell, H. Wan, Y. Araya, H. Song, D. R. Perez, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 7565 (2009).
9. N. Van Hoeven *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 3366 (2009).
10. T. R. Maines *et al.*, *Science* **325**, 484 (2009).
11. T. M. Tumpey *et al.*, *Science* **315**, 655 (2007).
12. T. R. Maines *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **103**, 12121 (2006).
13. Y. Gao *et al.*, *PLoS Pathog.* **5**, e1000709 (2009).
14. E. J. Schrauwen *et al.*, *Emerg. Infect. Dis.* **17**, 200 (2011).
15. WHO Media Centre, WHO concerned that new H5N1 influenza research could undermine the 2011 Pandemic Influenza Preparedness Framework [statement], 30 December 2011; www.who.int/mediacentre/news/statements/2011/pip_framework_20111229/en/index.html.
16. Agricultural Research Service, *USDA Security Policies and Procedures for Biosafety Level-3 Facilities* (USDA, Washington, DC, 2002); www.ocio.usda.gov/directives/doc/DM9610-001.htm.
17. D. Baxby, *FEMS Immunol. Med. Microbiol.* **16**, 1 (1996).
18. A. Abelin *et al.*, *Vaccine* **29**, 1135 (2011).

Published online 19 January 2012; 10.1126/science.1219066

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Life Sciences at a Crossroads: Respiratory Transmissible H5N1

Release of details of recent research on affecting influenza transmissibility poses far more risk than any good that might occur.

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Two recently submitted manuscripts to *Science* and *Nature* report success in creating mutant isolates of influenza A/H5N1 that are able to be transmitted by respiratory droplet or aerosol between mammals (ferrets). The studies imply that human-to-human transmission could be possible as well. Shortly after the submission of the papers to the journals, the National Science Advisory Board for Biosecurity (NSABB) was asked by the U.S. government to address this question. The NSABB recommended that the papers not be fully published; rather, the basic results of the studies should be communicated without methods or detailed results but in sufficient detail to maximize the benefits to society of the studies' findings. In turn, these recommendations were accepted by the U.S. government and shared with the authors and the editors of *Science* and *Nature*.

Some have asserted that these recommendations represent unwarranted censorship of scientific research and that the sharing of the results, particularly the specific viral mutations, is necessary to protect global public health. They argue that sharing the virus mutation information with global influenza surveillance organizations would result in the rapid identification of a potential H5N1 pandemic virus in birds or humans. This early information might permit health authorities to quash an emerging human influenza pandemic. In addition, they believe that knowledge of the mutations could enhance H5N1 vaccine research and manufacturing.

While considering the possible merits of a wider dissemination of more complete information regarding mutational changes of the newly created H5N1 strains, one fact must be kept in mind. The current circulating strains of influenza A/H5N1, with their human case-fatality rate of 30 to 80%, place this pathogen in the category of causing one of the most virulent known human infectious diseases.

Disseminating the entirety of the methods and results of the two H5N1 studies in the general scientific literature will not materially increase our ability to protect the public's health from a future H5N1 pandemic.

Moreover, detecting an emerging pandemic virus in animals before the occurrence of a human pandemic is unrealistic; rather, the pandemic virus documentation will be "an after-the-fact record of what just happened." For example, in the six countries of the world where highly pathogenic avian influenza H5N1 is endemic (Bangladesh, Cambodia, China, Egypt, Indonesia, and Viet Nam), the quality of public and private veterinary and animal production services is variable and low in some places (*1*). These countries are not often able to detect and respond to influenza A/H5N1 infections in birds. When H5N1 isolates are obtained, little to no gene sequencing is conducted, meaning that a mutation map of possible prepandemic viruses will not be generally available. Even if such laboratory support were readily available and samples from ill birds were processed in a timely manner, these countries lack the commitment to deal vigorously with H5N1. This conclusion was recently highlighted by the United Nations Food and Agriculture Organization (*1*, *2*).

The World Health Organization (WHO) is also well aware of the magnitude of the challenge of identifying an emerging human influenza pandemic and stopping it before it spreads globally. Experiences with pan-

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