

Restricted Data on Influenza H5N1 Virus Transmission

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Authors of a debated flu transmission study discuss why such work is important and should be published.

Since its first detection in 1997, highly pathogenic avian influenza (HPAI) H5N1 virus has devastated the poultry industry of numerous countries of the Eastern Hemisphere. As of January 2012, HPAI H5N1 virus caused 577 laboratory-confirmed human cases of infection, of which 340 were fatal. Sustained human-to-human transmission has not been reported. Whether this virus may acquire the ability to be transmitted via aerosols and cause a future pandemic has been a matter of intense debate in the influenza field and in general public health research communities.

Scientific advice about the risk of HPAI H5N1 virus to cause a future pandemic is largely based on expert opinion rather than facts. Some experts have judged this risk to be low on the basis of the following assumptions stemming from historical data: (i) only virus subtypes H1, H2, and H3 cause pandemics; (ii) influenza viruses do not cause pandemics without reassortment (“genetic mixing”) of human and animal viruses; and (iii) pigs are required as an intermediate host to yield pandemic viruses (1). Partly as a consequence of inconsistent scientific advice, H5N1 virus outbreaks in poultry are not always stamped out with a sense of urgency for human health (2).

Estimates of the impact—including the death toll—of a possible future H5N1 virus pandemic for use in (inter-)national pandemic preparedness plans do not generally exceed those of the H1N1 Spanish influenza pandemic of 1918 (3). Although it is recognized that the case-fatality rate of current H5N1 infections is much higher than that of the Spanish influenza pandemic, experts have argued that an aerosol-transmissible H5N1 virus would probably be less virulent than the currently circulating HPAI H5N1 viruses. However, there is no scientific evidence to support this assumption.

Our research program on H5N1 virus transmission, which led to submission of one of the papers that has stirred up so much recent controversy, aimed to investigate whether and how HPAI H5N1 virus can acquire the ability to be transmitted via aerosols among mammals and whether it would retain its virulence. If H5N1 virus can acquire the

ability of aerosol transmission with few mutations without significantly losing virulence, the existing assumptions should no longer be used as the basis for scientific advice. Furthermore, pandemic preparedness plans would then need to be revised globally to account for much higher numbers of hospitalized cases and deaths. These are important issues in risk communication and in preventing a future pandemic or handling it as well as possible if prevention fails.

In addition, our research project has direct practical implications. Currently, our knowledge of determinants of airborne transmission of influenza virus is virtually nonexistent. If we knew which mutations and biological traits can change the zoonotic H5N1 virus into a virus with major public health impact, detection of specific mutations in circulating avian viruses should trigger more aggressive control programs than those employed currently. Moreover, if a HPAI H5N1 virus has the potential to cause a future pandemic, our last resort would consist of implementing societal measures (such as quarantine and travel restrictions), surveillance, vaccination, and the use of antiviral drugs. Diagnostic tests, antiviral drugs, and prepandemic H5N1 vaccines are currently evaluated using HPAI H5N1 strains with biological properties that are similar—but may not be identical—to the strain that would cause the pandemic. Because the surveillance and effectiveness of vaccination and antiviral drugs may depend on the virus lineage and its specific mutations, these measures need to be evaluated in the context of viruses with the most relevant genetic and biologic properties.

Oversight, Biosafety, and Biosecurity

Our work on aerosol transmission of HPAI H5N1 virus was done completely openly, and the decision to perform the work was reached upon serious local, national, and international consultation. The work has been discussed among staff members of the Department of Virology at Erasmus Medical Center (MC) since 1997, followed by consultation with local biosafety officers and facility managers. Over a period of several years, numerous international influenza specialists and other virologists operating in class 3 and class 4 facilities were consulted, and a plan was drawn to obtain adequate research facilities in Rotterdam.

After a Broad Agency Announcement of the National Institute of Allergy and Infectious Diseases and National Institutes of Health (BAA NIH-NIAID-DMID-07-20) in 2005, the Department of Virology along with partners in the United States drafted a research proposal to become an NIAID/NIH Center of Excellence for Influenza Research and Surveillance (CEIRS) to support the research agenda of the U.S. Department of Health and Human Services (HHS) Pandemic Influenza Plan in the United States. The proposal was reviewed favorably with the help of external reviewers, and the research contract was awarded.

An explicit permit to work with aerosol-transmissible H5N1 virus was obtained from the Dutch Ministry for Infrastructure and the Environment (I&M) in 2007. To this end, I&M was advised by the Commission on Genetic Modification (COGEM), an independent scientific advisory committee for the Dutch government. I&M and COGEM concluded that the proposed work could be performed with negligible risk to humans and the environment under the conditions outlined in the application.

The facility that was designed for the work consists of a negative-pressurized laboratory in which all work is carried out in class 3 isolators or class 3 biosafety cabinets, which are also negative pressurized. Only authorized personnel that have received the appropriate training can access the facility, which has state-of-the-art security systems. All facilities, personnel, procedures, and records are subject to inspection and oversight by the institutional biosafety officers of Erasmus MC in close consultation with the facility management. In agreement with the U.S. select agent regulations for overseas laboratories, the facilities, personnel, procedures, and records are further inspected by the U.S. Centers for Disease Control and Prevention every 3 years. The most recent inspection took place in February 2011, at which time no shortcomings in biosafety and biosecurity measures were identified.

It is important to emphasize that other research institutes—following similar but independent routes in the United States and elsewhere—have also come to the conclusion that this type of research is important, is of major interest to public health, and can be performed safely (4–8).

Dissemination of Results

After the decision was made that the research project was important and could be performed safely, the next question to address was whether the methods and results should be published in detail. We decided to describe our data, although not in complete detail, during a keynote lecture at the influenza conference organized by the European Scientific Working Group on Influenza (ESWI) in Malta in September 2011 to inform the influenza field as well as policy makers of our results. About the same time, a manuscript was submitted

for publication. We consulted with NIAID/NIH staff, collaborators within our CEIRS center, and organizers of the ESWI meeting about the decision to make our results available to the public.

In agreement with the Dutch Code of Conduct for Biosecurity and the U.S. regulations on “dual use” research, *Science* first conducted its own biosecurity review and the manuscript was independently sent to the National Science Advisory Board for Biosecurity (NSABB) for advice. The NSABB drafted recommendations for the U.S. government suggesting that the conclusions of the manuscript could be published, but without experimental details and mutation data that would enable replication of the experiments. It was recognized by NSABB that detailed information about the results (specific mutations) should be shared under confidentiality with parties that “need to know.”

Important questions that stem from the draft NSABB recommendations are who will identify the parties that need to know, how, and what mechanism can be used to share classified information? In our opinion, identification of relevant parties should be done liberally and should include the public health services of countries where H5N1 virus has infected humans, poultry, and other animals in recent history. According to the databases of the World Health Organization (WHO) and Food and Agriculture Organization (FAO), these countries span Bangladesh, Cambodia, China, Egypt, Hong Kong SAR-PRC, India, Indonesia, Iran, Israel, Japan, Korea, Mongolia, Myanmar, Nepal, Palestinian Autonomic Territories, and Vietnam (9, 10). WHO and FAO reference laboratories around the world and other expert laboratories affiliated to affected countries need to know. Affected countries and affiliated laboratories require detailed knowledge of our results to ensure implementation of the most up-to-date molecular diagnostics and virus genome sequence interpretation. Companies and research organizations with research and development programs aiming at the development of diagnostic tests, vaccines, and antiviral drugs for H5N1 virus need to know if the effectiveness of such tools depends on the virus lineage or specific mutations. Finally, research laboratories that study H5N1 virus host adaptation, H5N1 virus in mammalian model systems, or use the same virus lineage that was the subject of our studies have a need to know because they may unknowingly develop high-risk variants. The latter group is not hypothetical, as we have identified, from the published literature, laboratories working with H5N1 viruses that may only require one to three mutations before the viruses used may become transmissible via aerosols. It is important to note that the WHO-coordinated Pandemic Influenza Preparedness (PIP) Framework went into effect at the World Health Assembly in May 2011 after 4 years of intense international negotiations. The PIP was implemented

to promote the sharing of influenza viruses and to provide the member states access to vaccines and other benefits. Withholding information from the countries that share influenza viruses and their sequence data would be a major step backward in the field of global infectious disease surveillance and research.

Biosecurity experts have argued that the methods we have used represent a recipe to create biological weapons and that information about the specific mutations that determine transmission of H5N1 virus could also be misused for this purpose. However, it is important to emphasize that we did not develop novel methods and that we only used information and methods that are available freely from the scientific literature. The logic in this work is sufficiently obvious that virologists could perform experiments similar to ours even if our method is not published.

Perspective on Dual Use Research

The recent recommendation of the NSABB to restrict publication of research results is unprecedented and is a major deviation from common practice in the life sciences. Among thousands of manuscripts that describe potential dual use research according to the NSABB guidelines (11), only a handful has raised questions (7, 8, 12) and none has triggered similar advice. In dual use research, weighing the risks and benefits of the research is the crux. Biosecurity experts are more likely to lean toward (near) zero tolerance with respect to risk, whereas for infectious disease specialists, incremental risks may be waived in the light of potentially important public health benefits. Reaching consensus among scientific disciplines—let alone among the public at large—is virtually impossible.

We do not agree with the NSABB recommendations. Nevertheless, we have respected their advice. Together with the NSABB, NIAID/NIH, and *Science*, and in close consultation with key parties in the public health field, we hope to find a solution for disseminating key information to those who need to know while shielding this information from potential misuse. However, we cannot rule out the possibility that new scientific research, outbreak events, political sensitivities, or other circumstances may call for deviation from this route.

As we compare the current threat posed by bioterrorism and our past experience with the threat of influenza, we would argue that nature itself should be considered the prime bioterrorist. Viruses emerging from animal reservoirs have killed many millions of people around the globe without the help of direct human interference, and we need to be prepared for other naturally occurring events similar to those caused by influenza A virus, HIV, SARS-coronavirus, West Nile virus, filoviruses, and henipaviruses. Infectious disease specialists have a moral obligation to perform dual use research in the

interest of public health and to communicate the results of their work responsibly.

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