COMMENTARY

Biosafety Considerations of Mammalian-Transmissible H5N1 Influenza

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ABSTRACT The ability to produce an H5N1 influenza virus that can be transmitted from human to human raises both biosecurity and biosafety concerns. After analyzing the biosafety risks of such a virus, we propose that it be handled at biosafety level 4 (BSL4) containment until and unless it becomes clear that the risks to humans and other mammals can be mitigated.

The recent reports of experiments aimed at demonstrating the ability of avian H5N1 influenza virus to become transmitted from human to human have generated a vigorous and important debate. While the details of the work remain largely undisclosed, both the Fouchier and the Kawaoka laboratories were able to take this virus, which to date has infected humans through direct contact with birds, and make it able to transmit from ferret to ferret, an experimental animal model for human-to-human transmission. Much of the debate has focused on biosecurity issues. The National Science Advisory Board for Biosecurity was asked to review the manuscripts and advise the U.S. government about the security risks; its conclusion was that, at this time, the risks presented by these findings outweigh the benefits to society (1, 2).

Many influenza virologists have countered that the risks are minimal and that there is a greater risk of not making the results available through the normal publication route (3). Largely missing from these discussions, however, has been the topic of biosafety.

Useful starting points for any consideration of laboratory biosafety are Biosafety in Microbiological and Biomedical Laboratories (BMBL) (4) from the U.S. Department of Health and Human Services and the Laboratory Biosafety Manual (5) from the World Health Organization. Paramount to the determination of biosafety containment is a careful risk assessment of the agent. There are four questions that are generally considered. First, does the agent cause disease in healthy humans, animals, or plants? Second, if so, how severe is the disease? Third, how transmissible is the agent, and what is the route of transmission? Fourth, are preventative or therapeutic interventions available and, if so, how widely? The BMBL notes that one must consider the risks to both laboratory personnel and the community.

The H5N1 influenza viruses under discussion fall in the category of highly pathogenic avian influenza (HPAI). As such, these viruses have high virulence and need to be handled with caution. The BMBL recommends biosafety level 3 (BSL3) containment for HPAI, noting the risk to humans and to agriculture. It is of interest to note that, due to its pandemic potential, work with the 1918 H1N1 strain, which arguably would be less lethal today than it was in 1918 due to improvements in medical care, is also recommended to occur at BSL3.

The question is, does making the H5N1 virus transmissible among mammals change its biosafety profile? Let us begin by answering the questions posed above. H5N1 influenza clearly causes disease in otherwise healthy humans and animals. That disease is severe: the case fatality rate (CFR) in humans with H5N1 influenza virus is reported to be over 50% (World Health Organization, Confirmed human cases of H5N1 2003–2012; http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/index.html). While there has been debate regarding the true number of infected humans, it is evident that the CFR is certainly above that of the 1918 strain, something about which most experts agree (6). Until additional data are collected, we must assume that a large percentage of infected individuals will not survive H5N1 infection. The third question deals with transmission. This new influenza virus is spread through a respiratory route and, therefore, will be present in aerosols created in the laboratory. The BMBL makes special note of agents that can be transmitted by the aerosol route, categorizing them as “serious laboratory hazard[s].” Some scientists have suggested that transmission between ferrets does not necessarily translate into human transmissibility (7). While acknowledging that the ferret is indeed an experimental model, we must assume that it is a valid model and therefore that this virus would spread similarly to other pandemic human strains in history. Finally, there is the issue of treatment and prevention. To date, a vaccine against H5N1 influenza virus has not been available, ruling out immunization of laboratory workers or the general public. While the virus does respond to commonly used antivirals, it is reasonable to assume, based on experience with the 2009 H1N1 pandemic, that virus spread would outpace the capacity of the public health system. In addition, if there were an H5N1 pandemic, drug resistance would undoubtedly evolve.

Overall, then, we believe that the newly derived H5N1 HPAI virus should be handled at the highest biocontainment level, BSL4. This is largely based on a comparison to the natural H5N1 influenza virus. For example, the human-to-human transmissible form is, by definition, able to spread more readily. If a BSL3 worker were to be infected with natural H5N1 virus, the infection would likely stop in that individual. With human-to-human aerosol transmission, others could become infected. It has been argued that by the time the nonspecific symptoms of influenza have been confirmed to be bona fide influenza, it is too late for drugs to be effective (8). Subsequent transmission could occur rapidly, outpacing the public health system’s capability to contain it. Given

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the mortality rate, such a laboratory exposure event could lead to unacceptable numbers of deaths. Once outside the laboratory, there is also a threat to farm animals such as pigs. We also note that in addition to the enhanced biosafety procedures in a BSL4 facility, the agent would have more physical security.

These considerations and the assumptions used to analyze them have become more public over the past decade as high-level pathogen work has found its way into academic settings, outside the traditional boundaries of government laboratories. The environmental impact statements required for these projects, prepared by expert panels and made public to the surrounding communities, have raised the bar considerably for those who wish to have their safety assumptions and scenarios vetted in the public light. Although the matter at hand is not yet subject to those regimented assessments, it is not exempted from the same public scrutiny and the same need for high-level safety assurance.

Of course, one could argue that we may be wrong in our assumptions regarding the validity of the ferret model and that better serological studies may indicate that the CFR is more like that of seasonal influenza. In the meantime, why not follow the precautionary principle? We would draw an analogy to the early days of recombinant DNA work. It is almost hard to believe today that the cloning of the herpes simplex virus thymidine kinase gene in 1979 was carried out at BSL4 (or P4, as it was then known) containment (9). This experiment was originally judged to be high risk, but over time we came to understand that it is not; today, the same work would be performed at BSL1 containment (NIH guidelines, Section III-E-1). Perhaps an H5N1 vaccine will soon be available, making high-level containment no longer necessary. Until data are obtained to show that human-to-human transmissible H5N1 influenza is not as dangerous as it seems, however, we must be prudent. We owe it to the public worldwide to demonstrate that we are working with these viruses in a responsible manner.

REFERENCES


M.J.I. is a member of the NSABB, but the opinions in this piece are his own. Both authors are members of the University of Michigan Institutional Biosafety Committee. The views expressed in this Commentary do not necessarily reflect the views of the journal or of ASM.