Mammalian-Transmissible H5N1 Virus: Containment Level and Case Fatality Ratio

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The life sciences, and the field of microbiology in particular, are in the midst of an unprecedented debate regarding the risks posed by the publication of two studies that report the generation of mammalian-transmissible H5N1 virus in the laboratory. The controversy was precipitated when the National Science Advisory Board for Biosecurity (NSABB) advised the U.S. government that the best course of action was to seek a redaction of the manuscripts to delete important details that could be used for nefarious purposes (1, 2). In a recent issue, *mBio* published pro- and anti-NSABB decision commentaries (3–6) with the goal of informing the debate and the hope that airing these views would lead to the best decisions. At the time of this writing the issue remains unsettled, and a fierce debate is raging in government and academic circles on the best course of action. Even with the question of how to publish these studies unsettled, two other issues have quickly emerged: (i) the appropriate biosafety containment level (BSL) to be used for studies with mammalian-transmissible H5N1 viruses and (ii) the case fatality ratio of human H5N1 infections.

The question of the appropriate level of containment is both a biosafety and a biosecurity issue. Although "biosafety" and "biosecurity" are sometimes used interchangeably, it is important to recognize that they denote very different concerns (7). The existence of mammalian-transmissible H5N1 immediately brings about the question of whether the current biosafety level of containment is adequate. Currently, studies with mammalian-transmissible H5N1 are being done at BSL3 or higher (8). However, Canada has already moved to institute the highest level of biosafety containment for research work involving mammalian-transmissible H5N1 virus (see http://www.phac-aspc.gc.ca/lab-bio/res/advi-avis/sbn-asb-2012-01-31-eng.php). It is important to understand that the choice of BSL has profound implications for society. BSL4 containment would theoretically protect society by increasing both biosafety and biosecurity. However, at the same time, this very high level of containment would make society potentially more vulnerable, since critical experimental work will not get done simply because BSL4 facilities are few in number and already engaged in research with numerous other pathogens. Hence, no matter what decision is made, we face a tradeoff with regards to safety and future preparedness. There is also the possibility that assigning mammalian-transmissible H5N1 to BSL4 containment would affect vaccine production given that the pharmaceutical vaccine industry may not have such facilities and/or choose not to take vaccine projects under such restrictions. The more stringent containment conditions could also deter the recruitment of investigators to this field and thus hinder future preparedness. On the other hand, maintaining the current BSL3+ regulations would allow much of the ongoing research to proceed unhindered but at higher risk for accidental releases. Given the importance of the containment issue for biosafety, biosecurity, and future preparedness against influenza, we have invited two sets of investigators to discuss the pro and con arguments for each containment level (8, 9).

At the heart of the controversies on the disposition of the two manuscripts and the containment issue is the presumed case fatality ratio of human H5N1 infection. Clearly, much of the debate is driven by the concern that any H5N1 pandemic would be accompanied by unacceptable mortality and morbidity, although estimates of expected mortality differ widely. Whereas clinically documented cases of H5N1 infection in humans have a case fatality ratio of 50 to 60%, this number has been questioned on the grounds that many infections are subclinical (10). A meta-analysis of case fatality has also argued for a significantly lower mortality rate for H5N1 infection in humans (11). In contrast, an article in *mBio* by Osterholm and Kelley argues that the only known reliable mortality numbers are those provided by the World Health Organization, which show a mortality rate of 59% for humans with documented H5N1 infection (12). Furthermore, these authors argue that current global countermeasures in the form of vaccines and antiviral drugs are inadequate for coping with an H5N1 pandemic.

One area of agreement between the two camps is the need for more information on all aspects of H5N1 biology, pathogenesis, and epidemiology. In essence, the debate on the case fatality ratio is really a debate on the value of the epidemiology tools used to define and discriminate between infection and disease. Hence, no matter what choices are made regarding containment level, we urge that great consideration be given to protecting the influenza research enterprise, since increased knowledge is critical for the defense against future pandemics. If BSL4 containment is indeed mandated for studies of virulent mammalian-transmissible H5N1, then we urge that low-virulence strains be identified that would permit much of the work at current facilities that have access to BSL3+ containment to continue. Protection against current and future influenza threats is critically dependent on a vigorous research environment that can produce new vaccines and provide new understanding of viral pathogenesis that can lead to better therapies. We know from experience with select agent regulations that as research is made more difficult, less work is done (7). On the other hand, we know that when researchers can carry out basic studies with attenuated strains much work can be done unencumbered. For example, in the case of *Bacillus anthracis*, approximately ten times as many papers have been published on the anthrax toxin relative to its capsule, a discrepancy that has been attributed to the fact that attenuated toxin-producing capsule-deficient strains are available for study in BSL2 containment outside the select agent regulations (7). In contrast, all work with encapsulated *B. anthracis* strains must be done under select agent rules.

For the H5N1 and influenza field in general, we urge that the

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debate be expanded to discuss the mechanisms, requirements, and infrastructure required for maintaining a healthy international research enterprise in the coming years, since this is ultimately the best preparedness for coping with an ever-changing pathogen that has already shown capable of producing devastating pandemics.

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