New H5N1 viruses: How to balance risk of escape with benefits of research?

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In the controversy surrounding the newly developed strains of avian H5N1 flu viruses, scientists and policy makers are struggling with one question in particular: what level of biosafety is best for studying these potentially lethal strains of influenza? In a pair of commentaries, researchers from the Mount Sinai School of Medicine in New York and the University of Michigan argue their different views of how to safely handle H5N1 flu viruses. The commentaries will be published in *mBio*, the online open-access journal of the American Society for Microbiology, on Tuesday, March 6.

This fall, the U.S. National Science Advisory Board for Biosecurity (NSABB) set off a debate when it asked the authors of two recent H5N1 research studies and the scientific journals that planned to publish them to withhold crucial details of the research in the interest of biosecurity. The researchers had taken H5N1, a virus that cannot easily transmit from human to human, and developed strains of the virus that can transmit easily between ferrets, which are a common model for human influenza.

These H5N1 strains and others like them that might be developed in the future could pose a grave threat to human life, but researchers and others argue that studying these H5N1 strains could help bolster preparedness efforts and vaccine development to help fend off a potential H5N1 pandemic. How can we balance the need to protect human life from the accidental escape of an H5N1 strain with the need to continue research that might prevent a naturally occurring outbreak? Which biosafety level

(BSL) is right for the H5N1 virus?

In the commentaries appearing in *mBio*, two experts offer opposing views of the appropriate level of security for dealing with H5N1 viruses. The authors agree that, with a reported case fatality rate that could be as high as 50% or more, H5N1 could create a pandemic of disastrous proportions, but they differ in their opinions of how to strike a balance between biosecurity and potentially life-saving research.

"The existence of mammalian transmissible H5N1 immediately poses the question of whether the current biosafety level of containment is adequate," writes *mBio®* Editor in Chief Arturo Casadevall in an accompanying editorial. "It is important to understand that the choice of BSL level has profound implications for society."

Under current U.S. guidelines H5N1 is classified as a select agent and must be worked with under BSL-3 with enhancements. The BSL-3 designation is given to pathogens that can be transmitted through the air and can cause serious or fatal disease but for which treatment exists. Most facilities in the United States with infectious disease research programs have BSL-3 laboratories. In addition, many hospitals have areas that can be operated at this level; these areas are used for isolating patients with highly contagious diseases. In contrast, BSL-4 is reserved for pathogens for which there is no known treatment and BSL-4 laboratory requirements are such that there are only four working BSL-4 laboratories in the United States.

Adolfo García-Sastre of the Mount Sinai School of Medicine argues that the H5N1 viruses in question may well be less pathogenic than they were before passage through ferrets, but they could still be quite dangerous, so preventing human exposure is crucial. However, he says, the ultimate level of biosecurity, BSL-4, is excessive in this case and would stifle the pace of discovery. There are both therapeutics and vaccines available for

H5N1, says García-Sastre, so he advocates for conducting the research in enhanced BSL-3 facilities, which he says offer the necessary security measures, including interlocked rooms with negative pressure, HEPA-filtered air circulation, and appropriate decontamination and/or sterilization practices for material leaving the facility.

Michael Imperiale and Michael Hanna of the University of Michigan, on the other hand, make their case that the H5N1 viruses merit BSL-4 containment. Although H5N1 that cannot be transmitted from human to human would normally be handled in a BSL-3 facility, researchers changed the virus' biosafety profile when they enhanced its ability to transmit between mammals. According to Imperiale and Hanna, the vaccine for H5N1 is not widely available, and drug resistance and a slow distribution system for antiviral drugs mean a small outbreak could never be contained.

Since the controversy began in December, H5N1 viruses and flu research continue to be the source of much debate. *mBio®* and the American Society for Microbiology present these commentaries as a means of fostering a discussion and eventually achieving consensus about H5N1 biosecurity that is based on the scientific facts surrounding the subject.

More information: mbio.asm.org/

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