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The Decision to Publish an Avian H7N1 Influenza Virus Gain-of-Function Experiment

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Dr. Simon Wain-Hobson has written an opinion piece (1) questioning the decision of the American Society for Microbiology to publish in the *Journal of Virology* a paper by Sutton et al. that reports mutations in H7N1 influenza virus associated with airborne transmission in ferrets (2). We, the group of editors constituting an ASM committee that evaluates papers containing potential dual-use research of concern (DURC), provide responses to the three main concerns offered by Dr. Wain-Hobson and explain the rationale underlying the decision to publish this paper.

The underlying science. Dr. Wain-Hobson questions the importance of this work given the paucity of human infections with H7N1 influenza virus and the absence of human-to-human transmission of H7N1 strains. There appears to be confusion between the scientific value and rigor of the work and the medical importance of the virus studied. We used standard practice to assess the scientific quality of the Sutton et al. (2) study, which consisted of anonymous review by experts in the field and editorial evaluation of those reviews. The paper was reviewed twice by three senior influenza virologists with ample experience in studies of influenza transmission and pathogenesis. These reviewers concurred that the results were novel, significant, and scientifically sound. Furthermore, the experiments described are consistent with normative and epistemic standards in the field of molecular microbiology currently used for establishing causation (3). The editor handling the manuscript agreed with the opinions of the reviewers and recommended publication on scientific grounds. As the work raised a concern about the possibility of DURC, an additional evaluation of the manuscript was conducted by the ASM DURC Review Committee. This committee obtained opinions from the University of Maryland Institutional Biosafety Committee and the U.S. Department of Health and Human Services. After substantial deliberation, the committee reached consensus to publish the paper. With regard to the science, the *Journal of Virology* published the paper because the work was sound.

The internal review process and assessment of DURC. The U.S. Government defines DURC as "Life sciences research that, based on current understanding, can be reasonably anticipated to provide knowledge, information, products, or technologies that could be directly misapplied to pose a significant threat with broad potential consequences to public health and safety, agricultural crops and other plants, animals, the environment, materiel, or national security." Evaluation for the possibility of DURC consists of asking three specific questions as specified by the 2012 U.S. Government DURC policy (4). First, does the work involve one of the 15 listed agents and toxins? Second, does the work involve one of the seven specified experiments (or "effects")? Third, does the resulting knowledge, information, products, or technologies meet the definition of DURC as defined in the policy? Questions 1 and 2 are objective, but question 3 requires an interpretation of what precisely a criminal needs to know to perpetrate a crime. This is a judgment call for which reasonable people may not come to consensus. Therefore, it should be not be surprising that individuals and institutions can disagree about whether a particular study constitutes DURC. In the case of the Sutton et al. article, the ASM DURC Review Committee did not reach consensus about whether the work represents DURC entirely on the basis of disagreement about the answer to the third question. Importantly, the categorization of scientific work as DURC does not preclude publication and, consequently, the decision to publish such work should be made independently of whether a study is considered DURC. As we have noted previously (5), the DURC definition is problematic for journal editors, and we have called for the formation of a national board to help with these decisions. In the meantime, journal editors will continue to judge studies with the potential of DURC based on the quality of the science and, given recent precedents, work found to be scientifically meritorious should be published. In this regard, we note that the National Science Advisory Board for Biosecurity recommended unredacted publication of two controversial H5N1 papers in 2012 reporting DURC (6, 7) and that other papers reporting potential DURC have been published since that time (8). Thus, our decision to publish the Sutton et al. paper is consistent with contemporary practice.

Lack of a quantitative risk-benefit analysis. Although risk-benefit analyses have value because they foster discussion and can potentially identify important parameters that should be considered, we do not think an accurate (i.e., quantitative) risk-benefit analysis can be performed when neither the risk nor the benefit can be measured in a meaningful way (9). In our deliberations about the Sutton et al. paper, we relied on the funding agency (NIAID), the U.S. Department of Agriculture, and the University of Maryland Institutional Biosafety Committee to adjudicate biosafety risk. As noted in our editorial explaining the decision to

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publish the Sutton et al. paper (10), the authors incorporated several features in the experimental design to mitigate risk. "First, the A/ostrich/Italy/2332/2000 (H7N1) parental strain and the variants insolated in this study display avian (α2,3-linked sialic acid) and not human (α2,6-linked sialic acid) receptor-binding specificity. Second, the parental A/H7N1 virus is susceptible to oseltamivir and antigenically matched to an A/Netherlands/219/2003 (H7N7) experimental vaccine. Third, all experiments in this study were conducted in an enhanced animal biosafety level 3 laboratory appropriate for highly pathogenic avian influenza virus strains and routinely inspected by both institutional biosafety and United States Department of Agriculture officials." The risk of some type of laboratory accident is not zero, but we think that appropriate steps were taken to diminish risk to a minimum degree. Benefits are similarly difficult to quantify. In addition to possible contributions to influenza virus surveillance and vaccine development, we think that knowledge of specific sequences in influenza virus proteins that are altered during selection for replication and transmission in mammals might identify virus-host interfaces (i.e., points of contact between virus and host proteins) that may provide clues about antiviral drug targets. This may not prove to be the case, but we wonder if the pioneering molecular biologists studying restriction in bacteria dreamed that discoveries made about mechanisms of bacterial resistance to phages would pave the way for a revolution that has enhanced human health immeasurably, with the hepatitis B vaccine as just one example that stemmed from this research. In the end, we reached consensus that the potential risks of the study were low (as defined by the appropriate experts) and mitigated further by the experimental strategy used and that there were indeed potential benefits that might lead to improvements in human health. Based on this reasoning, which represents a form of risk-benefit analysis, we moved forward to communicate the results.

We thank Dr. Wain-Hobson for his critique, which has given us the opportunity to clarify the process used to publish the Sutton et al. study in the *Journal of Virology*.

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