cover in order to prevent the next influenza pandemic. We failed at containing the 2009 pandemic influenza simply because, among other factors, we do not have a comprehensive understanding of what makes an influenza strain transmissible in humans. We still do not know whether an H5N1 virus that gained the capacity to transmit by respiratory droplets in ferrets can effectively transmit by the same route in humans. We do know that the potential is there, but it is not through fear that we will stop H5N1 from becoming pandemic. The pursuit of knowledge is what has made humans resilient—a species capable of overcoming our worst fears.

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PUBLIC HEALTH AND BIOSECURITY

Life Sciences at a Crossroads: Respiratory Transmissible H5N1

Release of details of recent research on affecting influenza transmissibility poses far more risk than any good that might occur.

Michael T. Osterholm* and Donald A. Henderson

Two recently submitted manuscripts to *Science* and *Nature* report success in creating mutant isolates of influenza A/H5N1 that are able to be transmitted by respiratory droplet or aerosol between mammals (ferrets). The studies imply that human-to-human transmission could be possible as well. Shortly after the submission of the papers to the journals, the National Science Advisory Board for Biosecurity (NSABB) was asked by the U.S. government to address this question. The NSABB recommended that the papers not be fully published; rather, the basic results of the studies should be communicated without methods or detailed results but in sufficient detail to maximize the benefits to society of the studies' findings. In turn, these recommendations were accepted by the U.S. government and shared with the authors and the editors of *Science* and *Nature*.

Some have asserted that these recommendations represent unwarranted censorship of scientific research and that the sharing of the results, particularly the specific viral mutations, is necessary to protect global public health. They argue that sharing the virus mutation information with global influenza surveillance organizations would result in the rapid identification of a potential H5N1 pandemic virus in birds or humans. This early information might permit health authorities to quash an emerging human influenza pandemic. In addition, they believe that knowledge of the mutations could enhance H5N1 vaccine research and manufacturing.

While considering the possible merits of a wider dissemination of more complete information regarding mutational changes of the newly created H5N1 strains, one fact must be kept in mind. The current circulating strains of influenza A/H5N1, with their human case-fatality rate of 30 to 80%, place this pathogen in the category of causing one of the most virulent known human infectious diseases.

Disseminating the entirety of the methods and results of the two H5N1 studies in the general scientific literature will not materially increase our ability to protect the public's health from a future H5N1 pandemic.

Moreover, detecting an emerging pandemic virus in animals before the occurrence of a human pandemic is unrealistic; rather, the pandemic virus documentation will be "an after-the-fact record of what just happened." For example, in the six countries of the world where highly pathogenic avian influenza H5N1 is endemic (Bangladesh, Cambodia, China, Egypt, Indonesia, and Viet Nam), the quality of public and private veterinary and animal production services is variable and low in some places (*1*). These countries are not often able to detect and respond to influenza A/H5N1 infections in birds. When H5N1 isolates are obtained, little to no gene sequencing is conducted, meaning that a mutation map of possible prepandemic viruses will not be generally available. Even if such laboratory support were readily available and samples from ill birds were processed in a timely manner, these countries lack the commitment to deal vigorously with H5N1. This conclusion was recently highlighted by the United Nations Food and Agriculture Organization (*1*, *2*).

The World Health Organization (WHO) is also well aware of the magnitude of the challenge of identifying an emerging human influenza pandemic and stopping it before it spreads globally. Experiences with pan-

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demic H1N1 [influenza A(H1N1)pmd09] show the problems of a strategy based on the assumption that an emerging influenza pandemic could be identified quickly in a localized geographic area with no, or very limited, travel in or out of the pandemic zone (*3*). As a result of extensive global travel, influenza A(H1N1)pmd09 infection was already occurring in a number of countries before the first isolate was identified (*4*). That experience dashed WHO's expectations of using antiviral drugs to stop initial outbreaks of an emerging pandemic influenza virus (*3*).

With regard to H5N1 vaccine research, licensed influenza vaccines for human use, whether inactivated or live attenuated, are based on the use of the hemagglutinin and neuraminidase antigens, not on the other novel antigens that are potentially altered by mutational changes. Although H5N1 candidate vaccines using the isolates from these studies should be developed and tested, this does not require sharing all of the mutational data outside of a small select group of established researchers already working within the WHO network. Rather, the real challenge that we face in preparing for the next influenza pandemic is developing, licensing, and manufacturing 21st-century game-changing influenza vaccines that are effective against multiple strains and readily available on a global basis in time for the earliest days of the pandemic. One of us (M.T.O.) recently summarized the serious challenges we face with the relative effectiveness and availability of our current hemagglutinin antigen vaccines (*5*). First, the effectiveness of vaccines both with and without adjuvant against influenza A(H1N1)pmd09–related illness was limited despite the very close match between the circulating virus and the vaccine strain. In the United States, the effectiveness of the vaccine without adjuvant in children and adults 10 to 49 years was 59%, and for mostly vaccines with adjuvant in Europe and Canada in those primarily under 65 years of age, the median effectiveness was 72%. In addition, influenza vaccines produced for each of the last three pandemics (1957, 1969, and 2009) prevented very little disease, because supplies of vaccine were not available until after most of the cases had occurred because of lengthy manufacturing requirements (*6*–*9*).

In summary, disseminating the entirety of the methods and results of the two H5N1 studies in the general scientific literature will not materially increase our ability to protect the public's health from a future H5N1 pandemic. Even targeting dissemination of the information to scientists who request it will likely not enhance the public's health. Rather, making every effort to ensure that this information does not easily fall into the hands of those who might use it for nefarious purposes or that a biosafety accident resulting in an unintended release does not occur should be our first and highest priority. We can't unring a bell; should a highly transmissible and virulent H5N1 influenza virus that is of human making cause a catastrophic pandemic, whether as the result of intentional or unintentional release, the world will hold those who work in the life sciences accountable for what they did or did not do to minimize that risk.

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PUBLIC HEALTH AND BIOSECURITY

The Obligation to Prevent the Next Dual-Use Controversy

Ruth R. Faden[1]*† and Ruth A. Karron[2]

The recent debates over H5N1 experiments highlight current shortcomings in oversight of potential dual-use research.

For the first time, the U.S. National Science Advisory Board for Biosecurity (NSABB) has recommended that research done by two separate groups be redacted, an unprecedented caution that has unleashed debate over the proper balance of global security, public health, and the integrity of science. Currently, the avian influenza virus H5N1 is not easily transmitted from human to human, but a high mortality rate in those who have been infected with H5N1 viruses has raised fears of possible naturally occurring mutations that would increase transmissibility (*1*). This concern prompted research conducted by Fouchier and colleagues and Kawaoka and colleagues, with funding from the U.S. National Institutes of Health (NIH), to understand the molecular characteristics underlying transmissibility. However, the NSABB found sufficient cause for concern over potential use of this research by terrorists looking to unleash, rather than prevent, a lethal influenza pandemic to warrant restrictions on access to critical technical details. Although *Science* and *Nature* agreed to redact the research for publication to help prevent the misuse of this science by hostile actors, they made that agreement contingent on establishment of a mechanism to allow appropriate researchers and public health officials access to the complete information.

Although the dilemma over publication of these research projects has generated substantial concern in the bioscience community, this challenge was neither unanticipated nor previously unexamined. In part because of the anthrax attacks in 2001, the National Academy of Sciences convened a committee to analyze how best to minimize

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