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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Published online 19 January 2012; 10.1126/science.1218612

PUBLIC HEALTH AND BIOSECURITY

The Obligation to Prevent the Next Dual-Use Controversy

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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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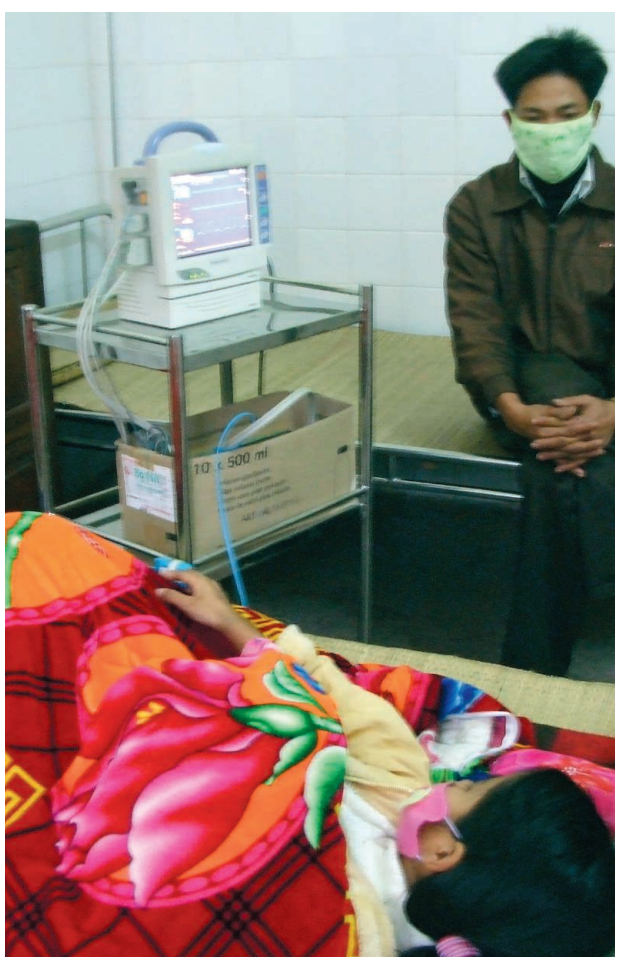
the biosecurity threats posed by dual-use research of concern without undermining biomedical science. In 2004, the committee published its analysis—now popularly called the Fink report after its chair Gerald Fink—that included recommendations amounting to a new system of oversight and biosecurity risk management for the life sciences and calling for the establishment of the NSABB (*2*).

In the 8 years since [publication of the Fink] report, no coordinated system for oversight of dual-use research, either national or international, has been implemented.

The specific and immediate question posed by the H5N1 studies is how to ensure appropriate access to the details of a study when a determination has been made by NSABB that these details should not appear in the public scientific literature so as to protect against misuse. This question should not have caught the NSABB or the NIH by surprise. Although the NSABB determined that all previous studies it had been asked to review could go forward to full publication, there was always a possibility that in the next case they would find otherwise. According to the chair of the NSABB, that committee was not given the job of developing a system for distributing sensitive information (*3*). But if that is the case, then this remit should have been given to some other identified entity when the NSABB was established.

However, the current debate about these H5N1 studies is as much about whether they should have been conducted at all, as about who, after the fact, should have access to the details of the research (*4*, *5*). There are increasing calls for some kind of prospective screening to identify higher-risk research proposals and subject them to special review and oversight (*6*–*8*). The Fink report put forward one blueprint for how this might be done that included guidelines to help identify research that has the potential for diversion to offensive aggressive uses, tasking Institutional Biosafety Committees to employ these guidelines in the first stage of review of experiments, and expanding the remit and membership of NIH's Recombinant DNA Advisory Committee (RAC) to make it an appropriate body for the next stage of review. That blueprint is far from perfect. For example, whereas the Fink report rightly acknowledges that any effective system of biosecurity oversight of the life sciences must have a global structure, its recommendations for international coordination are at best underdeveloped. Nevertheless, the central point is this: In the 8 years since that report, no coordinated system for oversight of dual-use research, either national or international, has been implemented. Although the current controversy may finally spur the adoption of some kind of prospective screening process, we now run the risk that heightened public attention will result in an overcorrection that is more restrictive of the conduct or communication of biological science than appropriate concern for biosecurity requires.

In the case of the H5N1 studies, scientists and security experts have the same aim: to reduce the risk of a global, highly lethal pandemic, whether naturally occurring or the intentional consequence of bioterrorism or biowarfare. Framed this way, the dilemma becomes a familiar problem of benefit-risk assessment and risk management, in which properly constructed prospective review can play an important role. Although nations differ in their tolerance for the risks of new biotechnologies (*9*–*11*), no society does or should operate with a true "zero-risk" approach to science, just as no society can responsibly ignore the biosecurity risks posed by some work in the life sciences. The challenge is to implement effective practices to properly assess and manage these risks that allow for the vigilant stewardship of both the institution of science and public safety.



CREDIT: STRINGER/REUTERS

Bird flu patient. Bui Thi Thao is lying in a hospital. His sister, who was the first confirmed bird flu patient in Vietnam, died the week before.

Two ethical dimensions of this challenge deserve particular mention. First, when dual-use research of concern is allowed to go forward, those responsible for managing any subsequent threats to biosecurity have a moral obligation to ensure that the results of that research are used to help reduce risks to global health. This obligation is grounded in two mutually reinforcing arguments. First, the prospect of such a benefit is at the heart of the ethical justification for conducting the research in the first place. Unless the biosecurity risk turns out to be more grave and more difficult to manage than was reasonably foreseeable, it is ethically unjustifiable to run the risks but not realize the benefits that justified their assumption. Second, particularly when there is any prospect that the research might be of near-term public health benefit, to withhold such scientific findings violates both general moral duties of beneficence to prevent harm to others and the specific forms of this duty that fall on the scientific community to use new knowledge to help prevent human suffering.

The details of the recent H5N1 studies may be of particular utility to countries where H5N1 in birds is prevalent and the risks to humans are of most immediate concern. The structure that will control access, must, as a moral matter,

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ensure that the global and national public health officials and scientists responsible for influenza control in these countries are included in the community of people authorized to know the research details. To do otherwise risks the ethically unacceptable prospect, if one assumes that this research turns out to have sufficient practical utility, that people will die from cases of avian flu that might otherwise have been averted (see the photo). Although current surveillance systems may not be sophisticated enough to make optimal use of these findings (*12*), that is an argument for investing in enhanced surveillance and molecular diagnostics, rather than withholding potentially valuable information. Withholding data from countries where highly pathogenic H5N1 has been detected also threatens the World Health Organization's (WHO) Pandemic Influenza Preparedness (PIP) Framework (*13*), a fragile global agreement on influenza information sharing that is vital to pandemic prevention. Established in May 2011 and adopted by all WHO member states, PIP states that laboratories conducting research on viruses obtained through WHO have an obligation to collaborate with scientists in countries where the virus originated, a response to Indonesia's position that supplies of its domestic virus strains would cease unless it was given access to the vaccines created from them (*14*).

The structure that will control access, must, as a moral matter, ensure that the global and national public health officials and scientists responsible for influenza control in these countries are included in the community of people authorized to know the research details. To do otherwise risks the ethically unacceptable prospect, if one assumes that this research turns out to have sufficient practical utility, that people will die from cases of avian flu that might otherwise have been averted.

Another ethical dimension centers on the responsibilities of individual scientists. The Fink report makes the point that all scientists have an affirmative ethical obligation to avoid contributing to the advancement of biowarfare and bioterrorism. This obligation and its implications for the conduct of scientists deserve greater attention in the life sciences literature. Fouchier and his colleagues have described their efforts to obtain consensus on the necessity of these experiments within the community of influenza virologists, to develop adequate containment facilities, and to obtain the necessary reviews and approvals from Dutch and U.S. government officials (*15*). These efforts are laudable and likely represent all of the options that were reasonably available to the investigators. However, the processes used did not have the features of the kind of review and oversight envisioned by the Fink report, including interdisciplinary and global participation.

In addition, Fouchier, Kawaoka, and more than 30 other influenza scientists recently announced a voluntary 60-day moratorium on research involving the generation of highly pathogenic H5N1 viruses that are more transmissible in mammals and on the viruses generated in the current research to give "organizations and governments around the world … time to find the best solutions for opportunities and challenges that stem from the work" (*16*). The moratorium, first suggested by the NSABB, is not the first such effort by life scientists at self-regulation. From July 1974 to February 1975, scientists refrained from conducting some types of recombinant DNA research to allow for the establishment of an appropriate oversight system in the interests of public safety (*17*). The current influenza research moratorium is not unproblematic. Sixty days may not be nearly enough time to establish a similar system for influenza research of concern, and the language used to announce the moratorium is troubling for its failure to confront the possibility that this research may pose real biosecurity concerns. Nevertheless, it illustrates one path for scientists wanting to take seriously their ethical obligation to avoid contributing to biosecurity threats while endeavoring to conduct research to protect public health.

Ethics does not demand the impossible, however; scientists cannot ensure or guarantee that their work will never be applied intentionally or accidentally to harm society. They can only take reasonable steps to minimize the chances that such harm will occur. Moreover, there are real limitations to what individual scientists or even groups of scientists can do on their own, as this recent H5N1 case illustrates vividly. Managing the biosecurity and biosafety risks posed by some life science research without unduly hampering the good that such research can produce is a classic, and daunting, collective action problem that cannot be solved without global cooperation and coordination. Just as the potential benefits of this type of research cannot be realized without providing information to international groups of scientists and public health officials with expertise in multiple disciplines (*15*), so, too, an adequate assessment of potential societal risks requires prospective review by an international body with a range of expertise, including in this case influenza virology and biosecurity. There is no doubt that there are formidable obstacles to developing such a global oversight body. But that the challenge is hard is no excuse. What we could not accomplish between 2004 and today can no longer be delayed.

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Published online 9 February 2012; 10.1126/science.1219668

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