Engineered H5N1: A Rare Time for Restraint in Science

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Two scientific teams have recently engineered the H5N1 virus to make it readily transmissible between ferrets. Given that ferrets are considered the most reliable animal surrogate for human influenza infection, the newly engineered H5N1 strain is probably transmissible between humans as well. The potential consequences of an engineered human-transmissible H5N1 strain are stunning. Although seasonal flu infects as much as 20% of the world’s population—more than 1 billion persons—each year, only a small fraction of those with seasonal flu dies, most often the oldest, youngest, and sickest. If the newly engineered strain were to escape the laboratory (either by design or by accident) and spread as widely as seasonal flu with anywhere near the current confirmed H5N1 human case-fatality rate, it could endanger the lives of hundreds of millions of persons. The possible benefits of this work do not justify taking such risks. As clinicians, we have a stake in this issue with our responsibilities for the diagnosis and treatment of influenza. We embrace the principle of free and open exchange of scientific information, but we also believe in the principle of “first, do no harm.” These 2 principles have come into a moment of rare conflict. It seems most reasonable and prudent to request that the involved scientific community and its institutions exercise restraint by restricting dissemination of the experimental results and discontinuing work on the engineered H5N1 strains. If a highly compelling case is made for continued work on this strain despite the risks, the work should be controlled and should merit the greatest scrutiny.

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Recent experiments to engineer an H5N1 influenza virus that is transmissible between humans have generated intense scientific, public health, and ethical debate around the world. The World Health Organization (WHO) recently weighed in on the issue with an uncommon statement of concern: “... studies undertaken by several institutions on whether changes in the H5N1 influenza virus can make it more transmissible between humans have raised concern about the possible risks and misuses associated with this research. WHO is also deeply concerned about the potential negative consequences” (1). On this exceptional occasion, there is sufficient reason for concern, and it seems reasonable to request that the involved scientific community and its institutions exercise restraint and restrict dissemination of the experimental results and that the continued use of the engineered H5N1 strains cease.

As clinicians, we have a stake in this issue with our responsibilities for the diagnosis and treatment of influenza. We strongly support research and the accrual of new scientific information. We embrace the principle of free and open exchange of scientific information, but we also believe in the principle of “first, do no harm.” These 2 principles have come into a moment of rare conflict.

A Virus Like No Other

The currently circulating H5N1 bird flu virus has an extraordinarily high case-fatality rate, killing nearly 60% of the 574 confirmed human cases (2). Fortunately, unlike seasonal influenza, the H5N1 virus circulating in nature has not spread readily between humans. At the time of this writing, the most recently reported death was a man in China who died on 25 December 2011. According to Chinese authorities, none of the man’s more than 100 close contacts developed symptoms of bird flu (3).

Two scientific teams have recently engineered the H5N1 virus to make it readily transmissible between ferrets. Ferret models are considered the most reliable surrogate for human influenza infection. Thus, it is reasonable to extrapolate that the engineered H5N1 strain would be transmissible between humans. One of the investigators reported that his engineered strain spread as efficiently as seasonal flu (4).

The potential consequences of the engineered H5N1 strain are stunning. Although seasonal flu infects as much as 20% of the world’s population—more than 1 billion persons—each year, only a fraction of those with the infection dies, most often the oldest, youngest, and sickest. If the newly engineered H5N1 strain were to spread as widely as seasonal flu and have a case-fatality rate anywhere close to 60%, it could endanger the lives of hundreds of millions of persons.

How Could Things Go Wrong?

The engineered strain could begin to spread in society in 2 ways: by accident or by design. Modern approaches to biosafety are excellent. Even in the rare event of an accidental infection of a laboratory, the societal consequences of an escaped pathogen would normally be minimal or nil because most pathogens have little capacity for spread. However, the escape of a mutant, highly contagious H5N1 strain with a high case-fatality rate into a population with little or no immunity could result in a catastrophe. The probability may be small, but the consequences would be
A HARD LOOK AT THE BENEFITS

One reason that some scientists have supported these experiments and believe the full details should be published is that this work will increase basic scientific understanding of the H5N1 virus. The premise that all fundamental scientific knowledge is important and can ultimately lead to human benefits is a rationale for much of scientific research. Although I support this principle generally and believe in the many benefits of basic research, my view in this specific case is that we would need a more direct and urgent rationale to justify the risks of working with a transmissible H5N1 strain that could have an unprecedented global effect.

Others support this work with the expectation that new knowledge might provide benefits for disease surveillance and vaccine development. In terms of surveillance, no certainty exists that a strain with mutations similar to the new laboratory-engineered strain will ever emerge naturally. It is also possible that a differently configured H5N1 strain will emerge naturally. Consequently, we must remain alert and sustain control efforts for avian flu with or without knowledge of these newly engineered mutations. H5N1 vaccine development does not depend on knowledge of these mutations or on testing animals with an engineered contagious strain of H5N1. Work is under way to develop new H5N1 vaccines and more universal flu vaccines. This is critical work that deserves greater support and funding.

If we are asking society to take the substantial and unprecedented risks associated with a human-transmissible H5N1 strain with this kind of case-fatality rate, we had better have a compelling, concrete, and realistic public health justification for it.

LIMITING ACCESS

It would have been preferable if these engineered, human-transmissible strains had not been created. But now that they have, deliberations are under way regarding how to proceed with publication. The U.S. Department of Health and Human Services, at the recommendation of the National Science Advisory Board for Biosecurity, has asked the authors of the reports and the editors of the journals that are considering publishing them to make changes to the manuscripts so that they do not include methodological and other details that could enable replication of the experiments by those who would seek to do harm. The journals Science and Nature are now considering these recommendations. The National Institutes of Health has said that it will establish a mechanism to allow secure access to the details of the experiments to investigators with a legitimate need for use in achieving important public health goals (5).

Although the recommendation to create a system for sharing the experimental details with other legitimate scientists seems to be a reasonable effort at a compromise in this difficult situation, implementation and ongoing enforcement of such a system seems unrealistic. How can it be decided who is a “legitimate” scientist with a need to know? If a scientist is determined to have a need to know, do all of her or his institutional colleagues have a need to know? What are the ongoing obligations to keep these details secure? Is there any mechanism that will prevent further sharing of the information?

A TIME FOR RESTRAINT

If an experiment in chemistry or physics were performed with good and honorable purpose but the outcome created the potential to threaten the lives of hundreds of millions of persons by either accident or malicious intent, what would be the appropriate response? Would scientists around the world with a “legitimate need” to know be allowed to have the results? Would further research be allowed in additional laboratories?

If a highly compelling case is made for continued work on this strain despite the risks, the work should be controlled and should merit the greatest scrutiny. Restricted use of a particularly dangerous pathogen does have a precedent. As a result of international consultations and agreement, smallpox virus is now restricted to only 2 laboratories. Protocols for all proposed experiments must be approved by an independent international committee. This arrangement, which has been in place for more than a decade, is an example of the international scientific community and governments agreeing to curtail the risks surrounding a contagious and highly lethal agent. A genetically modified, human-transmissible H5N1 strain with a high case-fatality rate could arguably be as threatening as smallpox.

Clearly, urgent and serious deliberation about how to proceed is needed. This is a rare moment when scientific restraint and reflection are in order.
References


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