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Oversight required on Influenza research

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Executive Summary

Recent research on the H5N1 influenza virus has raised serious questions about the dangers of certain types of experiments involving specific pathogens. In response, U.S. officials have called for the drafting of global guidelines for conducting and disseminating such research. The outlines of a global oversight system are apparent and could build on existing practices of institutional and peer review. The World Health Organization has a vital role to play in developing and operating such a system, which would inevitably require significant innovation in the management of scientific information. A broad public discussion, one that involves the scientific establishment, is necessary to ensure that any oversight provides continued support for public health initiatives, while ensuring global security.

Introduction

Genetic manipulation of the H5N1 influenza virus is looming as a seminal case in the sobering annals of disaster prevention. As has been widely reported, laboratory experiments have rendered the highly virulent avian strain transmissible among ferrets, strongly suggesting that it would be transmissible among humans as well. The potential is alarming. The 1918 H1N1 strain is believed to have killed some 20 million to 100 million people worldwide with a case fatality rate usually estimated in the range of 2 percent to 4 percent. The victims were disproportionately young adults. The naturally occurring H5N1 virus has so far infected only about 600 people, but half of them have died. If the virus could achieve efficient transmissibility while retaining anything like a 50 percent case fatality rate, or even half of that, it could inflict global disaster of unprecedented proportions. In principle there is a life-threatening risk to billions of people and a correspondingly large risk to the global economy.

Implications

The principal U.S. government entity seized with the matter – the U.S. National Security Advisory Board for Biosecurity (NSABB) – initially attempted to remove details of the experiments from published reports, an action it imagined would prevent replication. It then abandoned that effort and has now indicated it will initiate a process to draft global guidelines for conducting and disseminating research on dangerous pathogens. That step, which it had previously resisted, implicitly concedes that the United States alone cannot exercise comprehensive jurisdiction.

At the moment, some prudential oversight of highly consequential biological research is being practiced in some countries, but prevailing procedures are largely voluntary, are not consistently applied, and do not have global scope. A more effective arrangement would have to be obligatory and would have to be based on the principle of independent oversight applied to other matters of great consequence. Those who handle large sums of money are subjected to audit. No single individual is ever allowed exclusive control of a nuclear weapon.

General parameters for oversight. The basic features of an appropriate oversight arrangement are evident. Established procedures for peer review of scientific merit would be extended to questions of social consequence and made mandatory. A record of judgment would be recorded in each instance. For lines of research of moderate concern, a process would be created for comparing judgments across local and national jurisdiction in order to encourage harmonization. For lines of research of extraordinary danger, such as the H5N1 experiments, the review process would be globally representative, and access to the results would be restricted to globally vetted public health professionals whose use of the results would be globally monitored. That degree of enforced transparency would require legislative action with appropriate regulatory specification to assure compliance and prevent misuse, but less than 1 percent of current biomedical research efforts would be affected.

The impediments to such an arrangement are largely matters of attitude, but they are formidable. Some research scientists recognize the need for oversight, but many are concerned about the implications of oversight for basic research, no matter how limited. Their concern is understandable, yet the risks are grave. In addition, the challenge of international coordination poses a danger of competitive national biological weapons development programs, a danger that so far appears to be largely unrealized but is not reliably prevented.

The question, then, is whether we can get from where we are to where we need to be before a disaster occurs. It is worth some effort to imagine how a reasonably robust protection schema might be worked out before there is immediately insistent demand to do so.

Practical steps

A role for the WHO. The most logical place to locate a protective oversight arrangement with global scope would be the World Health Organization (WHO), a U.N. agency established in 1948 that now includes all generally recognized nation states and many other political entities. International collaboration on the prevention, detection and treatment of infectious disease primarily occurs through the WHO whose seminal accomplishment has been the eradication of smallpox.

As an international bureaucracy beholden to the instructions of the member states, WHO is not likely to be the source of an advanced oversight initiative, but it is the inevitable venue for implementation. Acting so far in character, it has convened discussions of the H5N1 experiments and has endorsed the legitimacy of the work without attempting to determine how the dangers involved are to be managed. If the WHO is to do more in that latter regard, it will have to receive authoritative instructions to do so from the member states through the World Health Assembly that represents them.

Those instructions would necessarily focus on procedural guidelines. There is no categorical basis for judging the merits of fundamental research. Lines of inquiry that could enable exceedingly dangerous applications could also enable compellingly therapeutic ones. Judgments of consequence depend on the specific details of individual projects and have to be made by people capable of understanding not only the science involved but also the broader social implications. The WHO can and must set a process in place whereby appropriate judgments are made on a case-by-case basis. That process needs to assure that informed judgments are exercised in advance by qualified people not directly involved in the research in question. It also needs to assure that records are kept enabling comparison across cases over time. That is the only way that appropriate and consistent substantive research guidelines can evolve.

Up to this point, the WHO has not been given any mandatory authority, and there would be strong categorical resistance to doing so. It is also unclear how the WHO would enforce such authority. Its ability to achieve compliance has depended on setting standards that command voluntary adherence. The notable example is the standards it set for the containment of highly infectious pathogens in the research laboratories that hold them. They are widely accepted and reasonably well enforced by national and local authorities. To be sure, it is questionable whether standards for protective oversight could achieve the same degree of compliance or whether that degree would be sufficient. Failures of containment are inherently prominent events that trigger immediate reactions; failures of oversight are not as feared and unlikely to be noticed. Nonetheless, voluntary oversight guidelines issued by the WHO would be a constructive first step if they were accompanied by a budget for implementation. A core problem with voluntary measures is that they typically are not financed.

There is an embryonic precedent in that the WHO is supposed to exercise oversight of all research on smallpox viruses kept under containment at two designated locations pending their ultimate elimination. A committee was appointed to exercise that responsibility, but it rarely meets and does not have assertive means of assuring compliance. In a more advanced arrangement, an oversight committee would meet more often, would have dedicated staff support, would have the ability to initiate inquires about compliance, and would have a budget sufficient to support continuous attentiveness. Fortunately an institutional unit at the WHO dedicated to protective oversight could and should be very modest in size and resource requirements. Its activities would largely be restricted to influenza research. A CISSM manuscript, "Controlling Dangerous Pathogens: A Prototype Protective Oversight System" outlined notional criteria for the type of research activities that could be eligible for oversight (see Table 1).

Information protection. Any oversight unit would need the capacity to initiate and sustain a very significant innovation in the management of scientific information. As the NSABB deliberations revealed, there is no currently available means of controlling dissemination of inherently dangerous public health information. National security classification is fundamentally inappropriate for matters of vital global interest and for that reason unlikely to be effective. Practicing scientists and most other people as well will not keep secrets they do not accept as legitimate. Attempting to delete detail from published papers that need to document scientific results is similarly inappropriate and ineffective. Those who perform public health functions have legitimate claim to relevant scientific information whatever their national identity and are likely to acquire it given the free flow of information across the Internet. Although malicious misuse cannot be decisively precluded in a situation with so many legitimate claimants, standards of accountability could be set and enforced if publication

Table 1. Notional Criteria for Risk-Benefit Assessment of Dual-Use Research

Biosafety Issues
(1) Does the proposed research plan contain appropriate protections to minimize risk to the public or environment? • *Proposals receiving a "no" answer would have a low biosafety rating*
Evaluation of Research Plan
(1) Are the proposed research plan and stated rationale for the work consistent with one another? (2) Are the risks posed by the agent (either from the perspective of public health or bioterrorism) and the stated rationale for the work consistent with one another? (3) Is the proposed research plan logically sequenced? (4) Are there scientific reasons why the same outcome cannot be pursued through alternate means? For example, could other methods or materials be used? • *Proposals receiving two or more "no" answers would have a low research plan evaluation rating*
Public Health Considerations
(1) Do agents to be constructed currently exist in nature? (2) If not, are said agents expected to be generated by natural processes? (3) Will the research advance our understanding of disease-causing properties of currently existing agents? • *Proposals receiving "no" answers either to questions (1) and (2) or to question (3) would have low public health rationale*
Biodefense Considerations
(1) Do agents to be constructed currently exist in nature? (2) If not, is the work being done in response to a "validated threat" (i.e. one for which there is credible information) or "theoretical threat" (i.e. one that is possible but for which there is no credible information)? (3) Will the countermeasures that are expected to result from the work significantly reduce the threat posed by the agent? • *Proposals receiving two or more "no" answers would have low biodefense rationale*
Current Necessity
(1) Are countermeasures against agents to be constructed currently unavailable? (2) Are there scientific reasons why countermeasures cannot be developed without access to such agents? • *Proposals receiving one or more "no" answers would be of limited current necessity*
Potential Impact
(1) Will the proposed research contribute to new knowledge (e.g., by furthering our understanding of basic life processes or pathogenesis) rather than primarily confirm work already done? (2) Are the research results likely to be definitive enough to inform policy decisions (e.g., vaccination strategies)? (3) Are there significant obstacles to using the research results to develop a more dangerous pathogen or to overcome current countermeasures? • *Proposals with two or more "no" answers would have limited positive impact*

John Steinbruner et al., "Controlling Dangerous Pathogens: A Prototype Protective Oversight System," CISSM, 2007.

was in controlled-access form whereby only licensed – that is, identified and vetted – individuals could acquire it and their use would be documented. Advanced information-handling technology would enable oversight managers to know who has had access to highly sensitive information and to monitor their use of it. That arrangement would have to be accompanied by oversight of the oversight monitors themselves to protect against regulatory abuse as distinct from scientific misuse. There is a strong presumption that very powerful biomedical technology will ultimately force the development of sophisticated regulatory designs of that sort.

But if the WHO is unlikely to initiate the oversight process it would have to implement, then who might? From where might the necessary leadership arise? In principle, one can say it would come from within the biomedical establishment, which has a much greater stake in the matter than it has yet acknowledged. The potential consequence of rapidly advancing knowledge, especially within molecular biology, is bound eventually to seize attention, and practicing scientists have a huge interest in organizing tolerable protective procedures. Otherwise they are likely to get ones that justify their fears of interference. The initiative required has more to do with policy, however, than with science, and effective policy is something that must engage entire societies. Rather than pining wistfully for some visionary politician to lead a parade, we first need to organize a public discussion worthy of the topic.

About the author

John Steinbruner is Professor of Public Policy at the University of Maryland and Director of the Center for International and Security Studies at Maryland (CISSM). He is co-author of a research monograph *Controlling Dangerous Pathogens* and author of a recent novel, *The Secular Monastery,* both of which deal with the issues of biotechnology oversight.