Can Limited Scientific Value of Potential Pandemic Pathogen Experiments Justify the Risks?

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Casadevall et al. (1) argue for the value of the scientific findings of gain-of-function experiments to render avian influenza viruses transmissible in ferrets and further argue that the value of this knowledge should be weighed against the quantifiable risk (2) that such experiments might lead to an accidental pandemic.

Herein I contend that the scientific or epistemic gain from such experiments is limited by several factors, and I question whether such knowledge can carry substantial weight in a risk-benefit assessment where the risks to life and health are large, as they are in the case of potential pandemic pathogen creation.

Modification of an avian influenza A/H5N1 virus (referred to here as H5N1) to achieve respiratory droplet transmission in ferrets is a proof by example that such transmission is possible. This is indeed a piece of new scientific knowledge with relevance to the more pressing question of whether efficient respiratory droplet transmission in humans is possible for strains closely related to existing avian H5N1. However, the scope of the new knowledge is restricted for two reasons.

The first is limitations of the ferret model, compounded by small sample sizes. The adequacy of animal models for human disease phenotypes has come under growing criticism in recent years (3–5). Specifically, the quantitative correspondence between respiratory droplet transmission in ferrets under precise laboratory conditions on one hand and human-to-human transmission in the field on the other is uncertain (6). Relatively few of the possible influenza virus strains of interest have been tested in the ferret model, making the generality of any relationship a matter of speculation and the quantitative correspondence unknown. For example, there are only a few inferred examples of human-to-human transmission of influenza virus A/H7N9 by any route, yet isolates from human cases were transmitted with moderate or high efficiency in three laboratory ferret studies (7–9). Stronger scientific claims, such as the existence of a minimal set of mutations to confer transmissibility, have been asserted (10) but are not supported by statistically sound evidence, which would be arguably prohibitive to gather due to the large numbers of experimental animal pairs required (16).

The second is the generality of results. The generalizability of findings in a single influenza virus A/H5N1 isolate to other variants of influenza virus A/H5N1—and indeed other influenza virus A subtypes—is uncertain. Introducing the mutations observed by Imai et al. (11) and Herfst et al. (17) into a different influenza virus A/H5N1 isolate did not change sialic acid receptor specificity in the same way as in the variants used by those authors (13). More generally, epistatic interactions that modify the phenotypic or fitness effect of mutations depending on their genetic context are frequent in influenza virus (2, 18), including for other loci deemed important in the gain-of-function studies (10), such as the PB2 E627K mutation (12). The molecular Koch's postulates proposed by Falkow (14) were, as Casadevall et al. state (1), a tremendous step forward for the field. In the presence of very strong epistatic interactions, it seems that there may be a need to add to these postulates some consideration of the generalizability of a phenotype within a microbial species or clade.

A separate issue reflects the difference between the high standards for certainty that are appropriately required for scientific claims in microbiology and the requirements for evidence-based policy-making that routinely require decision-making under uncertainty. It is true that before the gain-of-function (GOF) studies with H5N1, some experts hypothesized that this virus could not be modified to be transmitted in mammals. The GOF experimental results definitively prove this hypothesis wrong. Scientifically, the scope of our knowledge has grown and the scope of our uncertainty correspondingly narrowed, at least for ferrets.

From a decision maker's perspective, that additional scientific evidence can do little to alter the choice of policies. When the potential for transmissibility of H5N1 in ferrets was unknown, a responsible and rational decision maker would have had to consider the possibility that H5N1 could become pandemic, notwithstanding the existence of an untested hypothesis that it could not. Indeed, the United States, for example, stockpiled vaccines against this eventuality. Following the GOF experiments, we know that one variant of H5N1, with a small number of mutations, can be transmitted in ferrets. The responsible and rational decision maker is in nearly the same position, still needing to plan for the possibility of a pandemic from H5N1, perhaps with slightly greater urgency, but still uncertain whether any H5N1 strain has the capacity to evolve into a human-to-human-transmitted pathogen. Science proceeds by answering precisely defined questions with a high level of certainty—in this case the question of whether a particular strain of H5N1 can be modified with a small number of mutations to become transmissible in ferrets under laboratory conditions. Policy must consider much "messier" questions that cannot be answered with such certainty—what are the chances that any H5N1 variant will evolve in nature (perhaps through major changes involving reassortment) to become readily transmissible in humans under field conditions? From a policy maker's perspective, the answer to this question is only modestly clearer than it was before the GOF experiments, and it is difficult to imagine how it could become significantly clearer with any practicable number of future such experiments.

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This consideration leads to a further question raised by the essay of Casadevall et al. They state that the epistemic benefit of answering a scientific question with certainty must be weighed against the risks to life and health posed by the possibility of accidental or deliberate release of a potential pandemic pathogen. This is a strong claim in bioethics, and it raises an essential question that has not been well addressed in research ethics in general: can a risk to the life and health of large numbers of people ever be balanced by the benefit of pure scientific knowledge? Casadevall et al. note that researchers place themselves (and, one could add, sometimes their unknowing colleagues [15]) at risk whenever they work with dangerous pathogens, even nontransmissible ones. However, the scale of risk from a potential pandemic pathogen is much greater than the occupational risk run by those who work with dangerous, nontransmissible pathogens. Moreover, it could be argued that the voluntary nature of the risk undertaken by such researchers places it in a different category from the pandemic risk imposed on uninformed, unconsenting persons who may be geographically and culturally remote from the scientists undertaking the experiments. In clinical studies that deliberately place enrolled humans at health or life risk, generally accepted ethical principles state that the benefits of such studies must be humanitarian, not merely scientific, and must be unachievable by safer means. In the relatively uncharted ethics of research that places unspecified humans at such risk, it has been argued that the same principles should apply (2), which would imply that the pure epistemic value of PPP (pathogens with pandemic potential) experiments could not outweigh the risks of pandemic release. The contention that epistemic benefits might carry such significant weight requires an argument for why the model of research placing identified human subjects at risk should not be extended to research placing unidentified ones at risk.

Finally, in a world of scarce resources for science, it is essential to judge the epistemic value of a particular experimental program in comparison to that of alternative experimental programs. The question is not whether GOF/PPP experiments have epistemic value; they surely do. But so do other experimental approaches that compete with GOF/PPP experiments for resources. Doing GOF/PPP experiments has an opportunity cost. In choosing how to allocate limited scientific resources, the question is whether the benefits of the GOF/PPP approach exceed those of other approaches (including GOF studies in safer viral genetic backgrounds) to an extent that is sufficient to justify the unique risks they entail (2).

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