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

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We thank Dr. Lipsitch for his comments (1). Dr. Lipsitch does not argue with the notion that gain-of-function experiments are epistemologically valuable, but he does feel that their practical value is limited. Likewise, we would not argue that reasonable people cannot come to different conclusions about the relative epistemic value of any given experiment. He makes several points to which we will respond.

The first point is that the epistemic yield of influenza virus GOF experiments in ferrets is limited. Dr. Lipsitch questions the value of the experiments establishing H5N1 transmissibility in ferrets (2, 3) on the basis of underpowered experiments and the possibility that the information is limited to ferrets. That may be true for quantitative data, although arguments have been made to the contrary (4), but the experiments on H5N1 transmissibility unequivocally established that H5N1 had the biological potential to become mammalian transmissible, and that observation was a qualitative, all-or-nothing, result for which there is no need for statistical analysis: it happened. The fact that it happened is the epistemic gain, and the definitive nature of the result makes it of high epistemic value. Prior to these experiments, the question of whether highly pathogenic avian influenza viruses (HPAIV) had the biological potential for mammalian transmissibility was in doubt. Since the completion of these experiments, we know with great confidence that H5N1 can mutate to achieve mammalian transmissibility, and that knowledge is new, important, and actionable. In addition, we note that influenza virus infection in ferrets closely mimics that of humans, and ferrets are the most widely accepted small animal model for this virus (5).

The second point is the generalizability of the results. Dr. Lipsitch questions whether the results obtained with a single strain are generalizable. We agree that one should not extrapolate from single strains and that the epistatic effects Dr. Lipsitch notes limit the value of the mutational information. However, the simultaneous work from the Fouchier and Kawoaka laboratories used different strains, obtained similar results, and thus confirmed one another (2, 3). Since those experiments were reported, additional work has been done with strain H7N1, which was also shown to be capable of mammalian transmissibility (6). Hence, we now have information that three different strains in three different laboratories can become mammalian transmissible and appear to be generalizable to other influenza virus strains. The reproducibility of the major findings with a different strain using gain-of-function experiments in ferrets highlights the high epistemic value of the original findings.

The third point is that the information is of little relevance to a policy decision maker. We disagree with the notion that the information is of little use, since prior to the experiments, the question of whether H5N1 could become transmissible in mammals was uncertain. Now there is no question that it can happen. Before the experiments a decision maker had to deal with the uncertainty of whether HPAIV had the capacity for mammalian transmission. Would Dr. Lipsitch argue that the risk of a pandemic is the same with and without the possibility of the mammalian transmission demonstrated in GOF experiments? After the experiments were reported, a decision maker would know that the virus has the capacity for mammalian transmission, and this reduction in uncertainty has to be helpful in making decisions as to whether and how to prepare for a pandemic.

The fourth point concerns ethical choices involving experimentation. Dr. Lipsitch writes "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?" Dr. Lipsitch appears to have misread our editorial, since nowhere in the text did we argue that information gathered for pure scientific knowledge can justify putting at risk the lives of humans (7). In fact, our arguments in support of the epistemic value of GOF experiments rest solely on the benefit of the information to humanity and never on "pure scientific knowledge" (7). We argued that these experiments are directly beneficial to humanity because they have informed on the capacity of high pathogenicity avian influenza viruses to become mammalian transmissible and thus warned humanity of this potential danger (7, 8). Additionally, we did not ignore the difference between individuals knowingly putting themselves at risk and putting others at risk without their prior knowledge.

In addition to these responses, we note an apparent contradiction in the letter by Dr. Lipsitch. In the early paragraphs he criticizes the value of ferret experiments with the implication that this information cannot be extrapolated beyond the results presented. However, later in the letter he takes us to task for suggesting that these experiments have epistemic value despite the potential for a laboratory accident that could cause a pandemic. This position is not consistent, for if there is no value beyond ferrets, there is no threat of a pandemic from a laboratory accident. In fairness to Dr.

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Lipsitch, we know what he means, but we also point out that he cannot have it both ways.

We also note that Dr. Lipsitch employs the strategy of raising the specter of global pandemic—a real concern, to be sure—as an eventuality with consequences so dire as to overwhelm any conceivable good flowing from GOF/PPP experiments. The rhetorical device of evoking overwhelming suffering ramps up the cost, however large or small the probability, and severely downplays any gain from the practice under debate. We caution against the repeated use of this strategy in the GOF debate, since this rhetorical device turns risk analysis into a parlor game by invoking the prospect of infinite suffering. As we have written previously (7, 8), we urge that the debate refocus on making these very valuable experiments even safer, through the development of new tools such as safer strains and experimental strain vaccines for investigators, which would provide a ring of immunity to contain a laboratory accident.

Finally, Dr. Lipsitch argues that resources spent on GOF experiments are best used in other ways. In response, we argue that there is currently no alternative to GOF experiments for answering certain questions. In this regard, we have noted that short of waiting for a human H5N1 pandemic to occur, with its associated mortality and morbidity, no other technology is available to definitively answer the question of whether HPAIV had the potential for mammalian transmission. The GOF experiments carried with HPAIV strains provide unequivocal evidence that this could occur, and this is information that humanity can use to prepare itself for such an eventuality with better therapeutics, vaccines, and increased surveillance. Moreover, it is misleading to argue that we are involved in a zero-sum game. Public concern about pandemic influenza is so acute that it is not at all implausible that additional resources might be made available to fund multiple experimental and epidemiological studies.

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