Assessing and Managing the Risks of Potential Pandemic Pathogen Research

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The ongoing controversy surrounding highly pathogenic avian influenza virus research has generated considerable discussion among virologists, public health researchers, and biosafety/biosecurity experts (1–3). The most recent pause in research instituted by the U.S. Office of Science and Technology Policy calls for an independently performed risk-benefit analysis (RBA) to be completed within a year. The RBA, administered by the NIH Office of Science Policy, is supposed to be "comprehensive, sound, and credible" (4). A brief review of some of the risk assessments performed so far suggests that the typical RBA approach is unlikely to build consensus or resolve this controversy.

While the NIH requests both qualitative and quantitative risk-benefit assessments if possible, the general expectation among scientists involved in the avian influenza research debate is that a quantitative assessment should be performed (5) under the assumption that numbers carry more credibility and may suggest solutions. Klotz and Sylvester (6) performed a simple probabilistic risk assessment to argue that gain-of-function (GOF) research with potential pandemic pathogens (PPPs) should be restricted. Starting with the assumption that the probability of release from a laboratory each year is 0.003 and that at least 42 labs worldwide are working with PPPs (in this case, viruses causing highly pathogenic avian influenza, Middle East respiratory syndrome [MERS], or severe acute respiratory syndrome [SARS]), there is an 80% likelihood of a release every 13 years. An updated calculation (7) estimated a 5% to 27% probability of a pandemic over a 10-year period due to laboratories working with PPPs.

Using biosafety level 3 (BSL-3) lab infection data (8), Lipsitch and Inglesby (5) estimated a probability of between 0.01% and 0.1% per laboratory-year of creating a pandemic which would cause between 2 million and 1.4 billion fatalities. This yields an expected fatality rate of 2,000 to 1.4 million per BSL-3 laboratory-year. Alternatively, using data from the National Institutes of Allergy and Infectious Diseases, the probability of a pandemic would be between 0.05% and 0.6% per worker-year, with a resulting expected fatality rate of between 10,000 and 10 million per laboratory worker. When Lipsitch presented these calculations at a December 2014 National Research Council (NRC) symposium, Ron Fouchier, the lead researcher for the original controversial H5N1 paper (9), responded, "I prefer no numbers rather than ridiculous numbers that make no sense" (10). Even if we assume these calculations are credible, Fouchier makes a fair critique in that using expected utility to express low-probability–high-consequence events can be quite unhelpful for decision-making. For example, an event with a 0.1% chance of 999 fatalities has the same expected fatality rate as an event with a 99.9% chance of 1 fatality. However, these events are ethically distinct, as are their policy implications.

A subsequent risk estimate from Fouchier (11) started from the same data (8), but then Fouchier argued that highly pathogenic H5N1 virus experiments occur in special facilities (BSL-3+) and, using the Erasmus MC facility as an example, he estimated that the risks are much lower due to extra physical barrier biosafety measures, lab personnel vaccinations, and available antiviral therapeutics. Thus, he estimated the risk of a laboratory-acquired infection (LAI) to be less than 1×10^{-7} per person-year. Taking into account that any infected lab worker would have already been vaccinated against a homologous H5N1 virus, would be taking antiviral medication, and would be quarantined, Fouchier estimated that a lab-induced pandemic would occur every 33 billion years—more than twice the known age of the universe. He concluded with the observation that there have been no confirmed influenza virus LAIs or releases in decades, which suggests current measures are sufficient.

A reply by Lipsitch and Inglesby (12) questioned Fouchier's claim that virology labs are safer than other BSL-3 labs. They also noted that Fouchier's calculations incorrectly accounted for the uncertainty associated with 0 observed events (13). Furthermore, the assumption of 0 events was claimed to be unreasonable, because viral LAIs have occurred in non-U.S. facilities (14). In separate comments, Klotz (15) argued that Fouchier's calculations were based on the wrong method of calculating the elapsed time of escape for an LAI and that the estimate for an LAI was too low. A reply by Fouchier (16) argued that Klotz did not provide "scientific justification" for higher estimates.

Within this debate among competing risk estimates, there appears to be disagreement as to not only what constitutes the appropriate methodology, but also what constitutes evidence. For example, Fouchier (16) does not believe that recent laboratory errors (most notably at the CDC) constitute relevant data, because either the errors did not result in LAIs, the pathogen was not an engineered avian influenza virus, or the work was not conducted specifically in a BSL-3+ laboratory. However, critics contend that these errors demonstrate the general failure of laboratory safety procedures upon which Fouchier's calculations depend. Adding to this concern is a study (17) that estimated a 5% to 15% probability that a laboratory escape event would go undetected. Likewise, investigative reporting on U.S. labs (18) suggested that laboratory accident records are poorly tracked, generally underreported, and difficult for the public to access.

A review of these various assessments suggests that the most useful contribution of a single independent quantitative risk as-

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sessment may be to standardize the language of the debate. It is difficult enough to assess the quality of the data and validity of assumptions of each risk assessment. Further comparisons are made nearly impossible because of use of inconsistent units (e.g., escape probability, risk per lab-year, and risk per worker-year) and different treatments of uncertainty (e.g., point estimates versus 95% confidence intervals). By using a single RBA as a starting point, hopefully the various stakeholders will at least be able to argue using the same mathematical framework.

Despite the NIH request for a comprehensive quantitative risk-benefit analysis, there is acknowledgment that this may not be possible. During the NRC symposium (10), both Baruch Fischhoff and Ronald Atlas discussed the difficulty of estimating benefits from the GOF research or, more generally, any basic research, due to its unpredictable and serendipitous nature. Likewise, the public health benefits of GOF research are difficult to estimate because they are conditioned on factors outside the laboratory (19). That is, while the risk of accidental release is largely controlled by laboratory conditions, the beneficial use of any discovered knowledge depends on the existing public health system, which varies widely among communities, regions, and nations. For example, 1 year into the 2009 influenza pandemic, there was still only enough vaccine for one-quarter of the world's population (20).

Further complicating a benefits analysis are the multiple ways in which evidence can be interpreted. For example, during the NRC symposium, it was widely acknowledged that genetic analysis of PPPs currently could not predict the resulting phenotype (21). Critics of GOF research argued that this lack of predictive ability severely limits the benefits of this line of research for any practical therapeutic purposes (e.g., vaccine design). However, proponents argued that this lack of knowledge was the very reason that GOF research should continue. Thus, an argument against the current practical value of the research is being interpreted by others as a supportive argument from the perspective of basic science. In this case, interpretation of a benefit is a subjective value judgment.

The GOF controversy includes many other value-laden debates regarding risks, benefits, and assessment methodologies. For example, proponents argue that GOF research has a unique scientific value (22), while critics argue that the scientific value may be no greater than that of safer alternatives, which should be considered an opportunity cost in an RBA (23). The debate also extends to disagreements regarding: the practical value of GOF experiments to policy makers (23, 24), how we should count and compare the various ways of valuing research (e.g., intrinsic value versus instrumental value) (25, 26), and how publication criteria should compare public health risk(s) to scientific merit (27, 28). Considerable disagreement even exists regarding ancillary effects, such as the impact of the various moratoria and regulations on the decisions of young scientists to work in virology (29–31).

The GOF controversy even includes debates over definitions. As discussed at the NRC symposium (10), GOF research is already widely used for multiple beneficial and largely benign purposes, including increasing vaccine yields (32), expanding genomic sequence surveillance databases (33), and creating animal models of human viral infections to aid further research. Furthermore, naturally arising GOF mutations are common in research labs that work with RNA viruses. Because the current state of science is unable to predict what genomic changes will increase danger, we cannot be sure what experiments will result in new undesirable traits. Proponents of the 2014 moratorium argue that the wording was specific enough that only 18 federally funded projects were affected and that public health surveillance and vaccine development activities were exempt (5). Rather, proponents accuse critics of the moratorium of attempting to widen the definition of what might be banned in hopes of weakening support for any restrictions.

This is not the only debate over terminology. It has been argued that the use of the term "pandemic" itself is an "apocalyptic rhetorical device" (24, 34) that preempts any reasonable discussion of risks and benefits by appealing to our innate fear of rare but catastrophic events. However, this assumes that the risk of a pandemic is actually rare, despite considerable disagreement among informed scientists regarding the likelihood of such an event. Ironically, labeling the use of "pandemic" as rhetorical sophistry may itself be a rhetorical trick if it is used to dismiss a category of serious claims without due consideration of merit.

Ultimately, the purpose of summarizing and critiquing some of the arguments within the GOF/PPP debate is to emphasize the many epistemic and ethical value judgments inherent to RBA and to provide evidence for prior claims that a consensus-building quantitative assessment is unlikely (1). This naturally leads us to wonder if there is a better alternative.

Fischhoff suggests that, rather than use RBA to only inform the eventual policy decision, it should instead be used to improve research design (10). Lipsitch and Galvani (35) made the same argument for improving GOF/PPP research design, but in the context of responsible research principles. They argued that most GOF/PPP experiments are not ethically justifiable because they do not meet the criterion of yielding humanitarian benefits not attainable by safer alternatives.

One approach to improving research design is to use the design principle of inherent safety (36–38), which focuses on attempting to eliminate material hazards in research and manufacturing. In contrast, conventional risk management generally focuses on reducing the likelihood of an accident through safety procedures and equipment. The formal inherent safety concept is frequently used in the chemical and nuclear engineering communities but it has not been widely adopted by scientists and engineers in other fields (39). While this idea seems to be common sense, it is a departure from most previous work on biosafety and biosecurity (14, 40), which was focused on improving risk management through formalized processes and training. The continued emphasis on these methods is unfortunate, given the generally poor record of implementation (41, 42).

An additional benefit of the inherent safety concept is its ability to address security concerns (43). For example, a traditional safety measure, such as removing all ignition sources near an explosive material, is of little security value; malevolent actors will bring their own ignition source. Likewise, terrorists are attracted to hazards that already instill public dread. Inherently safe design makes terrorism more difficult by removing the exploitable hazard.

Because safety has traditionally been the concern of engineers at the production level, the R&D community often fails to consider these principles in the early stages of research when the most impact can be made (44). However, inherent safety in research is sometimes recognized in hindsight. A CDC report (45) that summarized an internal review of the June 2014 exposure of laboratory workers to potentially viable *Bacillus anthracis* at a CDC bio-

terrorism response lab noted that an avirulent strain could have been used as a substitute in the experiment. It is also interesting that in its list of responses, the report focused primarily on revised biosafety protocols and procedures. A reference to reducing the hazard (i.e., inherent safety) was made only within the fifth of eight recommendations.

The calls for inherently safe design appear to have yielded some consensus from the opposing camps in the GOF/PPP controversy. One sign during the NRC symposium was provided by Yoshihiro Kawaoka, a principal investigator of one of the two original studies that started the debate (46), who endorsed the idea that some research could be conducted with alternative techniques, such as loss-of-function studies, use of less-pathogenic viruses, and phenotypic analyses (10). Proponents of inherently safe PPP research have also been buoyed by recent successes. For example, Langlois et al. (47) showed that species-specific microRNA targeting can be used to conduct relevant animal model PPP research that still poses low risks to humans. As Michael Imperiale stated, "You can develop safer approaches to do these types of experiments; it just needs a little bit of imagination on the part of researchers" (10).

As summarized here, many of the disagreements within the GOF/PPP debate involve epistemic and ethical value judgments that suggest that definitive quantitative risk-benefit analysis is not possible. This does not devalue RBA; it is still useful as a tool for engaging experts and the public in a conversation about risk-benefit tradeoffs. However, if calls for RBA become knee-jerk responses to what are essentially quantitatively intractable technological risk problems, everyone will be disappointed. RBA works best when expectations are realistic. When data are plentiful and there are no moral or cultural differences among the stakeholders, RBA can generate "answers" for policy formulation. However, for emerging technologies and controversial research where data are sparse and uncertainty is high, putting a number on a subjective quantity only engenders suspicion.

The question of whether the benefits of GOF/PPP outweigh the risks is unlikely to be resolved by an independent formal RBA. However, this question may become less relevant if safer approaches can achieve the same goals. That is, inherently safe design may be the best compromise solution for the GOF/PPP controversy. Because the inherent safety principle will not be invoked unless a risk is perceived, the appropriate next step is to regard the eventual results of the RBA as a tool for risk exploration, which then inspires more inherently safe research. Over the long term, changing the biosafety/biosecurity culture in the life sciences to emphasize inherent safety principles will help avoid similar heated controversies in the future.

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