A Simple Benefit Assessment Framework to Support Decisions on Human Pathogen Research

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Abstract

Research on human pathogens can provide profound public health benefits and pose substantial public health risks. Key actors involved in human pathogen research (such as life scientists, biosafety professionals, administrators, publishers, funders, and policy makers) must weigh benefits to public health and scientific knowledge against biosafety and biosecurity risks to make informed choices about how to perform, support, publish, or regulate it. Currently, scientific merit is evaluated alongside biosafety and biosecurity risks, but no method has been adopted to assess benefits to public health. Assessing the public health benefits of research is difficult because benefits typically unfold over long time scales, with great uncertainty, and unevenly across the global population, and they depend upon disputable technical details of the research in question. As a result, the claimed public health benefits of human pathogen research are often vague or underspecified, complicating a comparison to risks.

To aid decision-makers, we describe a framework for qualitatively estimating a research project's *maximum* expected public health benefits. The framework is deliberately designed as a set of six simple yes-or-no questions that can be answered by reviewers who are not experts in the scientific field at issue. Underpinning the framework is the idea that the expected benefits of human pathogen research are larger when the pathogen (and the specific variants under study) are or will be circulating in humans and domestic animals. For example, the maximum benefits of research are larger (and tolerance for risk is therefore higher) when that research involves pathogens that are present threats to humanity, and benefits are smaller for research on pathogens that are unlikely to naturally evolve. We intend for this framework to be implemented alongside existing methods to evaluate scientific merit, biosafety risks, and biosecurity risks to strengthen the risk-benefit assessment process for pathogen research.

Background

This project focuses on assessing the benefits of human pathogen research. Key actors involved in human pathogen research (such as life scientists, biosafety professionals, administrators, publishers, funders, and policy makers) must weigh its benefits and risks together to make informed choices about how to perform, support, publish, or regulate it. The benefits of this research have been discussed most extensively - and defended most vigorously - for projects that are also claimed to pose significant risks, such as gain-of-function research involving potential pandemic pathogens and research to discover new viruses in wildlife or predict risks of zoonotic spillover.[1,2] For this reason, we will draw heavily on

[1] Duprex WP et al. (2015) Gain-of-function experiments: time for a real debate. *Nat Rev Microbiol.* 13 (1)**:** 58-64.
[2] Sandbrink JB et al. (2022) Mitigating biosecurity challenges of wildlife virus discovery and characterisation. *SSRN.*

discussions of controversial pathogen research to describe the benefits that are most frequently cited, the methods used to assess them, and the arguments used to weigh them against risks.

Public health is the central benefit of human pathogen research

Public health is routinely framed as the central benefit of human pathogen research. While scientific research is formally evaluated for many types of benefits, including contributions to scientific knowledge[3,4] and economic impact,[5] human pathogen research has had a profoundly successful track record of improving human health and wellbeing.[6] Major funders, researchers, and journals involved with human pathogen research prioritize public health in their organizational missions.[7,8,9,10]

The potential benefits of human pathogen research for public health are particularly salient when that same research is claimed to pose substantial *risks* to public health. For example, gain-of-function research involving potential pandemic pathogens is claimed to pose risks of laboratory accidents, deliberate release, and dual-use information risks, while its benefits are framed in terms of biosurveillance, medical countermeasure development, and public health policymaking.[11,12] Claims about the unique value of gain-of-function research for scientific knowledge have been met with questions about whether such knowledge is intrinsically valuable vs. instrumentally valuable for public health.[13,14]

Public health benefits are assessed via speculative qualitative arguments

To date, the public health benefits of human pathogen research are assessed primarily via qualitative arguments from subject-matter experts, rather than quantitative estimates of outcome measures such as expected values of quality-adjusted life-years or lives saved. This type of approach is used not only for

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[3] Ahmadpoor M, Jones BF. (2017) The dual frontier: Patented inventions and prior scientific advance. *Science.* 357 (6351)**:** 583-587.
[4] Wang D, Song C, Barabási AL. (2013) Quantifying long-term scientific impact. Ibid.342 (6154)**:** 127-132.
[5] Rozell DJ. (2020) *Dangerous Science*. Vol. Ubiquity Press.
[6] Koppaka R. (2011) Ten great public health achievements--worldwide, 2001-2010.
[7] International Journal of Pathogen Research. International Journal of Pathogen Research: About the Journal. https://journalijpr.com/index.php/IJPR. Accessed 12/13/2022.
[8] National Institutes of Health. Mission and Goals. https://www.nih.gov/about-nih/what-we-do/mission-goals. Last Updated 7/27/2017. Accessed 12/13/2022.
[9] PLOS Pathogens. Journal Information - PLOS Pathogens. https://journals.plos.org/plospathogens/s/journal-information. Accessed 12/13/2022.
[10] Wellcome Trust. Our vision and strategy | Who we are. https://wellcome.org/who-we-are/strategy. Accessed 12/13/2022.
[11] Board on Life Sciences et al. (2015) The National Academies Collection: Reports funded by National Institutes of Health. In *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop*. Washington (DC): National Academies Press.
[12] Gryphon Scientific LLC. (2016) Risk and Benefit Analysis of Gain of Function Research. Prepared for.
[13] Casadevall A, Howard D, Imperiale MJ. (2014) An epistemological perspective on the value of gain-of-function experiments involving pathogens with pandemic potential. *mBio.* 5 (5)**:** e01875-01814.
[14] Evans NG. Ibid.Valuing knowledge: a reply to the epistemological perspective on the value of gain-of-function experiments. e01993-01914.

high-profile examples of controversial human pathogen research,[15,16,17,18] but for standard approaches to academic review of grant proposals and manuscripts.[19] Qualitative judgment is popular because precisely predicting the successful completion and practical application of research is extremely difficult, as many commenters in the gain-of-function debate have noted.[20,21,22,23] The results of research are inherently uncertain and typically rely on outside economic and geopolitical factors to mature into real-world public health benefits.[24]

However, qualitative predictions of research benefits are also extremely difficult. Experts in a wide range of fields struggle to predict technology development and geopolitical outcomes, even over relatively short timescales.[25,26] Qualitative judgment is also difficult to use as a basis for resolving disagreement because judgments cannot easily be reviewed by outsiders and judges can be perceived as biased. For example, experts have disagreed in their qualitative judgments of the value of gain-of-function research for medical countermeasure development, with no obvious path toward resolution.[27]

Moving debates forward: strictly-dominating options and upper bounds

In summary, the benefits of human pathogen research are typically framed in terms of public health and assessed with qualitative expert arguments, but the limits of qualitative judgment can make risk-benefit assessment difficult when research may also pose non-trivial risks to public health.

Participants in the debates regarding controversial human pathogen research have struggled between multiple options for managing risks, such as stopping research entirely, allowing it to proceed, or requiring modified research designs. They have used two complementary strategies to help compare their options.

The first strategy is to argue that one option *strictly dominates* another – that it clearly poses both less risk and greater benefit (or vice versa). In theory, this approach obviates the need to accurately estimate

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[15] Fouchier RA et al. (2013) Gain-of-function experiments on H7N9. *Science.* 341 (6146)**:** 612-613.
[16] Board on Life Sciences et al. (2015) The National Academies Collection: Reports funded by National Institutes of Health. In *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop*. Washington (DC): National Academies Press.
[17] Sandbrink JB et al. (2022) Mitigating biosecurity challenges of wildlife virus discovery and characterisation. *SSRN.*
[18] Carroll D et al. (2018) The Global Virome Project. *Science.* 359 (6378)**:** 872-874.
[19] Rozell DJ. (2020) *Dangerous Science*. Vol. Ubiquity Press.
[20] Board on Life Sciences et al. (2015) The National Academies Collection: Reports funded by National Institutes of Health. In *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop*. Washington (DC): National Academies Press.
[21] Rozell DJ. (2015) Assessing and Managing the Risks of Potential Pandemic Pathogen Research. *mBio.* 6 (4)**:** e01075.
[22] Casadevall A, Howard D, Imperiale MJ. (2014) An epistemological perspective on the value of gain-of-function experiments involving pathogens with pandemic potential. Ibid.5 (5)**:** e01875-01814.
[23] Gryphon Scientific LLC. (2016) Risk and Benefit Analysis of Gain of Function Research. Prepared for.
[24] Selgelid MJ. (2016) Gain-of-Function Research: Ethical Analysis. *Sci Eng Ethics.* 22 (4)**:** 923-964.
[25] Tetlock PE. (2017) Expert political judgment. In *Expert Political Judgment*. Princeton University Press.
[26] Bonaccorsi A, Apreda R, Fantoni G. (2020) Expert biases in technology foresight. Why they are a problem and how to mitigate them. *Technological Forecasting and Social Change.* 151**:** 119855.
[27] Board on Life Sciences et al. (2015) The National Academies Collection: Reports funded by National Institutes of Health. In *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop*. Washington (DC): National Academies Press.

the benefit of either option. For example, Lipsitch and Galvani have argued that "PPP experiments should be performed [only] if the public health benefits envisaged cannot be obtained by safer methods," and they provided a list of such methods that they claim are "not only less risky [than gain-of-function research], but also more likely to generate results that can be readily translated into public health benefits."[28] While strictly-dominating options are clearly not always available, and are themselves subject to debate, they can help identify and rule out other inferior options.

The second strategy is to treat the expected amount of harm caused by a pathogen as an *upper bound* on the magnitude of benefits of research on that pathogen. For example, if the intended benefits of H5N1 research are to protect the public against H5N1, then it seems reasonable to estimate the maximum benefit of such research as preventing the expected amount of harm that H5N1 would inflict on humans. The idea of upper bounds is intuitively captured by the sixth point of the Nuremberg Code, which states "The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment".[29]

Like the previous strategy, upper-bound arguments will clearly not resolve all risk-benefit debates about human pathogen research, but they might sometimes help. For example, Klotz and Sylvester have made upper-bound arguments to question the value of gain-of-function research,[30] and Esvelt has argued that the plausible risks of spillover prediction research outweigh even the maximum possible benefit of the prevention of all future zoonotic spillovers.[31] As discussed above, debates about the benefits of human pathogen research often become mired in difficult technical disagreements about the value or effectiveness of particular research approaches. Upper bounds allow evaluators to avoid these disagreements by assuming that research is maximally effective. Finally, upper bound arguments also help to alleviate concerns about the equitable distribution of benefits, because the assumption of the argument is that the harms of the pathogen are entirely erased for all people.[32,33]

Our approach

Goal, intended users, and context

Disagreements about the public health benefits of pathogen research have led biorisk management scholars to call for more "specific and standardized" approaches to benefit assessment.[34] Building on the work described above, we designed a framework to evaluate the public health value of research on pathogens, which can be used to inform levels of risk tolerance. Reviewers can use this upper bound to

[28] Lipsitch M, Galvani AP. (2014) Ethical alternatives to experiments with novel potential pandemic pathogens. *PLoS Med.* 11 (5)**:** e1001646.
[29] National Institutes of Health Office of NIH History and Stetten Museum. The Nuremberg Code. https://history.nih.gov/display/history/Nuremberg%2BCode. Accessed 12/13/2022.
[30] Klotz LC, Sylvester EJ. (2012) The unacceptable risks of a man-made pandemic. *Bulletin of the Atomic Scientists.* 7.
[31] Esvelt K. (2021) Manipulating viruses and risking pandemics is too dangerous. It's time to stop. *Washington Post*.
[32] Board on Life Sciences et al. (2015) The National Academies Collection: Reports funded by National Institutes of Health. In *Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop*. Washington (DC): National Academies Press.
[33] Selgelid MJ. (2016) Gain-of-Function Research: Ethical Analysis. *Sci Eng Ethics.* 22 (4)**:** 923-964.
[34] Pannu J et al. (2022) Strengthen oversight of risky research on pathogens. *Science.* eadf6020.

more easily judge whether some risk-management options clearly offer less risk and greater potential benefit than others.

Our framework is easy to use. It consists of six yes-or-no questions that are arranged and repeated in multiple branches of a flowchart. The questions ask for basic information about the pathogen under study and are simple enough that they could be incorporated into a checklist in a grant application or manuscript submission and answered by reviewers without significant technical expertise. The result is a ranking on a five-point ordinal scale from "Extremely uncertain benefits" to "More certain benefits."

Importantly, the questions in this framework are all answerable during the proposal stage of the research and do not require predicting the results of the research. Anticipating the results of research is extremely difficult and a source of challenges with regulatory frameworks such as DURC and P3CO.[35,36,37,38]

The framework is intended to be used as part of a larger risk-benefit assessment. For evaluating human pathogen research, risk-benefit assessment can be compared to a four-legged stool in which all four legs are necessary and should be assessed separately:

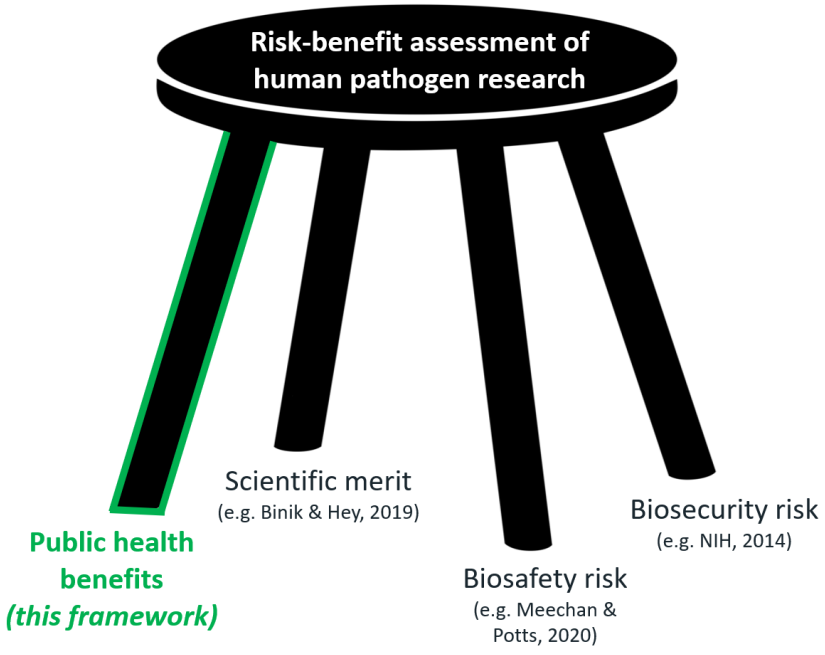

Figure 1: Four "legs" of risk-benefit assessment for human pathogen research. All four legs are necessary for accurate assessment; the framework described in this paper is for assessing public health benefits.

- *Public health benefits* are the sole focus of the framework described in this white paper. In the framework, we assume that the maximum possible benefits that could plausibly be accrued by

[35] Selgelid MJ. (2016) Gain-of-Function Research: Ethical Analysis. *Sci Eng Ethics.* 22 (4)**:** 923-964.
[36] Rozell DJ. (2020) *Dangerous Science*. Vol. Ubiquity Press.
[37] Palmer MJ. (2020) Learning to deal with dual use. *Science.* 367 (6482)**:** 1057.
[38] Branswell H. (2022) Boston University researchers' testing of lab-made version of Covid virus draws government scrutiny. *Stat*.

the research are the complete protection of all humans and domestic animals from the relevant target disease.

- *Scientific merit* refers broadly to the contributions of the research to scientific knowledge unrelated to public health. This concept incorporates both the intrinsic value of scientific knowledge from the research AND the likelihood that the research will successfully attain that knowledge. Assessing the scientific merit of any particular project requires specialized technical expertise and is outside the scope of this paper but is already a component of current funding/publication decisions.[39]
- *Biosafety risk* and *biosecurity risk* refer broadly to risks of accidental or deliberate misuse of the materials and/or information provided by the research. Assessing biosafety and biosecurity risks is also outside of the scope of this paper but also already a component of current funding/publication decisions.[40,41,42]

While public health benefits are often described as the central benefit of pathogen research, assessing these benefits is difficult in practice, and research is often evaluated instead in terms of scientific merit.[43,44] Our intention is to provide a streamlined and non-technical method of assessing public health benefits.

Crucially, risk-benefit assessment always requires all four legs of the stool. The framework in this paper can provide an estimate for maximum potential public health benefits of a human pathogen research project, but this information is *never* sufficient on its own for a complete risk-benefit assessment decision. Risks must always be compared to benefits to make informed decisions about research. Moreover, scientific merit must be assessed because other experimental approaches may be suited to gain the same knowledge.

Using the framework

To use the framework, start at the top and answer each question on your path, following the arrows as indicated. The green area in the upper-left indicates the most certain benefits, the red area in the bottom-right indicates the least certain benefits, and the diagonal lines distinguish five different qualitative levels of benefit from ”More certain” (green) to “Extremely uncertain” (red). As we explain below, the horizontal and vertical axes of the flowchart also reflect two key ideas for assessing public health benefits - whether the pathogen in question is likely to cause harm to public health without human intervention, and the likelihood that the specific genotypes under study will evolve in the population of the pathogen in question.

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[39] Casadevall A, Fang FC. (2009) Important science--it's all about the SPIN. *Infect Immun.* 77 (10)**:** 4177-4180.
[40] Meechan PJ, Potts J. (2020) Biosafety in microbiological and biomedical laboratories.
[41] Salerno RM, Gaudioso J. (2015) *Laboratory biorisk management: biosafety and biosecurity*. Vol. CRC Press.
[42] National Institutes of Health. (2014) Tools for the Identification, assessment, management, and responsible communication of dual use research of concern: A companion guide to the United States Government Policies for Oversight of Life Sciences Dual Use Research of Concern. Prepared for. https://www.phe.gov/s3/dualuse/Documents/durc-companion-guide.pdf.
[43] Casadevall A, Fang FC. (2009) Important science--it's all about the SPIN. *Infect Immun.* 77 (10)**:** 4177-4180.
[44] Binik A, Hey SP. (2019) A Framework for Assessing Scientific Merit in Ethical Review of Clinical Research. *Ethics Hum Res.* 41 (2)**:** 2-13.

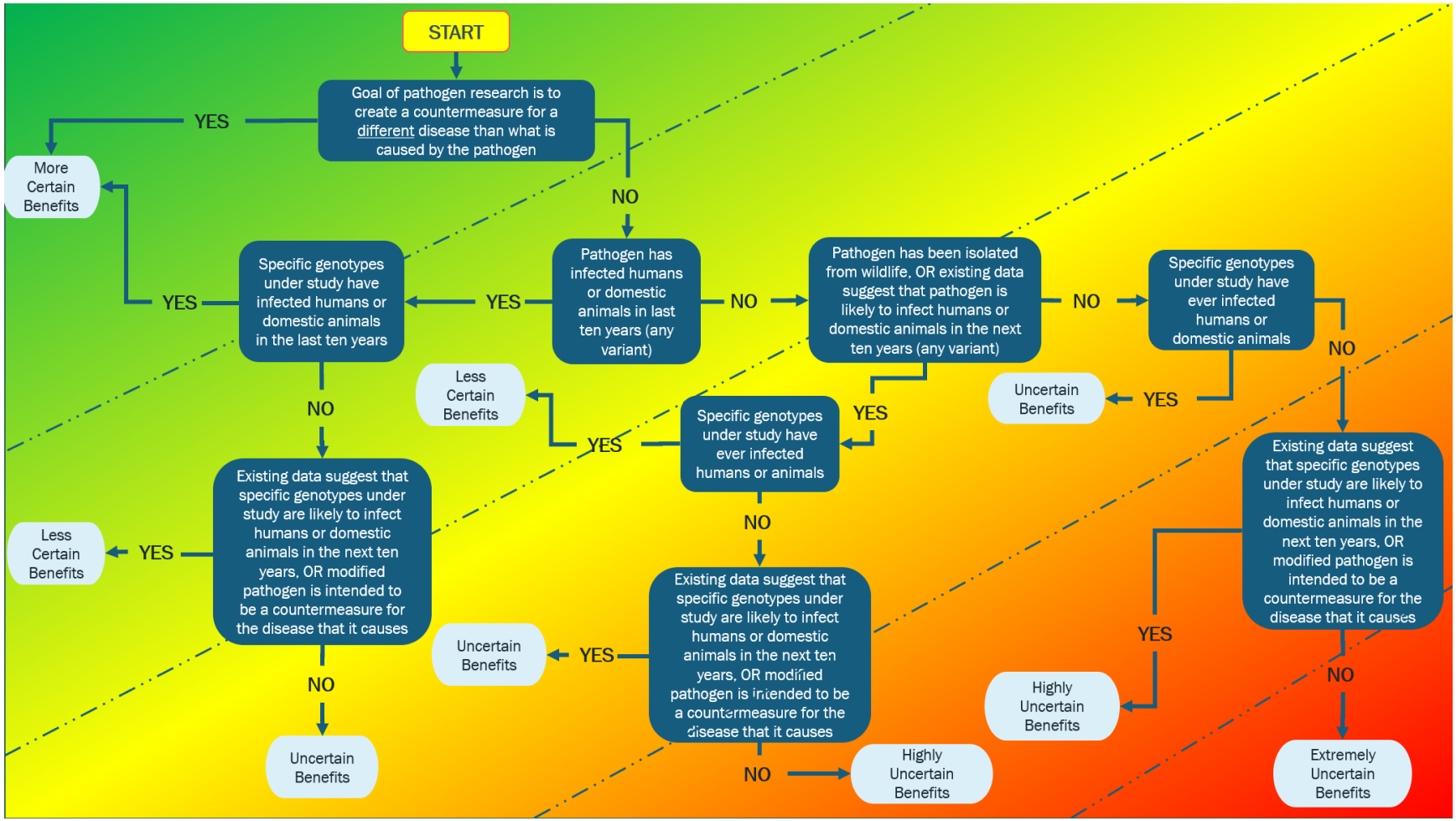

Figure 2: A framework for assessing the maximum potential benefits of a human pathogen research project without needing to predict the results of the project. The framework is organized around two key ideas: whether the pathogen in question is likely to cause harm to public health without human intervention (reflected in the horizontal axis of the flowchart), and the likelihood that the specific genotypes under study will evolve in the population of the pathogen in question (reflected in the vertical axis).

Key ideas

The framework is based around the following key ideas:

Key idea 1: Presence of pathogen

The potential benefits of human pathogen research depend heavily upon whether the pathogen in general (any variant) is, has been, or could be predicted to soon be circulating among humans and/or domestic animals. Clearly, potential benefits are greater for research on present or imminent threats, compared to research on those that are merely anticipated to emerge or re-emerge in the future, or even pathogens that are extinct or merely conceptual.

This idea is represented by the two questions in the upper-middle that move the user left or right on the horizontal axis of the flowchart by asking about "any variant" of the pathogen under study. On the leftmost side of the flowchart are pathogens that are causing public health harm today, while on the right are those that are extinct or novel (such as highly chimeric viruses).

Key idea 2: Presence of specific pathogen genotypes

The potential benefits of human pathogen research also depend heavily upon the past, present, and future circulation of all *specific* pathogen variants whose genotypes are being studied as part of the research. For example, the benefits of research are less clear if it involves modifying an existing pathogen into a form that would be unlikely to emerge naturally in the near future.

This idea is represented by the questions that move the user up or down on the vertical axis of the flowchart by asking about "specific genotypes." At the top are variants that are currently causing infections in the population, while the bottom is populated by variants that are unlikely to evolve by natural means.

Key idea 3: Countermeasure development

Sometimes human pathogen research is undertaken to develop countermeasures for a different disease than the one caused by the pathogen under study, and its potential benefits for addressing this disease should be recognized. Research can sometimes also create specific modified pathogens as potentially-beneficial countermeasures for the original pathogen, even if those modifications are unlikely to come to exist naturally.

This key idea is represented by the first question in the flowchart and by the second halves of the questions along the bottom of the flowchart.

Definitions and qualifications

Human pathogen research is complex, varied, and constantly changing, which creates challenges for cleanly categorizing research projects. The following definitions and qualifications are intended to clarify ambiguities in the language of the benefits assessment framework:

- The term "pathogen" here refers to a species as a whole and includes all variants that have been isolated and sequenced from humans or non-human animals outside of the laboratory. It does not include quasi-species variants, variants only created in a research setting, or hypothetical

variants that are expected to exist in humans or non-human animals but have never been isolated and sequenced from natural infections.

- "Domestic animals" includes all commercial species of animals outside of laboratories, but not wildlife.
- "Specific genotypes under study" refers to all variants of the pathogen that are studied or created as part the research in question.
- "Existing data" refers to presently-existing data at the time that the framework is used. Existing data do not include data that could potential be generated by the research under question.
- Pathogens that are studied because they are convenient models of human diseases (such as Feline Immunodeficiency Virus in cats) should be scored as the pathogen/disease that they are intended to study. For example, surrogates for HIV would run down the left side of the chart, while surrogates for smallpox virus would run down the right side of the chart.

Using the framework to consider risks of research

The framework in this paper is designed to estimate the chance that a pathogen is expected to harm public health. It uses this information to estimate the benefits of research on that pathogen, but it can also illuminate some of the biosafety and biosecurity *risks* of this research, as described below. While a more detailed biorisk assessment is necessary to properly weigh risks and benefits, the framework in this paper can also provide reviewers with starting points for further consideration.

In general, moving to the right on the horizontal dimension of the flowchart indicates that the pathogen under study is not recently, currently, or soon likely to circulate in humans or domestic animals in any variant. This fact implies increasing potential for *biosafety* risks because a laboratory accident could release a pathogen than is not already present in the environment.

Similarly, moving downward on the vertical dimension of the flowchart indicates that the *specific pathogen genotypes under study* are not recently, currently, or soon likely to circulate in humans or domestic animals. Indeed, near the bottom of the chart may be those modified pathogens that arise from the mind of just a handful of researchers and are not broadly known. This fact implies increasing potential *biosecurity information risks* from a malicious actor deliberately synthesizing the pathogen to cause harm, because the research could reveal specific pathogen genotypes that were not previously known to the scientific community.

There are some exceptions to this framework when considering risks. For example, research that is intended to create a countermeasure for a different disease that what is caused by the pathogen under study is judged to have "more certain benefits" in the top left of the flowchart. However, this research may also potentially carry a biosecurity information risk – for example, if it describes gain-of-function manipulations for the pathogen under study that others could recreate for malicious purposes. With that said, research in the top left of the flowchart is still more likely to provide benefits, and these benefits must be considered against potential risks.

The overall scoring of research benefits by this framework suggests a corresponding level of tolerance for biosafety and biosecurity risks. Assuming that the research has scientific merit, projects that are scored into the top left of the chart are likely to also have benefits to public health, and therefore reviewers should tolerate some inherent biosafety and biosecurity risks of the project. In contrast,

research projects that are scored into the rightmost or bottom of the chart are very unlikely to benefit public health, and therefore only research with minimal residual biosafety or biosecurity risks should be furthered.

Due to its simplicity and transparency, we hope that this framework can be used along with existing systems for the evaluation of scientific merit and biosafety/biosecurity risks to obtain holistic risk-benefit assessments. This framework should clarify that much of the pathogen research undertaken today merits tolerance for some residual biosafety and biosecurity risks. In contrast, as judged under this framework, some pathogen research projects do not warrant the attendant risks. These projects should only be conducted if the biosafety and biosecurity risks are extensively mitigated and should only be published if the information risks can be addressed.

Although we have socialized this approach with more than a dozen biosafety/biosecurity experts, policymakers and researchers, much work is needed to gain further buy-in and foster implementation. As a next step, an international workshop should be conducted in which researchers, policymakers and biosafety/biosecurity experts gather to discuss how various, notional research proposals would be scored under this scheme. By using concrete examples, nuances of the scoring can be elucidated, vagaries can be addressed and a better understanding of the types of research would be affected can be gained.

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