B.2 Definitions and Scope of Category 2 Oversight

B.2.1 Definition #1: Pathogen with Pandemic Potential (PPP)

A pathogen with pandemic potential (PPP) as defined in the Policy is a "pathogen that is likely capable of wide and uncontrollable spread in a human population and would likely cause moderate to severe disease and/or mortality in humans."

A pathogen's capability for "wide and uncontrollable spread in a human population" is a function of the pathogen's ability to spread in a human population through an efficient means of transmission (e.g., via aerosol, respiratory droplets, direct contact, fomites, etc.). As a general benchmark, "wide and uncontrollable spread" typically refers to pathogens expected to exhibit sustained human-to-human transmission in a population under specific conditions, or an effective reproductive number (R_t) greater than one. Conditions that aid wide and uncontrollable spread include a relative lack of pre-existing population immunity to the pathogen, environmental stability of the pathogen, respiratory route of transmission, and lack of availability of or access to non-medical and medical countermeasures (MCMs) to contain the pathogen. Once a population has been exposed to a pathogen over multiple years or seasonal cycles, the ability for that pathogen to spread disease throughout the human population and cause moderate to severe disease in humans may diminish. However, the absence of one of these conditions alone is insufficient to rule out pandemic potential. For example, Influenza A virus subtype H1N1 (1918) is considered to have pandemic potential because it may be able to spread widely in a population despite the existence of MCMs.

A pathogen's capability to cause "moderate to severe disease and/or mortality in humans" may be estimated by comparing case hospitalization rate (CHR) and/or case fatality rates (CFR). These comparisons may not be clear-cut or relevant in every circumstance, but rather can provide a high-level guideline to help PIs, IREs, and federal funding agencies assess which pathogens are included and excluded from the PPP definition.

While R_t, CHR, and CFR are key tools for determining whether a pathogen is a PPP, it is important to note that these metrics can vary widely based on a range of factors (e.g., levels of population immunity, access to health care, community behaviors, etc.), and relevant data on these metrics may not be available for many pathogens under study in the laboratory. Other pathogen characteristics for determining moderate to severe disease potential may include types of symptoms, duration of disease, or long-term symptoms that persist after infection.

Classification of a pathogen as a PPP can evolve over time, including during the course of a pandemic, due to changing levels of population immunity, development of MCMs, and emergence of variants with differing levels of transmissibility and pathogenicity. Cumulatively, these metrics are meant to help broadly establish a reference class of pathogens that fit in the PPP definition, to help PIs, IREs, and federal funding agencies determine whether a particular pathogen fits the PPP definition based on what is known about the transmissibility and disease characteristics of that pathogen. For additional guidance on assessing the pandemic potential of a pathogen, refer to Part B.2.4.1 of this *Implementation Guidance*.

B.2.2 Definition #2: Pathogen with Enhanced Pandemic Potential (PEPP)

A pathogen with enhanced pandemic potential (PEPP) as defined in the Policy is "a type of PPP resulting from experiments that enhance a pathogen's transmissibility[7] or virulence, or disrupt the effectiveness of pre-existing immunity, regardless of its progenitor agent, such that it may pose a significant threat to public health, the capacity of health systems to function, or national security. Wild-type pathogens that are circulating in or have been recovered from nature are not PEPPs, but may be considered PPPs because of their pandemic potential."

"Progenitor agent" within the PEPP definition refers to the starting pathogen of the proposed experiment, which may be a PPP in its wild-type form or a pathogen that is not considered a PPP in its wild-type form, but that when modified meets the definition of a PEPP.

B.2.3 Definition #3: Eradicated or extinct PPP

Category 2 oversight is also required for experiments that generate, use, reconstitute, or transfer an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security, regardless of whether the experiment enhances the PPP. Current eradicated and extinct PPPs include Variola major and minor,[8] and Influenza A virus subtypes H1N1 (1918) and H2N2 (1957-1968). Any research with these PPPs is considered Category 2 because of the heightened consequences of biosafety or biosecurity incidents that could occur from directly handling or possessing such pathogens, even without any enhancement to virulence or transmissibility.

B.2.4 Research Subject to Category 2 Oversight

Research that is subject to Category 2 oversight must meet the following three criteria:

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[7] Experiments that enhance a pathogen's transmissibility (refers to Section 4.2.2 i of the Policy) include those that enhance environmental stability of the pathogen or change the tropism or host range of the pathogen in a way that enables an increased ability to infect humans.

[8] The Centers for Disease Control and Prevention (CDC) is one of only two World Health Organization (WHO) Collaborating Centers approved for Variola virus research in the world. All research using Variola virus at CDC is overseen by the WHO and required by the World Health Assembly resolution 52.10 to have immediate public health impact. The WHO Advisory Committee on Variola Virus Research reviews all research that is proposed by CDC each year. This review and risk assessment may be deemed by HHS as satisfying the review requirements outlined in the Policy for Category 2 research with Variola virus.

- Involves, or is reasonably anticipated to result in, a PPP as specified in Section 4.2.1 of the Policy;

- Is reasonably anticipated to result in, or does result in, one or more of the experimental outcomes or actions specified in Section 4.2.2 of the Policy; and

- Based on current understanding, the research institution, federal funding agency, and/or Departmental multidisciplinary review entity assesses that the research is reasonably anticipated to result in the development, use, or transfer of a PEPP or an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security as specified in Section 4.2.3 of the Policy.

PIs and IREs should also assess Category 2 research for potential DURC risks, and if applicable, include appropriate risk mitigation measures, such as responsible research communication, in the Category 2 research draft risk mitigation plan.

Table 3 provides examples of risks posed by each type of Category 2 research experimental outcome listed in Section 4.2.2 of the Policy that, when conducted with pathogens described in Section 4.2.1 of the Policy, may be assessed as being reasonably anticipated to result in the development, use, or transfer of a PEPP or an eradicated or extinct PPP that may pose a significant threat to public health, the capacity of health systems to function, or national security. These examples are provided to illustrate the types of risks associated with each experimental outcome and may not represent the full range of possible risks.

Table 3. Examples of Potential Risks Posed by Category 2 Experimental Outcomes

Category 2 Experimental Outcomes	Examples of Associated Risks
i. Enhance transmissibility of the pathogen in humans	• Creates a pathogen more transmissible than the wild-type pathogen such that it is able to spread widely and uncontrollably in the human population. • Creates a pathogen able to survive outside the host and/or withstand environmental conditions longer than the wild-type pathogen, facilitating transmission such that it is able to spread widely and uncontrollably in the human population. • Creates a pathogen with altered tropism (i.e., tissue tropism or host range), that could change the route of transmission, resulting in increased transmissibility relative to the wild-type pathogen such that it is able to spread widely and uncontrollably in the human population. • Increases transmissibility of an animal or zoonotic pathogen, such that it can now utilize new non-human vectors or reservoirs to spread widely and uncontrollably in the human population.
ii. Enhance the virulence of the pathogen in humans	• Creates a pathogen more virulent than the wild-type pathogen (i.e., resulting in higher morbidity or mortality) such that it is able to cause moderate to severe disease in humans.
iii. Enhance the immune evasion of the pathogen in humans such as by modifying the pathogen to disrupt the effectiveness of pre-existing immunity via immunization or natural infection	• Modifies a pathogen such that it is able to spread widely and uncontrollably in the human population, and cause moderate to severe disease, despite existing population immunity against the wild-type pathogen.
iv. Generate, use, reconstitute, or transfer an eradicated or extinct PPP, or a previously identified PEPP	• Reconstitutes or creates a pathogen for which little or no natural immunity exists. • Transfers a reconstructed eradicated or extinct PPP or a previously identified PEPP to another laboratory with or without further experimentation.

B.2.4.1 Pathogens that May be Subject to Category 2 Oversight

Category 2 oversight may be required in three cases:

A) When the starting agent is a PPP **and** the research is reasonably anticipated to result in one of the experimental outcomes to produce a modified pathogen that meets the definition of a PEPP;

B) When the starting agent is a not a PPP **and** the research is reasonably anticipated to result in one of the experimental outcomes to produce a modified pathogen that meets the definition of a PEPP;[9]

C) When one transfers, generates, uses, or reconstitutes an extinct or eradicated PPP, regardless of whether the extinct or eradicated pathogen will be enhanced relative to its wild-type form.

The paragraphs below provide high-level rationale for why certain pathogens are considered PPPs in their wild-type form and others are only considered PPPs after experimental modification. These examples are intended to assist PIs and IREs in their determination of whether their research involves, or is reasonably anticipated to involve, a PPP, and may be reasonably anticipated to result in a PEPP due to expected experimental outcomes. The paragraphs below illustrate some of the considerations that may be taken into account when determining if the pathogen and proposed research should be included in Category 2 research assessment. The rationales in this part of the *Implementation Guidance* are not fully comprehensive but can provide general guidelines for how available quantitative metrics can, on a case-by-case basis, help inform the assessments.

Examples of Pathogens with Pandemic Potential (PPP) in wild-type form

SARS-CoV: SARS-CoV is the etiological agent that causes severe acute respiratory syndrome (SARS). It is an RNA virus transmitted person-to-person most readily through respiratory droplets. During the 2003 outbreak, its basic reproduction rate (R0) was estimated to be about 3 in the absence of controlling measures, giving it potential for wide and uncontrollable spread.[10] However, the lack of transmission before symptom onset allowed for effective implementation of non-pharmaceutical interventions (NPI) to disrupt disease transmission in humans. SARS-CoV is characterized to cause severe disease, given its outbreak case-fatality rate (CFR) was estimated near 10%, with two-thirds of probable cases

[9] The assessment of whether modification of a starting agent that is not a PPP would be reasonably anticipated to result in a PEPP relies on the specific traits of the pathogen and on the type and degree of enhancement being made. For example, enhancing only the virulence of a pathogen that is already highly virulent, but retains limited transmissibility abilities, would not be expected to meet the definition of PEPP and thus not require Category 2 oversight.

[10] Zhang Z. (2007). The outbreak pattern of SARS cases in China as revealed by a mathematical model. Ecological modelling, 204(3), 420–426. https://doi.org/10.1016/j.ecolmodel.2007.01.020.

in the U.S. resulting in hospitalization.[11] While the general population did not have immunity to SARS-CoV,[12] NPIs prevented the 2003 outbreak from reaching pandemic levels. Generally, modifications to SARS-CoV that increase its virulence, transmissibility, or disrupt the effectiveness of pre-existing immunity in humans may be reasonably anticipated to result in a PEPP.

SARS-CoV-2, ancestral lineage, in the absence of population immunity and MCMs: SARS-CoV-2 is the etiological agent that causes coronavirus disease 2019 (COVID-19). It is an RNA virus transmitted person-to-person most readily through respiratory route, with the capability of spreading from infected persons without symptoms. During its emergence in humans in early 2020, the R0 of SARS-CoV-2 was heterogeneous and context dependent, but was greater than 1 and resulted in wide and uncontrollable spread globally. During that time of the pandemic (i.e., January to May 2020), the population had little to no pre-existing immunity and effective countermeasures were not available. The ancestral lineage of SARS-CoV-2 caused moderate to severe disease in individuals at that time: for example, among laboratory-confirmed infections with case reports submitted to CDC between January and May 2020, the case hospitalization rate was estimated at 14% and the CFR at 5.4%.[13] Additionally, pre-symptomatic and asymptomatic transmission dynamics and a range of virulence from asymptomatic to lethal disease contributed to wide and uncontrollable spread on a global level significantly impacting public health, the capacity of health systems to function, and national security. Within the context of early 2020, the ancestral lineage of SARS-CoV-2, or emerging pathogens with comparable characteristics, would be characterized as a PPP due to lack of population immunity and effective medical countermeasures. As of May 2024, SARS-CoV-2 would not be considered a PPP because of the development of vaccines and other effective medial countermeasures, as well as the rise of population immunity. If SARS-CoV-2, regardless of lineage, were genetically modified to enhance transmissibility, virulence, and disrupt effectiveness of pre-existing immunity in humans, it could still be anticipated to result in a PEPP.

Examples of non-PPPs that could result in a PEPP after modification via listed experimental outcome

Ebola virus: Ebola is a term commonly used for disease caused by filoviruses in the genus *Orthoebolavirus*, including most prominently Ebola virus (*Orthoebolavirus zairense*) as well as several other species. These RNA viruses are transmitted person-to-person most readily through direct contact with blood or body fluids from symptomatic infected persons rather than through respiratory route. One review of published estimates proposed a pooled mean R0 for the two most common species of about 2, with high heterogeneity and variability across countries, while acknowledging its R_t can be affected by other characteristics

[11] Update: Severe Acute Respiratory Syndrome --- United States, 2003. MMWR. CDC. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5218a2.htm.

[12] Exposure to other coronaviruses may lead to cross-protective immunity.

[13] Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020. Morbidity and Mortality Weekly Report (MMWR). CDC. https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm.

modifying population susceptibility.[14] Ebola virus causes severe disease. CDC lists outbreaks with estimates of CFR typically greater than 30% and sometimes greater than 80% depending on the outbreak,[15] and essentially all diagnosed illnesses result in hospitalization. Ebola viruses have also caused reoccurring outbreaks since the first recognized cases in 1976, with the largest in 2014-2016 totaling about 28,000 cases and 11,000 deaths. None of these outbreaks progressed to pandemic-level spread, even though specific MCMs were generally not available and resources for implementing NPIs were often limited. Some preventive and therapeutic countermeasures for *Orthoebolavirus zairense* have been approved in recent years that might further help with containment of outbreaks. Based on historical experience with the nature and extent of spread and on the potential for improved control measures, the wild-type Ebola virus is not considered a PPP; however, significant modification to the virus, particularly enhancing transmissibility or disrupting the effectiveness of pre-existing immunity, may result in an Ebolavirus with enhanced pandemic potential, i.e., a PEPP.

SARS-CoV-2, Omicron lineage, given population immunity as of May 2024: SARS-CoV-2 is the etiological agent that causes COVID-19. It is an RNA virus transmitted person-to-person most readily through respiratory route, with the capability of spreading from infected persons without symptoms. The omicron lineage of SARS-CoV-2 became dominant in late 2021 and has spread widely and uncontrollably, with some R0 estimations around 10, but an Rt ranging from 10 to less than 1 depending on levels of pre-existing immunity and other factors.[16] Given population immunity as of May 2024, its CFR is generally considered to be less than 0.5% and it generally is not considered to cause moderate to severe disease in most of the human population.[17] Due to MCMs, including approved vaccines and therapeutics, and the existing population immunity, the circulating omicron lineage of SARS-CoV-2 is currently not considered to pose a significant threat to the capacity for health systems to function or national security. Experiments that are reasonably anticipated to enhance the virulence of or evade pre-existing immunity to the omicron lineage SARS-CoV-2, or other emerging variants with similar characteristics, may result in a PEPP.

Highly Pathogenic Avian Influenza A(H5) and A(H7) subtypes: Avian influenza A viruses may cause severe (highly pathogenic avian influenza, HPAI) or mild/inapparent (low pathogenic avian influenza, LPAI) infections in poultry, can infect and be transmitted by wild birds, and occasionally spill over to sporadic mammalian, including human, infections. Either HPAI or LPAI can cause either mild or severe infections in humans. Particular concern has been raised regarding the potential for severe and fatal human infections with H7N9 and H5N1, with estimated CFRs of about 40-50% of detected cases, although the completeness of

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[14] Basilua Andre Muzembo, Kei Kitahara, Debmalya Mitra, Ngangu Patrick Ntontolo, Nlandu Roger Ngatu, Ayumu Ohno, Januka Khatiwada, Shanta Dutta, Shin-Ichi Miyoshi, The basic reproduction number (R0) of ebola virus disease: A systematic review and meta-analysis, Travel Medicine and Infectious Disease, Volume 57, 2024, 102685, ISSN 1477-8939, https://doi.org/10.1016/j.tmaid.2023.102685

[15] History of Ebola Outbreaks. CDC. https://www.cdc.gov/vhf/ebola/history/chronology.html.

[16] Liu, Y., & Rocklöv, J. (2022). The effective reproductive number of the Omicron variant of SARS-CoV-2 is several times relative to Delta. Journal of travel medicine, 29(3), taac037. https://doi.org/10.1093/jtm/taac037.

[17] Horita, N., & Fukumoto, T. (2023). Global case fatality rate from COVID-19 has decreased by 96.8% during 2.5 years of the pandemic. Journal of medical virology, 95(1), e28231. https://doi.org/10.1002/jmv.28231.

detection is unclear and milder cases have also been reported. However, human-to-human transmission has been rare and non-sustained. There are several MCMs or candidate MCMs that might also help to limit transmission depending on specific circumstances. Because A(H5) and A(H7) viruses do not transmit efficiently in humans, they are not considered PPPs in their wild-type state.[18] However, because they can cause moderate to severe disease in humans, modification of A(H5) and A(H7) viruses that facilitate enhanced human-to-human transmission compared to their parental strains could reasonably be anticipated to pose a significant threat to public health, the capacity of health systems to function, or national security, and result in a PEPP. This type of research would be considered Category 2 and necessitate department-level review before the research commences or proceeds.

Note: Research that is reasonably anticipated to result in one or more of the experimental outcomes listed in Section 4.1.2 of the Policy on an HPAI virus such as A(H5) or A(H7), if not designated as Category 2 research, may be considered Category 1 research due to the viruses' potential to pose a significant threat to animals.

B.2.4.2 Experiments that May be Subject to Category 2 Oversight

Examples of experiments that could be reasonably anticipated to result in creation of a PEPP, include but are not limited to:

- Certain serial passaging experiments to select for increased virulence and/or transmissibility in animal models and/or cell and organoid systems that are designed to model human pathogenesis or transmission[19]
    a. Examples of serial passaging experiments that could fall under Category 2 oversight include:
        i. Serial passaging a respiratory pathogen that replicates in ferrets to select for increased transmissibility between animals, as ferrets have a similar lower and upper respiratory tract as humans and are often used as human surrogates for transmission studies.
        ii. Serial passaging experiments in primary human cells or human organoid systems that are reasonably anticipated to select for increased virulence or transmissibility in humans.
    b. Examples of serial passaging experiments that are not included in Category 2 oversight:

[18] Should any variant HPAI A virus emerge that similarly causes moderate to high disease in humans and gains efficient human-to-human transmission with potential for wide and uncontrollable spread, these emergent wild-type viruses would be considered PPPs; and in many cases, modification that is reasonably anticipated to, or does, enhance transmission, virulence, or immune evasion would make resulting product a PEPP and be considered Category 2 research.

[19] Note: Not all human transgenic animal models or species used for animal models are designed to accurately model the complexity of human pathogenesis. Similarly, not all human transgenic animal models or species used for animal models are necessarily appropriate surrogates for studying transmissibility in humans.

i. A mouse model designed to overexpress a human receptor to study viral infection that result in abnormal pathogenesis (e.g., encephalitis). Increased virulence in the mouse model does not necessarily represent increased virulence in humans due to differences in receptor expression compared to humans.
ii. Serial passaging in animal models to adapt the virus to that system in order to develop a model for pathogenesis often results in mutations that improve replication for that species and diverge away from infecting humans.

- Experiments deliberately generating PPP strains that are resistant to FDA-approved, cleared, or licensed MCMs, when such resistance trait(s) are not known to occur naturally and such resistance trait(s) could compromise the ability to control the morbidity, mortality, or spread in humans.
- Modifying the host range of highly virulent animal pathogens (e.g., avian influenza) to increase transmission between humans or animal reservoirs and humans.
- Creating a chimera from two PPPs such that the resulting pathogen could have enhanced transmission or virulence as compared to at least one of the progenitor pathogens.
- Assembling and rescuing infectious 1918 pandemic influenza virus through a reverse genetics protocol.

B.2.4.3 Experiments that are Not Typically Subject to Category 2 Oversight

The following types of experiments are not typically within scope of Category 2 research because the outcomes or actions typically do not result in the enhancement of a pathogen's transmissibility or virulence or a disruption of the effectiveness of pre-existing immunity resulting in a PEPP as outlined in Section 4.2. However, PIs are expected to exhibit vigilance and evaluate research in case unexpected results warrant Category 2 review for the development, use, or transfer of a PEPP.

Note: Category 1 Research oversight may apply if the agent is on the Category 1 list and genetic manipulation or laboratory adaptation is reasonably anticipated to result in one of the experimental outcomes listed in Section 4.1.2 of the Policy in a manner that would constitute DURC. These protocols should be evaluated for Category 1 designation by the PI and IRE and a risk mitigation plan should be developed, as appropriate.

- Surveillance activities, including collection of diagnostic and clinical specimens, sampling and sequencing, and basic viral characterization, in which the pathogen or toxin is not modified via genetic manipulation or laboratory adaptation to enhance transmissibility or virulence in humans such that it can spread uncontrollably in human population and cause moderate to severe disease.

- Research on evaluating, testing, and/or producing vaccines and related biologics such as immunoglobulins and the generation of high-growth strains, with the attenuation of virulence and transmissibility below wild-type levels.

- Experiments focused on evaluating and developing antivirals for the treatment or prevention of disease caused by circulating human viruses, when generation of antiviral resistant strains are not reasonably anticipated to result in a PEPP.

- Basic viral characterization studies, including but not limited to, pseudotype virus studies with proteins from laboratory-adapted strains, human receptor binding studies, animal model susceptibility studies that do not involve serial transmission, and *in vitro* experiments with human cell lines or primary human cells that do not involve certain types of serial passage that would be considered higher risk.

For further examples on how to identify and assess Category 2 research, refer to Appendix D of this *Implementation Guidance* for illustrative scenarios.

B.3 Explanation of Reasonably Anticipated

As described in the Policy, the phrase "reasonably anticipated" describes "an assessment of an outcome such that, generally, individuals with scientific expertise relevant to the research in question would expect this outcome to occur with a non-trivial likelihood. It does not require high confidence that the outcome will definitely occur and excludes experiments in which experts would anticipate the outcome to be technically possible, but highly unlikely."

This definition is meant to capture several important features of the assessment:

"Generally, individuals with scientific expertise relevant to the research in question": Relevant scientific expertise is required to anticipate the potential and plausible results of an experiment. Scientists may have differing views on possible and likely outcomes of any particular experiment, so the general assessment of multiple individuals is likely to be more robust than the views of any single individual. The PI is not required to seek assessment from a group of individuals, but rather to use the PI's individual expertise and experience to consider the range of assessments that individuals with relevant scientific expertise would likely make.

"Expect this outcome to occur": While it is impossible to know for certain the result of any experiment in advance, experiments are typically conducted to test specific hypotheses. These hypotheses constitute expectations about the possible results of an experiment, and should be included in the range of results that are "reasonably anticipated" may occur. The PI may consider, if applicable, leveraging existing literature that may have analogous experimental design and/or similar pathogens or toxins to determine potential expectations.

"Non-trivial likelihood": A "reasonably anticipated" outcome is not necessarily the most likely outcome, nor is it necessarily an outcome with greater than 50% likelihood. Rather, it is an outcome that has a reasonable, non-negligible chance of occurring. For example, consider an experiment on pandemic influenza that experts anticipate is most likely to result in a loss

of function, but that experts also believe could possibly increase transmissibility of the pathogen. An indication of generating a pandemic influenza virus with enhanced transmissibility represents a risk of high consequence to the public if that agent were to be accidentally released. Such a study should therefore undergo Category 2 oversight because, despite the fact that generating a PEPP is not the likeliest outcome, it has a non-trivial likelihood of resulting in a PEPP.

"Excludes experiments in which an expert would anticipate the outcome to be technically possible, but highly unlikely": For many experiments it may be possible to imagine a scenario, however unlikely, in which a genetic mutation surprisingly results in an increase in virulence or transmissibility against all reasonable expectations and prior evidence. The purpose of the Policy is to prioritize oversight for experiments that may pose the greatest risks. Technically plausible outcomes with very low likelihoods, as assessed based on pre-existing evidence, are not subject to Category 2 oversight. As per the Policy, if such a result unexpectedly arises during the conduct of research, the study should be halted, immediately be flagged for the IRE and funding entity, and be subject to Category 2 assessment and risk mitigation.