

## Category 2 Agents and Experiments

**“Pathogen with pandemic potential (PPP)”** 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

### **“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, and Influenza A virus subtypes H1N1 (1918) and H2N2 (1957-1968).

**“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, but excludes experiments in which experts would anticipate the outcome to be technically possible, but highly unlikely.

**Key to this Category 2 determination** is an assessment of whether the research involves a pathogen that, through one or more of the listed experimental outcomes, may pose a significant threat to public health, the capacity of health systems to function, or national security. Research involving PPPs, whether eradicated, extinct, or existing, may not always rise to the level of posing this type of significant threat as indicated above. In such cases, the research would not be considered to reasonably result in the development, use, or transfer of a PEPP or extinct or eradicated PPP needing Category 2 oversight. Factors that could be useful in determining these types of significant threats include the pathogen’s cumulative capability for wide and uncontrollable spread, extent of disease, the degree of pre-existing population immunity, and the availability of MCMs to provide preventative and treatment interventions, and other public health and social considerations.

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

- SARS-CoV
- SARS-CoV-2, ancestral lineage, in the absence of population immunity and MCMs

**“Pathogen with enhanced pandemic potential (PEPP)”** is a type of pathogen with pandemic potential (PPP) resulting from experiments that enhance a pathogen’s transmissibility 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.

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

- Ebola virus
- MERS-CoV
- SARS-CoV-2, Omicron lineage, given population immunity as of May 2024
- Highly Pathogenic Avian Influenza A(H5) and A(H7) subtypes

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 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;
- 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.

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
  - 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.

- 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.

## Category 2 Research Experimental Outcomes or Actions

Research within the scope of Category 2 are those experimental outcomes or actions with a pathogen outlined above that are reasonably anticipated to result in one of the experiments below in the table. Please review the examples provided to make the determination if this applies to your research. If you are uncertain, please contact the EHS Biosafety Office at 203-785-3550.

### Examples of Potential Risks Posed by Category 2 Experimental Outcomes

| Category 2 Experimental Outcomes                       | Examples of Associated Risks                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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| i. Enhance transmissibility of the pathogen in humans; | <ul style="list-style-type: none"><li>• Creates a pathogen more transmissible than the wild-type pathogen such that it is able to spread widely and uncontrollably in the human population.</li><li>• 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.</li><li>• 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.</li><li>• 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.</li></ul> |
| ii. Enhance the virulence of the pathogen in humans;   | <ul style="list-style-type: none"><li>• 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.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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| <p>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; or</p> | <ul style="list-style-type: none"> <li>• 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.</li> </ul>                                  |
| <p>iv. Generate, use, reconstitute, or transfer an eradicated or extinct PPP, or a previously identified PEPP.</p>                                                                                 | <ul style="list-style-type: none"> <li>• Reconstitutes or creates a pathogen for which little or no natural immunity exists.</li> <li>• Transfers a reconstructed eradicated or extinct PPP or a previously identified PEPP to another laboratory with or without further experimentation.</li> </ul> |