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## Requirements for COVID-19 research

### Table of Contents

Containment levels at a glance .....	1
Institutional Biosafety Committee review and approval .....	2
Background on COVID-19 and SARS-CoV-2 .....	2
General considerations for COVID-19/SARS-CoV-2 research .....	3
Research involving live SARS-CoV-2 .....	4
Research involving pandemic human samples .....	6
Research involving inactivated COVID-19 samples .....	9
Research involving nucleic acids from SARS-CoV-2 .....	9
Research involving proteins from SARS-CoV-2 .....	10

### Containment levels at a glance

Research type	Containment level
Live SARS-CoV-2	BSL3/ABSL3
Pandemic human samples	BSL2 with enhancements (varies by sample type)
Inactivated COVID-19 samples	BSL2
Nucleic acids from SARS-CoV-2	BSL1 (individual genes) or BSL2 (extracted/full genome)
Proteins from SARS-CoV-2	BSL1

### **Institutional Biosafety Committee review and approval:**

As an institution that receives federal funding, UW-Madison is required to comply with the [\*NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules \(NIH Guidelines\)\*](#). Experiments that fall under sections III-A through III-D of the *NIH Guidelines* require approval from the UW-Madison Institutional Biosafety Committee (IBC) prior to initiation, even if low risk. Experiments that fall under section III-E of the *NIH Guidelines* may commence simultaneously with IBC notification (i.e., assignment of a biosafety protocol or amendment to an IBC meeting), but still require IBC review and approval.

Experiments that fall under section III-F of the *NIH Guidelines* (i.e., exempt experiments) or that are not subject to the *NIH Guidelines* because they do not involve recombinant or synthetic nucleic acids may still require a biosafety protocol and be subject to IBC review and approval. The IBC is charged by the Chancellor with responsibility for oversight of biological materials that entail a potential risk to humans, animals, plants, or the environment. The IBC is authorized to approve, require modifications to secure approval, or disapprove work with biohazardous materials. The IBC is also authorized to suspend or revoke authorization of work that is not conducted in accordance with their requirements. To determine if your planned research requires a biosafety protocol, please refer to the [Bio-ARROW webpage](#) or contact OBS at 608-263-2037 or [biosafety@fpm.wisc.edu](mailto:biosafety@fpm.wisc.edu).

The IBC meets the first Wednesday of every month. Protocols and amendments are pre-reviewed by OBS staff prior to assignment to an IBC meeting. The cutoff for assignment to an IBC meeting is two weeks prior to the meeting date. **To allow time to complete the pre-review process it is recommended that new protocols and amendments are submitted at least one month prior to the IBC meeting date.** The IBC understands the importance and urgency of COVID-19 research. OBS staff will work with researchers and the IBC to expedite the review process and consider late submissions, but IBC review cannot be guaranteed for protocols and amendments submitted less than three weeks prior to the IBC meeting date.

### **Background on COVID-19 and SARS-CoV-2:**

COVID-19 is an emergent respiratory disease that is caused by infection with the coronavirus SARS-CoV-2 (previously called “2019 novel coronavirus” or 2019-nCoV). Infection with SARS-CoV-2 results in a range of symptoms from none to mild to severe. Symptoms may include fever, chills, cough, shortness of breath or difficulty breathing, nasal congestion, muscle pain, headache, fatigue, sore throat, loss of taste or smell, and diarrhea. In most individuals, COVID-19 produces only mild flu-like symptoms. Older adults and people of any age who have serious underlying medical conditions are at higher risk for severe illness. Severe illness can lead to hospitalization, need for ventilation, and in the most severe cases, death. Medical conditions known to increase COVID-19 risk include chronic lung disease, asthma, heart conditions, diabetes, chronic kidney disease, liver disease, obesity, and compromised immunity. Many things can cause a person to be immunocompromised, including pregnancy, cancer treatment, smoking, bone marrow or organ transplantation, immune deficiencies, AIDS, and prolonged use of corticosteroids or certain other medications. Employees are not required to disclose pregnancies, medical conditions, or their immune status, and if they have concerns, they should consult their physician.

COVID-19 is thought to spread primarily through respiratory droplets produced when an infected person coughs or sneezes. Other possible means of transmission include aerosols (e.g., an infected person

exhaling), transfer of virus through touching the mouth, nose, or eyes after touching a contaminated surface, and fecal-oral transmission. Symptoms may appear 2-14 days after exposure, and some infected individuals never exhibit symptoms. Infected individuals may transmit the disease even if pre-symptomatic or asymptomatic.

SARS-CoV-2 is a betacoronavirus in the *Coronaviridae* family. It is closely related to SARS-CoV, the coronavirus that causes severe acute respiratory syndrome (SARS). Like SARS-CoV, SARS-CoV-2 is believed to have a zoonotic origin, perhaps originating in bats. SARS-CoV-2 is a positive-sense single-stranded RNA virus. It has four structural proteins: S (spike), E (envelope), M (membrane), and N (nucleocapsid). S, E, and M along with the lipid bilayer form the viral envelope, and N interacts with the RNA genome to form the helical nucleocapsid. The virus is believed to enter human cells by binding of the spike protein to the receptor angiotensin converting enzyme 2 (ACE2). SARS-CoV-2 produces at least three virulence factors that promote shedding and inhibit the host immune response. Multiple genetic variants of SARS-CoV-2 have been documented throughout the pandemic. Much is still unknown about these emerging strains of SARS-CoV-2, including their pathogenicity, transmissibility, and effect on the efficacy of diagnostic tests, therapeutics, and vaccines.

COVID-19 vaccines are now available. Although studies indicate these vaccines are safe and highly effective at preventing illness, they do not guarantee protection from infection. It is also unknown how long immunity lasts after vaccination, or whether vaccination prevents transmission of the virus. More information on COVID-19 vaccines can be found on the CDC's [COVID-19 vaccine](#) webpage.

### **General considerations for COVID-19/SARS-CoV-2 research:**

There are currently no standardized antiviral treatments for COVID-19, and many people have not yet been vaccinated. **SARS-CoV-2 has been classified as a risk group 3 (RG3) virus.** When planning any COVID-19 research project, the following should be considered:

- In the event of an exposure to research materials, is there a risk of a lab-acquired COVID-19 infection (i.e., will you be working with live SARS-CoV-2 or materials that contain or potentially contain live SARS-CoV-2, such as clinical samples)?
- If exposure to live virus is possible, then:
  - What is the level of exposure risk? (e.g., Will the virus be isolated or cultured? Will samples come from known COVID-19 patients or are they unknown diagnostic specimens? What type of tissue samples or bodily fluids will be used?)
  - What is the laboratory's experience with coronaviruses or other respiratory pathogens?
  - Who will train personnel to work with the virus/potentially infectious materials?
  - Has the laboratory developed all the necessary SOPs for working with the virus/potentially infectious materials (e.g., donning and doffing personal protective equipment (PPE), disinfection, spill protocols)?
  - Does the laboratory have a COVID-19 occupational health plan?
  - Have laboratory staff been offered COVID-19 vaccine? For information on vaccine availability, please check the [PHMDC COVID-19 vaccine webpage](#) or contact University Health Services at uhs@uhs.wisc.edu.
- Does the laboratory have the facilities and containment equipment appropriate for the level of risk (as outlined in the sections below)?
- Does the laboratory have access to PPE appropriate for the proposed work (e.g., PAPR, Tyvek)?

- What other hazards are associated with this research (e.g., bloodborne pathogens, viral vectors, sharps), and how will their risk be mitigated?
- If you will be using human subjects or samples collected from human subjects, do you have Institutional Review Board (IRB) approval for this research?
- If you will be using animal models, do you have Institutional Animal Care and Use Committee (IACUC) approval for this research?

The sections below outline the typical requirements for different types of COVID-19 research. As many factors affect risk (e.g., genetic modifications, equipment, assays and procedures), OBS and the IBC will work with you to determine the appropriate containment level, location, practices, and PPE needed for your specific research. Additional guidance and tools can be found on the [Biosafety COVID-19 information webpage](#). For questions, please contact OBS at 608-263-2037 or [biosafety@fpm.wisc.edu](mailto:biosafety@fpm.wisc.edu).

### **Research involving live SARS-CoV-2:**

Research involving the isolation, enrichment, culture, or concentrated stocks of live SARS-CoV-2 requires BSL3 containment and must be approved by the IBC prior to initiation.

### **Facility requirements**

Not all UW-Madison BSL3 laboratories are suitable for work with high risk respiratory pathogens. If you are planning research with SARS-CoV-2 please contact Christina Pier at 608-712-2359 or [pier@wisc.edu](mailto:pier@wisc.edu). For live SARS-CoV-2 work, a BSL3 laboratory must meet the following requirements:

- Fan failure testing has been performed within the last 12 months
- Laboratory must have room pressure monitoring
- Air must be single-pass (100% exhausted) and not re-entrained or recirculated into any part of the building
- Exhaust air must be HEPA-filtered
- Laboratory must have an anteroom that is large enough to change out of street clothing, don and doff PPE, and provide adequate storage for PPE

Please note that other aspects of the laboratory layout and workflow (e.g., location of an autoclave) will be considered as part of the risk assessment by the IBC.

### **Administrative controls and practices**

Good microbiological practices must be followed when working with any microorganism, though this is especially true when working with an RG3 virus. Due to the COVID-19 pandemic, work with live SARS-CoV-2 additionally requires the following:

- The laboratory must have established processes to address occupational health considerations for personnel involved in the research. The occupational health plan must include:
  - Hazard communication that includes the risk and symptoms of COVID-19
  - Signed informed consent for those working with SARS-CoV-2
  - Pathogen-specific emergency response procedures in the event of known potential exposures and development of symptoms with no known exposures

- Laboratory staff should be prepared to self-isolate following any known exposure to SARS-CoV-2 or development of COVID-19 symptoms until released by Occupational Medicine or Public Health
- If working with SARS-CoV-2 that has been mutated via serial selection in cells or animals or through site-directed mutagenesis of infectious clones or animals infected with SARS-CoV-2 that are housed in open cages, exposures and development of symptoms require reporting through the UW-Madison Responsible Official/Alternate Responsible Officials (RO/AROs)

OBS has developed occupational health plan templates that may be used for this purpose:

[Occupational health plan template for mutant/recombinant SARS-CoV-2 and SARS-CoV-2-infected animals in open caging](#)

[Occupational health plan template for wild type SARS-CoV-2/COVID-19 and pandemic samples](#)

- Individuals may not travel outside the state of Wisconsin within 14 days of working with live SARS-CoV-2 if either of the following is true:
  - The SARS-CoV-2 has been mutated via serial selection in cells or animals or through site-directed mutagenesis of infectious clones. Travel restrictions are required in this case due to the potential for an increase in pathogenicity or transmissibility of the virus, which could be transmitted to the public.
  - Animals infected with SARS-CoV-2 are housed in open cages (i.e., the room serves as primary containment in a BSL3-Ag facility or equivalent). Travel restrictions are required in this case due to the greater risk of lab-acquired infections with open caging.
- Access to the laboratory must be controlled and restricted to those involved in the research while active work (i.e., hands-on manipulation) with SARS-CoV-2 is being performed
- Signage should be posted at the laboratory entry regarding the restricted access. [Signage for SARS-CoV-2 work](#) can be downloaded from the EHS website.
- Concomitant work with SARS-CoV-2 and other viruses in the same laboratory space is prohibited unless a plan to avoid cross-contamination is approved by the IBC
- All aerosol-generating activities (e.g., pipetting, homogenization) should be performed inside a certified class II biosafety cabinet (BSC) or other approved containment device
- Training on SOPs for lab entry/exit including donning and doffing PPE should be documented
- [EPA-registered disinfectants effective against SARS-CoV-2](#) should be used for decontamination of work surfaces and equipment.

## PPE

Street clothes are not permitted in the BSL3 laboratory when working with SARS-CoV-2; dedicated shoes and dedicated scrubs with full Tyvek coveralls or equivalent is required. Other required PPE include disposable shoe covers, two layers of disposable gloves, face and respiratory protection. A powered air purifying respirator (PAPR) with full head shroud is preferred for face and respiratory protection over N95/N100 respirator with safety glasses and face shield. The entering and exiting of the BSL3 laboratory should allow for the proper donning, doffing, disinfection, storage, and disposal of PPE.

## Animal models of COVID-19

Research animals that are experimentally infected with SARS-CoV-2 require ABSL3 containment. Where possible, animals infected with SARS-CoV-2 must be housed in microisolator cages. For species that do not have microisolator caging available, animal cages or pens must be housed within an approved HEPA-filtered containment device or within a BSL3-Ag facility. Please note that not all UW-Madison BSL3

laboratories are considered suitable for housing animals, and locations for animal use must be approved by both the IBC and IACUC. Additional administrative controls (e.g., showering out) and PPE (e.g., Tyvek sleeves) may be required for animal work.

### **Research involving pandemic human samples:**

For the purposes of this guidance, pandemic human samples are defined as mucosal swabs or washes, sputum, blood, serum, plasma, feces, urine, other tissues or bodily fluids collected from November 1, 2019 onwards. **All pandemic human samples should be treated as potentially infectious for COVID-19 unless collected from individuals that have tested negative for COVID-19 at the time of sample collection or the samples are confirmed to be negative for SARS-CoV-2 using a validated method.**

Research involving pandemic human samples requires BSL2 containment with enhancements (which will vary depending on sample type, see below) and must be approved by the IBC prior to initiation.

In addition to the precautions outlined in this document for handling pandemic human samples, the risk of exposure from being in the presence of a participant that could transmit COVID-19 (i.e., through coughing, sneezing, exhaling, touching) should be considered during sample collection. Guidance for minimizing the risk of COVID-19 transmission during face-to-face research activities can be found on the [Returning to Campus Safely website](#).

### **Facility requirements (all sample types)**

Air should be single-pass (100% exhausted) and not re-entrained or recirculated into any part of the building. Please note that other aspects of the laboratory layout and workflow should be considered as part of the laboratory's risk assessment.

### **Respiratory and gastrointestinal samples from COVID-19 patients**

Since SARS-CoV-2 is a respiratory pathogen, nasal swabs, nasal washes, nasal secretions, sputum, saliva, and lung or respiratory tract tissue present the highest risk of exposure. Information on shedding of SARS-CoV-2 in feces is currently limited, though live SARS-CoV-2 has been detected in fecal samples from COVID-19 patients and diarrhea is a possible clinical sign of COVID-19. Work with nasal swabs, nasal washes, nasal secretions, sputum, saliva, lung or respiratory tract tissue, feces, and gastrointestinal tract tissue collected from patients known or suspected to have COVID-19 requires a minimum of BSL-2 containment with the following enhancements:

- The laboratory must have established processes to address occupational health considerations for personnel involved in the research. The occupational health plan must include:
  - Hazard communication that includes the risk and symptoms of COVID-19
  - Signed informed consent for those working with COVID-19 respiratory/gastrointestinal samples
  - Pathogen-specific emergency response procedures in the event of known potential exposures and development of symptoms with no known exposures
  - Laboratory staff should be prepared to self-isolate following any known exposure to COVID-19 respiratory/gastrointestinal samples or development of COVID-19 symptoms until released by Occupational Medicine or Public Health

OBS has developed an [occupational health plan template for wild type SARS-CoV-2/COVID-19 and pandemic samples](#) that may be used for this purpose.

- Access to the laboratory must be controlled and restricted to those involved in the research while active work (i.e., hands-on manipulation) with COVID-19 respiratory/gastrointestinal samples is being performed
- Signage should be posted at the laboratory entry regarding the restricted access while active work with COVID-19 respiratory/gastrointestinal samples is being performed. [Signage for work with COVID-19 samples](#) can be downloaded from the EHS website.
- All aerosol-generating activities (e.g., pipetting, homogenization) should be performed inside a certified class II BSC or other approved containment device
- Concomitant work with COVID-19 respiratory/gastrointestinal samples and cells permissive to COVID-19 infection is prohibited
- [EPA-registered disinfectants effective against SARS-CoV-2](#) should be used for decontamination of work surfaces and equipment.
- Required PPE includes disposable lab coat, gown, or coveralls and two layers of disposable gloves. Additional PPE such as an N95/N100 respirator or PAPR, dedicated lab shoes or disposable shoe covers, and face shield may be required if activities with COVID-19 respiratory/gastrointestinal samples will be performed outside of containment.

### **Pandemic respiratory and gastrointestinal tract samples**

Work with potentially infectious nasal swabs, nasal washes, nasal secretions, sputum, saliva, lung or respiratory tract tissue, feces or gastrointestinal tract tissue collected during the pandemic from the general population or a patient population not known to have COVID-19 requires BSL-2 containment with the following enhancements:

- The laboratory must have established processes to address occupational health considerations for personnel involved in the research. The occupational health plan must include:
  - Hazard communication that includes the risk and symptoms of COVID-19
  - Signed informed consent for those working with pandemic samples
  - Pathogen-specific emergency response procedures in the event of known potential exposures and development of symptoms with no known exposures
  - Laboratory staff should be prepared to self-isolate following any known exposure to pandemic samples or development of COVID-19 symptoms until released by Occupational Medicine or Public Health

OBS has developed an [occupational health plan template for wild type SARS-CoV-2/COVID-19 and pandemic samples](#) that may be used for this purpose.

- Access to the room should be restricted when active work (i.e., hands-on manipulation) with pandemic samples is being performed
- Signage should be posted at the laboratory entry regarding the restricted access while active work with pandemic samples is being performed. [Signage for work with pandemic samples](#) can be downloaded from the EHS website.
- All aerosol-generating activities (e.g., pipetting, homogenization) should be performed inside a certified class II BSC or other approved containment device
- Samples discovered to be positive for SARS-CoV-2 must be destroyed, inactivated by a validated method, or handled using the enhanced precautions described above for respiratory and gastrointestinal samples from COVID-19 patients
- Concomitant work with pandemic samples and cells permissive to COVID-19 infection is prohibited

- [EPA-registered disinfectants effective against SARS-CoV-2](#) should be used for decontamination of work surfaces and equipment.
- Additional PPE such as a disposable lab coat, gown, or coveralls, an N95/N100 respirator or PAPR, dedicated lab shoes or disposable shoe covers, and face shield may be required if activities with pandemic respiratory/gastrointestinal samples will be performed outside of containment.

### **Non-respiratory/gastrointestinal samples from COVID-19 patients**

Work with blood, plasma, serum, organs and tissues that are not part of the respiratory or gastrointestinal tracts, and non-respiratory/enteric bodily fluids and secretions (e.g., cerebrospinal fluid, urine) obtained from known or suspected COVID-19 patients with an active infection requires BSL-2 containment with the following enhancements:

- The laboratory must have established processes to address occupational health considerations for personnel involved in the research. The occupational health plan must include:
  - Hazard communication that includes the risk and symptoms of COVID-19
  - Signed informed consent for those working with COVID-19 samples
  - Pathogen-specific emergency response procedures in the event of known potential exposures and development of symptoms with no known exposures
  - Laboratory staff should be prepared to self-isolate following any known exposure to COVID-19 samples or development of COVID-19 symptoms until released by Occupational Medicine or Public Health

OBS has developed an [occupational health plan template for wild type SARS-CoV-2/COVID-19 and pandemic samples](#) that may be used for this purpose.

- Access to the room should be restricted when active work (i.e., hands-on manipulation) with COVID-19 samples is being performed
- Signage should be posted at the laboratory entry regarding the restricted access while active work with COVID-19 samples is being performed. [Signage for work with COVID-19 samples](#) can be downloaded from the EHS website.
- All aerosol-generating activities (e.g., pipetting, homogenization) should be performed inside a certified class II BSC or other approved containment device
- Concomitant work with COVID-19 samples and cells permissive to COVID-19 infection is prohibited
- [EPA-registered disinfectants effective against SARS-CoV-2](#) should be used for decontamination of work surfaces and equipment.
- Additional PPE or higher containment levels may be required under the following circumstances:
  - Aerosol-generating activities with COVID-19 samples will be performed outside of containment
  - Cells from COVID-19 patients will be isolated and cultured
  - Cells from COVID-19 patients will be administered to animals

Exceptions for low-risk samples may be considered on a case-by-case basis.

### **Other non-respiratory/gastrointestinal pandemic human samples**

Work with blood, plasma, serum, organs and tissues that are not part of the respiratory or gastrointestinal tracts, and non-respiratory/enteric bodily fluids and secretions (e.g., cerebrospinal fluid)

obtained from the general population or a patient population not known to have COVID-19 requires BSL-2 containment with standard precautions equivalent to those employed to protect from bloodborne pathogens. This includes human samples not considered to be potentially infectious for bloodborne pathogens that can be handled at BSL1 when known to be negative for COVID-19 (e.g., urine). Additional PPE may be required if activities with human materials will be performed outside of containment.

### **Research involving inactivated COVID-19 samples:**

Although it is typically not required to list inactivated materials (e.g., fixed tissues) on a biosafety protocol, since SARS-CoV-2 is a pandemic RG3 pathogen, investigators are asked to list inactivated COVID-19 samples. Relevant samples include cells, tissues, or fluids from COVID-19 patients or animals experimentally infected with SARS-CoV-2, and cultured cells or tissues experimentally infected with SARS-CoV-2. In accordance with [CDC biosafety guidelines](#), work with inactivated COVID-19 samples require BSL2 containment using standard precautions. OBS will determine whether IBC review is required for approval to work with inactivated materials based on risk assessment.

Inactivation of COVID-19 samples should be performed using a method with demonstrated efficacy against SARS-CoV-2, related coronaviruses (SARS-CoV or MERS-CoV), or other highly pathogenic viruses with a lipid envelope. The lab should provide a published reference or data demonstrating viral inactivation, including inactivation time and concentration of reagents. If the laboratory is receiving inactivated COVID-19 samples from a collaborator or commercial source, they should request and retain documentation verifying inactivation of the samples using a validated method. More information on inactivation can be found in the “Frequently Asked Questions for Pandemic Research” on the [Biosafety COVID-19 information webpage](#).

If you will be working with only inactivated COVID-19 samples, please do not list SARS-CoV-2 on the Microbes page in Bio-ARROW. Rather, please list the inactivated materials in the “Organs, tissues or biological specimens” section and provide a description of the samples, their source, and the inactivation method used in the “Organs, tissues, or biological specimens other information” text box.

### **Research involving nucleic acids from SARS-CoV-2:**

Research involving the subcloning, expression, or analysis of individual genes from SARS-CoV-2 *in vitro*, in microbes, or in cultured cells may be performed at BSL1 if no other agents used in the experiments require a higher level of containment. Recombinant or synthetic nucleic acid constructs and recombinantly modified microbes and cells must be listed on your biosafety protocol and may require concomitant notification of the IBC or IBC approval prior to initiation.

In accordance with [CDC biosafety guidelines](#), research involving nucleic acids extracted from COVID-19 samples require BSL2 containment using standard precautions. Relevant samples include cells, tissues, or fluids from COVID-19 patients or animals experimentally infected with SARS-CoV-2, and cultured cells or tissues experimentally infected with SARS-CoV-2. Concomitant work with full-length genomic RNA and cells permissive to COVID-19 infection is prohibited at BSL2; experiments involving full-length genomic RNA and cells permissive to COVID-19 must be handled at BSL3 following the requirements outlined above for work with live SARS-CoV-2.

If you will be working with only extracted SARS-CoV-2 RNA or cDNA (e.g., deep sequencing experiments), please do not list SARS-CoV-2 on the Microbes page in Bio-ARROW. Rather, please list the nucleic acids in the “Organs, tissues or biological specimens” section and provide a description of the material and its source in the “Organs, tissues, or biological specimens other information” text box.

**Research involving proteins from SARS-CoV-2:**

Research involving only isolated SARS-CoV-2 proteins does not require a biosafety protocol or OBS/IBC review if all the following are true:

- The proteins are being produced in cells or RG1 microbes through expression of recombinant protein and no SARS-CoV-2 is involved in any step of their production
- Your laboratory is not doing any of the recombinant work but is just receiving the purified protein from a collaborator or commercial source\*
- The research does not involve any other recombinant or biohazardous materials

By themselves, SARS-CoV-2 proteins do not cause disease. Therefore, there are no enhanced biosafety requirements for experiments involving only SARS-CoV-2 proteins in the absence of its RNA genome.

\*If you will be expressing recombinant SARS-CoV-2 proteins in cells or microbes in your laboratory, please refer to the “Research involving nucleic acids from SARS-CoV-2” section for requirements.