Biospecimen Collection During the COVID-19 Pandemic
Considerations for Biobanking

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Key Words: COVID-19; Biobanking; Biosafety; Biomarkers; SARS-CoV-2; Coronavirus

ABSTRACT

Objectives: Millions of biospecimens will be collected during the coronavirus disease 2019 (COVID-19) pandemic. As learned from severe acute respiratory syndrome (SARS), proper biospecimen handling is necessary to prevent laboratory-related infections.

Methods: Centers for Disease Control and Prevention and World Health Organization severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) interim biosafety guidelines continue to be updated. Presented here are additional considerations intended to complement the interim guidance. These considerations draw on prior SARS recommendations and recent COVID-19 reports.

Results: SARS-CoV-2 viral RNA has been detected in various biospecimen types; however, studies are needed to determine whether viral load indicates viable virus. Throughout the pandemic, biospecimens will be collected for various purposes from COVID-19 known and suspected cases, as well as asymptomatic and presymptomatic individuals. Current data suggest the pandemic start may be as early as October 2019; thus, all biospecimens collected since could be considered potentially infectious.

Conclusions: All entities handling these biospecimens should do risk assessments in accordance with institutional policies and adhere to any guidance provided. The scientific community has a responsibility to safely handle and maintain all biospecimens collected during the COVID-19 pandemic. Soon, it will be imperative to convene expert working groups to address the current and long-term storage and use of these biospecimens. Ideally, worldwide guidelines will be established to protect the personnel handling these biospecimens and communities at large.

Key Points

- Current data suggest the earliest cases in the COVID-19 pandemic may have been as early as October 2019.
- Millions of biospecimens have been and will be collected from known and suspected cases, as well as asymptomatic and presymptomatic individuals for various purposes.
- Biosafety considerations intended to complement evolving CDC and WHO guidelines are presented.

COVID-19 Pandemic

On December 31, 2019, Wuhan, China, reported a cluster of pneumonia cases. A week later, the cluster was confirmed to be associated with a novel betacoronavirus, 2019-nCoV, now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On January 20, 2020, the first case in the United States was reported in Washington state. The World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a global pandemic on March 11, 2020. As of this writing (July 10, 2020), there are 12.3 million cases and 556,211 deaths globally, with 3.1 million cases and 133,542 deaths in the United States.

SARS-CoV-2

Coronaviruses, which mainly cause mild to moderate respiratory and gastrointestinal tract infections, attracted little attention until the 2002 SARS outbreak and the 2012 outbreak of Middle Eastern respiratory syndrome (MERS). Like COVID-19, SARS and MERS are hallmarkcd by acute respiratory distress syndrome in severe cases. As with the SARS and MERS coronaviruses (SARS-CoV and MERS-CoV, respectively),
SARS-CoV-2 is highly pathogenic and classified as a risk group 3 biological agent.9,10

SARS-CoV-2 Transmission
Coronaviruses are generally transmitted via respiratory aerosols and the fecal-oral route.11 Initially, it was thought that SARS-CoV-2 spread through large respiratory droplets and close contact12; however, recent reports suggest aerosol transmission is also likely.13-18 SARS-CoV-2 remains stable up to 3 hours in aerosols, 4 hours on copper surfaces, 24 hours on cardboard, and 72 hours on plastic and stainless steel.19 This stability is similar to SARS-CoV and suggests that differences in transmission arise from factors such as viral loads in respiratory aerosols and presymptomatic and asymptomatic transmission. SARS-CoV-2 viral load has been reported as highest in throat swabs at symptom onset, suggesting that presymptomatic individuals are highly infectious.20 Reports also suggest that 30% to 60% of infected individuals are asymptomatic.21,22 This contrasts with SARS-CoV infection, where viral loads peak approximately 10 days after symptom onset.23

SARS-CoV-2 in Various Biospecimen Types
Nasopharyngeal swab testing is typically used to confirm COVID-19 diagnosis24 and SARS-CoV-2 has been detected in other biospecimen types. In one study, SARS-CoV-2 was isolated from 17% of nasopharyngeal swabs and 83% of sputum collected during the first week of symptoms. Stool biospecimens from these mildly symptomatic patients had high viral RNA load, but virus isolation was unsuccessful.25 Additional studies, however, have reported virus isolation from stool26,27 and that stool viral RNA load is generally lower than viral RNA load in respiratory biospecimens.28 Viral RNA has also been detected in urine.29

A study of SARS-CoV-2 viral RNA load in respiratory biospecimens reported higher viral load early in illness, as well as similar viral loads in symptomatic and asymptomatic individuals.30 While additional studies are needed, such findings are consistent with reports of asymptomatic transmission.31 In one report, an asymptomatic infant had persistently positive nasopharyngeal swabs through day 16 post admission, with the highest viral loads on admission day; blood collected from the infant early in illness was also positive.32

Together, these studies suggest that viral load in various biospecimen types is dependent on day and severity of illness; however, additional studies are needed to determine whether viral load indicates viable virus.

Biobanking in the Time of COVID-19
Biobanks were vital in the identification of Legionella pneumophila and hantavirus in serum collected prior to outbreaks in 1976 and 1993, respectively.33 Biobanks will likewise be crucial to COVID-19 vaccine and treatment development and have a valuable archive of biospecimens that could clarify details of SARS-CoV-2 emergence.

The past several decades saw tremendous biobank growth.34 The number of biospecimens that will be collected during the COVID-19 pandemic and stored in biobanks is not insignificant and will likely surpass the number collected during prior SARS and MERS outbreaks.

The impact of COVID-19 on biobanking is evolving but likely to be profound. Widespread distribution of biospecimens from known or suspected (eg, persons under investigation) COVID-19 cases, as well as presymptomatic and asymptomatic individuals, is inevitable. Critical to biobanking efforts during the pandemic is implementing the proper precautions, which may require changes to measures traditionally taken.

Lessons Learned From SARS
On July 5, 2003, WHO declared SARS contained.35 Research on the virus continued and three instances of laboratory-related infections were reported.36-38 While two incidences did not result in secondary transmission, one resulted in person-to-person transmission, including severe and fatal disease.39 Following the initial report of laboratory-related infection (later determined to be the result of accidental cross-contamination),40 WHO held an informal SARS Laboratory Workshop and subsequently issued recommendations.41

Transmission of the SARS virus occurs primarily via direct mucus membrane contact with infectious droplets. SARS-CoV has been detected in various biospecimen types and detection rate varies between biospecimen type and day of illness.42 The virus can survive in some biospecimen types for days at room temperature and up to three weeks at 4°C.43

SARS-CoV biosafety guidance issued by the Centers for Disease Control and Prevention (CDC)44 and WHO45 stressed the importance of using standard precautions, eliminating unguarded aerosol production, decontaminating workspaces, and treating waste to render viral particles inactive.

Additional CDC SARS guidance recommended that laboratory personnel have a baseline serum sample collected prior to working with SARS-CoV biospecimens.
and stored for future reference. All personnel working with these biospecimens should report any fever or respiratory symptoms. Any incidence of these symptoms should be evaluated for possible exposure and the personnel monitored. Local and/or state public health departments should also be promptly notified.

In December 2003, WHO recommended that unneeded biospecimens containing SARS-CoV be destroyed and national governments maintain a registry of laboratories approved to store infectious biospecimens. A 2006 review discussed the efforts to maintain SARS-CoV biospecimens in Hong Kong. In brief, all biospecimens from known or presumed SARS cases are handled in accordance with specific precautions, as well as all biospecimens collected during the SARS outbreak period. Infected or potentially infected materials are categorized as (1) cell culture virus isolates; (2) biospecimens from known SARS cases; (3) biospecimens collected from animals/environment that were tested and known to contain SARS-CoV; and (4) biospecimens from non-SARS cases collected November 1, 2002, to July 31, 2003 (time period defined using the emergence of the first SARS case). Following WHO recommendations, unneeded biospecimens from any category should be destroyed. Any biospecimens retained should be locked in a biosafety level (BSL) 3 laboratory (or BSL 2 with access control) and an inventory maintained. Periodic audits should be done to ensure compliance. Laboratory personnel working with these biospecimens should be monitored and any respiratory illness occurring within 10 days of handling SARS-CoV biospecimens investigated.

Additional Considerations for Biobanking During the COVID-19 Pandemic

The following are intended to complement interim biosafety guidance and provide additional considerations for handling biospecimens collected during the pandemic. All entities handling these biospecimens should always do risk assessments in accordance with institutional policies and adhere to any guidance provided.

Categorization of Biospecimens

In addition to biospecimens collected from known or suspected COVID-19 cases, there will be numerous biospecimens collected from asymptomatic and pre-symptomatic individuals. Symptom onset of the initial 41 cases in Wuhan ranged from December 8, 2019, to January 2, 2020. Given the 2- to 14-day incubation period between infection and symptom onset, it is likely these individuals were infected in mid-November 2019. Recent analysis of 7,666 SARS-CoV-2 genomes suggests the pandemic started in late 2019, specifically, October 6, to December 11, 2019.

Thus, similar to the categorization used in Hong Kong for SARS biospecimens, a third category should be considered, ie, all biospecimens collected internationally during the pandemic window of October 1, 2019, through a yet to be determined date. Testing of banked biospecimens collected in late 2019 may help define asymptomatic (or mildly symptomatic) circulation of SARS-CoV-2 prior to the presentation of severe cases in December; however, until a more accurate date is defined, use of October 1, 2019, as the start of the pandemic window is reasonable.
Categorization of Biospecimens Collected During the COVID-19 Pandemic

| Known COVID-19 | Suspected COVID-19 | Pandemic Window |
|----------------|-------------------|-----------------|
| Biospecimens from COVID-19 positive cases | Biospecimens from suspected individuals (eg, persons under investigation) who may or may not be later identified as COVID-19 positive or negative | Biospecimens collected internationally during the pandemic window—October 1, 2019, through a yet to be determined date |

Handling of Biospecimens Collected During the COVID-19 Pandemic

| Tissue | Blood and Other Biospecimens | Any Source |
|--------|-----------------------------|------------|
| FFPEa | Standard precautions | Standard precautions |
|       | Appropriate PPE (including surgical mask) | Appropriate PPE (including surgical mask) |
|       | BSL2 | BSL2 |
| Standard precautions | Any procedure capable of generating aerosols should be done in a class II BSC |
| Appropriate PPE | Bloodb | Stool | Urine | Other |
| Only frozen section known or suspected COVID-19 if absolutely necessary using cryostat that contains aerosols; thaw and thoroughly disinfect cryostat and materials after use64 |
| Any procedure capable of generating aerosols (eg, homogenization) should be done in a class II BSC |
| Standard precautions | Appropriate PPE |
| BSC, biosafety cabinet; BSL2, biosafety level 2; FFPE, formalin-fixed, paraffin-embedded; PPE, personal protective equipment. |
| aStudies are needed to address inactivation by routine fixation and processing; however, such processing should render SARS-CoV-2 inactive based on previous studies of other coronaviruses.61-64 |
| bStudies are needed to determine if presence of viral RNA29,32 indicates viable virus; however, until more information is available, all blood biospecimens and derivatives (eg, serum, plasma, peripheral blood mononuclear cells, buffy coats) should be handled in this manner, which is consistent with recent reports.57,59 |
| cBiospecimens used for nucleic acid extraction should be handled as described for the specific biospecimen type; nucleic acid extracts need no special precaution if handled correctly.64 |

Precautions for Biospecimens

Interim biosafety guidance48,49 recommends PPE consistent with standard precautions. This is similar to prior SARS guidance,44,45 which also specifically mentions donning surgical masks. Given similarities between SARS-CoV and SARS-CoV-2, along with the increased transmissibility of SARS-CoV-2,56 all personnel handling pandemic window biospecimens should consider donning surgical masks. This is consistent with recommendations in recent reports.57-60

Unlike the 2002 SARS outbreak, the current COVID-19 pandemic has caused widespread PPE shortages, including surgical masks. Thus, all personnel should seek institutional guidance and include availability of PPE in risk assessment.

Handling Biospecimens

Following CDC and WHO interim biosafety guidance when handling all fresh and frozen pandemic window biospecimens should be considered. While handling all fresh and frozen biospecimens as infectious may result in additional steps and procedure time, such handling eliminates the need to switch between protocols. Additionally, handling all fresh and frozen biospecimens as infectious minimizes exposure potential and the implications such exposure could have to laboratory personnel and the community.

Exceptions to such handling include formalin-fixed, paraffin-embedded (FFPE) tissue and nucleic acid extracts. If handled correctly, these processed biospecimens likely need no special considerations beyond the use of standard precautions and appropriate PPE. Studies are needed to address SARS-CoV-2 inactivation by routine histologic fixation and processing; however, such processing should render SARS-CoV-2 inactive based on previous studies of other coronaviruses.61-64 While nucleic acid extracts likely need no special considerations if handled correctly,64 the biospecimens used for extraction should be handled appropriately. Specific considerations for various biospecimen types are summarized in Table 2.

Labeling Biospecimens

Known or suspected COVID-19 biospecimens should be labeled accordingly at the time of collection. Suspected or pandemic window biospecimens later identified as SARS-CoV-2 positive, should be noted. At such time these biospecimens are processed, distributed, and/or tested, the appropriate labeling should be added. It is imperative all entities accurately maintain collection date.
Shipping Biospecimens

Consideration should be given to shipping all pandemic window biospecimens as UN 3373 Biological Substance, Category B, in accordance with International Air Transport Association (IATA) Dangerous Goods Regulations. Collection sites should notify receiving entities of shipments containing known or suspected COVID-19 biospecimens prior to shipping. Recipients should note the tracking number and ensure all precautions are taken when receiving and opening these shipments.

Storing Biospecimens

FFPE tissue can likely be stored per institutional policy. When storing frozen biospecimens, it should be considered that viruses stored in liquid nitrogen (LN2) retain pathogenic properties and can cross-contaminate biospecimens in LN2 tanks. Currently, there is no evidence that storage of SARS-CoV-2 positive biospecimens with uninfected biospecimens in the same LN2 tank results in cross-contamination. The possibility should be considered, however, as cross-contamination of biospecimens stored in LN2 liquid phase has been documented. As such, frozen biospecimens should be stored in LN2 vapor phase. Placing cryovials in a second, heat-shrinkable tube may protect from cross-contamination and accidental rupture. When possible, storing frozen biospecimens from known COVID-19 cases in dedicated LN2 tanks should be considered.

Considerations for storing and access to pandemic window biospecimens, as well as inventory information to be maintained, are guided by previously described strategies for laboratory containment of SARS-CoV and summarized in Table 3.

Table 3

| Storage of Biospecimens Collected During the COVID-19 Pandemic |
|---------------------------------------------------------------|
| Known COVID-19                                               | Suspected COVID-19/Pandemic Window*                         |
| FFPE storage and access                                       | As usual per institutional policy                          |
| Frozen storage                                                | As usual per institutional policy                          |
| Locked freezer/vapor phase of dedicated LN2 tank (when possible) inside BSL2 locked room with restricted access | Locked freezer/vapor phase of LN2 tank                     |
| Frozen access                                                 | Controlled room access; handling of biospecimens requires prior approval |
| Room entrance and handling of biospecimens requires prior approval; access record should be maintained | |
| Inventory information                                         | Case ID                                                     |
| Case ID                                                       | Biospecimen type                                            |
| Biospecimen type                                              | Biospecimen identifier                                      |
| Biospecimen collection date                                   | Biospecimen collection date                                 |
| Number of biospecimens                                        | Number of biospecimens                                      |
| Storage location                                              | Storage location                                            |
| Any movement of biospecimens, including distribution          | Any movement of biospecimens, including distribution         |
| COVID-19 testing result, if applicable                        | COVID-19 testing result, if applicable                      |

BSL2, biosafety level 2; FFPE, formalin-fixed, paraffin-embedded; LN2, liquid nitrogen.
*Collected October 1, 2019, through a yet to be determined date.
†Placing cryovials in a second, heat-shrinkable tube may protect from cross-contamination and accidental rupture.
*To be maintained in the biospecimen tracking system.

Ability to Follow Biosafety Recommendations

WHO suggests that laboratories unable to meet the recommended biosafety requirements consider transferring diagnostic biospecimens to laboratories with such capacity. While there is no mention of the ability to handle biospecimens for biobanking purposes, it should be considered that biobanks unable to meet the recommendations redirect or transfer biospecimens to biobanks that have such capability.

Per CDC and WHO SARS-CoV-2 interim biosafety guidance and reported COVID-19 experience, biobanks handling pandemic window biospecimens must:

- Be BSL2 (or higher) and have a certified BSC.
- Store biospecimens in a locked room with limited access.
- Properly train personnel and permit select staff to work with these biospecimens.
- Ensure all laboratory workers wear appropriate PPE (including surgical mask).
- Ensure laboratory doors remain closed while handling these biospecimens.
- Maintain physical distancing.

Distribution of Biospecimens

Testing laboratories may not be versed in handling biospecimens containing respiratory viruses. Review of proposals to utilize pandemic window biospecimens should include a review of the receiving laboratory risk assessment and biospecimen handling protocols. Whether testing laboratories can operate per all recommendations...
described in the preceding section should be considered. Additionally, proposal review should consider implications of SARS-CoV-2 infection on the biomarker(s) of interest. Investigators should, at minimum, address the potential scientific impact of including known or suspected COVID-19 and pandemic window biospecimens in their study.

Conclusions

SARS-CoV-2 is the highly transmissible respiratory virus that causes COVID-19, a disease hallmarked by asymptomatic infection in some, and severe symptoms, including death, in others. At present there is no vaccine or effective treatment. Current models suggest that until a vaccine is available recurring outbreaks are likely.73

Biobanks have a critical role in the COVID-19 pandemic, as biospecimens are necessary for diagnosis and research. During the pandemic, biospecimens will be collected from known or suspected COVID-19 cases, as well as asymptomatic and presymptomatic individuals. As such, all biospecimens collected internationally from October 1, 2019, through a yet to be determined date could be considered potentially infectious and handled accordingly.

Following the 2002 SARS outbreak, WHO convened an informal workshop and subsequently issued SARS-CoV biospecimen handling recommendations.41 As millions of biospecimens will be collected during the COVID-19 pandemic, similar working groups must be convened to address the immediate and long-term storage and use of pandemic window biospecimens. Such guidance will be necessary to protect the health and safety of the personnel handling these biospecimens, as well as communities at large. Until harmonized international guidance is established, entities should follow CDC and WHO interim biosafety guidelines.

Presented here are additional considerations intended to complement the interim guidance. These considerations draw on prior SARS recommendations, as well as reports on biospecimen handling during the COVID-19 pandemic. In summary, the following should be considered during risk assessment:

- All biospecimens collected during the pandemic window (October 1, 2019, through a yet to be determined date) should be considered potentially infectious.
- Appropriate PPE, including surgical mask, should be donned when handling these biospecimens.
- Known or suspected COVID-19 biospecimens should be labeled appropriately; suspected or pandemic window biospecimens identified as SARS-CoV-2 positive should be subsequently labeled.
- All biospecimens should be shipped UN 3373 Biological Substance, Category B.
- Frozen biospecimens should be stored in a locked freezer/LN2 vapor phase; placing cryovials in a second, heat-shrinkable tube may protect from cross-contamination and accidental rupture.
- Personnel handling these biospecimens should have prior approval.
- Access to rooms containing known or suspected COVID-19 biospecimens should require prior approval and an access record should be maintained.
- Detailed inventory information should be maintained for all pandemic window biospecimens, including any results of SARS-CoV-2 testing.
- Biobanks handling these biospecimens should be capable of following all recommendations; if unable, biospecimens should be redirected or transferred to a biobank with such capability.
- Pandemic window biospecimens should only be distributed to testing laboratories that can follow all recommendations.
- Review of proposals to utilize these biospecimens should include a review of the receiving laboratory risk assessment and protocols for biospecimen handling, as well as the potential scientific impact of including these biospecimens in the study.

These considerations should be updated as the SARS-CoV-2 and COVID-19 knowledge base expands. Per current understanding and lessons learned from SARS, personnel handling pandemic window biospecimens should adhere to all biosafety guidance and recommendations. It is recognized adoption of additional biosafety precautions may cause workflow disruptions for entities not currently operating in the recommended fashion. Given the highly transmissible nature of SARS-CoV-2 and lack of effective prophylaxis and treatment, exercising an abundance of caution is warranted. As such, all entities should do an institutional risk assessment prior to handling these biospecimens. Periodic risk assessments may also be needed as interim guidance is updated.

At present, the world is working to flatten the curve, adapt to a new normal, and conduct decades of research at lightning speed. In the past several months, hundreds of studies have been developed to test COVID-19 vaccines and treatments, as well as study the impact of viral infection. Many of these studies collect biospecimens, in addition to biospecimens collected for diagnostic purposes. Additionally, biospecimens continue to be collected for
research efforts “unrelated” to COVID-19. The scientific community has a responsibility to safely handle and maintain all biospecimens collected during the COVID-19 pandemic. Soon, it will be imperative to convene working groups of international experts to address the current and long-term storage and use of these biospecimens. Ideally, worldwide guidelines will be established, as they are needed to protect not only the personnel handling these biospecimens, but communities at large.

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