Received: 2 September 2020 | Revised: 21 November 2020 | Accepted: 29 November 2020

DOI: 10.1002/cyto.a.24280

SRL COMMUNICATION

ISAC CYTOMETRY Journal of Quantitative Cell Science PART A

Biosafety during a pandemic: shared resource laboratories rise to the challenge

Avrill M. Aspland[1] | Iyadh Douagi[2] | Andrew Filby[3] | Evan R. Jellison[4] | Lola Martinez[5] | Diana Shinko[1] | Adrian L. Smith[1] | Vera A. Tang[6] | Sherry Thornton[7]

[1]Sydney Cytometry Core Research Facility, Centenary Institute, The University of Sydney, Sydney, New South Wales, Australia

[2]Flow Cytometry Section, Research Technologies Branch, NIAID, NIH, Bethesda, Maryland

[3]Innovation, Methodology and Application Research Theme, Newcastle University, Newcastle upon Tyne, UK

[4]Department of Immunology, UCONN School of Medicine, Farmington, Connecticut

[5]Biotechnology Programme, Flow Cytometry Core Unit, Spanish National Cancer Research Center (CNIO), Madrid, Spain

[6]Faculty of Medicine, Department of Biochemistry, Microbiology, and Immunology, Flow Cytometry and Virometry Core Facility, University of Ottawa, Ottawa, Ontario, Canada

[7]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Department of Pediatrics, University of Cincinnati Medical Center, Cincinnati, Ohio

Correspondence
Avrill M. Aspland, Sydney Cytometry, Charles Perkins Centre D17, John Hopkins Drive, The University of Sydney, Camperdown, NSW 2050
Email: avrill.aspland@sydney.edu.au

Funding information
National Institute of Allergy and Infectious Diseases

Abstract

Biosafety has always been an important aspect of daily work in any research institution, particularly for cytometry Shared Resources Laboratories (SRLs). SRLs are common-use spaces that facilitate the sharing of knowledge, expertise, and ideas. This sharing inescapably involves contact and interaction of all those within this working environment on a daily basis. The current pandemic caused by SARS-CoV-2 has prompted the re-evaluation of many policies governing the operations of SRLs. Here we identify and review the unique challenges SRLs face in maintaining biosafety standards, highlighting the potential risks associated with not only cytometry instrumentation and samples, but also the people working with them. We propose possible solutions to safety issues raised by the COVID-19 pandemic and provide tools for facilities to adapt to evolving guidelines and future challenges.

KEYWORDS
COVID-19, SARS-CoV-2, biosafety guidelines, shared resource laboratory (SRL), pandemic, epidemic, emerging disease, cytometry, flow cytometry

1 | INTRODUCTION

Biohazardous materials are commonly encountered in flow cytometry SRLs. As with any laboratory setting, the standard approach to safety when working with potential hazards is to perform a thorough risk assessment on the infectious agents, reagents, standard operating procedures (SOPs), and the instrumentation proposed for use. Protocols are put in place to help reduce these inherent risks, managed through the implementation of primary controls, such as engineering controls, personal protective equipment (PPE), and SOPs (1). Biosafety considerations when handling samples before, during, and post-acquisition have always been front of mind in flow cytometry SRLs, particularly related to droplet-based cell sorters. The SRL, by its definition, handles a wide variety of samples and hosts users from many laboratories, universities,

All authors contributed equally to this study.

ISAC CYTOMETRY Journal of Quantitative Cell Science PART A

institutions and companies. Considering that the current pandemic is spread via respiratory transmission and remains viable on surfaces for prolonged periods (2), the actions of one individual can impact many with wide-spread downstream consequences. In times of epidemics, pandemics and emerging disease, the potential risks associated with working within an SRL are evolving, giving cause for re-evaluation of our practices to accommodate these new challenges.

2 | HUMAN-ASSOCIATED RISKS

The SRL, by its nature, is a multi-user environment that facilitates interaction between different members of a research community including SRL staff and users. In the case of COVID-19, a vaccine is currently unavailable against the causative agent (SARS-CoV-2), and it is currently not feasible to perform screening for asymptomatic or pre-symptomatic individuals. This pandemic has necessitated significant changes in the working environment and management of the workforce, with increased expectations put on staff and users. As a result of these changes, added attention needs to be given to the human contribution to the risks associated when working within the context of a shared-use space. With respect to biosafety risks, staff and users must now be included in this assessment and operational guidelines should be identified. For most institutions, these expectations are defined by the level of biosafety threat to individuals and the specific institution's approach to risk (1). We review below some simple strategies that can be employed to maintain a safe and healthy SRL working environment.

2.1 | RISK ASSESSMENT AND CONTACT TRACING

Perhaps one of the biggest changes in the pandemic SRL environment is the potential source of significant biosafety risks. In the pre-COVID-19 era, the focus was on the biosafety risks posed by the samples and reagents brought into the SRL. The standard mitigation approach was a detailed sample-associated biological safety assessment (3) that led to the application of engineering controls, PPE and SOPs for processing and analyzing samples. While communication between investigator, SRL, and safety officer remains critical to ensure a cohesive approach when defining a biological safety assessment in the context of an SRL (Figure 1), the COVID-19 pandemic has added additional considerations to this previously defined process. This global pandemic has caused a paradigm-shift whereby potentially the greatest sources of biosafety risks in an SRL are now the people who enter it; staff, users and external visitors such as field service engineers. The risk posed by an individual carrying SARS-CoV-2 must now be considered and integrated into risk assessments. Any risk assessments should include:

1. Identification of the workforce with potential for exposure—including competency and experience as well as enrollment in medical surveillance.

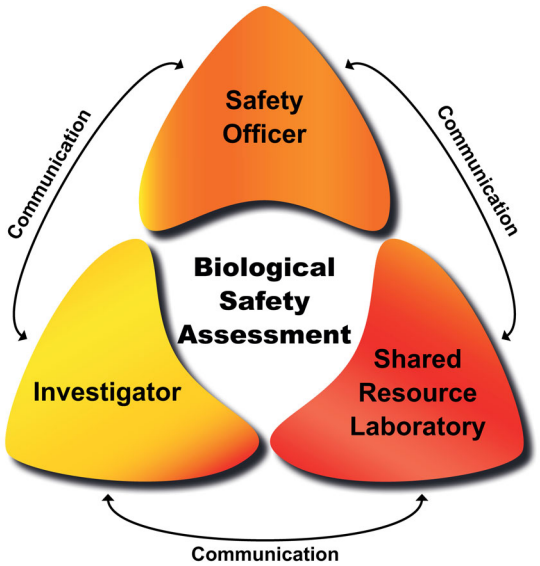

FIGURE 1 Effective communication between investigator, shared resource laboratory, and safety officer ensures a cohesive approach when defining biological safety assessment in the context of an SRL. As in everything we do, our ability to identify the risks, assess them, and then go on to manage them is limited by our ability to communicate with all involved parties. It is in the framing of these biosafety discussions that SRL staff can have the most impact, where the focus is understanding, communicating perceived risks, followed by collaborating to determine an appropriate safety response. While compromise may not always be possible, there are invariably instances where inclusion of users leads to innovative solutions and new approaches to safety. There is a certain amount of trust required between users and SRL staff. This trust is developed by having ongoing discussions around safety, developing a cultural expectation of safety and continued inclusive discussions. There is a significant mental and time burden to the maintenance and communication of appropriate biological risk management. However, it is imperative, especially during pandemics, that SRLs have effective processes in place to ensure the safety of everyone who uses their space [Color figure can be viewed at wileyonlinelibrary.com]

2. Characterization of the risk—including hazards, risk group of the agent, risk of exposure, activities that increase the risk of exposure, and an evaluation/prioritization of the risks.
3. Risk mitigation—including creating mitigation strategies, determining mitigation necessity, communication of strategies to affected personnel, and validation of mitigation strategies.

This new source of risk has necessitated the development of screening mechanisms to identify and exclude potentially infected individuals. These methods can range from high-tech approaches that use purpose-built programs for self-assessment, to low-tech paper versions (4, 5). More detailed screening methods, from sampling of body temperatures, as well as polymerase chain reaction and serological tests, have also been employed. Institutional and regional policies will dictate when this type of testing is warranted and provide guidelines regarding periods for self-isolation or quarantine. In many institutions, once a positive case has been identified, contact tracing is undertaken to identify individuals at risk so that they may follow the

TABLE 1 Software types, applications and important features for facilitating safe work practices during a pandemic

Category	Use cases	Examples Free	Paid	What to look for
Facility management	Bookings, Usage tracking User tracking Record user agreement with entry conditions; update users on changing requirements *Comments: None*	Quartzy (academic and non-profit) (quartzy.com/)	Stratocore (stratocore.com) iLabs (agilent.com/en/products/lab-management-software/core-facility-management) IDEA ELAN (ideaelan.com/) Agendo (agendo.science/) Calpendo (exprodo.com/calpendo)	Control bookings and instruments logins, e.g. require gaps between users Ability to group instruments into sets that cannot used at the same time Approval for bookings Management of safely approvals Document management with user response tracking
Collaborative communications	Shared inboxes allow centralization of email communications with users Mailing list software facilitates mass communications Wiki and blog software provides repository of facility information and communications *Comments: Ticketing systems (helpdesk/servicedesk) systems can also be useful*	Google Groups (groups.google.com)	*Shared Inboxes*: Front (frontapp.com) Gmelius (gmelius.com) *Mailing List Software*: Mailchimp (mailchimp.com) *Wiki/Blog Software*: Confluence (atlassian.com/software/confluence) Wordpress (wordpress.com)	Shared inboxes Shared drafts Assign emails to individuals Open/read tracking
Instant communications	Communication between facility staff Communication between users and staff "crowd-sourcing" support, for example, facilitates expert users helping other users when facility staff are not on-site) *Comments: Many of the commercial products have free tiers that have been expanded during COVID-19*	Slack Google Chat	Slack (slack.com) Microsoft Teams (microsoft.com/teams)	Ability to support multiple organizations, for example, users may already be using a product with other groups and need to be able to quickly switch between accounts
Remote control	Observe and control instrument PCs remotely, for example, for trouble shooting Remote setting of sort regions *Comments: Security is critical when enabling remote access across the internet; look for security focused reviews and seek approval from cyber-security team*	Chrome Remote Desktop (remotedesktop.google.com) No Machine (nomachine.com) MeshCentral (meshcommander.com/meshcentral2)	TeamViewer (teamviewer.com) SplashTop (splashtop.com) Remote Utilities (remoteutilities.com) ConnectWise Control (connectwise.com/software/control)	Multi-factor authentication Support for a wide-range of operating systems
Remote meetings and assistance	Remote meetings and assistance *Comments: Many of the commercial products have free tiers that have been expanded during COVID-19*	Jitsi (meet.jit.si)	Google Meet (meet.google.com) Zoom (zoom.us) GoToMeeting (gotomeeting.com) WebEx (webex.com.) Microsoft Teams (teams.microsoft.com)	Direct use in a browser (no download required) Persistent meeting URLs
Digital check-in and visitor management	Track people who have entered the facility in order to facilitate contact tracing Pre-entry screening questions and reminders *Comments: These products can raise serious privacy concerns that need to be considered in the light of local guidelines or national regulations: for example, see this guidance for Australians—www.oaic.gov.au/engage-with-us/consultations/guidance-for-digital-check-in-providers-collecting-personal-information-for-contact-tracing/*	Google Forms with a QR Code	Swipedon (swipedon.com) Sine (sine.co) COVID19 Tracker (covid247.org)	Ability to pre-screen visitors with questions Mobile apps to facilitate contactless check-in Geofencing for automated cheek-in/out High-resolution tracking (using beacons/tags) to facilitate contract tracking

Additional Notes
Many vendors offer discounted rates/free plans for educational or non-profit use.
Care must be taken when evaluating license agreements, for example, some products may claim to be free for non-commercial use but these free plans do not cover use within an SRL.
There are many review sites that aggregate user reviews for Software-as-a-Service (SaaS) products; for example, getapp.com or capterra.com.

ISAC CYTOMETRY Journal of Quantitative Cell Science PART A

recommended procedures for testing and self-isolation (6). SRL facility management systems can help to quickly determine who should be contacted when a user or staff member tests positive (7). Some SRLs have access to high-tech methodologies that enable contact tracing such as badge scanners at the door of the SRL. Low-tech solutions should also be considered including having a sign-in/sign-out log. This manual system is important for users who come to the SRL for purposes other than to utilize an instrument, such that usage would not be recorded in instrument booking systems. For further details on possible booking systems and visitor tracking options please refer to Table 1.

Additional consideration should be given to those who must enter the SRL to provide specialist services, such as instrument maintenance and installation. Prior to their arrival, these individuals should be informed of the institution's screening process, escort rules, and other relevant guidelines for working within the facility. In the case where they are arriving from another country or region, government travel regulations must be considered and adhered to.

While every effort can be made to identify all potential contacts of a positive case, this may not always be all-encompassing. Thus, having in place a policy that assumes anyone may be infectious (similar to standard precautions when handling biological samples) is crucial to ensure a safe SRL working environment.

2.2 | Minimizing Transmission

Many facilities have put in place operational policies that help to control the spread of SARS-CoV-2. Although the specific policies and recommendations may vary between institutions, they all serve to reduce transmission through: (1) physical distancing of individuals; (2) improved decontamination of common workspaces; and (3) the use of PPE.

1. *Physical distancing*: There are different methods that can be employed to physically distance users and operators within an SRL. If space is not an issue, instruments can be relocated to other spaces or moved further apart to facilitate physical distancing. Rotating shifts for both core facility staff and users can help to reduce the number of persons in a given lab at one time. To complement this, strategies should be employed to minimize possible overlap of users and the number of users in a space by preventing the simultaneous booking of instruments in close proximity. The companion manuscript on regulatory measures (7) covers these issues in detail. Remote support can further reduce physical contact, while maintaining training and support. These same software solutions can also be employed by users who often will work side by side on an instrument to demonstrate data acquisition to new colleagues. These strategies can be encouraged to allow for mentoring to continue, while taking place remotely. There are a number of easy-to-use software platforms (see Table 1) that can be used to facilitate remote sessions between SRL users and staff alike, as reviewed in detail by Daniels et al. (8).
2. *Environmental decontamination procedures*: Cleaning procedures will vary between facilities; however, these typically include cleaning protocols for high-touch surfaces such as instrument keyboards, mouse, webcams, headsets, as well as all surface areas of the instrument contacted by a user (9–14). A list of surface disinfectants shown to be effective against SARS-CoV-2 can be found in Table 2. Enhancement of ventilation in SRL spaces is also recommended to further reduce the risk of environmental contamination (19, 20). Reducing back-to-back bookings by providing a 15 to 30 min gap between bookings on an instrument allows time for air exchange, sanitization of work surfaces, limits overlap between users and reduces the number of individuals within the SRL at any one time. All of these measures in combination are designed to reduce the concentration of potentially contaminated droplets and aerosols.
3. *Personal protective equipment*: The recommendations for the type of PPE and when to use them vary widely and can be conflicting between institutions and countries around the world. SRLs should refer to and follow the policies as dictated by their own local institutions. Examples of common PPE used in SRL include masks and other suitable face coverings, face shields, disposable gloves, clean lab coats, and safety goggles. Studies have shown effective reduction in the transmission of particulates through the use of masks (21). Various kinds of face shields and masks are available and reduce droplet spread to different degrees as assessed by physical testing (22).

2.3 | Communication

Ensuring consistent uptake of new policies associated with pandemic working conditions, while maintaining strong working relationships requires consistent messaging, support and a good safety culture (1). Institutional policies tailored to the SRL should have the backing of the administration. These policies are best put into place if the SRL defines them in accordance with state and national, as well as institutional guidelines, and acquires approval from institutional administration (Supporting Information Table S1). Having a clear, well-thought-out plan is essential and takes time and feedback from key stakeholders, including SRL staff, biosafety officers, workplace health and safety committee, SRL support committee, and users of the SRL. This inclusion facilitates acceptance of the resulting plan and successful uptake by staff and users. These interactions should be structured with a focus on enabling user compliance (1) and are best supported with imagery, videos, demonstrations, and documentation, all of which help to facilitate the transfer of skills, techniques and ultimately behavioral changes. Structuring a plan that details what is expected, along with the reasons for these changes, and potential consequences, will aid in transitioning to new working conditions. Moreover, reminders of policies can aid in ensuring compliance as working conditions change. This important task could be complicated due to the reduced number of SRL staff at a given time to check that

TABLE 2 Inactivation of SARS-CoV-2 virus by commonly utilized active ingredients

Active ingredient	Surface/sample type tested	Concentration	Time (minutes)	Temperature (°C)	Log reduction	Reference
Ethanol	Hand sanitizer	49% w/w	1	21	≥4.2	(15)
	Surface disinfectant (non-porous)	62%, 70%, 75%, 80%	0.25, 0.5, 1	Room temperature	>4.0	(16)
		95%	0.25, 0.5, 1	Room temperature	>1.0–<3.0	
Formaldehyde	Tissue culture fluid	4%	15, 60	18–25	≥4.8, ≥5.0	(17)
		2%	15, 60	18–25	≥4.8, ≥5.0	
	Infected monolayer	4%	15	18–25	≥6.9 (live virus still detectable)	(17)
		4%	60	18–25	≥7.5	
		2%	15, 60	18–25	≥6.8, ≥7.3 (live virus still detectable)	
Formaldehyde + glutaraldehyde	Tissue culture fluid, infected monolayer	2%+ 1.5%	15, 60	18–25	≥5.0, ≥6.7	(17)
Glutaraldehyde	Surface disinfectant (non-porous)	2.4%	0.25, 0.5, 1	Room temperature	>4.0	(16)
Isopropanol	Surface disinfectant (non-porous)	70%, 75%, 80%	0.25, 0.5, 1	Room temperature	>3.0–>4.0	(16)
Methanol	Infected monolayer	100%	15	18–25	≥6.7	(17)
			30	Room temperature	>4.0	(18)
Para-chloro-meta-xylenol	Hand sanitizer	0.094% w/v	5	21	≥4.7	(15)
Quaternary ammonium compound	Surface disinfectant (non-porous)	0.077% w/w	5	21	≥4.1	(15)
Sodium hypochlorite	Surface disinfectant (non-porous)	0.0525%	0.25, 0.5, 1	Room temperature	>1.0–<3.0	(16)
		0.525%	0.25, 0.5, 1	Room temperature	>4.0	
		0.1%	0.25, 0.5, 1	Room temperature	>4.0	

the SRL room occupancy is correct and everyone works following the "new normality" policies. Encouraging a collaborative culture where users remind each other of the new behaviors can greatly aid in adoption.

The need for physical distancing means the majority of SRLs are operating with some level of remote support. There are added pressures at this time as research groups must keep working, often on rotating shifts, and under the expectation they will not exceed booking times in order to maintain compliance with room occupancy restrictions. This extra pressure may potentially impact users' abilities to correctly follow protocols. Thus, added precautions should be implemented to not only limit the frequency of potential errors, but also to limit their impact. For example, additional training time in the form of remote support by SRL staff can be included in the first few sessions a new user runs on their own. This also means that users should be trained to follow all new procedures and consistent communication should be implemented to support users in these new policies (1).

The strategies reviewed here aim to reduce person-to-person contact and subsequent spread of disease while maintaining interactions between members of an SRL. For SRLs, the challenge is to implement working policies that both safeguard the health and well-being of all staff and users, while maintaining a high level of support to ensure continuity of research services. This is a delicate balance as the measures put into place to reduce person-to-person contact can potentially also reduce the ability for SRL staff to provide support to their users. An example of a risk assessment for working with a SARS-CoV-2 infected user in an SRL setting is provided in Appendix.

3 | INSTRUMENTATION AND INHERENT RISKS

Historically, facilities have effectively managed inherent risks by implementing "Standard Precautions" in laboratories in line with their biosafety containment level. Standard Precautions are such that all

human specimens are assumed potentially infectious, and protective measures are implemented to reduce the risk of transmission (23). These precautions include the use of protective barriers such as: hand hygiene, gloves, gowns, masks, and protective eyewear or face shields. If procedures are likely to result in a higher risk of transmission, for example, producing droplets or aerosols, it is recommended that a Class II Biological Safety Cabinet (BSC) or physical barrier is used (23). As such, all human samples should be treated as potentially infected with any human pathogen, which now includes SARS-CoV-2. This creates a complex matrix in the assessment of potential risk for each sample. Scientific literature and sample history provide us with the information needed to populate this matrix and determine the level of risk presented by such a sample. This matrix feeds into the determination of appropriate controls for assessed samples. Due to the respiratory nature of SARS-CoV-2 transmission, this means we must maintain heightened awareness of all processes that may result in the generation of droplets and aerosols.

A number of factors interplay to determine the final risk associated with running a particular sample on a specific instrument. Effective communication between investigator, shared resource laboratory, and safety officer is critical to ensure a cohesive approach when defining a safety assessment in the context of an SRL (Figure 1). It is recommended that the SRLs, along with their biosafety officer, perform a biological safety assessment for each laboratory group and their specific samples (24, 25). A template for such a risk assessment has been described and reviewed in detail by Schmid, Merlin, and Perfetto (3). In the current time, it is important to pay close attention not only to the types of samples entering shared facilities, where those samples have come from and what risk they might pose, but also the user bringing those samples (Appendix). It is at this point that engineering controls, appropriate PPE and SOPs can start to be applied to control for these risks.

3.1 | Sorters

The ISAC Biosafety committee has written extensively on the assessment of aerosols created by droplet cell sorters and the dangers posed to the sort operator (26). In summary, prior to any cell sorting, a risk assessment needs to be performed that will help identify and mitigate the risks of operator exposure to infectious or potentially infectious aerosols. Once it has been determined that samples can be safely handled through the use of PPE and engineering controls (e.g., aerosol management systems, instruments installed in BSC, etc.), aerosol testing should be carried out to determine if the engineering controls are indeed functioning prior to working with biohazardous samples. The latest published protocol for aerosol testing uses a combination of 1um green fluorescent beads and a relatively inexpensive Cyclex-D aerosol sampling cassette (27). Critical in the aerosol testing procedure is the need to have both a positive control sample (e.g., failure of containment), a normal operation sample, and a sample that follows SOPs in the event of a nozzle clog. This may vary depending on the cell sorter operator, and each SRL needs to establish an SOP, which includes timing for opening the sort chamber door and handling a nozzle after a clog has occurred, to give the aerosol management system time to dissipate lingering aerosols. Each operator should be trained for the SOP prior to performing such a sort, and there may be a need to test each operator for compliance with the SOP, especially in situations where dedicated facility staff are not the only users operating the cell sorter.

Specific to SARS-CoV-2, it has been established by regulatory entities globally that samples containing replication-competent SARS-CoV-2 should be handled in BSL-3 laboratories (28–30). Recently, the ISAC Biosafety committee published an SOP for operation of a droplet cell sorter under BSL3 conditions (31). It is imperative that SRL staff know the source of samples that are coming into the facility. Requiring investigators to fill out pre-sort questionnaires can help the SRL identify sample sources and determine the level of containment required for cell sorting (3).

It should also be noted that a number of microfluidic and chip-based flow cytometry cell sorters have been brought to market in the last 5–10 years. Aerosol generation by these cell sorters is kept to a minimum due to their design; however, there is still a need to validate the sorting safety of these instruments in each environment and with individual users. The ISAC Biosafety Committee has published standards for testing of aerosol management and these standards should be used and adapted to fit each individual situation and instrumentation.

The SRL may decide that only facility staff will operate sorters and room requirements may dictate that only one person can be present. In this context, contact-free sorting can be facilitated by thorough documentation encompassing critical parameters such as the reagents used, the number of sorted cells requested, and suggested gates. Instant communication tools and remote control software (Table 1) are effective for the required interactions such as gate confirmation (8).

3.2 | Analyzers

As discussed above, the operation of cell sorters is well classified due to the significant risk of aerosol generation, with SRL staff trained to ensure safe operation in line with well developed, evidence based SOPs. The use of analyzers is generally considered low risk due to their enclosed systems and low pressures. However, there appears to be little empirical evidence to support this (32, 33). While analyzers can be considered a lower risk than cell sorters, at this time they pose an uncharacterized risk, often operated by a large volume of users with varying levels of experience. As such it is important that strategies are implemented to reduce the risk associated with pathogenic and human samples in the SRL setting (34). These strategies can be subdivided into two main areas: standard operating procedure controls and engineering controls.

3.2.1 | Standard operating procedure controls

Utilizing fixation as a SOP control allows facilities to minimize the risk of running hazardous and potentially hazardous samples in their SRL space. The most common inactivation process utilized for flow

cytometry analysis is the use of formaldehyde solution in various concentrations. Incorporating a fixation protocol into the preparation of samples is a procedure familiar to many users, making this a straightforward process for controlling risk.

Fixation is often performed with the primary goal of stabilizing samples for downstream assays (e.g., intracellular staining). However, fixation protocols designed for stabilization may not necessarily result in pathogen inactivation and special care is needed in the assessment and development of fixation protocols (14, 26, 34–45). Commercial products, both within and across companies, often contain varying concentrations of fixative. This information is often not immediately obvious, and it is therefore necessary to reference the Material Safety Data Sheets (MSDS) along with the protocol when performing fixation protocol assessments. It is important to note that there is inherent variability in the response of pathogen infectivity to inactivation. There is extensive literature detailing pathogen inactivation by varying compounds and this should be reviewed when determining the suitability of a fixation protocol (15, 40, 44, 46–49). We are now seeing literature emerging detailing inactivation of SARS-CoV-2 with formaldehyde solution (16–18, 50), this is summarized in Table 2. In instances where pathogens are emerging or classified as Risk Group 3/4, all fixation and inactivation protocols are recommended to be validated by the laboratory undertaking the research rather than relying solely on literature (28). Viral inactivation validation protocols vary and literature should be reviewed, and local safety officers consulted, when developing protocols for the local context. Viral inactivation validation protocols can be found in these references (15–18, 40, 44, 46–50). In all fixation protocols, it is imperative to consider the: (1) fixative used; (2) how fresh this fixative is; (3) the concentration of the fixative; (4) the time of incubation; and (5) the temperature maintained during incubation (40, 42, 43, 47, 49). Critically, it has been demonstrated in a number of publications that fixation at low temperatures, for example at 4°C, often results in insufficient inactivation of pathogens (42, 43, 47, 49).

It is important that protocols are reviewed and any required changes are identified. Implementing changes in policy can be met with reluctance on the part of the users due to fear of potential impacts on existing work. Facilities can ameliorate this concern by demonstrating that protocol changes do not impact results in any significant manner. Staining protocols, particularly for intracellular markers, may be impacted by additional fixation steps if not implemented with care. Some guidance on staining protocols can be found in this methodology publication (51). Preliminary data from a high-dimensional panel indicate that various fixation protocols do not necessarily alter signal intensity or interpretation of data (Figure 2). Results showed that fixation with a 4% formaldehyde solution (freshly prepared from paraformaldehyde (PFA)) under different incubation conditions did not alter the forward versus side scatter plots (FSC-A vs SSC-A; Figure 2A) or the identification and separation of immune cell populations compared to the unfixed sample (examples of populations can be seen in Figure 2B). Furthermore, the different fixation conditions did not affect the signal intensity of single or tandem fluorophores when the median fluorescence intensity (MFI) of the positive population or the separation between the positive and negative populations (calculated as a separation ratio) was examined (Figures 2C,D respectively).

Significant value lies in testing fixation protocols to determine potential impact on assays. It should be acknowledged that some protocols will not function on fixed samples. The situation may necessitate examination of alternative assays, for example, an apoptosis assay that allows for fixation (52) or a move to implementing engineering controls for such samples. Due to the pandemic, we are now working in an environment with significant inherent risks, so stakeholders will now be seeking out protocols and reagents that facilitate a reduction of this risk. This is an area in which manufacturers have the opportunity to expand their market by identifying new protocols, taking into account viral inactivation and identifying stability of their reagents after fixation.

3.2.2 | Engineering controls

While some engineering controls already exist on instruments, the most effective control for facilities looking to run unfixed hazardous samples may be (as per standard precautions) to enclose an analyzer and any potential aerosols inside a BSC (34, 53). Historically this was not possible due to the size of instrumentation (34), but this is no longer the case with many benchtop analyzers (Figure 3). The ability to enclose a benchtop analyzer in a BSC opens up options for users in the types of protocols and samples that can be run while maintaining biosafety containment. However, a number of factors need to be carefully considered before moving down this path:

1. *Biological safety assessment*: Determine if a BSC is required for the types of samples handled within the facility.
2. *Frequency of live hazardous samples*: Depending on how frequently a facility encounters live hazardous samples, the use of a cell sorter contained within a BSC may be sufficient to accommodate user needs.
3. *Accommodation of instrument within BSC*: Sufficient air flow around instrument within standard BSC for both heat dispersion and maintaining functional containment. Custom BSC options may need to be explored.
4. *Thermal load*: Instrument specifications, such as number of lasers, should be considered. For example, the more lasers, the more heat produced, and the less stable the system may be.
5. *Training*: Adequate training must be provided for appropriate use of the instrument inside the BSC to ensure containment of hazards is maintained.
6. *Accessories*: components such as vortex, pipettes, and tube racks will be needed within the BSC to ensure ease of use and reinforcement of safe behaviors.

Placement of an analyzer inside a BSC increases the burden on facility staff due to the need for additional sample handling training for users and ensuring continued compliance with these behaviors. Additional costs are also associated with the initial BSC purchase and

ISAC CYTOMETRY Journal of Quantitative Cell Science PART A

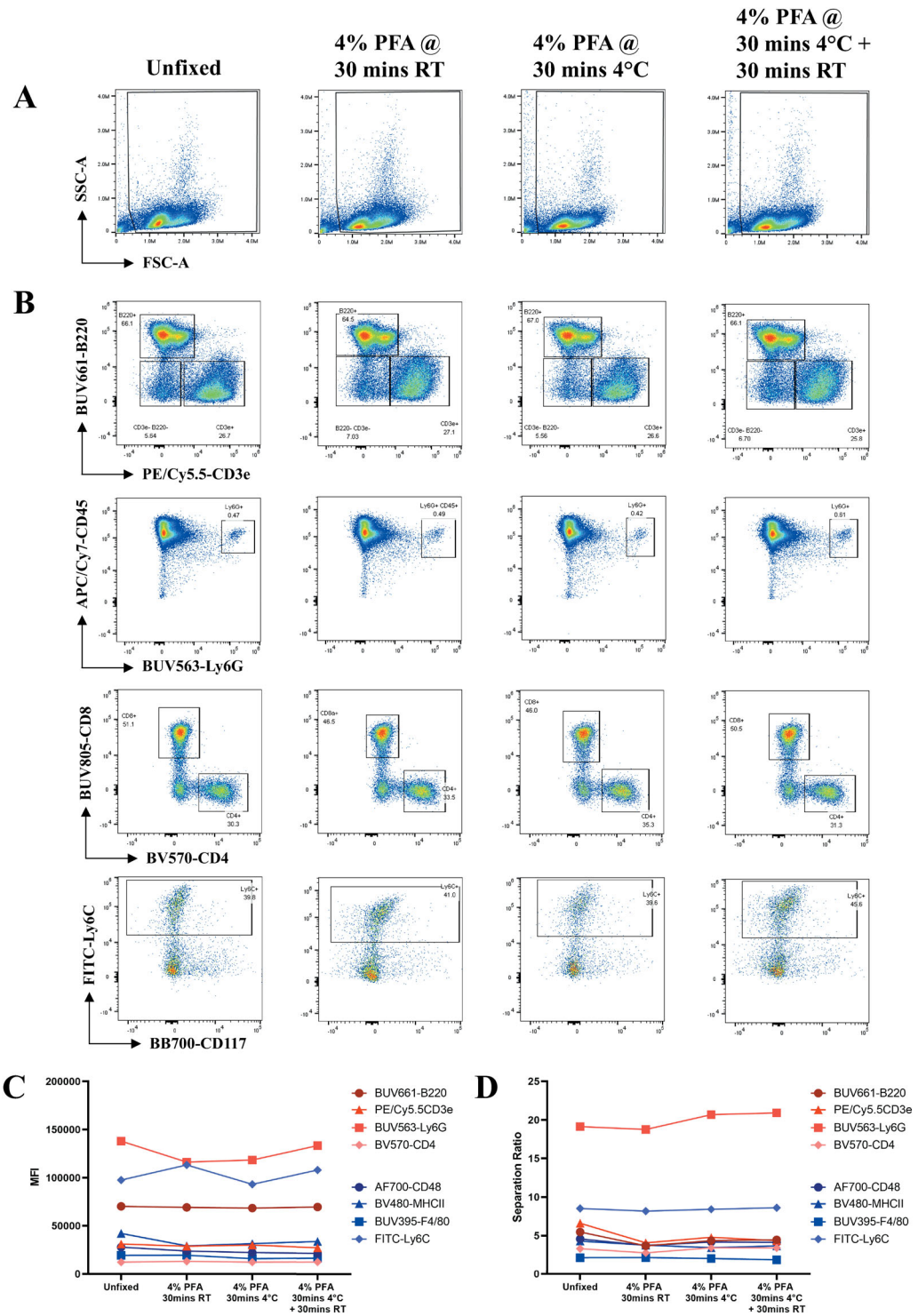

FIGURE 2 Murine spleen cells stained with 25-color high-dimensional panel and treated with four differing fixation protocols: Unfixed, fixed with 4% formaldehyde solution at room temperature for 30 min (4% PFA @ 30 min RT), fixed with 4% formaldehyde solution at 4°C for 30 min (4% PFA @ 30 min 4°C), or fixed with 4% formaldehyde solution at 4°C for 30 min followed by 30 min at room temperature (4% PFA @ 30 min 4°C + 30 min RT). After fixation, cells were washed and immediately acquired on a spectral cytometer, Cytek® Aurora (Cytek® Biosciences, Freemont, CA). The effect of the fixation was examined on (**A**) the forward versus side scatter plots (FSC-A vs SSC-A), (**B**) population identification, separation, and signal resolution of specific immune cell populations, (**C**) the median fluorescence intensity (MFI) of the positive population of single (blue) and tandem (red) fluorophores, and (**D**) the separation ratio between the positive and negative populations of single (blue) and tandem (red) fluorophores. Note: That autofluorescence was not used as a separate parameter for spectral unmixing [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 3 Example placement of a 3-laser benchtop analyzer inside a Class II Biological Safety Cabinet [Color figure can be viewed at wileyonlinelibrary.com]

continued certification. The need for such a set-up is limited and unlikely to be necessary for many SRLs if other measures can be effectively implemented.

3.3 | Instrument Waste

Inactivation of instrument waste is an important consideration for SRLs. Recommendations state that waste containers should hold enough bleach to result in a "10% final concentration of bleach" when the waste tank is full (26, 34). Local regulations and institution guidelines vary considerably and must be considered when developing a protocol for biohazardous waste disposal (54). A number of publications detailing wastewater pathogen inactivation are available and may be used as a guide when developing local protocols (54–59). It should be noted that the stability of bleach is impacted by a number of factors including, but not limited to, pH, temperature, exposure to light, and dilution (59). The management of waste in SRLs should be structured to ensure that waste is exposed to bleach for a sufficient period of time, at an adequate concentration of free chlorine (55). In some situations, such as in BSL-3 laboratory waste streams, autoclaving flow cytometry waste may be considered (26). However, this introduces some complexity due to the potential generation of hazardous gases, such as from wastewater containing formaldehyde or bleach solutions (60).

4 | CONCLUSION

The SRL is a hub for scientific activity, creating a centralized resource that investigators rely on for specialized equipment and technical expertise. The ability to pivot operational structures in response to a pandemic, communicate changed practices, and facilitate continued access has played an essential role not only for research in general, but also in developing our understanding of SARS-CoV-2. Every day we are seeing the emergence of new COVID-19 research, bringing with it potential changes in our understanding and subsequent changes to the safety measures implemented by SRLs. Biological safety assessment needs to consider not only samples and reagents but also the SRL staff, users and visitors as potential risks. Ensuring and maintaining adherence to standard precautions at all times while working within the SRL space will significantly reduce the risk for each individual and subsequently to the wider research community with whom they associate.

The ability of an SRL to rapidly respond to the emergence of a new pathogen centers on having established biological safety assessment procedures in place (3, 25, 34), along with a human risk assessment (Appendix). At this time, literature is starting to form a consensus around the stability and inactivation of SARS-CoV-2 (14, 16–18, 38–40, 43–45, 50). Exactly how these inactivation methods are applied in SRLs will relate directly to the sample type and the level of risk posed. Samples infected with cultured virus should be treated with significant caution, followed by SARS-CoV-2 positive human tissues known to generate propagative virus, and then those tissues not known to carry propagative virus (34, 61–70). Standard precautions apply to all human samples, with a biological safety assessment utilized to help guide the application of additional control measures relative to the local context (1) (Supporting Information Table S1).

Facilitating a safety conversation with users should be the foundation of safety within the SRL. Engaging those who must practice safety measures in the SRL space in these conversations encourages ownership and supports a culture of safety (1). Once a biological safety assessment (Figure 1) and human risk assessment (Appendix) has been completed and measures put in place, it is then the role of the SRL to ensure effective communication, and thus supports users in their ability to comply with these measures. Communication is the key component in ensuring safety during a pandemic.

ACKNOWLEDGMENTS

This research was supported in part by the Intramural Research Program of the NIH, National Institute of Allergy and Infectious Diseases.

AUTHOR CONTRIBUTIONS

Avrill Aspland: Conceptualization; project administration; supervision; writing-original draft; writing-review and editing. **Iyadh Douagi:** Conceptualization; project administration; supervision; writing-original draft; writing-review and editing. **Andrew Filby:** Conceptualization; project administration; supervision; writing-original draft; writing-review and editing. **Evan Jellison:** Conceptualization; project administration; supervision; writing-original draft; writing-review and editing. **Lola Martinez:** Conceptualization; project administration; supervision; writing-original draft; writing-review and editing. **Diana Shinko:** Data curation; formal analysis; visualization. **Adrian Smith:**

Conceptualization; project administration; supervision; writing-original draft; writing-review and editing. **Vera Tang:** Conceptualization; project administration; supervision; writing-original draft; writing-review and editing. **Sherry Thornton:** Conceptualization; project administration; supervision; writing-original draft; writing-review and editing.

ORCID

Avrill M. Aspland https://orcid.org/0000-0001-7406-0645
Iyadh Douagi https://orcid.org/0000-0002-3221-8667
Andrew Filby https://orcid.org/0000-0001-9078-4360
Adrian L. Smith https://orcid.org/0000-0002-0505-0344

REFERENCES

1. Kaufman SG. *Prepare and Protect: Safer Behaviors in Laboratories and Clinical Containment Settings*. Newark: ASM Press, 2020.
2. Van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N England J Med* 2020;*382*:1564–1567.
3. Schmid I, Merlin S, Perfetto SP. Biosafety concerns for shared flow cytometry core facilities. *Cytometry Part A* 2003;*56A*:113–119.
4. Budd J, Miller BS, Manning EM, Lampos V, Zhuang M, Edelstein M, Rees G, Emery VC, Stevens MM, Keegan N, et al. Digital technologies in the public-health response to COVID-19. *Nat Med* 2020;*26*: 1183–1192.
5. Mehring WM, Poksay A, Kriege J, Prasannappa R, Wang MD, Hendel C, Hochman M. Initial experience with a COVID-19 web-based patient self-assessment tool. *J Gen Intern Med* 2020;*35*: 2821–2822.
6. Cheng HY, Shu-Wan J, Ding-Ping L, Ta-Chou N, Wan-Ting H, Hsien-Ho L. Contact tracing assessment of COVID-19 transmission dynamics in Taiwan and risk at different exposure periods before and after symptom onset. *JAMA Intern Med* 2020;*180*(9):1156–1163.
7. Filby A, Haviland D, Jones D, Bedoya Lopez A, Orlowski-Oliver E, Rieger A. Modifying regulatory practices to create a safe and effective working environment within a shared resource laboratory (SRL) during a global pandemic. *Cytometry Part A* 2020.
8. Daniels K, Conway A, Gardner R, Martinez L, Price K, Schneider S, Sheridan R, Srivastava J, Thornton S. SRL staff and user training in a global pandemic. *Cytometry Part A* 2020.
9. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hosp Infect* 2020;*104*:246–251.
10. US EPA O. List N: Disinfectants for use against SARS-CoV-2 (COVID-19). US EPA 2020. Available at: https://www.epa.gov/pesticide-registration/list-n-disinfectants-use-against-sars-cov-2-covid-19. Accessed August 28, 2020.
11. Australian Government Department of Health Therapeutic Goods Administration. Therapeutic Goods Administration (TGA). Ther. Goods Adm. TGA 2020. Available at: https://www.tga.gov.au/. Accessed August 27, 2020.
12. European Chemicals Agency. ECHA. 2020. Available at: https://echa.europa.eu/en. Accessed August 27, 2020.
13. European Centre for Disease Prevention and Control. Disinfection of environments in healthcare and non-healthcare settings potentially contaminated with SARS-CoV-2. Eur. Cent. Dis. Prev. Control 2020. Available at: https://www.ecdc.europa.eu/en/publications-data/disinfection-environments-covid-19. Accessed August 27, 2020.
14. Chan K-H, Sridhar S, Zhang RR, Chu H, Fung AY-F, Chan G, Chan JF-W, To KK-W, Hung IF-N, Cheng VC-C, et al. Factors affecting stability and infectivity of SARS-CoV-2. *J Hosp Infect* 2020;*106*:226–231.
15. Ijaz MK, Whitehead K, Srinivasan V, McKinney J, Rubino JR, Ripley M, Jones C, Nims RW, Charlesworth B. Microbicidal actives with virucidal efficacy against SARS-CoV-2. *Am J Infect Control* 2020; *48*:972–973.
16. Meyers C, Kass R, Goldenberg D, Milici J, Alam S, Robison R. Ethanol and isopropanol inactivation of human coronavirus on hard surfaces. *J Hosp Infect* 2020;107:45–49. http://dx.doi.org/10.1016/j.jhin.2020.09.026.
17. Welch SR, Davies KA, Buczkowski H, Hettiarachchi N, Green N, Arnold U, Jones M, Hannah MJ, Evans R, Burton C, et al. Inactivation analysis of SARS-CoV-2 by specimen transport media, nucleic acid extraction reagents, detergents and fixatives. *J Clin Microbiol* 2020. Available at: http://jcm.asm.org/content/early/2020/08/21/JCM.01713-20.
18. Li Y, Leung GM, Tang JW, Yang X, Chao CYH, Lin JZ, Lu JW, Nielsen PV, Niu J, Qian H, et al. Role of ventilation in airborne transmission of infectious agents in the built environment a multidisciplinary systematic review. *Indoor Air* 2007;*17*:2–18.
19. Pantelic J, Tham KW. Assessment of the mixing air delivery system ability to protect occupants from the airborne infectious disease transmission using Wells–Riley approach. *HVACR Res* 2012;*18*: 562–574.
20. Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Shünemann HJ. COVID-19 Systemic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet* 2020;*27*: 1973–1987.
21. Verma S, Dhanak M, Frankenfield J. Visualizing droplet dispersal for face shields and masks with exhalation valves. *Phys Fluids* 2020;*32*: 91701.
22. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 guideline for isolation precautions: Preventing transmission of infectious agents in health care settings. *Am J Infect Control* 2007;*35*:S65–S164.
23. Iwen PC, Stiles KL, Pentella MA. Safety considerations in the laboratory testing of specimens suspected or known to contain the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Lab Med* 2020;*51*:239–242.
24. Pambuccian SE. The COVID-19 pandemic: Implications for the cytology laboratory. *J Am Soc Cytopathol* 2020;*9*:202–211.
25. Holmes KL, Fontes B, Hogarth P, Konz R, Monard S, Pletcher CH, Wadley RB, Schmid I, Perfetto SP. International Society for the Advancement of cytometry cell sorter biosafety standards. *Cytometry Part A* 2014;*85A*:434–453.
26. Perfetto SP, Hogarth PJ, Monard S, Fontes B, Reifel KM, Swan BK, Baijer J, Jellison ER, Lyon G, Lovelace P, et al. Novel impactor and microsphere-based assay used to measure containment of aerosols generated in a flow cytometer cell sorter. *Cytometry A* 2019;*95*: 173–182.
27. World Health Organization. Laboratory biosafety guidance related to coronavirus disease (COVID-19). 2020. Available at: https://www.who.int/publications-detail-redirect/laboratory-biosafety-guidance-related-to-coronavirus-disease-(covid-19). Accessed August 27, 2020.
28. Centers for Disease Control and Prevention. *Interim Laboratory Biosafety Guidelines for Handling and Processing Specimens Associated with Coronavirus Disease 2019 (COVID-19)*. Atlanta: Centers for Disease Control and Prevention, 2020.
29. ABSA International Emerging Infectious Diseases Consortium. *Considerations for Handling Potential SARS-CoV-2 Samples*. Mundelein: ABSA International, 2020.
30. Reifel KM, Swan BK, Jellison ER, Ambrozak D, Baijer J, Nguyen R, Monard S, Lyon G, Fontes B, Perfetto SP. Procedures for flow cytometry-based sorting of unfixed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected cells and other infectious agents. *Cytometry Part A* 2020;*97A*:674–680.

31. Carson CF, Inglis TJ. Air sampling to assess potential generation of aerosolized viable bacteria during flow cytometric analysis of unfixed bacterial suspensions. *Gates Open Res* 2018;*1*:2.
32. Evans MR, Henderson DK, Bennett JE. Potential for laboratory exposures to biohazardous agents found in blood. *Am J Public Health* 1990;*80*:423–427.
33. Schmid I, Kunkl A, Nicholson JKA. Biosafety considerations for flow cytometric analysis of human immunodeficiency virus-infected samples. *Cytometry* 1999;*38*:195–200.
34. Centers for Disease Control and Prevention. 1994 revised guidelines for the performance of CD4+ T-cell determinations in persons with human immunodeficiency virus (HIV) infections. 1994. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00030802.htm. Accessed August 27, 2020.
35. Kap M, Arron GI, Loibner M, Hausleitner A, Siaulyte G, Zatloukal K, Murk J-L, Riegman P. Inactivation of influenza a virus, adenovirus, and cytomegalovirus with PAXgene tissue fixative and formalin. *Biopreserv Biobank* 2013;*11*:229–234.
36. Sagripanti J-L, Eklund CA, Trost PA, Jinneman KC, Abeyta C, Kaysner CA, Hill WE. Comparative sensitivity of 13 species of pathogenic bacteria to seven chemical germicides. *Am J Infect Control* 1997;*25*:335–339.
37. Kariwa H, Fujii N, Takashima I. Inactivation of SARS coronavirus by means of povidone-iodine, physical conditions and chemical reagents. *Dermatology* 2006;*212*:119–123.
38. Rabenau HF, Cinatl J, Morgenstern B, Bauer G, Preiser W, Doerr HW. Stability and inactivation of SARS coronavirus. *Med Microbiol Immunol (Berl)* 2005;*194*:1–6.
39. Jureka AS, Silvas JA, Basler CF. Propagation, inactivation, and safety testing of SARS-CoV-2. *Viruses* 2020;*12*(6):622. http://dx.doi.org/10.3390/v12060622.
40. Pastorino B, Touret F, Gilles M, Luciani L, de Lamballerie X, Charrel RN. Evaluation of chemical protocols for inactivating SARS-CoV-2 infectious samples. *Viruses* 2020;*12*(6):624. http://dx.doi.org/10.3390/v12060624.
41. Chua J, Bozue JA, Klimko CP, Shoe JL, Ruiz SI, Jensen CL, Tobery SA, Crumpler JM, Chabot DJ, Quirk AV, et al. Formaldehyde and glutaraldehyde inactivation of bacterial tier 1 select agents in tissues. *Emerg Infect Dis* 2019;*25*:919–926.
42. Darnell MER, Subbarao K, Feinstone SM, Taylor DR. Inactivation of the coronavirus that induces severe acute respiratory syndrome, SARS-CoV. *J Virol Methods* 2004;*121*:85–91.
43. Gamble A, Fischer RJ, Morris DH, Yinda KC, Munster VJ, Lloyd-Smith JO. Heat-treated virus inactivation rate depends strongly on treatment procedure. *bioRxiv* 2020. Available at: http://biorxiv.org/lookup/doi/10.1101/2020.08.10.242206.
44. Chin AWH, Chu JTS, Perera MRA, Hui KPY, Yen H-L, Chan MCW, Peiris M, Poon LLM. Stability of SARS-CoV-2 in different environmental conditions. *Lancet Microbe* 2020;*1*:e10.
45. Kwon E, Minhas V, Phiri T, Wood C, Swindells S, Hunsley BA, Fernando MR. Inactivation and viral load quantitation of human immunodeficiency virus in blood collected into Cyto-Chex® BCT blood collection device. *J Virol Methods* 2014;*196*:50–55.
46. Möller L, Schünadel L, Nitsche A, Schwebke I, Hanisch M, Laue M. Evaluation of virus inactivation by formaldehyde to enhance biosafety of diagnostic electron microscopy. *Viruses* 2015;*7*:666–679.
47. Nicholson JK, Browning SW, Orloff SL, McDougal JS. Inactivation of HIV-infected H9 cells in whole blood preparations by lysing/fixing reagents used in flow cytometry. *J Immunol Methods* 1993;*160*:215–218.
48. Pawar SD, Murtadak VB, Kale SD, Shinde PV, Parkhi SS. Evaluation of different inactivation methods for high and low pathogenic avian influenza viruses in egg-fluids for antigen preparation. *J Virol Methods* 2015;*222*:28–33.
49. Patterson EI, Prince T, Anderson ER, Casas-Sanchez A, Smith SL, Cansado-Utrilla C, Solomon T, Griffiths MJ, Acosta-Serrano Á, Turtle L, et al. Methods of inactivation of SARS-CoV-2 for downstream biological assays. *J Infect Dis* 2020;*222*:1462–1467.
50. Sagripanti J-L, Hülseweh B, Grote G, Voß L, Böhling K, Marschall H-J. Microbial inactivation for safe and rapid diagnostics of infectious samples. *Appl Environ Microbiol* 2011;*77*:7289–7295.
51. Ashhurst TM, Cox DA, Smith AL, King NJ. Analysis of the murine bone marrow hematopoietic system using mass and flow cytometry. *Methods Mol Biol* 2019;*1989*:159–192.
52. Mariotti S, Pardini M, Teloni R, Gagliardi MC, Fraziano M, Nisini R. A method permissive to fixation and permeabilization for the multiparametric analysis of apoptotic and necrotic cell phenotype by flow cytometry. *Cytometry Part A* 2017;*91A*:1115–1124.
53. Holmes KL. Characterization of aerosols produced by cell sorters and evaluation of containment. *Cytometry Part A* 2011;*79A*:1000–1008.
54. Richardson S, Plewa M, Wagner E, Schoeny R, Demarini D. Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: A review and roadmap for research. *Mutat Res Mutat Res* 2007;*636*(1-3):178–242. http://dx.doi.org/10.1016/j.mrrev.2007.09.001.
55. Kim BR, Anderson JE, Mueller SA, Gaines WA, Kendall AM. Literature review—efficacy of various disinfectants against Legionella in water systems. *Water Research*, *2002*;*36*(18):4433–4444. http://dx.doi.org/10.1016/s0043-1354(02)00188-4.
56. Gallardo VJ, Schupp DA, Heckman JL, Krishnan ER, Rice EW. Inactivation of bacillus spores in wash waters using dilute chlorine bleach solutions at different temperatures and pH levels. *Water Environ Res* 2018;*90*:110–121.
57. Muhammad N, Gallardo VJ, Schupp DA, Krishnan ER, Minamyer KS, Rice EW. Inactivation of Bacillus spores in decontamination wash down wastewater using chlorine bleach solution. *Can J Civ Eng* 2014;*41*:40–47.
58. Örmeci B, Linden KG. Comparison of UV and chlorine inactivation of particle and non-particle associated coliform. *Water Supply* 2002;*2*:403–410.
59. Rutala WA, Weber DJ. Uses of inorganic hypochlorite (bleach) in health-care facilities. *Clin Microbiol Rev* 1997;*10*:14.
60. Hadar J, Tirosh T, Grafstein O, Korabelnikov E. Autoclave emissions—Hazardous or not. *J Am Biol Saf Assoc* 1997;*2*:44–51.
61. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, Niemeyer D, Jones TC, Vollmar P, Rothe C, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020;*581*:465–469.
62. Zheng S, Fan J, Yu F, Feng B, Lou B, Zou Q, Xie G, Lin S, Wang R, Yang X, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ* 2020;*369*:m1443.
63. Remmelink M, De Mendonça R, D'Haene N, De Clercq S, Verocq C, Lebrun L, Lavis P, Racu M-L, Trépant A-L, Maris C, et al. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. *Crit Care* 2020;*24*:495.
64. Chang L, Zhao L, Gong H, Wang L, Wang L. Severe acute respiratory syndrome coronavirus 2 RNA detected in blood donations. *Emerg Infect Dis* 2020;*26*:1631–1633.
65. Pham TD, Huang C, Wirz OF, Röltgen K, Sahoo MK, Layon A, Pandey S, Foung SK, Boyd SD, Pinsky BA. SARS-CoV-2 RNAemia in a healthy blood donor 40days after respiratory illness resolution. *Ann Intern Med* 2020;*173*(10):853–854. http://dx.doi.org/10.7326/l20-0725.
66. Andersson M, Arancibia-Carcamo CV, Auckland K, Baillie JK, Barnes E, Beneke T, Bibi S, Carroll M, Crook D, Dingle K, et al. SARS-CoV-2 RNA detected in blood samples from patients with COVID-19 is not associated with infectious virus. *MedRxiv* 2020.

Available at: http://medrxiv.org/lookup/doi/10.1101/2020.05.21.20105486.
67. Walsh KA, Jordan K, Clyne B, Rohde D, Drummond L, Byrne P, Ahern S, Carty PG, O'Brien KK, O'Murchu E, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. *J Infect* 2020;*81*:357–371.
68. Cento V, Colagrossi L, Nava A, Lamberti A, Senatore S, Travi G, Rossotti R, Vecchi M, Casati O, Matarazzo E, et al. Persistent positivity and fluctuations of SARS-CoV-2 RNA in clinically-recovered COVID-19 patients. *J Infect* 2020;*81*:e90–e92.
69. Zhu N, Wang W, Liu Z, Liang C, Wang W, Ye F, Huang B, Zhao L, Wang H, Zhou W, et al. Morphogenesis and cytopathic effect of SARS-CoV-2 infection in human airway epithelial cells. *Nat Commun* 2020;*11*:3910.
70. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* 2020;*323*:1843–1844.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Aspland AM, Douagi I, Filby A, et al. Biosafety during a pandemic: shared resource laboratories rise to the challenge. *Cytometry*. 2021;99:68–80. https://doi.org/10.1002/cyto.a.24280

APPENDIX: EXAMPLE RISK ASSESSMENT FOR POSSIBLE SARS-COV-2 INFECTED USER

This procedure has been developed as an illustrative example to help aid in the assessment of new risks that are now being experienced. Consideration needs to be given to the local context in which this will be applied, including: regional regulation, prevalence of the agent (e.g., SARS-CoV-2), the number of users moving through the space, what measures can be implemented effectively, etc.

Agent Description

Agent: SARS-COV-2
Origin: 2019–2020 pandemic
Susceptible host: Human—all staff, users, and visitors
Disease: COVID-19
Route of transmission: Aerosol, direct contact, fecal-oral, percutaneous
Infectious dose: Unknown
Agent stability: Varies. 3 days up to 28 days depending on surface type
Concentration: Unknown
Work performed at: Physically distant BSL2
Any additional information: Risk assessment assumes that prolonged exposure to infected individuals increases the likelihood of infection. In human populations, infected individuals may shed virus while remaining asymptomatic. Severe risk of illness exists for older adults, people with asthma, or other serious underlying medical conditions (especially those that affect the heart and lungs).

Procedure

Procedures and research goals: Safely open an SRL to provide users adequate access to highly specialized equipment and expert service.
Genetically modified pathogen? No
Containment level for all life cycle stages? All life cycle stages of the agent, including prior to disease onset, may result in high virus shedding. PPE including barriers, gloves, safety glasses, and masks must be used to prevent unintended exposure.
Containment breach: In the event of breach of containment or exposure to an infected individual, the local environment should be immediately cleared of all personnel for aerosol evacuation, followed by surface decontamination. Personnel should be equipped with full PPE as listed above prior to engaging in decontamination.
Pre-treatments and inactivation prior to disposal: Contaminated surfaces must be inactivated with an effective disinfectant for an appropriate length of time, for example, EPA-registered disinfectant active against SARS-CoV-2.
Laboratory testing: Molecular testing is available for SARS-CoV-2 detection in humans.
Environmental disinfection for SRL: EPA-registered disinfectant active against SARS-CoV-2 and accepted by instrument manufacturers will be used. Specifically, any high use areas will be routinely disinfected with 80% Ethanol by wiping with a saturated paper towel and allowing the area to air dry.

Safety Controls

Biosafety level practices: Users entering the facility shall participate in the institution's contact tracing and COVID-19 self-monitoring programs. Users will be allowed to operate instrumentation on an individual basis followed by surface disinfection. All users are required to wear masks and wash hands prior to operating instrumentation. Gloves are highly recommended. Consecutive users shall be separated by a minimum of 15-min intervals to allow aerosols to disperse and limit user–user contact.
Engineering controls: Masks, gloves, safety glasses, and plastic barriers placed between instruments in close proximity.
Clothing: Dedicated laboratory clothing, and dedicated laboratory shoes are recommended.

Personal protective equipment: Approved face mask appropriately fitted, gloves, clean laboratory coat, and safety glasses.

Personnel trained on associated hazards: Mandatory training on how to work with the potentially-infected users is required for all facility staff prior to commencement of research.

Personnel experience: SRL Staff are highly trained to work and adapt in an ever-changing world.

Medical surveillance: SRL staff will monitor incoming users and themselves for symptoms of COVID-19. Symptoms include fever, dry cough, fatigue, and shortness of breath but can also sometimes include headache, aches and pains, sore throat, nasal congestion, runny nose, and loose stool. Identification or self-reporting of any of these symptoms must be conveyed to the appropriate authority.

Region monitoring: Researchers from high risk regions will be asked to transport samples via courier to be run by SRL staff rather than attending the facility in person.

Incident reporting: Anyone experiencing symptoms should alert the laboratory director as well as institutional authority. If infection is confirmed by molecular testing, contact tracing of SRL users for up to 3 days prior to an individual's symptom onset should occur.

Vaccinations: None available

Post-exposure treatment: Contact your medical provider. Infected workers shall quarantine for a recommended period. Exposed individuals should continue to monitor for symptoms and should quarantine as recommended by the local authorities.

Surveillance practices: Users who develop symptoms must immediately report to the laboratory director and institutional authority.