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The COVID-19 pandemic: Implications for the cytology laboratory

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Review/Editorial

Title: The COVID-19 pandemic: Implications for the cytology laboratory

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Abstract

The coronavirus disease 2019 (COVID-19) is a pandemic with the SARS-CoV-2 virus. The infection has predominantly respiratory transmission and is transmitted through large droplets or aerosols, and less commonly by contact with infected surfaces or fomites. The alarming spread of the infection and the severe clinical disease that it may cause, have led to the widespread institution of social distancing measures. Due to repeated exposure to potentially infectious patients and specimens, healthcare and laboratory personnel are particularly susceptible to contract COVID-19. This review paper provides an assessment of the current state of knowledge about the disease and its pathology, and the potential presence of the virus in cytology specimens. It also discusses the measures that cytology laboratories can take to function during the pandemic, and minimize the risk to their personnel, trainees and pathologists. In addition, it explores potential means to continue to educate trainees during the COVID-19 pandemic.

At the time of the writing of this review, the COVID-19 pandemic, caused by a novel coronavirus, has already affected over 350,000 people in 192 countries and territories, and killed over 15,000 people worldwide. The number of cases reported worldwide and in the United States increase daily at an alarming rate, in part as a consequence of more widespread testing. As the fears of a global coronavirus COVID-19 pandemic, a disease caused by the SARS-CoV-2 virus continue to grow, the cytology laboratory must also brace itself to continue to offer the best service to patients, while in the same time protect its technicians, technologists, trainees and pathologists.

Recently, a series of public health measures have been taken to reduce the spread of the disease. These “social distancing” measures vary somewhat by state and city but are generally wide-ranging. They include cancelling sports, music, cultural and even political events, and the closing of gyms, schools and colleges, recommendations to work from home, to avoid discretionary travel, to avoid eating or drinking in bars, restaurants and food courts, and avoid social gatherings in groups of more than 10 people. This situation is not unprecedented, although the 100-year-old precedent is mostly forgotten. During the 1918-19 H1N1 "Spanish" influenza pandemic, which infected a fifth to a third of the world population, and during which 50 million people have died worldwide[1, 2], including an estimated 675,000 Americans, the United States has adopted a range of nonpharmaceutical (public health) interventions. These measures, which were similar to those currently adopted, included closure of schools and churches, banning of mass gatherings, mandated mask wearing, case isolation, and disinfection/hygiene measures[3]. However, these measures were not implemented at the same time or for the same duration in different cities, nor were they uniformly followed. A recent analysis concluded that in some cities (San Francisco, St. Louis, Milwaukee, and Kansas City), where the measures were implemented early, they reduced transmission rates by up to 30–50%[3]. Cities that implemented such measures earlier had greater delays in reaching peak

mortality, and had lower peak mortality rates and lower total mortality[4]. The duration that these "social distancing" measures were kept in place correlated with a reduced total mortality burden[4]. Although we still have no known effective therapy or vaccine prevention for this coronavirus, and the world is a quite different place than it was 100 years ago, the efficacy of the measures instituted during the 1918-19 pandemic gives us hope that the current measures will also limit the impact of the COVID-19 pandemic.

Because it is caused by a novel virus, the current pandemic has created plenty of anxiety, much of it due to the understandable fear of the unknown. We do not know how long this pandemic will last, and what its toll on communities will be in terms of fatalities, psychological, physical and economic well-being. Mathematical models using available data predict widely different outcomes, but worst-case scenarios, which have to be taken into account, predict the potential for millions of infected patients with an unacceptably high number of fatalities. The problem with such modelling is not only that different models make different projections, but that the basic assumptions about the virus, based on which these models were developed are far from certain. This is especially true for the two most basic values that predict the spread and impact of a virus: its basic reproductive number (R0) and its case fatality rate (CFR). The basic reproductive number (R0) is the number of secondary cases that one case would produce in a susceptible community. The value of R0 usually decreases during an outbreak of infection, as the susceptible population decreases, and measures to prevent the transmission are established. R0 values over 1 indicate a propensity for the infection to spread, while R0 lower than 1 indicate that the infection is likely to die out. The other important number is the CFR, which is calculated by dividing the number of deaths caused by the disease by the number of patients affected with that disease. For COVID-19, this number also varies greatly and is impacted by under-testing, the under-reporting of mild and asymptomatic cases, and the focus on more severe cases. This may be, at least in part, the reason why the CFR is much higher in studies from the Wuhan

province, where it was 2.3%, than in studies from elsewhere in China that show a CFR around 1%[5]. The case fatality rate is usually quoted to be around 2% and is similar in China[6], Iran[7] and Italy[8]. However, it varies between 0.25% and 3%, and lower estimates may be closer to the true value[9, 10]. The estimated infection fatality risk (IFR), i.e. the risk of death among all infected individuals (including those with no apparent disease) is 0.3% to 0.6%, which is comparable to the Asian influenza pandemic of 1957–1958[11]. However, other influenza pandemics had very different mortality rates and ranged from 0.001–0.007% for the 2009 H1N1 influenza to estimates ranging from 0.5 to 3%[12, 13] for the 1918 influenza pandemic. The high mortality rate of the 1918 influenza pandemic was related only in part to the pathogenicity of the virus itself, and the cytokine storm that it produced. Important contributors were the context in which the 1918 pandemic occurred, at the end of World War I, with overcrowded barracks, poverty, poor nutrition, poor hygiene, household/community-level crowding, lack of preparation of the population and decision-makers due to cognitive inertia[14], and poor medical and insufficient nursing care.

The case fatality rate also depends on the affected population, and is higher in hospitalized patients (4.3%)[15], in male patients (4.5% compared to 1.3% in female patients), in older patients (5.3% in patients ≥ 60 years compared to 1.4% in those < 60 years), and in patients with cardiovascular, diabetic and chronic respiratory comorbidities[16]. Given the fact that it appears that both the generally accepted R0 and the CFR are most likely overestimated, the impact of the pandemic may be severe, but will not attain the levels predicted in worst-case scenarios.

At this time, we still have many unanswered questions about this virus. For some of these questions we may not have answers based on hard data for months to come, maybe until the epidemic is over and an analysis of the worldwide data can be performed. However, even before we have all the answers, we should *neither panic, nor treat it too lightly.* We have to *"keep calm and carry on*" and continue to function as a cytology laboratory dedicated to provide

the best service to our patients in this health care emergency, but in the same time maximize the safety of health care workers and prevent unnecessary risks, which could help the dissemination of the virus.

Notwithstanding our imperfect understanding of the SARS-CoV-2 infection, we can summarize what we know from the current COVID-19 outbreak in China and the lessons from other outbreaks of severe respiratory diseases caused by coronaviruses. These include the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome-related coronavirus (MERS-CoV). SARS-CoV, SARS-CoV-2 and MERS-CoV, are all members of betacoronavirus genus While SARS-CoV has about 80% sequence homology with SARS-CoV-2, MERS-CoV has only about 50% sequence homology with SARS-CoV-2. These differences, as well as differences in the source of infection and cellular receptors for coronavirus, make the SARS outbreak a source of more relevant information to the COVID-19 pandemic than the MERS outbreaks. The other human coronaviruses, including the two alphacoronaviruses (HCoV-229E and HCoV-NL63) and two other betacoronaviruses (HCoV-OC43 and HKU1) do not appear to relate to the COVID-19, as these viruses continually circulate worldwide causing mild respiratory infections ("common cold") in adults and children.

Coronaviridae got their name from the club-shaped protein spikes on their surface, which give the appearance of a crown or "corona" in the two-dimensional image of transmission electron microscopy. They are rather large (120 nm) enveloped positive-sense single-stranded RNA viruses. Their specific tissue tropism, infectivity and species range are conferred by the spike protein, which interacts with a specific cell receptor. In the case of SARS-CoV and SARS-CoV-2, the receptor for the virus is the angiotensin-converting enzyme 2 (ACE2) receptor on ciliated bronchial epithelial cells, whereas for MERS-CoV, the receptor is DPP4/CD26 on nonciliated respiratory epithelial cells.

The fact that the receptor for SARS-CoV and SARS-CoV-2 is ACE2, a protein with a wide species distribution, may explain the observed cross-species transmission[17], as both SARS-CoV and SARS-CoV-2 viruses appear to have originated from animals. They derive most likely from bats, the mammals with the highest diversity of coronaviruses. The transmission may have resulted through the intermediary of civets, the pangolin, or other animals. This is supported by the fact that SARS-CoV-2 has a remarkable 96% genetic homology to a bat coronavirus[18], and a 99% sequence homology with a coronavirus from the pangolin species[6]. MERS-CoV, probably also originated from bats[17], but the intermediate hosts are the dromedary camels. Camel to human transmission of MERS-CoV may occur through contact with camels, unpasteurized camel milk and medicinal use of camel urine[19], but human to human transmission of the virus also occurs and has been documented in healthcare workers[20]. MERS has a much higher case fatality rate of about 35% for the 2,500 patients with clinical infections[21, 22]. All three diseases (SARS, MERS and COVID-19) have similar, but not identical, clinical manifestations, spanning the entire range from mild flu-like symptoms to severe pneumonia and acute respiratory distress syndrome. COVID-19 presents more frequently with lower respiratory system symptoms, including chest tightness, dry cough and dyspnea, and less commonly with gastrointestinal symptoms, like nausea vomiting and diarrhea.

While statistics usually include only patients who were tested for the disease because they were symptomatic and presented to their physician or health care facility, the infection is most likely much more prevalent, if one considers asymptomatic or subclinical infections. A recent study showed that 0.2% of healthy adult blood donors in Saudi Arabia have specific antibodies against MERS-CoV, suggesting the existence of a large number of asymptomatic or mild infections, which may act as an unrecognized source of infection[22]. Similar high numbers of asymptomatic or minimally symptomatic infections have probably occurred during the SARS epidemic. Although the exact incidence of such asymptomatic infection remains unknown, a meta-analysis of SARS data showed overall seroprevalence rates of 0.1% for the general population and

0.23% for health care workers[23]. It is therefore very likely that, when the dust has settled and serologic testing of populations exposed to SARS-CoV-2 is performed, we will realize than asymptomatic or subclinical cases of COVID-19 are much more common than clinical cases and may have played an important role in the spread of the disease.

SARS was a new human disease that first occurred in Southern China in the November 2002 and has apparently disappeared since 2003, but not before it had spread to 29 countries affecting 8098 people and resulting in 774 fatalities. Compared to SARS, COVID-19 appears to be much more widespread but less deadly. The case-fatality rate (CFR) of SARS was much higher than that of COVID-19, about 10%, compared to 2.3% for COVID-19[16]. The overall transmissibility of SARS was relatively low, with the basic reproductive number (R0) of around 3, i.e. one case would produce three secondary cases of disease in a susceptible community. However, this number was in large part determined by the much higher transmissibility in the hospital setting (R0 = 4). In the community setting, R0 of SARS was much lower, and may have even been less than 1, after the initiation of transmission control measures[24].

The most common form of spread of the SARS-CoV-2 causing COVID-19 has been from human to human transmission in settings that frequently involve close and prolonged (15 minutes or more) interaction between infected and uninfected people, facilitating large droplet and contact transmission. After exposure to an infected individual, or less likely a contaminated surface or fomite, the mean incubation period of COVID-19 is about 5 days, but can be much longer, up to 24 days. Nonetheless, 95% of patients who develop clinical disease do so within 12.5 days. The initial presentation is with fever (90-96% of cases[15]) and mild to severe respiratory symptoms including cough in 70%, dyspnea in 45%, and muscle soreness or fatigue in 40%[15]. 10% of patients or less have sore throat, headaches or diarrhea[25]. Imaging findings are usually those of pneumonia, with bilateral pulmonary infiltrates in 97% of cases[15] Compared to other pneumonias, COVID-19 pneumonia more frequently is more likely to have a peripheral

distribution, ground-glass or fine reticular opacities, and is less likely to have a central involvement, pleural effusion or lymphadenopathy[26]. Laboratory findings are nonspecific but usually include leukocytosis with lymphopenia, mildly increased liver enzymes, muscle enzymes, myoglobin, and LDH and increase in acute phase reactants. Increased procalcitonin, severe lymphopenia and elevated D-dimers were features that correlated with more severe disease. In severe cases, the disease may progress to respiratory, circulatory and renal failure, and ultimately death due to multiorgan failure.

A metaanalysis of 50 466 hospitalized patients showed that 18% had severe disease and 15% developed acute respiratory distress syndrome (ARDS)[15]. Among the cases reported to the World Health Organization (WHO), 3% were critical, 15% severe, and 82% were mild[27]. This distribution of cases shows that COVID-19 is on average less severe than the SARS, in which the majority of patients had moderate to severe disease, and 20%–30% required intensive care including mechanical ventilation. In the COVID-19 outbreak in China, the duration of viral shedding ranged from 8 to 37 days. Survivors had a median duration of viral shedding of 20 days, but viral shedding continued until death in fatal cases[28].

Due to the respiratory tissue and cell tropism seen in early infection, the virus can be isolated from saliva, nasopharynx and lower respiratory tract specimens. However, in advanced or severe cases, viral RNA can be found in the plasma of 15% of patients and may be found in feces, raising the possibility of fecal transmission. Since the receptor for SARS-CoV-2, ACE2, is also expressed on cardiac myocytes and vascular endothelial cells, the virus could, at least theoretically, directly involve the heart and vascular endothelium. This would explain the fulminant myocarditis that some patients clinically[29, 30], or show myocardial interstitial mononuclear inflammatory infiltrates. However, to date, no studies have been performed on cardiac tissue to determine the presence of the virus. Involvement of endothelial cells may be

implicated in the pathogenesis of the severe complications of the disease, including diffuse alveolar damage (DAD) and disseminated intravascular coagulation.

Based on the limited evidence available to date, the pathology of COVID-19 is similar to that of SARS and MERS[31, 32], which, in severe or fatal forms show lung injury in varying stages of exudation and organization[32]. These include acute fibrinous and organizing pneumonia, and diffuse alveolar damage, characterized by hyaline membrane formation, interstitial lymphocytic infiltrates, and desquamation of pneumocytes. In lung tissue, in situ hybridization and/or immunohistochemical stains demonstrated the presence of the virus in the cytoplasm of epithelial cells of the trachea (over 50% of ciliated cells), bronchi, and bronchioles, and in pneumocytes, both intact and degenerated, desquamated or forming syncytial giant cells[33]. They were also present in the lymphocytes located in the septal infiltrates and within blood vessels. The SARS virus could also be demonstrated in circulating lymphocytes and less frequently in monocytes. At autopsy, the virus was also found in the epithelial cells of the intestinal mucosa and distal renal tubules, and the neurons of the brain[33].

Superimposed infections with bacterial (*Pseudomonas aeruginosa, Staphylococcus aureus*), fungal (*Aspergillus* and *Mucor* species) and viral (cytomegalovirus, CMV) pathogens can occur as complications of severe lung disease[32, 34]. In some of these cases, especially those with associated bronchopneumonia, intraalveolar neutrophils may predominate. Lymphoid organs may show lymphoid depletion and the liver may show microvesicular steatosis, while the gastrointestinal tract and kidneys show no specific pathologic changes[35].

The few reports documenting the findings of COVID-19 show that the pathology is dominated by pulmonary findings, including pulmonary edema and prominent proteinaceous exudates, vascular congestion, and intraalveolar fibrinoid material and various degrees of organization

(fibroblastic plugs) corresponding to acute pulmonary injury patterns. In addition, there may be reactive type II pneumocyte hyperplasia, and atypical enlarged pneumocytes with large nuclei, amphophilic granular cytoplasm, and no definite intranuclear or cytoplasmic viral inclusions were identified[36, 37]. The inflammatory infiltrate is predominantly lymphocytic without significant neutrophil participation[38]. Immunohistochemistry for the Rp3 NP protein of SARS–CoV-2 showed staining of alveolar epithelial cells, including the damaged, desquamated cells present within alveolar spaces[39], but viral protein expression was only minimal in endothelial cells. This finding is similar to that seen in MERS, where immunohistochemistry with four antibodies against MERS-CoV showed the presence of the virus scattered in cytokeratin-staining pneumocytes and syncytial cells, but not in CD68-positive macrophages[40].

SARS-CoV-2 and the Cytology Laboratory

Our response to the COVID-19 pandemic can be regarded at the society level, the hospital level, laboratory level and the individual level. At the society level, local, state and federal governments have instituted travel bans, and either governments or various organizations have introduced restrictions or cancelled larger gatherings, including sports events and cultural events (music, theater, cinema), and even political rallies. These measures are meant mostly as a mitigation strategy, to limit transmission, and to prevent the fast spread of the virus and "level the infection curve" to prevent overwhelming of the health care system.

At the level of hospitals and other health care institutions, decisions are made to prioritize the essential health care work and reduce elective outpatient visits and inpatient admissions for elective interventions or operations. These measures are meant both to decrease the risk of infection to patients with routine annual and preventive health visits and elective procedures; and to increase the available capacity of the hospitals in case of a large surge of infections[41].

The abovementioned hospital measures to limit activities that can be safely postponed will undoubtedly affect the cytology laboratory, which will receive fewer specimens. This gives the cytology laboratory an opportunity to re-evaluate their staffing needs and maybe change the workflow. Measures may include working in shifts, and staggered meal breaks, to avoid contact between people, and having only the strictly necessary in the laboratory. A paper from Singapore advises that laboratory personnel should record their temperature twice a day, to allow early identification of COVID-19, but in the current US context it is uncertain if this measure, and especially the ensuing measures, including viral testing, isolation and quarantine measures are feasible and practical. Clearly, any person having respiratory symptoms that could be caused by COVID-19 should not come to work and should instead consult their physician or health care professional. Emergency plans and contingency plans should be made for the possibility that a large proportion of the laboratory personnel has either fallen ill or is under quarantine. Communicating any changes or delays in service to the clinical service providers and departments is particularly important, to avoid overwhelming the laboratory with inquiries about test results.

The role of the cytology laboratory in a patient with known COVID-19 is limited. In analogy to the role of the cytology laboratory in SARS, it is mainly to rule out superimposed pulmonary infections in sputum and other respiratory specimens. The cytologic features seen in sputa are nonspecific and reflect the underlying acute pulmonary injury pattern. They consist of the presence of increased number of macrophages, forming loose macrophage aggregates. The macrophages may also show cytoplasmic changes, including the presence of foamy cytoplasm or larger cytoplasmic vacuoles or nuclear changes, including multinucleation and ground glass appearance of nuclei[42]. Since bronchoalveolar lavage (BAL) fluid is sometimes obtained for viral identification[43-45] and is occasionally positive when nasopharyngeal and oropharyngeal swab

samples are negative[46], an aliquot may also be sent to the cytology laboratory. However, the cytologic findings of BAL samples of patients with COVID-19 were not yet reported. In patients with MERS, cytological examination of BAL fluid reportedly showed high numbers of neutrophils and macrophages[47]. Based on the histopathology of SARS, MERS and COVID-19, BAL specimens may also show squamous metaplasia, and features of repair, which together with the presence multinucleated cells and highly atypical alveolar type 2 pneumocytes showing cellular and nuclear enlargement, prominent nucleoli and chromatin clearing.[34] These cytomorphologic features may represent a potential diagnostic pitfall.

Laboratory measures (see Table 1)

Given the extraordinary fast spread of the disease and the pace of change in the information about it and guidelines on how to deal with various aspects of fighting it, one can only give general suggestions for the cytology laboratory's response. The recommendations are similar to those given for general and histopathology laboratories[48-50], but also include the situations in which cytology laboratory personnel is involved either in the care of patients potentially infected with SARS-CoV-2 during FNA procedures or rapid-onsite evaluation of aspiration or core biopsies or in the preparation of fresh specimens from such patients.

Although the situation is fluid and guidelines can change, making it imperative to keep up to date with high quality information and guidance from web sites like https://www.coronavirus.gov or https://www.nih.gov/coronavirus, as the pandemic unfolds, I believe the some general principles can be applied.

1. Use universal precautions

   While it is important to know which cytology specimens can contain viable and therefore transmissible virus, it is important to emphasize the use of universal standard precautions when dealing with any cytology specimen. From the experience with SARS

we can extrapolate that SARS-CoV-2 can be present in fecal and urine samples, in addition to peripheral blood and respiratory samples. SARS-CoV-2 may be present in samples in patients without known COVID-19, in undiagnosed patients, in pre-symptomatic patients, in patients with asymptomatic or minimally symptomatic infections, and in convalescent patients, who may still be shedding the virus. From the available data it is very likely that many, if not most, infections occur through contact with individuals who either don't have the disease or were not diagnosed with COVID-19. In addition, as with most specimens, the clinical diagnosis may not be indicated in the requisition. For all these reasons, all fresh specimens should be considered potentially infectious.

2. Special precautions should be taken handling specimens the preparation of which involves steps that can lead to aerosol formation. All technical procedures should be performed in a way that minimizes the generation of aerosols and droplets. Preparatory steps that may generate aerosols or droplets include expelling aspirates from the needle or syringe, smearing the aspirated material, and potentially air-drying or heat drying the smears, in which pathologists, trainees or cytotechnologists may be involved during rapid on site evaluation (ROSE). Air-drying or heat drying of smears is best performed under Class II Biosafety Cabinets (BSC)[51]. Agitating the smears by hand or using hand-held fans to speed up the drying of smears should be avoided. ROSE is an important measure to ensure the adequacy of specimens. However, during an epidemic of a virus with respiratory-transmission, like SARS-CoV-2, clinical judgement should be used to determine if ROSE is absolutely necessary for the success of the biopsy procedure. If ROSE is performed, it should be performed with appropriate personal protective equipment (PPE) including gloves, laboratory coat/gown and goggles or face shields for eye protection and respiratory protection using a properly fit-tested filter respirator (N-95

or higher level) or a powered air-purifying respirator (PAPR). The anticipated shortage of facemasks and filter respirators[52], makes a very selective use of this procedure important, as it is vital that we reserve this equipment for essential patient encounters and procedures. For similar reasons, it may be safer to suspend the activity of a pathologist-run FNA Clinic for the duration of the pandemic, and consider performing FNAs only on a case-by-case basis, weighing the risks and benefits of the procedure for each patient.

Cytopreparatory steps performed by technicians that can lead to aerosol/droplet formation include opening of containers and removing tube caps, blending, vigorous shaking or mixing, vortexing, pipetting, aliquoting, diluting or centrifugation of fluids and discarding the supernatant. All these cytopreparatory steps should be performed in Class II BSC, providing protection for the user, the sample, and the environment. The use of PPE, including gloves, gown, and face shield are also recommended for these procedures. Splash shields, sealed centrifuge rotors or sample cups are recommended for centrifugation; rotors and cups should be loaded and unloaded in a BSC[51].

3. The virus is inactivated by formalin and gamma irradiation. Therefore, according to the Centers of Disease Control and Prevention (CDC) guidelines[51], cytology laboratory activities, such as the pathologic examination and processing of formalin-fixed or otherwise inactivated tissues (cell block preparations), and the routine staining and microscopic analysis of fixed smears are assigned biosafety level 2 (BSL-2). This is the typical biosafety level of all pathology laboratories and is assigned when working with agents associated with human diseases that pose a moderate health hazard or when working with any human-derived sample, including blood, body fluids, or tissue, in which the presence of an infectious agent is unknown. Most cytology specimens are fixed in

either formalin or alcohol solutions with over 70% alcohol, which are considered effective to destroy this virus. It is not known if fixatives using much weaker alcohol solutions, such as PreservCyt® and CytoLyt® (Hologic, Inc. Marlborough, MA) and SurePath® (Becton, Dickinson and Company, Franklin Lakes, NJ) are adequately inactivating the virus. Therefore additional precautions, like the use of gloves may be indicated while handling and interpreting cytologic preparations processed with these fixatives. Some pathologists may prefer using gloves for all their slides, since glass slides are touched by multiple hands until they reach the pathologist's desk, and cannot be easily decontaminated. Although dipping the slides in 95% alcohol (or similar) for a couple of minutes would inactivate the virus, it would also erase the marks ("dots") on the slides. Other surface disinfectants, especially ones with short contact times, as mentioned below, can be tried to determine the practicality of their use on cytology slides.

4. General safe laboratory practices, especially procedures that are basic to good microbiological practices and procedures should be followed as recommended by the World Health Organization (WHO)[53] and the CDC[51, 54]. This includes training all personnel in the use of the protective equipment, limiting access to the laboratory, frequent handwashing, and wearing personal protective equipment (PPE). Handwashing should be performed thoroughly with soap and water for at least 20 seconds. Alternatively, an alcohol-based hand sanitizer containing at least 62% alcohol can be used, if soap and water are not available. The use of PPE includes wearing gloves for all procedures, wearing a buttoned lab coat or gown, eye protection and, when needed, wearing a mask. Touching mucosal membranes of the eyes, nose and mouth should be avoided. In addition, because the virus can remain viable on surfaces (especially plastic and stainless steel surfaces) for up to 72 hours[55], it is recommended to decontaminate all work surfaces multiple times per day, using EPA approved disinfectant solutions, wipes, towelettes or sprays. In addition to benches, this includes

decontamination of computer keyboards, phones, and frequently touched areas of microscopes. The chemical substances involved include, among others, ethanol (minimum concentration of 62%–71%), 0.5% hydrogen peroxide, quaternary ammonium, sodium hypochlorite (0.1%), and a variety of acid solutions in various concentrations. These substances should be used with the manufacturer-recommended disinfection directions and preparations for Human Coronavirus and the recommended contact time (i.e. the time the surface remains wet) which may range from 30 seconds to 10 minutes[56].

Educational measures in academic institutions (see Table 2)

Academic institutions should temporarily suspend, limit or move online activities involving over 10 people, such as lectures, Grand Rounds presentations, journal clubs, etc. Residents and fellows can be taught by using online lectures and unknown sessions using digitized slides and by facilitating and encouraging self-directed learning. Sign-out with trainees could be performed on a digital platform such as Zoom (Zoom Video Communications, Inc. San Jose, CA), although it might significantly slow the sign out. Finally, if allowed by existing rules and regulations, after prior validation, pathologists can sign out a portion of cases on virtual slides (whole slide images, WSI) in institutions equipped with FDA-approved high capacity whole slide scanners. Trainees could also be incorporated into the workflow to preview the WSI. It is obvious that most if not all of us have little experience with online teaching and the use of videoconferencing technologies for teaching pathology. Therefore, during these unprecedented times, we have to constantly seek to improve the delivery of online training by keeping in touch with colleagues using similar technologies and adopting or adapting the strategies that work best. Seeking feedback from trainees is essential, not only to assess the impact of the online teaching, but also to get advice on the use of technologies that the trainees may be more familiar with.

Communication

It is important to address the fact that this epidemic will unavoidably generate stress, fear and anxiety among the entire laboratory personnel, trainees and pathologists[57, 58]. Psychologic stress may be experienced differently by different people, and may be modulated by personal factors like age, sex, health status, baseline anxiety level and risk perception. More severe psychologic distress may be followed by increased levels of posttraumatic stress symptomatology[59]. Psychological distress may be related to increased work load due to co-worker absenteeism, lack of socialization with friends and colleagues, lack of recreational activities due to the closure of gyms, restaurants, movie theaters and other recreational avenues, and increased family stress and parenting issues due to children being at home as a result of school closings. It may also relate to having a friend or family member affected by the disease. All healthcare workers may also feel anxious and stressed due to the fear of contracting the disease, fear of transmitting the disease to members of the family, or financial fears related to the changes implemented during this period. During this period, laboratory directors and other pathologists should be prepared to provide up to date information regarding the most recent developments in our knowledge about the disease and candid information regarding all aspects of the personnel's job. Although such information may also be available from a variety of sources, including the CDC and the health care center's website, in order to alleviate the fear and anxiety, it is important to have clear channels of communication, transmit the information in person, and respond to any questions that may arise. Providing emotional support and an opportunity to discuss any personal and family concerns is crucial during these times. It is very important to communicate effectively the risk to laboratory personnel and trainees, without overly reassuring them, and acknowledging that a lot is unknown about this infection. It is equally important to communicate any changes in policy or schedule as soon as possible[60]. If physical meetings are not possible because of the social distancing measures

implemented, web-based conferences using a variety of platforms can be used. This can include SMS text messages, e-mails, using both institutional and personal email, if needed, small group discussions, and websites, in addition to online discussion through apps such as Skype or Microsoft Teams (Microsoft Redmond, WA), FaceTime (Apple Inc, Cupertino, CA), GoToMeeting (LogMeIn, Inc. Boston, MA), Zoom (Zoom Video Communications, Inc. San Jose, CA), Webex (Cisco Webex, Milpitas, CA), etc.

It is crucial to ensure efficient and redundant channels of communication, including lower-tech solutions to ensure the access of health care workers with all levels of technological skills and savviness. Remember that it may be difficult to access to the organization's intranet and email from home, and access to high-speed internet may be an issue too. When using any of these means of communication that are not secure or HIPAA compliant, use the same basic principles governing the use of social media[61, 62], i.e. do not use any specific patient information or data about the number or severity of patients treated at the health care center.

Finally, in addition to these measures meant to prevent infection in the workplace, all pathologists, trainees, cytotechnologists and laboratory personnel should also apply common-sense measures to prevent getting infected outside the laboratory environment. This may include, in addition to personal hygiene measures (handwashing, avoiding touching eyes, nose and mouth), "social distancing", avoiding close contact with other people, and, if possible, avoiding public transportation, avoiding crowds and gatherings of over 10 people, avoiding contact with people who might be sick (i.e. people having fever and respiratory symptoms).

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Table 1. Laboratory Measures

- Review your procedures and reduce or eliminate steps that could result in aerosol formation or creation of droplets
- Review the indications for rapid onside evaluations (ROSE), and reassess their need after discussions with the provides requesting these services to; eliminate unnecessary exposure
- Establish a chain of command, emergency plan and contingency plan
- Reassess the situation weekly or biweekly and make any changes necessary
- Implement measures to reduce crowding: review staffing and realign staffing needs with the workload; consider working in shifts to reduce overlap
- Follow CDC/WHO guidelines for routine specimen processing in accordance to biosafety level 2 guidelines
- Process all specimens that have steps that could result in aerosols or droplets (including making smears, staining them and air-drying or heat fixing them), in a Class II Biosafety Cabinet (BSC).
- Follow any additional or updated CDC guidelines
- Keep informed about the latest developments regarding the COVID-19 pandemic and inform the staff about any new scientific knowledge, dispel misconceptions
- Keep informed about the newest hospital policies and procedures and inform the staff of any changes
- Keep open communication channels with colleagues and staff and provide a virtual community through daily "fireside chats" including people working from home

- Don'ts
- Don't cause unnecessary concerns or panic, but be frank about the risks
- Don't disseminate or endorse rumors or information not coming from a reputable source (CDC, FDA, WHO, peer-reviewed publication)

Table 2. Educational measures: Dos and Don'ts for teaching/training residents and fellows

Dos

- Cancel educational session involving over 10 people, such as lectures, Grand Rounds presentations, journal clubs, etc.
- Limit face to face activities such as lectures or sign-out session in a multiheaded microscope
- Consider moving to sequential viewing of slides rather than "double-head" scoping or review
- Move online learning such as using online lectures and unknown sessions using digitized slides
- Make sure that trainees have access to the technologies used even from home
- Encourage and facilitate self-directed learning
- Identify "teachable moments" in your daily work and share them with the trainees
- Give brief "teaching points" summaries for more unusual or difficult cases
- Give mini-assignments; consider giving mini-quizzes
- Consider setting up discussion groups ("fireside chats") to maintain a sense of community
- Encourage questions and be accessible to provide answers
- Give regular and meaningful feedback; be as specific as possible
- Ask for informal feedback and try to make any changes suggested
- Use the best tools or platforms available for online teaching, reevaluating them frequently
- Keep up with developments in online teaching and adopt best practices for distance learning
- Keep in touch with your colleagues and adopt the techniques that work
- Consider providing an online "office hour", and to be available to answer trainees questions during this time
- Check on the mental and physical well-being of your trainees

Don'ts

- Don't abandon teaching during this undetermined period of time
- Don't forget about trainees working from home
- Don't use any protected patient information during teaching unless using an institution-approved VPN or a HIPAA compliant platform

Highlights

No highlights are required as this is not a research article, per
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