REVIEW ARTICLE

Mini Review on Laboratory Practices During Covid-19 Pandemic: From Microbiologists Perspective

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ABSTRACT

Laboratory practices in a laboratory have changed worldwide due to the emergence of the COVID-19 pandemic. The changes occur concerning specimen collection, handling, transportation, processing, and disposal. Infection control practices are applied in all aspects, starting from specimen collection until the clinician gets the results. A retrospective review of laboratory practices used in a tertiary teaching hospital laboratory from microbiologists' perspectives was performed, and the practices were compared with previously published articles.

Keywords: Laboratory practices, Microbiologists, SARS-CoV-2, COVID-19

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INTRODUCTION

SARS-CoV-2, like a virus under the β-coronavirus genus under the family of Coronaviridae, is an enveloped virus with an estimated length of 26-32 kilobases. As this virus was discovered in December 2019, the disease it caused was named Coronavirus disease -19 (COVID-19). It is currently causing outbreaks worldwide and causes significant mortality. To date, it has infected millions of people and caused significant mortality (1).

Transmission of SARS-CoV-2 is via respiratory droplets and close contacts. According to information gathered by World Health Organization (WHO), transmission from human to human was through respiratory droplets (the size is>5-10 μm in diameter) and direct contact routes with no airborne transmission reported so far (2).

With regards to clinical management of COVID-19, World Health Organization (WHO) has classified the disease severity into five categories; mild, moderate, and severe pneumonia, a critical disease with acute respiratory distress syndrome (ARDS), and critical disease in sepsis or septic shock (3)(4). In Malaysia, COVID-19 infections were staged clinically into five; asymptomatic, symptomatic without pneumonia, symptomatic with pneumonia, pneumonia requiring supplemental oxygen, and critically ill patients with multiorgan involvement (5). Since asymptomatic COVID-19 patients can transmit the disease, this staging system is taken into account to identify early stage of infection, contact tracing and public health preventive measures.

After full genome sequencing of SARS-CoV-2 shared by WHO and GISAID, validated real-time reverse transcription-polymerase chain reaction (qRT-PCR) is developed and considered a gold standard method in detecting SARS-CoV-2.(6) It is a highly sensitive and specific test for virus detection in the early phase of the illness. However, the process, right from sorting the samples, virus deactivation, extraction, and PCR itself, roughly took about six to seven hours. The method also depends on staff efficiency and time required for extraction, either manual or automated. However, recently, the US Food Drug and Administration has approved a rapid molecular COVID-19 detection kit that uses isothermal amplification. Using this kit, neither the RNA extraction process nor thermal cycler is needed, and it will shorten the turnaround time by half (7).

A new circular from MOH Malaysia has listed recommended kits for antigen, antibody, and RT-PCR that have passed the Medical Device Authority (MDA) requirement in December 2020. (8) Regarding antibody testing, SARS-CoV-2 IgM in the blood was detected approximately 7-14 days from symptoms' onset, followed by IgG around 10-21 days of illness (9). The advantages of antibody testing are cheaper cost, available in quick test form, and ability to identify past infection in an individual not previously diagnosed with SARS-CoV-2.(10) However, it may miss early COVID-19

disease when an antibody is not produced yet.

Even though previously there is no treatment approved for COVID-19 infection (11), however, approval of remdesivir on 22nd October 2020 by the US FDA gives light for patients 12 years and above, with the weight of at least 40 kilograms and COVID-19 adult patients requiring hospitalization (12)(13). Currently, clinical trials are on-going to find the potential therapies for COVID-19, such as using favipiravir, lopinavir-ritonavir, and antimalarials (chloroquine and hydroxychloroquine). Adjunctive medicines such as corticosteroids, anti-cytokine, or immune-modulatory agents, and immunoglobulin therapy are also under investigation for potential treatments in treating COVID-19 patients (11). Several vaccine candidates are still under investigation to determine the vaccine's safety profile and the vaccine's potential to activate an immune response in respective volunteers (14).

This review aims to share the changes in laboratory practices in laboratory preparation, preanalytical, analytical, and post-analytical aspects in response to pandemic COVID-19 disease. We also compare and contrast the methods with the recommended guidelines.

LABORATORY PREPARATION

In our hospital, a clinical microbiologist is in charge of an infection control unit. Our responsibility is to advise on general workflows of biochemistry, anatomical pathology, and haematology units in this situation. Guidelines were provided by Infection Control Unit, lead by a clinical microbiologist. General guidelines on donning and doffing of Personal Protective Equipment (PPE), handling possible infectious body fluids from patients, and safety precautions in aerosolized generating procedures (AGPs) in the laboratory were also provided. Several meetings were conducted when the first wave of COVID-19 hit Malaysia in February 2020. Several aspects, including Standard Operating Procedures (SOPs) development, team segregations (human resources), online educational talks, and COVID-19 testing, have been discussed. Clinical microbiologists, scientists, and medical laboratory technologists (MLTs) were divided into four main groups; one group for risk management, one group for technical aspects of PCR, one group for recruiting of staff and training purposes, and the last group for ensuring the current services offered in microbiology laboratory are still running and meet the turn around time of the respective tests.

For the risk management group, two clinical microbiologists work hand in hand as leaders. We have to identify the suitable laboratory, facilities, and types of equipment needed, workflow from specimen receipt until sample disposal, donning and doffing personal protective equipment (PPE), wastes disposal management, and cleaning of the environment and work surfaces. Risk management will be further discussed later.

Two scientists, two clinical microbiologists, and science officers chose and tested several kits for extraction and PCR. Positive control was obtained from a nearby government hospital. Protocols and standard operating procedures (SOPs) for PCR were developed and vetted in the department. Interpretation and troubleshooting of results were taught in several training sessions among science officers, medical officers, and clinical microbiologists.

Medical laboratory technologists (MLTs) were also recruited from other departments. Staff was trained in small groups (four-person per group) to limit the number of staff in the respective lab. A medical representative from the company was invited to provide the training. Besides, MLTs were also sent in batches to national public health laboratory Sungai Buloh and Kota Bharu for training purposes.

Another group is doing the down-scaling of the routine microbiology tests such as serological testing (HIV, Hepatitis B, Hepatitis C, etc.) from three times per week to one to two times per week, depending on the request. Other respiratory specimens, such as sputum culture, broncho-alveolar lavage (BAL) culture, etc., were held until the COVID-19 result available for safety purposes. In terms of training aspects, daily COVID-19 sampling training is carried out with the clinicians, especially on nasopharyngeal and oropharyngeal swabs collection. Besides, concurrent training of COVID-19 testing by the Institute of Medical Research (IMR) and companies providing the test kits were also provided to the science officer and medical lab technologists (MLTs).

To prevent cross-infection among the staff, several preventive measures have been introduced and implemented. A monitoring book with temperature recording has been placed in front of the laboratory counter. The movement of staff in and out of the lab is documented, as it is crucial for contact tracing later. Besides, physical distancing was also applied. Only two people are allowed in confined closed spaces such as in a pantry, prayer room, meeting room, and lecture room at one time. The chairs are arranged 2 meters apart in these confined spaces. Regular cleaning of frequently-touched areas using 70% alcohol (Micozid) was done twice a day.

RISK ASSESSMENT

Risk assessment is critical before setting up a COVID-19 laboratory. It is comprised of workforce, risk characterization, and risk mitigation strategies. We have to identify the personnel suitable for the work, assess the competency, and the personnel at risk to acquire the disease. Besides, we have to identify the hazard,

agent risk group, the potential for exposure (modes of transmission, spillage management), and activities that can increase exposure before evaluating and prioritizing the risk. Then, we have to develop the risk mitigation strategies, including PPE, SOPs, training, and assessment of staff proficiencies. The risks and mitigations strategies need to be communicated to all staff and recorded for reference. After that, the risk mitigation strategies need to be validated after implementation to ensure the effectiveness of the measures.

In terms of risk assessment, a team creates risk assessment SOPs and checklists to set up PCR and rapid test kit antigen facilities. Two assessors were appointed, comprised of an infection control unit team and a clinical microbiologist. Infrastructures, staff, and procedures were assessed for safety.

BSL-2 facilities are adequate for both antigen testing and PCR. The biosafety cabinet was checked to ensure it was working efficiently. The waste management area was also reviewed. Besides, a room for donning and doffing of PPE was also provided. Procedures for bench and workplace disinfection were also checked.

In term of staff safety, staff with comorbidity such as pregnancy was excluded from the team. The number of staff performing the test, donning and doffing PPE, and competency to complete the test were also observed. In terms of procedure, the flow of work from specimen registration until results delivered to the patient was also observed. Laboratory information system (LIS) requirement for providing the result to the clinician was also monitored. Notification of the result to the clinician, managing team, and national laboratory online system (SIMKA) was also observed.

PREANALYTICAL CONSIDERATION ON SAMPLES COLLECTION AND TRANSPORTATION

In a microbiology laboratory, we received various samples from the human body includes blood, respiratory specimens, cerebrospinal fluid, urine, and stool. All these specimens should be regarded as untreated specimens for COVID-19 and need to be handled in Biosafety level-2 (BSL-2) facilities following BSL-3 practices (15).

CDC has described four BSL categories named BSL-1, BSL-2, BSL-3, and BSL-4 (16). Minimum requirements for BSL-1 are handwashing area, laboratory bench, and minimum PPE without biosafety cabinet (BSC). Organisms that can be handled in the BSL-1 laboratory are *E.coli, K. pneumoniae*, and others that unlikely to cause disease. For BSL-2, the general requirement in BSL-1 is needed together with BSC. Organisms that can be handled in the BSL-2 laboratory are Influenza virus, HIV, and others with moderate risk to cause infection. BSL-3 need general requirements in BSL-2 plus double-door access, N95 mask/ respirator, personal shower out, exhaust HEPA filter, and effluent decontamination system. An example of the organism that can be handled in BSL-3 is tuberculosis that can cause aerosol transmission. For BSL-4, BSL-3 is needed together with positive pressure protective suit, physical containment device, chemical shower out, supply, and exhaust HEPA filters. Organisms handled in BSL-4 are exotic, high-risk, life-threatening agents such as Ebola and Marburg virus. SARS-CoV-2 is categorized under Group 3 organisms based on its global spread and mortality lower than Group 4 organisms, such as the Ebola virus (17). Therefore, an attempt to isolate this virus using cell lines needs BSL-3 facilities and trained staff (18). However, BSL-2 facilities are adequate for antigen testing and nucleic acid amplification (NAAT) (18). Recent guideline by WHO stated that point of care (rapid molecular) and quick test kit antigen do not require BSL-2 facilities in a well-ventilated space with full PPE (19).

SARS-CoV-2 has been recovered from upper respiratory specimens approximately 1-2 days before the symptom's onset. The virus's persistence has been seen for up to 7-12 days in moderately severe cases and two weeks for severe cases, respectively (20). According to several studies, apart from respiratory specimens, SARS-CoV-2 has been isolated from blood, stool, and urine specimens (9,21).

Regarding respiratory specimens, a clinician can send either upper (throat, nasopharyngeal swab (NP) oropharyngeal swab (OP), nasopharyngeal aspirate) or lower respiratory tract specimens (sputum, tracheal aspirate, and bronchoalveolar lavage (BAL). Before taking any swabs (nasopharyngeal, nasal, or oropharyngeal) from suspected COVID-19 patients, medical staff must don a full PPE, including a N95 mask/ respirator and face shield. Collection of sputum by hypertonic saline nebulizer, nasopharyngeal or tracheal aspiration, and BAL via bronchoscopy is considered AGPs (22).

In the context of AGPs, the WHO considers 'airborne precautions ' to the medical staff involved (23). If AGPs are needed for sample collection, we strongly encourage healthcare workers to wear full PPE gear, either N95 or powered air-purifying respirators (PAPRs), for respiratory protection. A systematic review showed no difference in either utilizing PAPR or other respiratory equipment (24). Besides, samples must be taken in an adequately ventilated room with minimal staff involved. These practices are currently being implemented in cases of ILI and SARI. All respiratory specimens must be sent in a triple layer packaging, as suggested by WHO (25).

MOH Malaysia is currently trying to use a deep saliva sample for COVID-19 RT-PCR (26). The patient can collect her or his saliva and help reduce the cost of the flocked swab, PPE, thereby reducing the risk of

transmission to healthcare workers. A recent study showed that more SARS-CoV-2 copies detected in saliva compared to nasopharyngeal swab (27) Besides, a review showed that saliva has good performance for the detection of SARS-CoV-2. However, a patient needs to be given education on correct sample collection for sampling. Apart from that, a comparison study must be conducted in a local setting to determine the agreement between the current sampling method with this new sampling method.

Few studies showed that up to 2-3 % of patients diagnosed with COVID-19 might present with diarrhea (28,29). From day five, following the onset of symptoms, viral RNA has also been recovered in faecal samples in up to 30% of patients and has been detected for up to 4-5 weeks in moderately severe cases (30). However, to date, no evidence can correlate viral SARS-CoV-2 RNA in the stool with infectiousness status (31). The faecal-oral route of transmission is questionable even though the live virus has been cultured from stool specimens. However, since the SARS-CoV-2 virus has been detected in urine and stool, both samples must be transported in triple-layer packaging (25).

Before sending the sample, the staff must ensure that the patient's identification is correct both at the sample and form using at least two identifiers such as name and hospital registration number to avoid sample lost or exchanged before specimen packaging. After a laboratory receives the samples, the patient's identification must be rechecked using two identifiers. Any confusion on the patient's label requires clarification with wards or may need a new sampling.

ANALYTICAL CONSIDERATIONS: SAMPLES PROCESSING

There are several problems encountered during specimen processing. Specimen processing starts with specimen sorting, which took about 1-2 hours depending on the amount of specimen and staff available. The team needs to sort the sample before the heat inactivation process and ensure that the specimen was labeled correctly as stated on the lab form. The missing specimen is one of the problems encountered, and staff needs to write a report later to document the incident.

Besides, the discordant result is one of the problems encountered. For example, if either the E gene or the RdRp gene is detected, the extraction needs to be repeated either with manual extraction or new samples before reporting the results.

Nucleic acid amplification test (NAAT) for SARS-CoV-2 detection

a. Virus inactivation

All samples from humans for SARS-CoV-2 detection are subjected to heat inactivation to kill the virus. The clinical samples were incubated in a 1.5ml Eppendorf tube at 65°C for 60 minutes using thermal heat rock to kill all viruses. Lyse buffer (protease) was added to enhance the virus's cell wall's breakdown to release the genomic materials. Then, the samples are safe for nucleic acid extraction. Even though WHO does not recommend heat inactivation before nucleic acid extraction,(6) the practice depends on every center running the test.

b. RNA extraction

Nucleic acid extraction was done manually using the Spinster extraction kit or via automation using Promega or Genolutions Extractor. Manual extraction takes about three to four hours, while an automation extractor takes about half the manual extraction duration.

c. Polymerase chain reaction (PCR)

PCR was carried out using Lytestar™ nCOV RT-PCR Kit 1.0 (Combo E gene and RdRp gene) kit. The target genes used were E-gene for screening and RdRp gene for confirmatory. The CT values cut-off point for positive E-gene was less than or equal to 40, and a positive result will be subjected to confirmatory RdRp gene detection. The CT values cut-off point for a positive RdRp gene was less than or equal to 40. Positive control for both the E gene and the RdRp gene is also included with an internal control (IC). This kit used a heterologous IC for sample preparation (nucleic acid extraction) and PCR inhibition control. There are three thermocyclers used in our laboratories, such as ABI7500, CFX 96, and QuantStudio5, by which the FAM channel is used for the E gene/ RdRp gene and VIC/HEX channel for IC. Two different targets of the COVID-19 virus are used to confirm positive NAAT in line with MOH and WHO, E, and RdRp genes.(6) However, a recent guideline from MOH stated that for rapid molecular tests, only one single confirmatory gene positive (RdRp) is adequate to confirm positive for SARS-CoV-2.(32) Any discordant result needs re-sampling from the patient or repeat extraction from the same sample.

COVID-19 antigen rapid test kit

As Malaysia has already recommended few rapid test kits for diagnosis of COVID-19, we use a kit with the sensitivity of 94.9% in patients exposed within 0-3 days. For samples with a CT value of less or equal to 33, the sensitivity is 94.1%. It is well correlated with several articles that showed CT value of more than 33 is no longer infectious (33,34). However, it is used as a screening and not a confirmatory test unless the prevalence of COVID-19 infection in that area is more than 10%.(35) The advantage of rapid COVID-19 antigen testing is cheaper, faster, needs minimal skill, and can facilitate infection control measures (36).

Other microbiological testing

Before doing specimen processing, laboratory personnel should oblige standard precautions, which comprise hand hygiene and PPE usages, such as lab coats, gowns,

gloves, and goggle-eye protection (37).

As a precautionary measure, after the opening of tertiary containers by laboratory staff, the secondary container must be sanitized with 70% alcohol before touching and transferring the secondary box inside a biosafety cabinet for further processing. Rapid test either immunochromatographic test (ICT) or lateral flow assay for enteric adenovirus or rotavirus detection and processing of stool and urine specimens for bacterial culture should be done inside a biosafety cabinet (BSC). Blood culture bottles need to be sanitized with 70% alcohol before touching and transferring into the BACTEC machine.

In the laboratory, many procedures may create infectious aerosols and droplets. For example, the procedures include pipetting, centrifugation, vortexing, shaking, mixing, removing caps, sonicating, preparing smears, flaming slides, a subculture of blood culture bottles, specimen spillage management, etc. (37). Centre for Disease Control and division (CDC) recommends a Class II Biological Safety Cabinet (BSC) with PPE gear (surgical mask and face shield) for AGPs procedure (38). Centrifugation is one of the most common procedures done in a laboratory. It is a process that can create aerosol. Samples for antigen and antibody testing require centrifugation to get the serum. Our suggestion is to use sealed centrifuge rotors, gasketed safety carriers, or sample cups (39). Filling the centrifuge tubes, loading, and unloading into and from the rotors, and opening the tubes must be done inside a BSC (40)(41). Any laboratory process outside the BSC must consider the safety of the personnel. We recommend one person per day to do centrifugation for all samples and their name recorded in the books for safety purposes. The name list will enable us to track the personnel involved if any breach of procedures occurs.

Few centers that attempted to cultivate SARS-CoV-2 on several cell lines on viral culture, including MDCK, MK2, A549, and Vero E6, showed that the cytopathic effect only observed with the Vero E6 cell line (40,42,43). Besides, one study showed that HEp2 (Human larynx carcinoma cell) and MDCK (Madin-Darby Canine Kidney) cell lines did not support SARS-CoV-2 replication (44). Therefore, continuing our practice using HEp2 and MDCK cell lines to culture other respiratory viruses such as influenza A, influenza B, respiratory syncytial virus, adenovirus, human metapneumovirus, and parainfluenza viruses will not isolate this virus unless a new strain or mutation reported.

Risk assessment procedures must be carried out. In the event of spillage of specimens, emergency precautionary measures must be carried out with the work's station and environmental decontamination. Supervisors and occupational health personnel must be notified. A schedule on staff involved handling samples to detect SARS-CoV-2 or AGPs procedures inside the laboratory must be documented. If the staff caught the virus, he or she might become symptomatic or asymptomatic. Therefore, the exposed laboratory personnel must be monitored and quarantine. Refer to Table I for risks addressed and the mitigation strategies.

Decontamination of work surfaces before and after specimen processing must be done using an appropriate decontamination solution. CDC has released the list of disinfectants approved for the decontamination of work surfaces for SARS-CoV-2 (45). In our center, we used a 70% alcohol solution (Micozid) for surface decontamination. WHO and the Ministry of Health Malaysia have recommended 0.1% sodium hypochlorite as one of the agents apart from 70% alcohol for surface decontamination (46,47). An ice pack used for triple packaging will be left soaked in 0.1% sodium hypochlorite solution. If there is a positive case found, the laboratory will be cleaned with Steriquat disinfectant. Surface screening and air sampling in hospital rooms occupied with infected COVID-19 patients showed that the most likely place to be contaminated was the floor, followed by other types of equipment such as air exhaust vent, bedside locker, and the bed rail (48). Therefore, in the middle of the COVID-19 pandemic, we must ensure these areas (i.e., floor, exhaust vent) are decontaminated regularly. A recent finding showed that the stability of the SARS-CoV-2 is the same as SARS-CoV-1, as it remained viable in aerosols for 3 hours (49). Therefore, laboratory technologists handling any procedures that generate aerosol (i.e., vortexing, centrifugation) need respiratory protection.

POSTANALYTICAL CONSIDERATIONS

CDC has launched an online reporting system to be used in the United States to facilitate COVID-19 disease reporting from healthcare to public health (50). The online reporting system has several advantages: paperless, easily accessible, faster-disseminating information, and more efficient and more straightforward record-keeping (51). However, several challenges are faced, such as system downtime, system investment cost, and data entry (51). Therefore, reporting positive and negative results needs an efficient online system so that MOH Malaysia captures the information.

The negative and positive results will be entered into the hospital Laboratory Information System (LIS). A positive result will be informed to the respective clinician, hospital director, and infection control team immediately. The result will also be conveyed to the Director-General Ministry of Health (MOH) via the nearest public health office (e-COVID notification system) for further actions, public health measures, and contact tracing. The results also entered into the national online Sistem Informasi Makmal Kesihatan Awam (SIMKA) outbreak system, MOH Malaysia for the

Table 1: Risks addressed and mitigation strategies

	Potential risk	Mitigation strategies
General risk	Transmission of SARS-CoV-2 among laboratory personnel	-All staff required to fill in health declaration form prior to entry to the laboratory -Regular cleaning of frequently-touched surfaces using 70% alcohol solution (Micozid) -Limit people in closed confined spaces -Frequent handwashing -Provision of hand sanitizer and infrared forehead thermometer -Documentation of staff movement in and out of the laboratory by provision of book -Staff with respiratory syptoms refered to COVID-19 screening clinic for assessment for testing, treatment or quarantine -Social distancing 2 metres apart -Team segregation -Educational talks via online platform (Webex)
Preanalytical phase	a. Risk of transmission while collecting samples from suspected COVID-19 patients b. Samples leakage during transportation c. Samples from severe acute respiratory infection (SARI) labelled clearly on the blood culture bottle	-Full PPE with respiratory protection (N95) or PAPR if taking sample via AGPs -Transport the specimen in a leak-proof polysterene container or cryobox -Applied triple packaging system with biohazard sticker -Red marker to label all samples drom SARI patients
Analytical phase	a. Samples not identified belonged to SARI patients arrived in the laboratory b. Identification of all procedures that can potentially generate aerosol (i.e: mixing, vortexing, pipetting) c. Surface contamination from specimen spillage	-Full risk assessment conducted in the laboratory. -All samples from SARI patients were kept until the COVID-19 testing turn out to be negative before processing -Spillage decontamination using 70% alcohol solution (Micozid) or 0.1% sodium hypochlorite
Postanalytical phase	Reporting of results	-Negative COVID-19 results conveyed to the clinician incharge immediately online via Laboratory Information system (LIS) -Positive COVID-19 results conveyed immediately to head of department for notification to the Director of Health Malaysia. Clinician was informed immediately for transportation of the patient to the COVID-19 designated hospital gazetted by Ministry of Health.

country daily census by authorized personnel only. The respective patient must be quarantined immediately to the COVID-19 designated hospital. The patient's result will be entered into the SIMKA system (an online course created by MOH Malaysia). It can only be assessed using a password to ensure the confidentiality of the patient's details.

SAMPLES DISPOSAL

Handling laboratory wastes from patients suspected of having COVID-19 infection or confirmed cases is like all other biohazard wastes in the laboratory. To date, no evidence suggesting that neither special additional packaging nor specific disinfection procedures needed for this type of laboratory waste (38). All tested specimens, remaining unprocessed specimens, and PPE have been disposed of into autoclave bags for autoclaving later before being disposed of as clinical waste.

CONCLUSION

In conclusion, these laboratory practices still need to be carried out even though effective treatment and vaccines already available to ensure healthcare personnel and laboratory personnel's safety while handling patient samples. Besides, every laboratory needs to carry out risk assessment procedures. The process starts from accepting the samples, processing the samples, and sample disposal must be discussed earlier with strict standard operating procedures (SOPs) on board. Besides, strict movement of staff, practicing hand hygiene, and social distancing are vital to prevent outbreaks at the workplace.

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