# The Role of Medical Microbiology Laboratories in Health Crisis

## Sağlık Krizinde Tıbbi Mikrobiyoloji Laboratuvarlarının Rolü

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**ABSTRACT** In facing an infectious pandemic, The World is watching for any progress on diagnosis and therapeutics. Clinical microbiology is first in line to detect the emerging trouble and promptly provide the information required to develop appropriate policies. In this review, we discuss the roles and functions of medical microbiology laboratories in facing a global health crisis. Prior to crisis, the laboratory must be prepared for an outbreak, and provide essential elements and comprehensive guidelines regarding validated diagnostic methods. When an outbreak happens, the early identification of causative agent, source of infection and also mode of spread allows for rapid implementation of strict policies and preventative strategies to limit its progress in countrywide. Also, timely recognition, clear and complete information result in public confidence, which is most needed in crisis. Laboratories aim to an urgent understands of antimicrobial susceptibility and also disease process to initiate appropriate treatment. The laboratories also observe appropriate biosafety guidelines, practices and equipment to reduce the exposure of staff and work place to hazardous agents. Finally, once outbreak happens, the medical microbiology laboratory should get involved as soon as possible to help for control of crisis.

**Keywords:** Health crisis; microbiology laboratory; pandemics; outbreak; infectious disease

**ÖZET** Bulaşıcı bir pandemiyle karşı karşıya kalan Dünya, teşhis ve tedavi konusunda herhangi bir ilerleme olmasını beklemektedir. Klinik mikrobiyoloji, sorunun tespit edilmesi ve uygun yaklaşımları geliştirmek için gereken bilgilerin acilen sağlanması noktasında ilk sırada yer almaktadır. Bu derlemede, tıbbi mikrobiyoloji laboratuvarlarının küresel bir sağlık kriziyle karşılaşma durumundaki rollerini ve işlevlerini tartıştık. Kriz öncesi, laboratuvar bir salgın için hazırlıklı olmalı ve geçerli tanı yöntemlerine ilişkin temel unsurları ve kapsamlı kılavuzları sağlamalıdır. Bir salgın meydana geldiğinde, neden olan ajanın, enfeksiyon kaynağının ve ayrıca yayılma şeklinin erken belirlenmesi, ülke çapında yayılımı sınırlamak için katı politikaların ve önleyici stratejilerin hızlı bir şekilde uygulanmasına imkan verir. Ayrıca, zamanında teşhis, açık ve eksiksiz bilgi halkın güveniyle sonuçlanır ki bu bir krizde en çok ihtiyaç duyulan şeydir. Laboratuvarlar, uygun tedaviyi başlatmak için antimikrobiyal duyarlılığı ve de hastalık sürecini ivedi bir şekilde anlamayı amaçlamaktadır. Laboratuvarlar ayrıca personelin ve işyerinin tehlikeli maddelere maruziyetini azaltmak için uygun biyogüvenlik yönergelerini, uygulamalarını ve ekipmanlarını da gözetir. Sonuç olarak, bir salgın meydana geldiğinde, tıbbi mikrobiyoloji laboratuvarı krizin kontrolüne yardımcı olmak için mümkün olan en kısa sürede devreye girmelidir.

**Anahtar Kelimeler:** Sağlık krizi; mikrobiyoloji laboratuvarı; pandemiler; salgın; bulaşıcı hastalık

One of the most important challenges that world encounters in the 21st century, is the global spread of infectious disease due to easy transportation possibilities. A tragedy that may cost millions of lives, greatly damages on national security, and even global economies.[1,2] There have been many considerable health crises recorded in the history, but over the last decades, the number of reported pandemics has increased. In facing an infectious pandemic, The World is watching for any progress on diagnosis and therapeutics.[3] Clinical microbiology laboratories are the first in line to detect the emerging trouble and promptly provide the information required to develop appropriate policies.[3,4]

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The clinical microbiology laboratory is complex and dynamic. It offers a variety of methods for accurate, rapid and consistent identification of microorganisms causing infection. The laboratory plays critical role in the diagnosis of infections caused by bacteria, fungi, viruses, protozoa and parasites. By providing pathogen identification and subsequent susceptibility testing, provides great information for targeted antimicrobial therapy. In addition, it provides periodic reports of antibiotic resistance patterns and reports unusual and increased resistance. The clinical microbiology laboratory is an important member of the infection control team, liable for preventing healthcare associated infections.[5,6] In addition to clinical aspects, microbiology laboratory provides epidemiologic data that is very important in global or country level. It also gathers data on the frequency of infectious disease and assists the hospital infection control epidemiologist in the prevention, detection, and termination of nosocomial outbreaks. The microbiology laboratory is also involved in the investigation of outbreaks. In this review, we discuss the roles and functions of medical microbiology laboratories in facing a health crisis.

## PRIOR TO CRISIS

In the 21st century, outbreaks become global, faster and the epidemics are spreading further than ever.[7] For example, the recent Novel Coronavirus disease (COVID-19) pandemic, according to WHO, made it all the way from China to Africa, Americas, South-East Asia, Europe, Eastern Mediterranean, and Western Pacific, in few months.

Since the pandemic preparedness is not a rapid procedure, the pre-existing facilities will be key factor in reducing the overall burden of pandemics. Long-term preparation before pandemic is essential to ensure that laboratory in all means is strong enough to withstand under disruptive pressure of crisis.[8] The microbiology laboratory's first role is anticipation for the re-emerging or emergence of a new disease. The lab must be prepared for an outbreak, and provide essential elements for prompt practice. These supplies include: equipments, materials, and reagent resources required for appropriate isolation, identification and antimicrobial susceptibility testing. Also, trusted and experienced staff is needed to provide quality-assured results. Pre-training of professionals is critical, since it takes years to educate.[9]

A set of written and step-by-step instructions, Standard Operating Procedures (SOPs), regarding the whole process from receiving and registration of the samples, validated methods, to the analyzing of the results should be prepared to reduce the risk of possible hazards and infection contamination.[10] Having a SOP in place, creates a safer work environment, simplifies the process and helps to complete the practice in the correct way and always in the same manner.[11] Standard Operating Procedures must be available at the place where the work is done and also be available to all laboratory personnel.[11] Moreover, based on lessons learned from previous pandemics, comprehensive guidelines should be intended primarily about already known pandemics, since re-emergence of previous outbreaks may happen or new ones are likely to behave similarly.

The clinical microbiology laboratories play an essential role in the treatment of disease, so have an ethical obligation to provide reliable information. The development of quality improvement programs lead to error-free and high quality results. The periodic laboratory quality control (QC) procedures help to ensure the accuracy of reported test results, and reduce possible laboratory errors, and delayed or incorrect reports.[12] All laboratories should participate in national and\or international external quality assessment programs and also perform appropriate internal QC. The laboratory staff should assure that testing protocols are validated and each step of the testing process is correctly performed. There is also the need to ensure that all materials, reagents, media and equipments are not outdated and meet all quality control standards.[13]

## CRISIS TIME

At the time of pandemic, the laboratory gets involved as soon as possible to determine the organisms causing the trouble, monitors and surveys its circulation among human population.

Identification of the agent is of central importance of pandemic control. Patient replacement precautions and initiating of treatment, primarily relies on detection. Effective response regarding infection prevention and management of pandemic is implemented followed by microorganism recognition.

Since the results accuracy in microbiology entirely depends on quality of specimens, the laboratories provide guidelines around appropriate specimen.[14] Laboratories define the proper type and source of specimen (e.g. midstream urine, nasal swap, stool sample etc.) and appropriate timing of specimen collection (e.g. before antimicrobial therapy or for blood sample in the acute stage of disease). Also, the adequate volume of specimen required for tests, and the correct transportation condition (for example, temperature, transport medium, aerobic or anaerobic condition, specimen container and many other factors) are determined by laboratory director.[15]

Regarding the large number of specimens referred to laboratory during the health crisis, laboratories select rapid, accurate (high sensitivity and specificity), reproducible, and low-cost techniques for specimen processing. Following detection, the laboratory performs antimicrobial susceptibilities to provide sufficient information for prompt antimicrobial treatment.

The staff of a microbiology laboratory provides an interpretation of the results and offers suggestions to physicians. This sense of teamwork and collaborative communication between laboratories, clinicians, epidemiologists, and other health workers help for preferable decisions and improved clinical outcomes.

Reporting of potential concern is of great importance, the acquired information is announced to regional and national health administers and policy-makers to make rational choices. International sharing of constantly updated information speed the provision of life-saving interventions such as diagnostics, therapeutics, and vaccines.[16]

Moreover, the laboratory periodically surveys any changes in antimicrobial susceptibility patterns. Continuous monitoring of the circulation of agent in the population and its susceptibility is considered as a strategy to make proper interventions. Control and surveillance measures are continued although the disease is no longer considered as a public health threat to prevent its re-emergence.

Cooperation of microbiology laboratories with health care providers is essential for surveillance data collection. Laboratories use standardized approaches to provide a full picture of pandemic epidemiology. The timely surveillance data informs about the number of infected cases, severity of pandemic, its progress and how the pandemic is evolving. It is also needed to monitor the potential impact of interventions, and vaccines or therapeutics effectiveness.[17] Recent experience of emerging viral threat, the COVID-19, has underscored the need for implementation of surveillance programs in both national and global levels.[18]

## DIAGNOSIS AND MONITORING

The Medical Microbiology Laboratories and Scientists (MMLS) are responsible for the validation and application of testing methods and vital for the infection disease diagnosis.

### AUTOMATED DIAGNOSTIC METHODS FOR BACTERIAL PATHOGENS

For the diagnosis of bacterial infections, culture-based methods historically have relied manual methods in microbiology laboratory testing. Rapid detection is significantly important in the diagnosis of pathogens and their drug resistance phenotypes. The rapidity detection in culture-based methods have challenged from many decades ago and are associated with the rate of division of the concerned microorganisms. In addition, these methods are basic approaches for each culture-based diagnostic methods such as isolation of mixed-cultures, detection of dominant pathogen in the infection and biochemical and drug susceptibility testing, which relied to achieve results among 2-3 days or longer.[19] In the last decades, automated methods have revolutionized clinical hematology and biochemistry and similar to these methods are largely absent in the most laboratories of clinical microbiology. The advantages of these automated methods include decreased turnaround time, improved standardization, increased capacity and reduced human errors.[20,21] However, these automated instruments typically account for a small fraction of the total work flow, automate a single process or test in a laboratory of clinical microbiology and cannot perform all necessary microbiology testing.[22-25] The automated systems must be flexible enough to collect phases of clinical microbiology laboratory. Laboratories of clinical microbiology receive many of the specimens from a variety of sources such as blood, sputum, urine, stool, cerebrospinal fluid, pus, tissue, bone etc., as well as, these specimens are submitted in different containers with a variety of forms such as swab, jars, tubes with or without medium. In addition, it is necessary to consider that wide ranges of specimens require different processing and incubation techniques. Therefore, there are many challenges in automating culture-based microbiology. However, total laboratory automation (TLA) systems such as Copan's WASPLab and Becton-Dickinson's Kiestra TLA could have an immediate impact on daily efficiency.[25,26] Croxatto et al. study demonstrated that inoculation and transfer of plates by staffs between incubators and benchtops occupied 10% and 33% of time of a technologists, respectively. While, TLA could reduce the hands-on time spent, and quantifying the isolate effect of TLA on efficiency is challenging.[25] A microbiology culture-based automation system is composed components including inoculation unit, track system, incubation system, high-resolution imaging system and work station, which could improve efficiency, reduce time to reporting of microbial growth, enhanced recovery, automated culture interpretation, reduce time to reporting of antimicrobial susceptibility and reduce exposure of technologists by pathogens.[20,21,25-31] Furthermore, there are other instruments, which could help clinical microbiology laboratory to reduce time to reporting, enhance accuracy of diagnosis of pathogens, as well as, can be used for serial identification, detection of patterns of antimicrobial resistance.[32, 33] These instruments are included BD Phoenix Automated, Microbiology System (PAMS, MSBD Biosciences, Sparks, MD, USA), Isoplater (Vista Technology Inc., Edmonton, Alberta, Canada), Isoplater (Vista Technology Inc., Edmonton, Alberta, Canada), BD KIESTRA™ InoqulA+™ (Becton-Dickinson, Dutch), Innova (Becton-Dickinson, Dutch).[34,35]

Owing to virulence of pathogen and existence of resistant pathogen phenotypes, rapid diagnosis of pathogen is important. In addition, some individuals are increasingly vulnerable to infections such as patients with immunocompromising and multi-morbid diseases, patients with implants and other foreign bodies and more elderly patients.

Polymerase chain reaction (PCR) technique was a revolution in detection of pathogens and could help to accelerate in detection of pathogens. PCR-based techniques with higher specificity and sensitivity were achieved for the detection of pathogens, which are fastidious and unculturable pathogens and also can help to detect new and unknown pathogens in crisis such as COVID-19 crisis.[19,35-38] Culture-based methods and PCR technique depending on the indication can contribute synergistically to identify the pathogen, to determine its antimicrobial susceptibility and to define further determinants of pathogens that are in crisis and common daily bench works in the clinical microbiology laboratory. These approaches require expert technicians, expensive materials, exact gene targeting, attention to pre-analytical issues and DNA extraction methods, and advance protocol development.[19,35] Matrix-assisted laser desorption/ionization-time to flight mass spectrometry (MALDI-TOF MS) is another successful systems in clinical microbiology laboratories, which have almost completely replaced culture- and uncultured-based biochemical identification of pathogens and its antimicrobial susceptibility patterns.[19,22] MALDI-TOF MS can increase the accuracy of diagnosis and reduce the time reporting of diagnosis and antimicrobial susceptibility of pathogens in crisis, while this system and other advanced methods such as next generation sequencing (NGS) and gen expert have high initial cost, low support cost by insurance and governments and require network analysis and expert technologists.[19,22,35] If all these new approaches and technologies are optimally embedded in the diagnostic process and paid attention in pre-analytical issues especially times of transport and storage, they will be realizable in practice and crisis.

### DIAGNOSTIC METHODS FOR THE VIRAL PATHOGENS

The medical microbiology laboratories have a critical role on the diagnosis of viral infections. The virus isolation in cell or tissue cultures, electron microscopy, immune fluorescent methods, nucleic-acid amplification assays, sequencing techniques, serological methods for antigen or antibody detection and immune chromatographic tests are commonly used in the diagnostic laboratories. Currently, the most commonly used methods in routine microbiology laboratories are PCR based methods with high sensitivity and specificity rates.[39]

Sequencing of the whole genome of the virus with new generation sequencing systems is very important in terms of determining the evolution of the virus, phylogenetic analysis, development of vaccine and therapy.[2,40]

Serological assay can be used to identify the antibody protein (Immunoglobulin) and can detect the immune response to a specific viral pathogen or vaccine, can investigate herd immunity in the community, identify the severe, mild, asymptomatic and potentially immune individuals, and contribute to the determination of potential plasma donors or development of therapeutic antibodies.

The laboratory monitoring of patients suffered from an infection is another crucial role of a MMLS in a pandemic. Medical microbiologists monitor the progression of disease, respond to antiviral therapy, detect post recovery complications by using laboratory tests with high sensitivity and specificity.[41]

## EARLY DETECTION, EARLY REACTION

### POLICY MAKING

The best chance for combating an outbreak is early detection of underlying agent. Early detection allows rapid containment measures, which are pivotal to reduce the risk of amplification and large scale epidemics. At the onset of an outbreak, laboratories aim for assessment of emerging problem and presenting health data to healthcare services. With the knowledge of type of infectious agent and how the disease is spreading, local and international healthcare organizations take preventative steps to limit its progress. Regarding the lessons from history, it is essential to take primary and strict policies and prevention strategies. Containment regulation is the first step to be taken to restrict the spread of disease across borders and continents.[42] Isolation and quarantine of infected or potentially infected persons is an integral part of control measures that should be implemented once outbreak appears.

In recent outbreak in Wuhan, China, as WHO announced the emergence of Corona virus outbreak, countries have restricted universal travels and trades to avoid importation or further spread of virus. Therefore, the not-yet-affected countries gained time to implement preparedness measures.

### PUBLIC CONFIDENCE

When a pandemic occurs, any initial delay in recognizing will spread false or misleading information, and therefore will cause a serious confusion and panic. Timely recognition, clear and complete information about the outbreak offers a view in the society that health services handle the situation effectively, public trust comes to result, which is most needed in crisis. The rate of adoption of preventative measures in the community significantly relies on society's confidence on health authorities. The epidemiological data emphasize on the importance of social behaviors such as using hand sanitizers, restriction on travels, social distancing, safe burial, and bans on public gatherings on disease spread. Any distrust or hesitancy will result in people's disregard to regulations, which can cause health programs to fail with harmful consequences.

The impact of public trust was obvious during the Ebola epidemic in the Democratic Republic of Congo. Due to the public distrust many people refused to get vaccination, resulting in epidemic's growth. According to WHO, that epidemic killed 2264 with 3444 number of infection cases, so far. By education about the disease and gradual increase of confidence, the epidemic began to come under control.

## IDENTIFICATION OF TRANSMISSION PATTERNS

When a newly emerging agent is identified, the transmission modes are not well recognized. Early and targeted control steps would be implemented if the transmission pattern is understood. Microbiology laboratories explain about the potential origin of emergence and reservoir to control the source of infection. Also, describes around the mode of spread, where and how transmission is taking place to cull of the animal-to-human or human-to-human transmissions. Timely predicting of transmission pattern has a significant impact on reducing the risk of contagion and limiting the outbreak.

## UNDERSTANDING OF CAUSE AND PROCESS

At the beginning of crisis, an early identification of infectious agent and its pathogenesis and progression within host can help to define exactly how the disease develops. Understanding the disease process plays crucial role in reaching a definitive diagnosis, and initiating appropriate treatment. It also avoids unnecessary hospitalization and treatment, results in significant reduced health-care expenditures. In the light of available evidence, many hospitals have indicated that timely diagnosis and assessment of infection can significantly impact morbidity and mortality rates.

## BIOSAFETY

### RISK ASSESSMENT

To deal with biological challenges, the laboratories observe appropriate biosafety practices. Biosafety programs eliminate or reduce exposure of man or environment to hazardous agents.[43] When an outbreak occurs, laboratories define a biosafety level 1 through 4 to the planned work for safe conduct.[44] Risk assessment is the backbone of biosafety practice, but there is not standard approach for its conduction. However, the consideration on the hazardous characteristics of agent, including origin of the agent, natural routes of transmission, the infectious dose and pathogenicity, capability of the agent to infect human or animal host, severity of the disease, and host range, is helpful for professional judgment and assignment of the most appropriate biosafety level.[45] Stability of the agent in the laboratory is also important in risk assessment. When the organism is unknown and there is not enough information available, biosafety level 2 is considered for handling of specimens. Followed by risk assessment, laboratory director provides standard guidelines, and also equipment, facilities, procedures and practices regarding to assigned biosafety level.[45]

### EQUIPMENT AND FACILITIES

Safety equipment and facilities together with adequate procedures and practices help to reduce the potential hazards. They not only protect personnel, but also protect work place and materials. The laboratory director provides adequate equipment according to assigned biosafety level, and ensures that it is used properly. Biological safety cabinets, high-efficiency particulate air (HEPA) filters, personnel protective equipment (including gowns, gloves, safety glasses, and face shield), a dedicated hand wash sink, and proper disinfectant with proven activity are highly effective in reducing of infection transmission.[44]

### LABORATORY STAFF

Laboratory staff are at the frontline on of exposure, so if measures are not properly implemented, laboratories can become source of transmission. At the start, personnel get aware of potential hazards, and required to follow the safety standard procedures. Laboratory director arrange the appropriate training of personnel, also provides protective clothing and equipment to protect them from exposure to microbial droplets and aerosols. Moreover, the director employs trained and competent staff, since the likelihood of errors is increased when staff training is inadequate and staffs are under pressure to deliver rapid results. Thus, well-informed employee with high technique is a key to the prevention of incidents and accidents.[46]

## AFTER CRISIS

The post pandemic world looks vastly different than it did before and its challenges are incomparable. The occurrence of a pandemic is an opportunity to grow, learn and innovate novel research strategies, vaccines and therapeutics. Attentive monitoring by medical microbiology laboratories is vital to inform about any unusual increase in the number of organisms and this is particularly true for both re-emergence or appearance of a new organism. The laboratories should notice the number of samples submitted, and elevated rate of an organism. When a pandemic comes to end, performance debilities of the last pandemic should be identified and improved before next crisis happen, since no one knows what and when is the next one.

## CONCLUSION

Infectious agents with a great potential to cause new outbreaks are already out there. It is impossible to predict the nature of next epidemics, its source or where it will start spreading. To maintain a laboratory's capability to confront with health-crisis, investments must be made in the infrastructure of the laboratory, in advance. During pandemics, laboratories should aim to early identification of infectious agents and provide information for implementation of strict policies and preventative strategies. The laboratories should detect source of infection and routes of spread to limit its transmission as soon as possible. They are required to provide the most appropriate diagnostic methods and antimicrobial susceptibility results for prompt initiation of therapy. The accurate and frequently updated information must be acknowledged by laboratories to maintain public trust. Biosafety guidelines, practices and equipment in laboratory are necessarily needed to reduce the exposure of staff and work place to hazardous agents.

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