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RESEARCH ARTICLE

Mitigation of the biosafety risks of SARS-CoV-2 at BSL-3 laboratories

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BSL-3 laboratuvarlarında SARS-CoV-2 biyorisklerinin azaltılması

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Öz

Amaç: Bu çalışmamın amacı biyorisk analizi yaparak SARS-CoV-2 virüsü kaynaklı laboratuvar egzoz hava tahliyesine ait biyogüvenlik risklerini COVID-19 pandemisine karşı aşı geliştirilen biyogüvenlik seviye-3 laboratuvarında azaltmaktır.

Gereç ve Yöntem: Çalışmada COVID-19 pandemisine karşı mücadelede spesifik laboratuvar çalışmaları için kullanımı hedeflenen biyogüvelik-3 seviyesinde yüksek güvenlikli laboratuvarın altyapısı ve organizasyonu risk değerlendirmesi için seçilmiştir. Risk değerlendirme matrisi ile yüksek güvenlikli laboratuvarlarda kritik bir öneme sahip ısıtma-ventilasyon-havalandırma sisteminin ilişkili alt bileşeni laboratuvar egzoz havasının tahliye prosedürü risk analizi ile değerlendirilmiştir.

Bulgular: Risk analizi sonrası risk azaltma stratejisi olarak biyogüvenlik-3 seviye laboratuvarın egzoz havasının, tahliyesi öncesi hava kanallarında 90 C° sıcaklığa maruz bırakılması belirlenmiştir. Çalışmada belirlenen proses uygulamaya alınarak egzoz havasının yüksek verimlilikteki partikül hava filtreleri aracılığıyla filtrasyonu ile tahliyesi öncesinde ilave bir biyogüvenlik bariyeri oluşturmuştur. Söz konusu yeni oluşturulan biyogüvenlik bariyeri, çalışmaya ait biyolojik riski düşürerek laboratuvar için daha güvenli bir çalışma ortamı sağlamıştır. Laboratuvar ile çevre arasında ise yeni ve ekstra bir biyogüvenlik önlemi oluşturularak mevcut biyogüvenlik statüsü güçlendirilmiştir. İlave alınan risk azaltma önlemi sonrası yenilenen risk değerlendirmesine göre nihai risk kabul edilebilir seviyeye düşürülmüştür.

Öneri: Yüksek güvenlikli laboratuvarda başarılı biyogüvenlik sistemleri için tesise ve uygulamalara spesifik risk değerlendirilmelerinin yapılması zaruridir. Çalışmada gerçekleştirilen risk değerlendirmesi sonuçlarına göre laboratuvarın özellikle pandemi döneminde riskten kaçınan bir yaklaşım ile ilave risk azaltma yollarını tercih etmeleri biyogüvenlik konusunda tesise fayda sunacaktır.

Anahtar kelimeler: Biyogüvenlik, biyorisk, , BSL-3, risk değerlendirmesi, SARS-CoV-2

Abstract

Aim: The aim of this study is to reduce the biosafety risks of laboratory exhaust air due to SARS-CoV-2 at a biosafety level-3 laboratory used for vaccine development against COVID-19 pandemic.

Materials and Methods: In this study, the infrastructure and the organisation of the containment laboratory, which aimed to be used to struggle with pandemic, was used for risk assessment. Assessment of the laboratory exhaust air procedure as a component of the heating-ventilation-air conditioning system, which is significant for high-level biosafety laboratories, was conducted through a risk assessment matrix.

Results: A heating system providing exhaust air exposure to heat at 90 C° before being discharged to the outside was selected as the risk mitigation strategy after the risk analysis. The system was established as an additional biosafety barrier before the discharge of laboratory exhaust air passing through high-efficiency particulate filters. The biosafety barriers provide a safer working environment by reducing the biological risk stemming from the laboratory work. It also strengthens the existing biosafety status by building a novel and extra biosafety barrier between the laboratory and the outside environment. The residual risk was reduced to an acceptable level with the help of an additional mitigation measure regarding reassessment.

Conclusion: Conducting risk assessment peculiar to practices and the facility is a necessity for the successful biosafety system at high-level biosafety laboratories. According to the risk assessment carried out in this study, creating additional risk mitigation at laboratories by the guidance of a risk-averse approach particularly during the COVID-19 pandemic might provide biosafety advantages.

Keywords: Biorisk, biosafety, BSL-3, risk assessment, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) which is the most recent pandemic, started in the late 2019 in Wuhan, China. The causative agent of the disease is a novel coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) which is a highly transmissible and threatening pathogen for human health (Harapan et al 2020, Hu et al 2020, Lv et al 2020,). In addition to SARS-CoV-2, there are other coronavirus species that can infect humans such as HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1 leading to mild upper respiratory diseases and SARS-CoV and MERS-CoV causing serious respiratory infections by infecting lower respiratory tract (Hasöksüz et al 2020).

Researchers from all over the world have been struggling against this pandemic. There are more than a hundred thousand publications available as the proof of these efforts in the WHO COVID-19 database. Studies focusing on diagnosis, therapy or prophylaxis of the disease are included as a significant part of these studies. (WHO 2020a). The abundance of the studies related to SARS-CoV-2 has drawn attention to the requirements within the scope of biosafety and biosecurity. Biosafety Level (BSL) 2 conditions are considered to be adequate for non-propagative practices such as handling samples for molecular analysis, sequencing and nucleic acid amplification. On the other hand, practices like cell culture, isolation and propagation which might be necessary for laboratory search related to SARS-CoV-2 should be conducted at BSL-3 laboratories (Kaufer et al 2020, WHO 2020b). Biosafety and biosecurity are the fundamental components to carry out biorisk management at high biosafety laboratories like BSL-3. These components should be taken into consideration while working with SARS-CoV-2 at the laboratory. BSL-3 laboratories are designed for use while working with Risk Group 3 microorganisms and with large amounts or high concentrations of Risk Group 2 microorganisms that can pose an increased risk of aerosol spread (WHO 2004).

It is a well-known fact that COVID-19 pandemic causes moderate or severe respiratory disease and even death. Transmission of the virus is possible through droplets, fomit and air (WHO 2020c). When the way of transmission of the virus is taken into consideration, the significance of the Heating, Ventilation, Air Conditioning (HVAC) systems becomes more apparent for the BSL-3 laboratory studies of COVID-19 (FAO 2018).

It is essential for the exhaust air of BSL-3 laboratory to be released away from inhabited buildings and air intakes or High Efficiency Particulate Air (HEPA) filtration must be used to discharge the air (WHO 2004). In a common facility design, HEPA filtering of exhaust laboratory air, which is considered to be potentially contaminated (UCOP, 2020; WHO, 2004), constitutes the final biosafety barrier. Air filtration by HEPA filters is conducted by three mechanisms: namely, diffusion, interception and impaction (Christopherson et al 2020, Nazarenko 2020, Yeo et al 2020). Predominant filtration mechanism for air particles depends on the particle size (Christopherson et al 2020). The size of SARS-CoV-2 virion varies between 60-140 nm in diameter as it is in the limits of penetrating sizes for HEPA filters. (Christopherson et al 2020, Nazarenko 2020). HEPA filters have 99.97% efficiency at least while filtrating aerosols with a 0.3 μm diameter to meet the requirements of approval (Nazerenko 2020). While final filtration of laboratory exhaust air through HEPA filters provides an effective risk mitigation measure, there may always be some additional measures to attach the biorisk management system regarding biorisk assessment.

Risk analysis and risk assessment are the most important elements of biosafety (WHO 2004). The analysis of biological risk is a process including identification and characterization of the risks associated with health, safety and security, implementation of control measures in order to lessen the risks to an acceptable level and measurement of the effectiveness of control assessments (OIE 2018). Proper risk assessment must be conducted regularly by the director of the laboratory and the principal investigator (WHO 2004). The risk belonging to a biohazard agent is the function of likelihood and consequences. In other words, the risk shows the possibility of occurrence and the impact of the harm related to the hazard (Astuto-Gribble and Caskey 2014, WHO 2020b)

Risk assessment is followed by risk mitigation which might actually indicate that the elimination of the risk rather than reducing it is the main aim. Establishing a new biorisk management and taking effective mitigation measures against recently emerging infectious diseases with novel microorganisms would be difficult to manage. This difficulty became apparent during COVID-19 with novel SARS-CoV-2 due to the unclarified characteristics of the virus, its virulence and transmission ways. In this sense, being proactive against this virus and building additional biosafety barriers to the facility while working with this biohazard seems to be a safer approach. This approach is critical for laboratories which are planning to reduce the risk as close as to the elimination level.

Furthermore, risk assessment is unique to every single laboratory depending on the hazards, procedures and threats. Parallel to this, it is an expected situation that assessment might have different results for each laboratory. In addition to these differences between ways of assessment, risk mitigation strategies might vary undoubtedly between countries and even with laboratories (Astuto-Gribble and Caskey 2014).

A biohazard agent or toxin poses risks not only to the laboratory workers in the facility but it also threatens animal and human health outside the laboratory (Astuto-Gribble and

Caskey 2014). Therefore, mitigation measures must provide protection for the humans and animals outside the laboratory as well as the workers in the laboratory (Astuto-Gribble and Caskey 2014). In this study, the risk assessment was carried out with the help of risk assessment template using the risk matrix included in the Interim Guidance of Laboratory biosafety guidance related to COVID-19 (WHO 2020b). Each equipment and procedure involved in the study has an effect on the risks stemming from biohazard. Therefore, a local risk assessment specific to laboratory for each procedure involving the pathogen was carried out as recommended by WHO (Astuto-Gribble and Caskey 2014, WHO 2020b). This study aimed to reduce the risks related to laboratory exhaust air with a maximum risk averse approach during COVID-19 vaccine production by the help of biorisk assessment.

Material and Methods

The laboratory in which this risk assessment was performed provides the requirements for BSL-3. The facility has been in use as a BSL-3 laboratory to work with risk group 3 microorganisms. All the applications with SARS-CoV-2 were practiced in a class II A2 biosafety cabinet with required personnel protective equipment. Biosafety cabinets were set up with H14 class HEPA filters. Each laboratory room was equipped with ultra low particulate air (ULPA) U15 filters. Laboratory air was not re-circulated and the filtration of exhaust air was done with H14 class HEPA filters.

This study includes an important point of risk assessment and risk mitigation for the laboratories; namely, the likelihood of virus release to the outside of the laboratory. It is possible to evaluate the risk in different ways such as using quantitative, qualitative and semi-quantitative methods. In this study, biorisk assessment was conducted through a qualitative risk matrix including likelihood and severity factors. This method was included in this study because it is a part of the laboratory biosafety guidance for COVID-19 (WHO 2020b) and it is both easy to follow and practical. In this study, risk assessment team includes the principal investigators, biosafety officers, institute directors, laboratory workers and other responsible researchers. Based on the risk assessment template, consequences of exposure or release are grouped into three categories, which are severe, moderate and negligible. Probabilities listed as unlikely, possible and likely are used to indicate the likelihood of exposure or release. After the assessment of these factors, the initial risk could be defined as very low, low, medium, high or very high (WHO 2020b). Risk assessment finally reveals whether the decision for the biorisk is acceptable or not (CEN 2011, Astuto-Gribble and Caskey 2014).

Risk acceptance depends on a subjective evaluation (Astuto-Gribble and Caskey 2014), which demonstrates that the risk acceptance criteria might vary based on the biosafety and biosecurity approach of the organization. According to the risk acceptance criteria of the organization, initial risk needs to be reduced by additional mitigation measures. In this sense, a coil heating system was attached to air ducts. The laboratory air was first filtered through U15 HEPA filter and then passed through heating coils at 90 C° temperature for 5 seconds. When the exhaust air reaches the final filter which discharges the air to outside, the temperature of the air decreases to room temperature. The heating system can be monitored and controlled by the help of programmable logic controller. The system makes it possible to switch on or off the heating based on the risky activities. The residual risk was reevaluated after the implementation of the additional measures.

Results

Discharging of laboratory exhaust air is one of the essential functions of the HVAC system. Exhaust air is discharged without recirculation. When considering the ventilation rate, which is at least 12 changes per hour, the amount of discharged air is significantly high. The consequence of exposure or release was identified as severe when we consider the virulence characteristics of the SARS-CoV-2 virus and the pandemic situation threatening the world human health.

Biosafety cabinets with HEPA filter and exhaust air HEPA filtration process have been used at the laboratory. These measures actually reduce the risk probability to unlikely level by affecting the likelihood of the risk rather than consequence. Despite the present measures taken for the likelihood of the risk, the initial risk related to the release of active virus to the outside accidentally was identified at 'medium risk level' as shown at Table 1.

The final decision for the defined risk level was not acceptable regarding the risk acceptance criteria of the organization. It was decided to take action against this result with a medium level priority. Risk assessment was carried out at the beginning of 2020 before the start of the work at the laboratory. At that moment, there were many unclarified issues about the disease and the virus which made the situation worse all over the world. Therefore, creating additional measures to provide safer working area for laboratory practices and to reduce the risk particularly for the environment was an appropriate approach.

To this end, a heating system detailed in the Materials and Method section as an additional process was utilized and no adverse effects were observed on HEPA filters. Moreover, the temperature used in this additional process is in line with the supplier's limits of the product. The risk was re-evaluated after the implementation of the measure. The residual risk was reduced by the help of this mitigation. The final risk was found to be acceptable and preparatory work continued in accordance with this result.

Table 1. Risk evaluation matrix

		Likelihood of exposure/release		
		Unlikely	Possible	Likely
Consequence of exposure/release	Severe	Medium	High	Very high
	Moderate	Low	Medium	High
	Negligible	Very Low	Low	Medium
Laboratory activity/procedure		Initial risk (Very Low, Low, Medium, High, Very High)	Is the initial risk acceptable? (Yes/No)	Priority (High/Medium/Low)
Exhaust air process		Severe+Unlikely : MEDIUM	NO	MEDIUM

Discussion

Establishing laboratory biosafety and biosecurity in the facility is a necessity because of the presence of the biological hazards. Laboratory biosafety involves the principle of containment and the required practices that will be used to be away from unintentional exposure to biological agents and toxins and also their accidental release (CEN 2011). Biorisk management helps to be well-prepared by the help of biorisk assessment to avoid the unwanted events related to biological hazard. The final aim of using risk assessment is the determination of correct risk mitigation measures to reach an acceptable risk level (WHO 2020b), which was also our purpose in this study. Risk evaluation is a crucial method for identifying emerging pathogens, such as SARS-CoV-2, due to the limited knowledge available on pathogens and diseases (Callihan 2020)

The significance of risk assessment as the cornerstone of any successful system of biorisk management was stressed (Callihan 2020). Measures could be created by taking the worst scenarios into consideration. Laboratory acquired infection or release of pathogen to the outside could be taken as examples for the worst scenarios of high containment laboratories. The worst scenarios like laboratory associated infection or unintentional release correspond to the risks, mitigation of which is also mentioned in the goals of ISO 35001. There has been a growing concern about bioterrorism and unintentional laboratory release of potential pandemic microorganisms (Peng et al 2018). To date, no cases of laboratory-associated SARS-CoV-2 infection have been documented in the scientific literature (Kaufer et al 2020). However, this present situation cannot guarantee that it will never happen because the first documented case of SARS-CoV infection in a laboratory environment was announced after the initial international outbreak ended (Lim et al 2004). Laboratory-acquired SARS-CoV-2 infection is possible if laboratory guidelines and safety procedures are not followed (Kaufer et al 2020). For this reason, we have evaluated the existence of such potential risks based on such scenarios and carried out the risk assessment.

The laboratory, in which the mentioned risk mitigation measure was implemented, has been used to develop vaccine against COVID-19 disease. Occurrence of the worst scenarios at such kind of laboratories might have negative effects on both disease transmission and social issues. Likewise, vaccine development studies encouraging people while struggling against pandemic might also be affected negatively. When there is an unforeseen risk, the necessity of high-level containment becomes clear. This level of necessity decreases as the characteristic of the novel pathogens becomes clarified (Callihan 2020).

HEPA filters utilized at high containment laboratories have 99.97% efficiency at least while filtrating aerosols with a 0.3 μm diameter to meet the requirements of approval (EPA 2009, Nazarenko 2020). While 0.3 μm is considered to be the most penetrating particle size (MPSS), the variability of this value should be taken into consideration due to the type of aerosol particles, filter type and flow rate (Nazarenko 2020). Predominant HEPA filtration mechanism for air particles depends on the particle size. Large particles with a size of more than 1 μm are associated with impaction and interception. On the other hand, particles with a size smaller than 0.1μm are mainly filtered by diffusion. (Christopherson et al 2020).

Using HEPA filter as an engineering control provides several benefits to maintain the biocontainment. On the other hand, high temperature, pressure and moisture might cause some failures. For instance, filter might be torn because of overpressure drops or getting wet (Bergman and Garcia 2018). The filter might also be ruptured by high operation pressure. Another point that must be evaluated is changing filters. Filter replacement without following bag in / bag out procedure may probably increase risk while working with hazardous

materials at the laboratory (EPA 2009). BSL-3 design must also be compatible with the zero-tolerance principle to maintain directional airflow. However, there may be some situations such as power cut leading to a positive pressure contrary to zero tolerance approach (CDC 2009, Memarzadeh 2010, NIH 2019).

Aforementioned issues related to accidental release of the virus to the outside guided this study to include a heating system as an additional measure for air discharging process. There are some studies in which the biorisk management system was revised or reinforced for COVID-19 by additional measures through biorisk assessment in different settings (Zorbozan et al 2020, Aspland et al 2021, Baclig 2021). For instance, Zorbozan et al (2020) performed a biorisk assessment at a routine diagnostic parasitology laboratory making use of the same risk assessment matrix as the one in this study. The 'high' or 'very high' risks of the procedures such as stirring and pipetting were mitigated to an acceptable level, which is also the procedure we followed in this study.

In the same manner, Aspland et al (2020) tried to identify and review the challenges for Shared Resources Laboratories (SRLs) have in maintaining biosafety standards. Afterwards, they came up with some possible solutions to the safety issues during COVID-19, which can be considered as possible mitigation strategies.

On the other hand, Baclig (2021) revealed the biosafety concerns related to the establishment of a COVID-19 laboratory. He also mentioned some mitigation control strategies for aerosol-generating procedures as well as some recommendations on this issue. Like the potential risk we considered, Baclig (2021) also focused on the potential transmission of the virus by aerosols.

The durability of virus depends on temperature and humidity. An increase in one of these critical issues might cause destructive effects on virus (Riddel et al 2020). The statement provided by CDC is that the degradation of coronavirus lasts shorter at elevated temperatures and moisture instead of cooler or dryer conditions (Abraham et al 2020).

There are some other studies which investigated the effects of temperature on the SARS virus (Chan et al 2011) or SARS-CoV-2 (Riddel et al 2020) and virus like particles of SARS-CoV-2 (Sharma et al 2021). One of these studies demonstrated that slightly higher temperature (34 °C) is significantly efficient for the breakdown of the structure of SARS-CoV-2 VLPs (Sharma et al 2021). Combination of high temperature (38°C) with a relative humidity (>95%) has got a serious impact to finish the persistence of SARS-CoV on contaminated areas (Chan et al 2011). In another study, SARS-CoV-2 was detected at the end of 28 days on the virus inoculated surfaces with 20°C temperature. When the temperature was increased to 40°C instead of 20 °C and 30 °C, a significant reduction was observed in virus survival rate (Riddel et al 2020).

Aforementioned studies revealed that the detrimental effect of temperature is commonly over 30 °C. On the other hand, higher temperature might be needed to achieve a quick 4 log reduction, as recommended by WHO, 56 °C heating lasts 15 minutes to kill SARS coronavirus (WHO 2003). It should be taken into consideration that small increases in temperature lead to quite serious effects on survival rate. In this sense, based on a fair estimation, temperatures above 65 °C might be required for the entire elimination of coronavirus (Abraham et al 2020). The temperature which was preferred in this study is clearly higher than the investigated or recommended temperature ranges. However, the duration of heat exposure is shorter than the ones used in previous studies.

There are several guidelines including a wide variety of recommendations instead of the specifications of BSL-3 (Memarzadeh 2010). Risk assessment is the starting point of biosafety. This assessment should also be based on procedures unique to facility to implement the most appropriate mitigation strategies (Baclig 2021). Keeping the goals of biorisk assessment and mitigation measure in mind, this study aims to reduce the risk parallel to these goals. There is always a residual risk which is impossible to eliminate while working with hazardous material. In this concept, this study is composed of strengthening the laboratory biosafety while following the risk reduction goal of the risk assessment.

Conclusion

To the best of our knowledge, this study is among the very few studies carried out with the risk assessment approach during COVID-19 pandemic in Turkey. As the findings we obtained are peculiar to our own setting, the findings cannot be generalized; however, it can serve as an example for future studies emphasizing a similar risk assessment in different laboratories. Establishing a heating system for the exhaust air might not provide a complete destruction of the virus as it is impossible to eliminate the risk. However, it is obvious that the new measure enables the reduction of risks related to this issue as it is carried out to protect biosafety by the help of biorisk assessment. In this sense, after performing a biorisk assessment specific to a facility and the activities, the reasonable approach is that the organization defines and fulfills its requirements in addition to the common recommendations to reduce the risks to an acceptable level like the process in this study.

Conflict of Interest

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An ethical statement was received from the authors that the data, information, and documents presented in this article were obtained within the framework of academic and ethical rules. All information, documents, evaluations, and results were presented according to scientific ethics and morals.

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