WHAT THE DEBATE ON THE ORIGIN OF COVID-19 HAS TOLD US ABOUT LABORATORY SAFETY AND SECURITY*

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Abstract

The world has witnessed the most devastating pandemic facing humankind in more than a century. A critical question remains as to the origin of the virus responsible for this tragedy. Two theories have been put forward; that the virus spilled over from wild animals and infected humans who then spread the new virus to others, or that the virus somehow escaped a research laboratory. Both theories are plausible. While there is no direct evidence to suggest that the virus originated from a laboratory, the theory does offer an opportunity to review safety and security protocols that are designed to keep biocontainment facilities and the staff that work within them safe and secure. Advances in science and technology are greatly outpacing our ability to establish policies to mitigate risks in life science research and solutions will require international consensus building, sustained commitment, and effective collaborations.

Key Words: COVID-19, SARS-CoV-2, Laboratory Biosafety, Biosecurity, Pandemic origin

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INTRODUCTION

We have all witnessed the most devastating pandemic to face humankind in more than a century. As the world begins to transition from the global pandemic of COVID-19 disease caused by the SARS-CoV-2 virus, a pathogen new to science, we are now faced with learning how to manage this still very dangerous virus as an endemic threat, one that will likely be with us for many years to come. At the same time, we must prepare to recognize and respond to future threats as new infectious diseases arise. While some countries had made limited preparations for a possible pandemic, thought likely to be caused by the influenza virus, no country was prepared to face the massive suffering and loss of life caused by this new virus, one that none of us had seen previously and one to which we were all susceptible. As a result, about 7 million people have died, and probably many, many more that were not officially counted. Today, the vast majority of us have been infected and/or been vaccinated and some are still suffering from associated lingering illnesses that are yet to be fully understood.

METHODS

The pandemic was first recognized in Wuhan, China in late 2019. The source of the SARS-CoV-2 virus remains unknown; however, two theories regarding its origin have been put forward. These include that the virus spilled over from wild animals and infected humans who then spread the new virus to others. This may have occurred in one or more live animal markets that were in operation in Wuhan before the start of the pandemic. Early human cases of COVID-19 clustered near the Huanan Seafood Market in Wuhan where the market sold live animals, including those known to be susceptible to SARS-like coronaviruses such as raccoon dogs, palm civets, and others. Environmental sampling after the start of the pandemic found specimens positive for the SARS-CoV-2 virus and the live virus was isolated from some samples (1, 2). However, it could not be determined with certainty if the virus detected was from wild animals or reflected infection among humans entering the market as the pandemic began. Some specimens collected at the market had genomic signatures of both SARS CoV-2 virus and animals sold there (3, 4). The spillover of a naturally occurring coronavirus from wild animals to humans is generally accepted as the way the original SARS coronavirus emerged in late 2002 and is thought by many experts as the likely route of introduction of the new virus into humans (5, 6).

The second theory is that the virus may have emerged from a laboratory accident, perhaps involving studies of naturally occurring bat-associated coronaviruses or created in the lab by recombining elements from existing viruses or manipulating sequences. Bat-associated coronaviruses were the likely source of the original SARS virus and another newly emerged coronavirus that causes Middle East Respiratory Syndrome (MERS). Viruses sharing significant genetic similarity to the SARS-CoV-2 virus were found among field-collected specimens obtained from wild-caught bats in southern China (7). Some of this work was done at the Wuhan Institute of Virology and perhaps elsewhere in China. As more information became available, the theory that the virus may have been created by molecular manipulation of an existing virus or created *de novo* has generally been discounted by most molecular biologists; however, the theory highlights an emerging challenge as technological advances make such studies increasingly feasible.

RESULTS

Both the natural spillover and the lab-associated theories are plausible; however, there is currently not sufficient evidence from inside China to draw firm conclusions on the origin of the pandemic (8). Nonetheless, there are several lessons to be considered that could reduce the risk of future pandemics. The focus of discussion here will be on those aspects of laboratory biosafety, biosecurity, and operations that if implemented might lessen the risk of future pandemics.

DISCUSSION

The first question is, "How might the activities of a virus research laboratory be associated with the introduction of a new virus into the community?" Bat-associated coronaviruses are known to exist in free-living bat colonies in China and field teams from the Wuhan Institute of Virology and perhaps other laboratories actively captured bats in southern China and obtained samples from them to look for bat-associated coronaviruses in the laboratory. Infection risks for humans involved in field studies are present from airborne droplets that might be inhaled while inside bat caves and field technicians may have inhaled infectious viruses while collecting bats and become infected. Bat guano is also potentially infectious and could have been a source of human infection. Humans may have been bitten or scratched by bats as they were being captured or handled, or as blood and other samples were obtained. Potentially infectious specimens may have leaked or spilled while being packed or in shipment, potentially leading to human infection as the field-collected specimens were transferred to the laboratory. A small cluster of cases of a disease some speculated was due to a bat-associated coronavirus infection occurred several years before the pandemic among persons working in or near a cave where bats were present, but the cause of these infections was never identified. Thus, a naturally occurring virus similar or identical to the SARS-CoV-2 virus may have infected a human while working near bat colonies, collecting field samples from bats, or while specimens were being transported to the laboratory. Such an infected person might then travel to Wuhan where they could have infected others in the laboratory or the community. Importantly, there is no evidence to suggest that any of these possibilities occurred.

Bat-associated coronaviruses very similar to the SARS-CoV-2 virus were studied at the Wuhan Institute of Virology, at the regional China Centers for Disease Control in Wuhan, and perhaps in other laboratories. Details of the exact work being undertaken in laboratories working with bat-associated coronaviruses are not well known; however, it is known that bat-associated coronaviruses are difficult to grow in cultures. Potentially risky research may have taken place to modify the virus to make it easier to grow and study in the laboratory; however, it is not clear that such risky research was ever actually attempted.

If the SARS-CoV-2 virus or a close relative was in a laboratory in Wuhan, a scientist or technician might have infected themselves or others while trying to grow the virus from samples collected from bats or from a strain that was modified to allow it to more easily infect mammalian cells. Perhaps a laboratory accident occurred such as a needle stick, exposure to infectious aerosol following a spill, or other incidents that could lead to symptomatic or asymptomatic infections of staff. An equipment or system failure might have led to the release of infectious virus into the laboratory or the local community, or infectious waste may have not been fully inactivated, leading to the release of infectious virus into the environment. The infectious virus might have been stolen or intentionally released by a disgruntled employee or bad actor, potentially exposing an individual or the entire community. Importantly, there is no evidence to suggest that the SARS-CoV-2 virus was intentionally created or released to cause the pandemic, or indeed that any of these potential accidents even occurred. Nonetheless, several possible events may have happened during routine laboratory investigations of bat-associated coronaviruses that could have led to human infections or release into the surrounding community.

A systematic review of laboratory operations and records might shed light on possible ways that a SARS-CoV-2-like virus might have escaped laboratory containment. Questions that the laboratory director or others might ask while investigating the possible origin of the virus from a research laboratory are listed below, along with comments on the type of information or records that could be reviewed to help determine areas of possible concern.

Questions about laboratory personnel

- Were staff appropriately trained in biosafety and biosecurity precautions and procedures?

  To do this, one might examine training records for each person working in the laboratory.

- Were lab workers or support staff sick with an illness that could be COVID-19?

  A medical surveillance program could provide a record of acute illnesses among staff, and a serum bank in which regularly collected samples were stored could provide critically important specimens to allow serological testing that could document infection at a particular time.

- Was there a laboratory accident?

  A program to document and record potential breaks in containment, needle sticks, spills, or other possible staff exposures could provide important information.

- Was appropriate PPE available and used correctly by staff?

  A record of PPE supplies and use could provide important information to assure that PPE was present and training records could suggest that they were likely appropriately used. Aerosols are not the only means of becoming infected. In addition to needle sticks, these viruses are prone to infection by mucosal contamination. Contaminated hands rubbed into the eyes or nose can lead to infections. Wearing masks or powered air-purifying respirators (PAPRs) inhibits this. What was the practice in the labs?

- Was there a disgruntled employee associated with the laboratory who may have had access to infectious material that could be misused?

  Personnel records could provide important information to help identify individuals for special consideration.

Questions about laboratory biocontainment and security

- Was there evidence of theft of infectious material?

  A review of physical security for the laboratory and records of controlled access to infectious material could provide important information to determine if a virus sample was lost or stolen.

- What level of biocontainment was being used when potentially infectious specimens were being handled?

  A review of research protocols could show where work with SARS-CoV-2-like viruses was done, by whom, and what biocontainment precautions were in place.

- Were laboratory containment systems functioning correctly?

  Biosafety cabinets are the first line of defense for an individual handling potentially infectious material. A record of annual inspections and certification of filters and air flow could document that these were in good working order.

Air handling and filtration systems ensure that any aerosolized infectious material is captured through filtration and removed before the air exits the facility. Inspections and maintenance records could provide evidence that these systems were functioning appropriately.

Laboratory equipment and instrumentation, including centrifuges and other mechanical devices that might be a source of potentially infectious aerosols, could serve as a source of infections. Having documentation of staff training on the standard operating procedures for the safe use of such equipment, a record of individuals using each piece of equipment, and a review of scheduled maintenance and servicing records could reduce the risk of accidents and potential release of infectious material.

Autoclaves and other equipment to inactivate infectious material. Documentation of staff training on the proper use of autoclaves and records of use, including a written record that documents that critical temperatures were reached to fully inactivate infectious material during each run would confirm that waste material was fully inactivated before leaving biocontainment.

A systematic approach allowing for careful examination and formal records of inspections, including specific examination of the many safeguards in place for the entire waste stream operations, records of maintenance of air handling systems, documentation of inspection and replacement as needed of filters and others would ensure that infectious material never leaves biocontainment.

Global surveillance of infectious diseases

Regardless of the controversy surrounding the origin of the SARS-CoV-2 virus, two major agendas should be addressed going forward (9). First, governments must improve their intelligence about infectious disease threats occurring both in their own country and in coordination with others around the world. Such situational awareness is critical for rapid recognition and coordinated, effective response to outbreaks before they become international tragedies. Heretofore we have relied on national governments to provide timely and complete reporting. Although there was early reporting and sharing of sequence information, subsequent sequestration and suppression of information seemed to replace early openness. Under these circumstances, the system failed decisively and it is clear that we need an alternative. The need for transnational biomedical surveillance, with open communications, clarity, and implementation by strong national systems is essential. The pandemic has spotlighted the need for better surveillance and situational awareness about emerging infectious diseases. The One Health approach that recognizes the interconnection between human and animal health and the interface with environmental conditions has helped to identify sites where spillover events might occur and is an especially valuable model for many countries to incorporate as they work towards implementing improved surveillance activities.

Laboratories play an important role in generating the data needed for effective global surveillance by identifying and characterizing pathogens found in nature or as causes of human infections. Genomic characterization of these pathogens and rapid sharing of specimens and sequence information is critical for the development of diagnostic tests, vaccines, and therapeutics, as well as for the implementation of targeted preventive measures. There will be a need to assist some countries in obtaining the technical skills and capabilities needed to allow national laboratories to meaningfully contribute to global surveillance efforts and strategies, along with resources that will need to be identified to support the creation of such a system. All laboratories will need to adapt and sustain a strong foundation in biosafety and biosecurity as global surveillance of emerging infectious diseases is advancing.

How information is to be assimilated and distributed internationally must be refined. The World Health Organization is the obvious organization to undertake this critical role; however, it is clear from the COVID-19 pandemic response that a tremendous amount of work still must be done to establish an accurate, timely, and equitable global surveillance system that is supported by all countries and free of political interference.

Regulation of “risky research”

Second, we need a large, multinational effort to regulate “risky research.” Risky research includes experiments that might intentionally or unintentionally enhance the transmissibility of a microbe, increase its natural host range, enhance pathogenicity, or further its ability to overcome natural or vaccine-induced immunity or the efficacy of proven therapeutics. Through the National Science Advisory Board for Biosecurity (NSABB), the United States government has proposed guidelines to reduce the risk of experiments dealing with or creating pathogens of pandemic potential. These guidelines are well-reasoned but are limited in scope in that they only address research undertaken within the United States or supported by the United States government when conducted by international grantees. These or similar guidelines must be discussed and incorporated into internationally accepted standards to reduce the risk of accidental or intentional creation of novel pathogens of pandemic potential. Such guidance must include ensuring that appropriate biosafety and biosecurity programs are in place wherever dangerous pathogens are being handled. It will be challenging to ensure that these safeguards are in place, but an essential first step will be to ensure that potentially risky research is fully vetted and assessed by qualified individuals and their host institutions *before* potentially risky studies are even begun.

Among the issues that must be considered are dual-use research of concern and gain of function research of concern, both of which can involve molecular modification of otherwise non-threatening microbes to create pathogens that might impact human health, animal welfare, or plant production. Gain of function studies are critical to modern virology and we need to ensure that efforts to reduce risk from these studies do not hinder beneficial research. Gain of function research of concern includes genetic modification of a potential pathogen that may result in increased transmissibility, enhanced virulence, or evasion of immunity or therapeutics. Substantial overlap exists with dual-use research of concern. Widespread concern was first raised following modifications made to avian influenza viruses in 2011 when two separate laboratories attempted to identify the molecular changes needed to allow avian influenza viruses to be efficiently transmitted among mammals. This led to a pause in some research supported by the US government and resulted in a comprehensive set of recommendations prepared by the NSABB that are included in the *Framework for guiding funding decisions involving pathogens of pandemic potential* (10).

Implementation of the 2017 NSABB Framework found that the recommendations were incomplete and that additional conditions were needed to further ensure the safety surrounding research activities on pathogens of pandemic potential. In March 2023, a reconvened NSABB released a new report, *Proposed Biosecurity Oversight Framework for the Future of Science* (11). The new report expanded the scope to include research that may enhance the transmissibility or virulence of *any* pathogen (recommendation 6) "likely to pose severe threats to human health, food security, economic security, or national security by its impacts on animals or plants or to animal or plant products." Further, it called for an integrated approach to research oversight that includes a "bottom-up" review involving investigators and institutions where the work is to be undertaken. This places greater responsibility on individual investigators, their parent institutions, and their associated biosafety review committees (recommendation 10.2) "Investigators and institutions should be aware of the potential risks of such research". The report further recommends (recommendation 3.2) "institutional compliance procedures must be better harmonized, strengthened…". The guidance is limited to research that is funded by the United States government; however, the need for international collaborations and consistent guidance throughout the global research community is recognized (recommendation 7): "Commitments to international engagement to harmonize and strengthen international norms, standards, education, and training related to biosafety and biosecurity must be renewed". Progress in science and technology is accelerating daily while our policy guidance to mitigate risks in life sciences research is failing to keep pace. There is a critical need for international collaborations and cooperation to establish norms and standards to effectively address "risky research". The 2023 NSABB report offers valuable recommendations to reduce the threat of "risky research" and to strengthen international biosafety and biosecurity.

The global proliferation of biocontainment laboratories

Today we are witnessing a global proliferation of biocontainment laboratories. There are about 70 maximum containment (Biosafety Level 4) laboratories in operation or advanced stages of planning or construction around the world (12). When operational, investigators in these laboratories will be handling the most dangerous pathogens known and potentially considering "risky research" that could lead to the creation of novel pathogens able to initiate another pandemic. There is a clear need for internationally accepted norms and standards of operations, biosafety, and biosecurity in biocontainment laboratories. Before the construction of a biocontainment laboratory, national leaders should consider the following:

- What will be the mission of the laboratory?

  Will it be strictly research-focused, provide clinical services such as diagnostics, or be involved in product development, for example?

- How will success be measured?

  Criteria might include the number and quality of scientific publications, the products developed, or the services rendered.

- Who will provide external oversight of the facility including safety, security, and standards of operation?

  Options might include the national government, a private business, or an academic enterprise. A reference framework of internationally agreed-upon standards for safe and secure laboratory operations could be helpful.

- How will construction costs be managed? Who will be responsible for the sustained operations costs?

  It is often easier to obtain one-time funding to build a facility than it is to be assured that the costs of routine operations and maintenance will be available year after year. These recurrent costs can approach 10% of the original cost of construction in some instances.

- Who will use the laboratory? Who will be the responsible person for directing the laboratory?

  Work in modern biocontainment laboratories requires not only technical skills in the field of research to be pursued, but also strong leadership, specialized training in biosafety and biosecurity, and a robust cadre of support personnel. Leaders who communicate effectively with both their staff and the local community are essential to the success of the laboratory (13). They must create a culture of safety and security that is the foundation of successful operations for the laboratory. Access to such skilled personnel may be challenging.

- How will the security of the lab be maintained?

  Assuring that dangerous pathogens are securely stored with limited access to only qualified personnel is expensive, but essential.

- Reliable supply chains for reagents, equipment, maintenance parts, supplies, and services are needed for the successful operations of the laboratory.

  Having access to these critical elements may be challenging in some parts of the world.

- Will laboratory animals be used?

  A host of special needs and regulatory requirements must be met if laboratory animals are to be used in research. This adds significantly to operations costs and manpower requirements.

- How will potentially infectious waste be managed?

  The safety of the surrounding community demands that infectious waste is completely inactivated prior to release into local sewage systems or solid waste management facilities. Ensuring that this is done safely and efficiently is essential.

- Is the power supply reliable and is there a system in place to provide backup power? Biocontainment at all levels depends on a secure power source to maintain negative pressure and directional airflow, in addition to operations of all the associated laboratory equipment, instrumentation, and security systems.

Finally, the overarching question is: What is the most appropriate level of biocontainment required to meet the needs of the organization?

CONCLUSION

Advances in science and technology are greatly outpacing our ability to establish policies to mitigate risks in life science research. Solutions will require international consensus building sustained commitment and effective collaborations. Overseeing risky research relies on a leadership culture committed to safety and security, and the individual researchers that accept and practice this culture. A "bottom-up" approach to ensure a critical review of proposed research by qualified local investigators and institutional officials before it is initiated is essential to reduce the risks from risky research. Laboratories with staff that have a strong safety culture, that don't view safety as a box-checking exercise, will be safer, more productive, and more rewarding places in which to work.

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S A Ž E T A K

ŠTO NAM JE RASPRAVA O PODRIJETLU COVID-19 OTKRILA O SIGURNOSTI I ZAŠTITI U LABORATORIJIMA*

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Sažetak
Svijet je svjedočio najrazornijoj pandemiji s kojom se čovječanstvo suočio u više od jednog stoljeća. Ostaje ključno pitanje podrijetla virusa odgovornog za ovu tragediju. Iznesene su dvije teorije; da se virus proširio s divljih životinja na ljude koji su zatim širili novi virus na druge ili da se virus proširio iz istraživačkog laboratorija. Obje teorije su moguće. Iako nema izravnih dokaza koji bi upućivali na to da je virus potekao iz laboratorija, teorija nudi priliku za pregled sigurnosnih i zaštitnih protokola koji su osmišljeni da bioistraživački instituti i osoblje koje u njima radi budu sigurni i zaštićeni. Napredak u znanosti i tehnologiji uvelike nadmašuje našu sposobnost uspostavljanja protokola koji bi uzeli u obzir rizike prilikom bioloških istraživanja, a rješenja će zahtijevati izgradnju međunarodnog konsenzusa, trajnu predanost i učinkovitu suradnju.

Ključne riječi: COVID-19, SARS-CoV-2, biološka sigurnost u laboratoriju, biozaštita, podrijetlo pandemije

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