



OPINION ARTICLE

REVISED High-level biocontainment laboratories: risks and necessity for society

[version 2; peer review: 1 approved, 1 not approved]

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Abstract

Advancements in the biological sciences have made it possible to manipulate life forms in unprecedented ways.. This activity, like working with pathogenic natural organisms is intrinsically dangerous. For this reason, countries have promoted the building of High Safety and High Containment Laboratories, classified as Biological Safety Levels 3 and 4.

In this article I briefly summarize the major features of these laboratories, and exemplify some of the research that they host. I then highlight the possible dangers, and argue for the opportunity of a reduction of possibly dangerous research. I argue for more transparency and openness about activities that imply risks not only for those involved, but for human and environmental health as well.

Keywords

BioSafety, Biosecurity, Biological risk, BSL-4, Gain of Function



This article is included in the **Research on Research, Policy & Culture** gateway.



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REVISED Amendments from Version 1

The revised version of the article is very similar to the original version, except for some additional information requested by Reviewer 1, and for the re-phrasing of some parts as requested by Reviewer 2.

The text was written in early 2001, at a time of major changes in the situation of High-level containment laboratories. It would be impossible to update all details, as it would imply the writing of a completely new work.

I thank the reviewers for their comments and insights.

Any further responses from the reviewers can be found at the end of the article

Introduction

Humans and infectious diseases have always cohabited. Understandably, humans have always tried to escape diseases and counter their effects as best as they could, with varying success.

With the advent of modern science, we have started a ‘fight on disease’ which, although it has not been won (and can never be), has brought much better means of escape and also has provided us with considerable knowledge. We now have a discrete understanding of many biological processes, with a significant part relating to pathogenic organisms.

The study of pathogens is useful and important, as it helps us prevent or cure many transmissible diseases through diagnostic, therapeutical and clinical research. However, studying pathogens is also intrinsically dangerous, as it poses the risk of contamination for laboratory workers (Laboratory Acquired Infections¹⁻⁴), possibly leading to community outbreaks. Furthermore, knowledge gained with the purpose of better understanding and managing disease may have the potential for malicious uses (known as dual-use research), which poses another layer of dilemma for scientists and science policy.⁵⁻⁷ However, it is difficult to trace a clear line separating danger and utility, and it often occurs that an activity is both dangerous and very useful, in science as in other fields (*e.g.* fire extinguishing). The risks and benefits of researching potentially pandemic pathogens has been the subject of several articles, documents and regulatory guidelines.⁸⁻¹¹

In order to mitigate the risks connected with exposure to pathogenic organisms, scientists perform studies and experiments in High Level Biosafety Laboratories (designated as BioSafety Level 3 or 4 (BSL-3 or BSL-4), also called High-Containment, Containment Level 3 or 4, Physical Containment Level 4 or similar). Depending on the perceived risk and danger, some experiments are done in labs with more or less stringent measures to control possible contamination of workers and the environment (see following section).

The perception of safety has fostered a number of experiments that could be extremely dangerous, such as so-called Gain of Function (GoF) or the creation of new, synthetic organisms with ‘designed features’¹² that will be discussed in the “Dangerous experiments” section.

Unfortunately, we have always lived with accidents and mistakes in addition to disease (see “Accidents”): in relation to laboratories, even the highest BSL labs cannot fully guarantee that no accident will ever happen, leading to escape of material from the lab.

The following questions then arise: to what extent is it acceptable that dangerous experiments are performed? Does the knowledge that we hope to gain from such experiments balance the risks? Who should decide? On which basis?

Answers to these questions are not easy, and depend on many different considerations, based on cultural, social and personal priorities. Yet, they demand answers at a global level. In this article, the following section reports a brief summary of the classification of laboratories at different safety levels, as well as their presence and distribution. The work performed in these laboratories is summarized in the third section, highlighting its role in health protection and its associated risks, with a few examples. The fourth section is dedicated to the occurrence of accidents, showing how they are unavoidable, with their possible consequences, and with some examples. Finally, we discuss the necessity and risks of dangerous research in the fifth section, and conclude (final section) with some considerations.

High-containment laboratories**Levels of containment**

The vast majority of experiments and studies on pathogenic organisms (mostly viruses and bacteria) is performed in laboratories at low bio-safety level (BSL-2); this is also where the vast majority of the knowledge that leads to the

development of treatments is produced. [Note. *The definition and designation of levels of containment vary in different countries, according to national definitions; we will refer to BSL Levels as defined in the Biosafety in Microbiological and Biomedical Laboratories—6th Edition*¹³]. The BSL designation can be replaced by a more functional approach, exposed in the Laboratory Biosafety Manual of the WHO- 4th Edition,¹⁰ in which a risk assessment process is the basis for the selection and implementation of control and containment measures. However, as BSL levels are still widely used, their designation will be used throughout this article.

In general, BSL-2 labs are built with a higher emphasis on the protection of biological cultures from contamination derived from researchers and the environment than vice versa: these are the typical laboratories in which most biological research is performed, spanning all fields of biology from plant biology to cancer, from cell biology to genetics. Cells and their guest pathogens are delicate material, prone to be spoiled from many possible sources of contamination. For this reasons, BSL-2 labs are separated from the other laboratories, are always kept very clean, workers wash their hands, use dedicate coats and wear gloves at all times; cultures are handled with care in specifically designed hoods or cabinets (with laminar air flowing away from the work surface towards a filter), and materials, both incoming and outgoing, are sterilized. These conditions are in general sufficient to protect the biological cultures from contamination, together with some additional precautions, such as using specific antibiotics and other compounds to impede growth of unwanted organisms like fungi. In BSL-2 labs, it is allowed to grow mildly pathogenic organisms that cause treatable diseases: the very precautions that protect the cultures also protect the workers; in case of accident, workers know how to respond because the cultured pathogens are well known, symptoms are recognized and treatments or cures are readily available.

More dangerous pathogens can also be studied in BSL-2 labs, because scientists can use versions modified to be non-pathogenic: deactivated versions (*i.e.* in which essential or pathological functions are disabled and/or replaced by reporter genes), or pseudotyped forms (in which a harmless virus is used as a carrier for only a subset of genes), or vectors that only contain one or few proteins (components of the toxins, or some enzymes necessary in the viral cycle).

In order to transform the information obtained through basic research performed in BSL-2 labs into usable therapeutic solutions, however, it is necessary to test their activity in conditions that better reproduce the pathogen's natural cycle, often involving live, fully infectious particles. These studies are usually performed in BSL-3 laboratories. Technical features of these labs are reported in [Table 1](#): it can be seen that the emphasis is on measures meant to protect workers and the environment from getting contaminated by the pathogens in culture. In addition to the measures of BSL-2, here we find: double doors (which cannot be open at the same time), negative pressure (so that eventual breaches would result in flow into rather than out from the laboratory, thus impeding escape), sealed piping for liquid waste (including hand washing, and the eventual shower on the way out), and special autoclave with double access (entry from the lab, exit to the rest of the world). Laboratory personnel (usually already expert biologists) receive specific additional training, which should be rehearsed regularly, and wear additional protective equipment: face mask, double gloves, shoe covers, among others. On top of the regular recording of experiments (normal good laboratory practice), detailed logs must be kept for all in- and out-going material, all the experiments, and all the times that any personnel spend in the BSL-3. BSL-3 laboratories can be 'enhanced' with additional precautionary measures, such as control cameras, respirators or other devices.

The most dangerous research is relegated to BSL-4 labs. In addition to the safety measures described for BSL-3, at Level 4 properly trained and approved personnel work wearing a positive pressure suit, connected to an external source of breathing air: in case of puncture or other damage, air will flow from the worker to the environment and not the other way round. The surface of their sealing coats is chemically sterilized before being removed, and they go through a shower before reaching the outside world. Not only objects and other items are sterilized through an autoclave (or by other approved means) on the way out, but the air is also filtered through double high-efficiency particulate air (HEPA) filters, and all effluents are decontaminated. Cameras monitoring work inside the BSL4 are always on, and special rules apply for workers: for example, the two-person rule states that nobody can work alone in these environments. The experiments performed in these laboratories often involve studies on transmission, meaning that live animals (mammals, birds, insects) are kept alive for certain periods of time; as experiments are larger and more complex, more workers need to access the facility and more often, increasing the complexity of management of both people and materials. These laboratories are often very large and articulate, including parts of high containment, as well as laboratories at lower level of containment.

Before moving forward, a note on safety and security; the two terms, in many languages, are expressed by the same word, sometimes creating confusion. Safety refers to the possible accidental or unintentional dangers that can arise during experimental procedures, and is pursued with the development of practical rules on equipment, maintenance, instruction and behavior of personnel, aimed at minimizing the risks of exposure. Security, on the other hand, is a term that refers

Table 1. Features of the laboratories at increasing level of biosafety.

	Level 2	Level 3	Level 4
Dedicated room(s)	+	Double doors	Double door, pass-through autoclave, pass-through chamber for material and equipment entry/exit. All internal surfaces designed for easy cleaning and decontamination
Air		HEPA filters for cabinets/incubators	HEPA filter for incoming air, Double HEPA filter for air outlet. Negative pressure inside the facility.
Access	Restricted while working	Restricted to authorized. Doors locked	Restricted to strictly necessary, authorized and properly trained and approved. Periodic rehearsal
Washing	Hands	Hand washing with automatic (hands-free) sink	Enter/exit is through shower passage. Clothes/suits used in the laboratory are decontaminated or disposed.
Medical	Surveillance	Info on agent symptoms and immunization (if available)	Surveillance, prior medical evaluation (for risk exposure), specific information on agent symptoms, immunization (if available)
Immunization	If available for specific agents	If available for specific agents present	If available
Decontamination	Routine after work	Frequent while working (spills, splashes, aerosol formation ...)	Frequent while working (spills, splashes, aerosol formation ...)
Waste	Sealed in the lab and autoclaved	Autoclaved within the facility	Autoclaved or inactivated within the facility
Work	Bench or Biosafety Cabinet	Strictly BSC	
Accidents	Procedure for reporting exposure	Specific procedure for reporting near misses, accidents, exposures. Any instance is recorded and evaluated at various levels.	Specific procedure for reporting and documenting near misses, accidents, exposures. Incidents are reported and evaluated at laboratory, institutional, and security level
Personnel	Warning sign on door	Personnel specifically trained	Record entry/exit times of all personnel
Log book – material	Good laboratory practice	Good laboratory practice. (detailed if working with Select Agent)	All work is recorded. Plates/vials/vessels are numbered and stored in specific locations. Each movement is recorded.
Log book – facility			Frequent (daily) inspection of all containments and equipment to ensure proper functioning
Certification		By institutional authority	Annual certification by external authority.
Lab coat, gloves	All the time	Solid front coat, only used in lab, decontaminated before laundry. Double gloves when appropriate	Single piece, sealed, positive pressured suit. Additional gloves worn all the time, decontaminated and changed frequently
Eye protection	During operations that may produce splashes, aerosol or while handling dangerous chemicals	For work that may produce splashes or spills of infectious material. Eyewash station in the laboratory	
Shoe cover	Not necessary	If necessary (e.g. working with animals, or in case of floor spills)	

to the possible intentional release or misuse of harmful biological material and is aimed at preventing theft, loss and other possible misuse; therefore, emphasis is placed on control, including authorizations. Checks are performed on the personal history of scientists and workers; biological material is controlled as much as possible, with numbered vials, plates and thorough recording of their use; responsibility and issues about the military potential of biological organisms are considered. In many countries, national authorities compile a list of organisms or toxins for which it is necessary to obtain clearance, including many deadly viruses, bacteria and toxins, on the basis of their perceived bio-warfare or bio-terror potential. These lists are regularly updated and are obviously different for different countries: in places where plague or Ebola are endemic, it would make no sense to 'prohibit' or 'control' a naturally occurring disease.

The discussion on Security is important also in light of the Biological and Toxin Weapon Convention (BTWC), which was established in 1972 and effective since 1975.¹⁴ It prohibits the development, production, acquisition, transfer, stockpiling and use of biological and toxin weapons, but does not restrain research on potential weaponizable organisms as long as their type and quantity is justified for 'prophylactic, protective, or other peaceful purposes'. The convention is periodically reviewed in the Review Conference, in which the operation of the convention is updated to keep pace with the development of biological science and technology. For example, the origin of the ISO 35001 standard on biorisk management, originates in the 7th of the BTWC, held in 2001.

How many and where

High-level biosafety labs are present in many institutions around the world: they are used for the characterization and identification of pathogens from clinical sources, for research on therapeutics, for vaccine testing, and for surveillance, among other practices. Most countries keep a register, and guidelines for their maintenance and control are issued by national and other authorities, although a role for international and supranational organizations is growing, as shown by the recent publication of International Organization for Standardization on Biorisk Management, ISO 35001.¹⁵

For the highest level of security (BSL-4), a precise count of their number is difficult: a very recent resource for information about the major complexes can be found at globalbiolabs.org,¹⁶ which lists 59 locations (August 2021), most of them in Europe, North America and Asia. Many of the facilities in the list include two or more independent units, and sometimes few adaptations are sufficient to upgrade a lower-level laboratory into one with high-containment capacity.¹⁷ Furthermore, they are sometimes hidden under some layer of secrecy, as could be the case for some of those managed by the military (that operate 20% of the facilities¹⁸), connected with industrial property protection or considered easily amenable to misuse by clandestine operators.¹⁹

Recent estimates¹⁷ indicate that there are over 3,000 BSL-3 laboratories in 86 countries worldwide. The distribution of the highest containment laboratories reflects the fact that high containment does not come cheap: their cost, in fact, can reach hundreds of million US dollars (USD), depending on the size and equipment (they are all custom built). As an example, the Australian Animal Health Laboratory (AAHL) in Geelong, Australia (now renamed Australian Centre for Disease Preparedness), a facility with 15,000 m² of lab space, including 2,900 m² of BSL-3 space (28 rooms) and 100 m² of BSL-4 space, two BSL-4 animal rooms, one of which can hold up to six horses, and 955 m² of animal biosafety level (ABSL)-3 space, cost 200 million Australian dollars (AUD) to build in 1985,²⁰ equivalent to about 350 million USD today. The smallest BSL-4 labs can be small enough to be transported on trucks, as the self-contained portable cabinets used for rapid identification and work during the latest (and ongoing) Ebola outbreaks. Large facilities (among which are probably those run by the military) may include hospital beds for human patients, indoor agriculture, animal husbandry for small and large mammals, birds, and insects.

Once built, the running costs, often not anticipated when the lab is built, easily reaches 10 million USD per year.²¹ This is due to both the continuing running expenses and the necessity to keep the personnel technically proficient, to avoid losing skills.

Most BSL-4 labs reported in Ref. 16 are hosted in public health hospitals, about 20% in university buildings, two of them are privately owned, and the remaining 20% are linked to military facilities. The location of such facilities poses important issues of public safety: ideally, perfect isolation of the labs is achieved through built-in measures. However, even a minor accident resulting in infection of a single person can have very different outcomes in relation to where the facility is located: big cities, university setting or public hospitals are the ideal places to spread infections; more secluded locations, such as islands or isolated compounds could mitigate the risk, even if it would be less practical for workers.

Work in high-level biosafety labs

Research on dangerous pathogens

Working with biological material requires attention, training and experience with various laboratory practices, in order to manage all the small steps involved in growing live and very delicate material, even before considering aspects of

research (organizing the proper experimental design, including for example dose/response scale and proper controls). From careful cleaning and sterilization of all materials, surfaces, liquids etc., to understanding how the many machines work, beyond deep knowledge of the organism subject of study, scientists that work in high containment laboratories are typically senior experts. However, the work conditions are quite demanding: all workers always wear gloves and goggles, and time is often a limit, forcing people to work fast, while at the same time clean, and, of course, without making mistakes.

At the highest level of biocontainment (BSL-4) all difficulties are amplified: people are enclosed in a completely sealed 'astronaut suit' with internal pressure; breathing air is delivered through pipes, gloves are doubled, making it harder to handle plates, bottles, vials and other materials, including the microscope knobs. Some people may feel re-assured by the camera watching and recording their work, but others could feel harassed and nervous by the constant control.²² Furthermore, additional stress could be related to the known dangers associated with each specific organism, typically dangerous for oneself and for the community.

So, why are people willing to expose themselves and others to danger? The benefits of research that cannot be conducted in other settings are related to human and animal health: identification of pathogens, and development of diagnostics, vaccines, new therapies and treatments for new and very dangerous diseases, for which there are no available treatments nor vaccines. An obvious example is Ebola, that, with a high infectivity and lethality, would not be investigated in less safe conditions. Other diseases include the severe acute respiratory syndrome and Middle East respiratory syndrome (SARS and MERS, respectively) particularly virulent strains of influenza virus such as the H5N1, other hemorrhagic fever virus related to Ebola, including Marburg, Crimean Congo, Lassa and Yellow fever, and Zika, among others. Studies are aimed at understanding the pathogen's biology, the immunology of host defense, the mechanisms of transmission of the pathogens and the diseases they produce, with the objective of identifying measures of detection, prevention and/or intervention. Therefore, experiments can be conducted *in vitro*, *in vivo* and in animal models. In the latter case, animal models can be naturally occurring (for example the wild reservoir of a zoonotic pathogen), or can be specifically developed for these studies. In some cases, it can be necessary to also include the vectors that transmit the pathogen, like ticks and mosquitoes (see Discussion). Organisms under study belong to the Risk Group 3 or 4, defined, respectively, as "high individual risk, low community risk" and "high individual and community risk: A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available".¹⁰

The decision on the appropriate safety level for any given study depends on a number of considerations, and varies according to local regulations; in general, and in accordance with the latest indications from the WHO guidelines,¹³ the process implies a Risk Assessment procedure that takes into account the organism, the experiment, the facility and the worker(s).

Unfortunately, these risk assessment procedures are rarely available to the public; it is therefore impossible to evaluate how the risks balances with the societal value of the expected benefits. This issue is further worsened by the fact that many high-level labs are engaged with secret work, be it because of security concerns, industrial protection, or military reasons.

Despite the general opacity, some information can be accessed from the annual reports of the Federal Select Agents Program (FSAP) of the USA. The reports are not solely concerned with high-containment labs, and are focused on security: they report the number of entities (facilities and personnel) that obtained permission to work with material listed as 'select agents', *i.e.* agents (viruses, bacteria, toxins or prions) potentially dangerous for humans, other animals or plants, and for which there is a potential for intentional abuse, or that pose a particularly severe threat from the point of view of the USA. Not all select agents belong to high-risk group, and it is permitted to work with some of them (once clearance from the relevant authority is obtained) in lower safety level laboratories. The latest edition of the FSAP report²³ reports that in the USA, during 2019, there were 247 entities and 8,360 individuals "approved to access biological agents and toxins". Although there is no complete overlap between high-containment laboratories and workers and the number of laboratories and workers approved for access to select agents, these numbers, which refer to the USA only, provide indication about the extension of the high-containment issue.

It must be noted that, in many countries, besides the research described above, an unknown fraction of the work performed in BSL-4 laboratories is related to biodefense, and is even less accessible. In some laboratories, in addition to safety, security concerns induce a high level of secrecy, especially where the subjects of study are agents with a strong potential to be used in war or bioterror settings. As mentioned above, the BTWC does not prohibit research on pathogens with the potential to be used as a means of aggression, it is therefore considered legitimate to study organisms for 'defense purposes'. However the distinction between offensive and defensive research rests largely in the intention of the user, a problem that will be address in the Discussion.

Dangerous pathogens

What is a dangerous pathogen? In some sense, all pathogens are dangerous, but the degree of danger is related to a number of features. Danger for whom? human health; economically important agricultural species; farmed animals; environment or wild species.

In parallel with the definition commonly used in the financial setting, we can define risk as the product of the possible harm if something happens, by the probability that it will happen. The problem is that both terms are hard to quantify: different people can quantify harm in different ways, and they may be more or less prone to accept probability and the resulting risk.

The first half of the term (the possible harm) considers gravity of the disease (from minor, like a head ache, a short burst of fever, to mortal), infectivity (how easily the pathogen spreads), transmissibility (the mean of transmission, *e.g.* by breath, by ingestion or by mucosal contact, via insects, etc), treatability (the availability of treatment or cure, its ease of production and cost), susceptibility of a specific population. For example, malaria is transmitted by some species of mosquitoes (*Anopheles*): in places where those species do not thrive, it is safe to work at a low to medium level of safety; in places in which transmission *could* occur, but the disease has been eradicated, it is more important to keep it enclosed; finally, in places where the disease is still endemic, precautions always make sense, but might not be the prime thought for workers which could be already naturally infected. The human immunodeficiency virus (HIV) is a lethal virus (nearly 100% mortality if untreated), but it does not easily spread (it requires mucosal contact), and since the 1990s has been manageable through medications: it is classified as a Risk Group 2 pathogen. The virus responsible for the 2002–2004 pandemic of SARS, is in itself less lethal than HIV (30–40%); however, there are no known cures, and it spreads easily through the air: it is therefore in the Risk Group 3. As mentioned in the second section, some work can be performed in less stringent environment, by exploiting techniques that exclude the possibility of infection. Poliovirus is nowadays almost extinct, except for a few cases in remote areas in which vaccination is difficult; precisely because it is almost extinct, a large fraction of the population is not vaccinated against it anymore, and the extremely rare cases could pose a serious danger. For this reason, surveillance is still active, and is in part dependent on work performed in BSL-4 laboratories, despite being in itself considered in the Risk Group 2.^{24,25} The case of Polio highlights the difficulty of interpreting risk: in this specific case the possible harm is very high, and the probability very low.

As a reference, the American Biological Safety Association maintains a database²⁶ with the risk classification of a large number of organisms, as classified in different countries. Furthermore, it must be kept in mind that risk, its perception and the way we deal with it are subjective evaluations, that depend on many factors, including personal, cultural and political situations. Furthermore, it can change in time and according to circumstances.

Dangerous experiments

Medical practice is largely based on scientific understanding of diseases: here we only consider infectious diseases, which are mostly caused by bacteria, viruses and, occasionally, prions. This understanding spans from the molecular (including the genetic features of the pathogen and its cellular interactions), to the physiological (the clinical manifestations of the diseases), and the epidemiological (how the disease spreads) dynamics.

Not all research however is necessarily or directly connected to health, or even presents any ‘use’: curiosity is a strong driver, and it has served us well in innumerable cases.²⁷ Studies based on non-pathogenic viruses, in particular, have fostered a very large base of information, knowledge, and understanding, very often leading to use way downstream of the initial research: possibly the best-known case nowadays is the CRISPR-Cas9 system and its analogues, derived from the study of a phenomenon linked to bacterial phages (virus) and the response actuated by the infected bacteria.²⁸

Gain of function

Gain of function (GoF) experiments are intended to force a system (virus, bacterium, or even an artificial construct) to acquire new functionalities, more or less well defined *a priori*. It can be achieved through different means, including genetic manipulation (*e.g.* inserting specific genes to induce a new activity), or through ‘directed evolution’, in which an organism is grown in conditions presenting features that ‘push’ selection towards specific traits.²⁹ Considering the almost inconceivably high number of single individual organisms (that count in the 10^{6-10} or even more) that can be grown in a laboratory, it is possible to produce events that in nature would occur at an extremely low frequency. Procedures of selection or amplification makes it easier for researchers to isolate the resultant ‘new’ variant, which can then be studied in detail.^{7,30}

The possible risks and possible benefits related to GoF research, and of other applications of biotechnology, have been and still are discussed extensively.^{7-9,30-34} With new scientific developments, regulations and guidelines are updated regularly (for example, the Biosafety in Microbiological and Biomedical Laboratories reached its 6th edition in 2020¹³),

and for GoF research that carries a possible dual use capability, additional regulations apply, for example in Europe³⁵ and in the USA.³⁶

The case of the Influenza A H5N1 virus, also called ‘avian flu’, is worth considering. H5N1 first appeared in the 1970s, showing mildly pathogenic features. By the end of last century, after decades of circulation among birds, a new strain appeared in East Asia that was highly infectious and lethal to birds, also causing sporadic infections in humans (18 infected people, six of whom died in Hong Kong, in 1997); as a containment measure, all domestic birds of Hong Kong were culled (killed and destroyed).³⁷ However, the measures could not completely stop the circulation of the strain, which reappeared in the early 2000s worldwide, in both domestic and wild birds, also infecting other animals such as pigs. Human infections increased in frequency,³⁸ prompting research on a vaccine and drugs.^{39,40} Human to human transmission had not been observed (except for possibly few cases,³⁷). In 2012 scientists managed to obtain an outcome that had not occurred in nature: direct airborne transmission of the highly virulent strain among mammals.^{41,42} This case is further addressed in the Discussion.

Resurrecting extinguished influenza virus

Another example of dangerous experiments is the work aimed at recreating the ‘Spanish flu’, an influenza strain that in the years 1918–20 killed an estimate of 20–60 million people worldwide (1 to 3% of the human population at the time). The pandemic naturally extinguished over a couple of years, to never resurrect, at least so far. At the time, samples were taken and conserved in paraffin. These samples, together with ‘naturally conserved samples’ in the graves of a victim in Alaska, have been used extensively in the laboratory to recreate the virus, whose molecular features were characterized by numerous research groups as reviewed in Watanabe and Kawaoka.⁴³ Also, this research has been the subject of discussion, and has contributed to a debate that led to an initial self-imposed year-long moratorium on flu research established in 2012.⁴⁴ Subsequently, the US Government imposed a moratorium on GoF research also involving SARS and MERS,⁴⁵ which remained in place until the new policy was released in 2017, with the Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens.³⁶

If there is a gun in the scene ...⁴⁶

Bacillus anthracis is a prominent member in the list of the FSAP, which regulates the agents and toxins considered to pose severe threats to human, animal or plant health. In other words, it is considered a potential biological weapon. The only intentional use of Anthrax spores on record is the episode of 2001, soon after the 9/11 attacks. As it became evident after few years of investigations, reported in the Amerithrax investigation,⁴⁷ the origin of the material was a military high-containment laboratory in the USA, in which research had been conducted on ‘methods of weaponization’, aimed at identifying and understanding vulnerability to possibly weaponized bacteria (presumably by other countries or terrorist groups).^{47,48} The result of such research is precisely what made it possible for what the Federal Bureau of Investigation (FBI) says was a single American scientist, Bruce Ivins, to kill five people, to disseminate terror, and to cause a major economic disruption by mailing letters containing somehow weaponized spores.⁴⁷ Apparently, the scientist suffered from mental health disorders, but the Army (his employer) failed to recognize them.⁴⁹ A secondary outcome was that this episode strongly contributed to the USA deciding to spend 60 billion USD on research related to biodefense,⁵⁰ aimed at protecting the country from biological agents, including purchase of antidotes, vaccines and any medical countermeasure, and starting the new wave of building of several high-containment laboratories.

Other experiments that can be considered dangerous, or unreasonably risky, are conducted with other select agents, such as the botulinum toxin,⁵¹ which was mutated (via directed evolution) to attack several different protein substrates, or the modification of insects to deliver viral vectors with human specified genetic material to plants.⁵²

The most dangerous

Possibly the most dangerous studies are those on smallpox, an organism that is listed both among the 66 pathogens in the select agents of the FSAP,²³ and in the Risk Group 4. Smallpox virus (*Variola major*) has circulated in humans for centuries, sweeping in waves that infected between a third and half of the populations, killing many of the infected and leaving the survivors blind, deformed and/or disfigured. It has been used as a biological weapon by the British against Native American people in the XVIII century,⁵³ and it was eradicated from the wild, thanks to a major vaccination campaign, completed in the 1970s.⁵⁴ Nowadays most humans are not vaccinated against it, and many voices in the WHO have repeatedly requested the destruction of the viral samples still existing in some freezers in the USA and Russia.^{55,56} The request has not been satisfied for the opposition mainly from the USA delegates, who claim that, in case of a resurgence (which they are *de facto* encouraging simply by thawing the samples), the knowledge gained with their experiments would be of medical interest.^{57–59} The possibility of finding live smallpox virus in quantity sufficient to start even a single infection is extremely low to nonexistent, as demonstrated by the difficulties encountered by scientists in recovering fragments of viral genome from multiple sources.⁵⁹

Accidents

Accidents happen

People that work in BSL-4 labs are usually experienced biologists who have completed additional training both on general safety and on the specific organism used. However, they are humans and, precisely because they are experienced, they know well that accidents and mistakes do happen.⁶⁰ One might be distracted because of personal reasons (a date in the evening, or a sick child at home, a recent argument with a boss), or might be in a hurry, or may feel slightly sick, possibly in a way that would not be a problem in normal conditions: consider a sneeze in the positive-pressure personnel suit. Rules may well contemplate some of the situations, and suggest that work is handed to colleagues who should be able to perform equally well. But who would leave to someone else the final steps of an experiment that they have cultivated for months? Each one of us is naturally inclined to consider that no one could be as careful as oneself, when our own study is being performed, and an incipient cold might not seem problematic. Or one could think it unfair to call someone else to do our work, just because of a slight headache. Or an expert colleague might not be available at the requested time.

Accidents are frequently the result of several contributing factors, among which are human errors, which are typically due to carelessness, inadequate training and knowledge, poor judgment, fatigue, distraction, and high stress level.⁶¹⁻⁶³ The most frequent small accidents involve spills or drops, sample mix-up, handling needles and sharps, and animal bites or scratches.⁶⁴ Other occurrences are linked to incomplete inactivation, leading to work being performed in conditions that, although safe for the inactive virus, can lead to infection from an active pathogen: this case is frequent in diagnostic and in vaccine research, and is due to non-compliance with rules that (should) impose verification of full inactivation of samples; multiple cases have been described in the 2016 report of the United States Government Accountability Office on high-containment laboratories.⁶⁵

However, a small mistake is often easily corrected, but not always; sometimes, it represents the beginning of a chain of events, that can lead to disastrous consequences (see next section).

Other sources of accidents are machine failures, power outages, or structural breakages, as exemplified by the release of foot-and-mouth disease from a major animal research institute in Pirbright, UK, where in 2007 a leakage from a drainage pipe released enough virus to start an outbreak that lasted several months, involving eight farms, over 200 animals (cattle and sheep)⁶⁶ and costed an estimate 200 million UK pounds.⁶⁷

A third source of accidents is related to natural factors: earthquakes, floods (including hurricanes, tornadoes, and storms), and fires. A record of the instances involving select agent facilities which were affected by such events is made available, for the USA, by the Annual Reports of the Federal Select Agent,²³ which reveal that around one hundred events are reported each year. Buildings that host high-containment laboratories have additional safety measures to ensure secondary containment, according to national legislations. Fortunately, up to now, no cases of release due to accidents caused by natural disasters have been recorded. But this is no guarantee for the future: major climate disruption will lead to an increase in the frequency, in the geographical expansion and in the severity of weather extremes, including floods, heat waves and fires.⁶⁸ On the other hand, the lesson from Fukushima should warn that, although rare, “double-hit” are not impossible, and major accidents can never be excluded. In the Fukushima event of 2011, the nuclear power plant resisted the magnitude 9 earthquake: emergency procedures were activated, operations were stopped, and systems for colling the plant were started. However, the subsequent tsunami wave compromised the cooling operations, leading to a series of events that produced the nuclear meltdown of three units of the plant, the explosion of containment chambers and the dispersion of radioactive material. The episode highlights the vulnerability of complex systems. In the case of a major flooding, the last thing that people might want is the circulation of mice or rats bearing a lethal disease.

Once the accident has happened

It is obvious that occasional mistakes and small accidents happen, including in BSL-4 labs. But what happens in these cases? First of all, if they are aware of the mishap, the researcher(s) involved try to fix it. They should report the case to the lab supervisor; however, according to expert estimates (see, for example, the WHO report of the Consultative Meeting on High/Maximum Containment cited before²¹) they often refrain from doing so, fearing the consequences (temporarily isolation, restriction of permission to work in lab), or for a sense of shame, or for lack of understanding the relevance.²¹ A non-punitive method for reporting might encourage a more thorough assessment of problematic instances, and lead to a safer environment and procedures.⁶⁹

Often, researchers are quick to react: minor accidents can be easily ‘fixed’, for example by mopping up the spill, or drying the drops. If they are not aware of the accident, or if the ‘fix’ does not work, the most likely next step is that the workers themselves become infected. Well-known examples are the case of *Brucella* episode at Texas A&M university (TAMU,⁷⁰) and the case of SARS in 2004.⁷¹ At this point the chain of events can take a more serious path: if the disease is easily transmitted, a chain of infection might start, leading to local or large outbreaks. This path has been suggested as

the possible source of the ongoing COVID-19 pandemic, prompting many scientists to request a deeper investigation.⁷²⁻⁷⁴

When an accident leads to problems, a possible, and possibly frequent reaction by all involved (sometimes including the personnel directly involved) is to hide it: investigations are dreaded because they slow down work, and might uncover responsibility of laboratory directors, control system, failure of maintenance, among others. They may lead to suspension of permissions, fines and even criminal charges.⁶⁵ Furthermore, bad reputation might compromise the possibility of future work, raise public attention, opposition and mistrust, and jeopardize future grant acquisition, as in the examples below.

A common solution is to blame the victim and close the case without much publicity; we cannot know how many and which cases were concluded with this modality.^{62,75} Some cases, however, do come to light: for example, the well documented case of *Brucella* infection at Texas A&M University, in which one worker became ill and at least three other showed signs of previous infection with another bacterium listed as select agents.⁷⁶ The episode was revealed months later, thanks to the activity of a watchdog organization, now unfortunately closed (The Sunshine Project⁷⁷). It prompted a major investigation by the US Center for Disease Control (CDC), which ordered the closure of all work performed at the facility, in which at least five laboratories were working with select agents.⁷⁶ A second episode⁷⁸ in which the classical procedure of hiding the fact, blaming the victim, then admitting and finding a scapegoat happened in Boston, with the Tularemia case starting in May 2004 (first infection of three), which became public only in January 2005, with publication in a local newspaper.⁷⁸

It is fortunate that up to now no major laboratory-induced outbreak has happened. However, the list of accidents is long, even considering only those that have been publicly reported, most likely only a fraction. A possible exception to the statement above is related to the origin of SARS-CoV-2, the cause of the current COVID-19 pandemic, which is at present unknown. Some investigation has been conducted, with no conclusive result.⁷⁹ It has been proposed^{73,74,80} that the virus may have originated during some of the research aimed at ‘investigating new emerging viruses’ carried out in research institutions in Wuhan, including the Wuhan Institute of Virology, which have been studying SARS and other coronaviruses from bats, and keeps the largest collection of this viral family. Curiosity, or the drive to explore the unknown is a natural human drive,⁸¹ and it is only natural that Chinese scientists may have wanted to gather new information and knowledge about a family of viruses that already demonstrated its lethality with SARS and MERS; the fact that in Wuhan SARS strains were studied does not necessarily imply, nor exclude, that a leakage has been at the origin of the pandemic. The origin of SARS-CoV-2 from a natural spillover is favoured by many scientists,⁸² but the precise route is still unknown, and both hypotheses (a lab and a natural origin) should be investigated.

A selection of publicly accessible episodes of accidental release of dangerous pathogens is reported in Table 2. The table is compiled from information gathered from several sources, including publications from the [Government Accountability Office of the USA](#), in the “High Containment Laboratories” series, and collected information from the FSAP program and CDC reports. In these reports, the Office repeatedly remarks that the extent of occurrences is not known. Another public repository of Laboratory-Acquired Infections (LAI) is maintained by [ABSA](#),⁴ where an impressive list of 524 episodes of exposures is reported, not necessarily leading to actual infection, including diseases ranging from Ebola^{2,83,84} to Influenza A and B.

Table 2. A selection of recent known accidents involving pathogens from laboratories worldwide.

CDC: American Center for Disease Control.

Year	Pathogen	Brief description	Reference
1978	Smallpox	Smallpox release, leading to short chain of infection. University of Birmingham, UK	54
1979	Anthrax	Anthrax release from bioweapon production facility in Sverdlovsk, >100 cases, a total of 68 deaths confirmed. Russia	101
1990	Marburg	Laboratory acquired Marburg infection, not lethal	102
1995	Venezuelan equine encephalitis virus (VEE)	Venezuela and Columbia large outbreak, linked to laboratory strain used for testing. Estimated 100.000 human infections, >300 reported deaths	67,103
2003	SARS	SARS escape (workers infected) in BSL-4 laboratory in Taiwan	1

Table 2. *Continued*

Year	Pathogen	Brief description	Reference
2004	SARS	SARS incomplete inactivation, two workers infected in Beijing Virology Institute, starting a chain of infections. Finally 11 infections, 1 death	67,104
2004	Tularemia	At least 3 cases of Tularemia in Boston university workers, due to sample mix-up	78,105
2004	Ebola	Exposure to needle while puncturing an animal in Germany	2
2004	Ebola	Ebola infection causes death of Vector scientist in Novosibirsk, Russia	3
2004	Ebola	Exposure to mouse-adapted strain of Ebola virus at US Army Medical Research Institute of Infectious Diseases	83
2006	Brucella	Brucella infection of worker, Texas A&M University	70,76
2006	Coxiella	Q Fever exposure of three workers, Texas A&M	87
2007	Foot-and-mouth disease	Leak from drainage at Pirbright (UK veterinary high containment facility), leading to culling of thousands sheep and cattle	66
2010	Prion (CJD)	At least two people, contaminated in a laboratory in France, develop disease after >10 years. One death.	106
2014	Influenza virus	CDC shipping of Flu sample contaminated with H5N1 highly pathogenic strain	107
2014	Anthrax	Exposure of >50 staff to potentially live anthrax in CDC laboratory in Atlanta	108
2014	Ebola	Sample contaminated with active Ebola virus delivered to BSL-2 lab in CDC laboratory in Atlanta	84
2002–15	Anthrax	Anthrax live shipping (failure of inactivation) to almost 200 labs worldwide from Fort Detrick	65
2019	Brucella	Release from vaccine production facility in China, over long period, leading to >4600 human infections.	109,110

Discussion

Necessity

Basic knowledge

Modern medicine is largely based on a detailed understanding of pathogen biology: genetic (sequence identification, used for molecular and evolutionary studies), biochemical (proteins' role, structural and topological information, for development of drugs and vaccines), cellular and physiological (interactions with host components and reaction of the organism, for drugs and patient management), and epidemiological (for societal management).

Each pathogen differs from any other by some of the aspects broadly described above, and a good knowledge of each one is the best basis on which to build a response in case of an outbreak, or, worse, a pandemic.

Some experimental knowledge can be acquired in safe conditions, while other requires the handling of live pathogens and animal models, sometime including vectors, as explained in the previous pages. In the latter cases, a balance between the opportunity of (possibly) getting the desired knowledge and the risks associated with conducting the research⁶⁴ must be found (see below). High-containment laboratories provide the safest conditions for performing experiments that, although dangerous, are considered necessary.

The case of Smallpox, mentioned before, represents a case worth discussing. Its presence in nature has not been documented for over 40 years. An effective vaccine has been available for over 200 years, and, along with others (possibly based on mRNA technology), it can be produced relatively fast. Infected people present highly characteristic symptoms and the disease is easily recognized: any small outbreak would be quickly identified, isolated and treated. The opportunity for further research, as requested by some scientists,^{57–59} is therefore doubtful.

Treatments and vaccines

The COVID-19 pandemic is an ongoing demonstration of what the scientific community as a whole can do to face a new pathogen. The effort has been huge, with thousands of world scientists switching from their current focus to research on COVID-19; however, we should not forget that any new knowledge is based on previous knowledge. Coronaviruses have been extensively studied (just like many other viruses, *e.g.* Influenza) for many years, especially after the SARS and MERS emergencies.⁸⁵ Similarly, platforms for vaccine development have been pursued in the last 20 years, providing a solid base for new preparation, such as in this case.⁸⁶ Thanks to this knowledge base, it has been possible, in less than two years, to produce several vaccines (10 currently approved for Emergency Use by WHO⁸⁷), based on different technologies, and tested rapidly using the actual pandemic virus. Pharmaceutical interventions are based mainly on repurposed drugs⁸⁸ and have been characterized *in vitro* and in cell culture in several laboratories at BSL-2 and BSL-3 levels, respectively. Patient management has been learned ‘the hard way’ by countless medical staff, engaged night and day for many months. The case of COVID-19 makes it very obvious that, in case of a new pandemic, the last concern will be with shortage of material for study and research.

Highly lethal hemorrhagic fevers (Ebola being a prime example) for which we do not yet have a safe vaccine nor a cure, must be studied at the highest level of containment. The possibility of accidents must always be kept in mind, and risks should be minimized not only by safety measures but also by careful experimental design, *i.e.* choosing the least dangerous experimental options.

Surveillance

The possibility of controlling any emergent or re-emergent disease is linked to the capability of rapid identification and diagnosis. The case of poliomyelitis, caused by poliovirus and described earlier, is an example of a disease that is still circulating in some parts of the world and requires growing suspect samples,^{24,89} which must be done in fully safe conditions. Other pathogens can be more difficult to spot, in particular those not yet known (as was the case of SARS-CoV-2 at the start of the pandemic), and maximum precaution is warranted when analyzing unknown samples.

Gain of function research

Research on enhanced potential pandemic pathogens (PPP), also known as Gain of Function by virtue of the technique applied, explores possible emerging diseases by essentially ‘constructing’ new pathogens, that may (or may not) arise in nature. This research is subject to regulation. For example, the USA framework governing research on ‘enhanced Potential Pandemic Pathogens’ (P3CO), released in 2017 by the US Department of Health and Human Services (HHS)³⁶ allows “research that involves [...] enhanced PPPs” in the case that the pathogen created is “reasonably judged to be a credible source of a potential future human pandemic”.

Some examples of GoF research have been mentioned in the third section, and all have raised discussions. The case of Influenza A H5N1, called avian flu and mentioned earlier, is an interesting example: the genome of influenza virus is composed of eight different parts, circulating in several variations (for example, there are 16 HA and nine NA types), that can recombine in a very large number of ways, even without considering further mutations arising along the way.⁹⁰ Most of the combinations are unproductive and will never develop into a disease that infects humans; however, this still leaves the ‘possibly productive’ number at a level that cannot be possibly experimentally explored. The purpose of the studies that led to the generation of a strain H5N1 which can be directly transmitted among a mammal model (ferrets),^{41,42} was to “address the concern that the virus could acquire this ability under natural conditions”, and reached the tautological conclusion that Influenza A H5N1 “constitutes a risk for human pandemic influenza”.⁴² Nature has always surprised scientists, and it is sure to continue doing so, as most recently demonstrated with the emergence of COVID-19 and its thousands of mutations⁹¹: the number of possible emerging diseases is so high that it is extremely unlikely that the very disease created in the labs will arise spontaneously, while others are to be expected. In the case an outbreak was to emerge spontaneously, as the COVID-19 experience shows, much of the knowledge already obtained (largely from non-GoF experiments) would be helpful for fast reaction and, to understand the mechanism that led to human transmission, the outbreak strain itself could be studied. The risks associated with the creation of previously unknown pathogen must be weighed in relation to the possible utility of the knowledge gained. As nature is much more creative than humans in a lab, we can reasonably expect that, given the appropriate conditions, adaptive solutions will emerge that were not forecast by experts.

As mentioned, GoF research is strictly regulated,^{35,36} yet decisions on what research is worth pursuing (considering risks and benefits) is always based on expert judgment. In this respect, it is remarkable that a document released in 2016, the final report on Risk and Benefit Analysis of Gain of Function Research,⁸ concluded that “the coronaviruses are

insufficiently transmissible to have a significant chance of causing a global pandemic” (page 2). This example illustrates how difficult it is, even for competent experts, to foresee evolution, and how their judgment cannot always be fully trusted.

It is also important to consider that any new disease developed in the laboratory, even in the case that it actually coincides with a natural pandemic one, poses the risk of escape and spread long before the identification of treatments and/or vaccines.

Defense

Another reason that leads to perform risky research relates to biowarfare and bioterror. It is true that we can hardly think of a means of aggression that has never been used, but in relation to biological warfare, while several countries in Europe, Asia and North America developed bioweapons programs, especially in the first half of the past century,^{48,53,92,93} very few episodes of effective use have been documented: the distribution of smallpox-tainted blankets to Native Americans by the British colonizers in the XVIII century,⁴⁸ and some attempts during World War II especially by Japan, but also by Germany and possibly others. Nowadays, scholars, notably Cross and Klotz,⁹⁴ doubt that biological agents will be used in warfare, due to “the widespread belief that biological weapons have no military utility”,^{94,95} and thanks to the fact that the Biological Weapon Convention has been signed by almost all countries.¹⁴

The possible use of biology for terrorism, or by non-state actors, can be considered somewhat easier, as it would “only” take few knowledgeable scientists to prepare a sufficient amount of an agent capable of infecting a few people, sufficient to disseminate terror. In the last 50 years or so, documented episodes include the intoxication of over 750 people in 1984 in Oregon (USA)⁹⁶ and the 2001 mailing of letters containing anthrax spores produced in a military facility in the USA, to politicians and members of the media in the USA.⁴⁷ The former episode involved a non-lethal bacterium (*Salmonella*), released by members of a religious sect whose aim was to debilitate the local population on occasion of local elections. The episode of the so-called ‘anthrax letters’, which caused 22 infections, including 5 lethal, prompted a vast program of biodefense research in the USA aimed at developing countermeasures for possible further attacks. During the last 15 years in the USA, biodefense programs have been developed for the detection, identification, and characterization of an attack; prophylaxis against and treatment of cases of illness; and decontamination/recovery from an attack. These programs also contributed to the proliferation of high containment laboratories, at both the BSL-3 and BSL-4 level.

Still, the use of biological agents as bioterror cannot be excluded: single persons or small organizations willing to disrupt ordinary life by seeding fear might pursue this option. Nowadays, with modern techniques, it is certainly possible for an expert biologist to ‘create’ a pathogen (likely a virus) with specific properties, but it is also certainly not easy. Previous research could ‘guide’ the activity,⁹⁷ but it would still require an expert virologist, a complex and expensive facility, supply of materials and reagents not easily obtained, and years of work. The few documented cases mentioned above,^{47,96} and other failed attempts such as those pursued by the Japanese sect Aum Shinrikyo,⁹⁸ indicate that the use of traditional weapons vastly exceeds the use of biological ones. Even in the case that such individuals or groups were to develop their programs, what are the chances that it could be prevented by biodefense research?

The proliferation of laboratories and personnel authorized and capable of handling dangerous pathogens also poses the issue of the distinction between defensive and offensive research, which is defined by the ‘intention’, and is therefore prone to interpretation: a country’s defensive research program may be viewed by other countries as a threat,⁹⁹ with consequences that could lead them to start their own defensive research, possibly triggering a vicious circle.

We can also note that the word ‘defense’ has been used as a euphemism for ‘war’ since after World War II,¹⁰⁰ with the renaming of ministries in many countries (UK, Italy, USA and more). Indeed, the concept of defense implies a situation of hostile aggression and is strongly associated with weapons and war.

Risks

Accident reports

In section 4 the conditions that can lead to accidents have been explored. [Table 2](#) reports examples to illustrate the variety of situations that represent danger. Documented accidents have happened in research laboratories, in military facilities, in vaccine production and/or in surveillance entities. Causes include scratches with needles and other equipment, leaks through exhaust of air and liquids, failure of inactivation (often coupled with failure to check), or has sometimes remained unexplained. Consequences can be minor in the luckiest cases, or can lead to widespread infection of humans and/or animals, leading to loss of lives and considerable costs.

At least 59 maximum containment laboratories exist worldwide

The globalbiolabs.org website¹⁶ reports the list of all publicly known laboratories registered as BSL-4 or equivalent. Possibly dangerous research is also performed in lower-level laboratories, and it is impossible to estimate how many people (scientists, technicians and other staff) have access, are trained and can handle dangerous pathogens.

In the WHO report from the consultative meeting cited before,²¹ as arguments in favor of the large number of high-containment laboratories, were mentioned ‘benefits at global level’ such as the availability of “highly trained bio-containment workforce [that] can be deployed in emergency outbreaks and provide expertise based on experience with diagnostics, packaging of samples for shipping, and correct PPE usage for people at risk”. It seems that such ‘benefits’ could be obtained in much less dangerous conditions and lower cost, and that this reason hardly justifies the building and maintenance of large numbers of BSL-4 labs. At the same time, having more people handling dangerous material statistically augments the risk of actual contamination, as well as of intentional theft. Furthermore, the know-how of experimental practices constitutes a risk (or a valuable asset) if terrorist groups were to recruit scientists with practical knowledge (and little ethical concern).

It is therefore legitimate to ask if the number of BSL-4 labs is proportionate to the needs. Arguably, a reduction of authorized laboratories would allow for better control and more efficient performance. Similarly, a reduction in the number of personnel with both authorization and experience in handling dangerous pathogens would greatly reduce the risk of malign use. It would also limit the number of travelling samples, a critical time in which dangerous material exits the high-containment labs. Furthermore, reduction of the number of BSL-4 laboratories might also facilitate interaction among the labs, possibly leading to the adoption of a set of best practices. At present, there is little international governance for such facilities, and although any kind of binding international regime seems highly remote, there could be prospects for informal coordination among the labs that could improve safety. In this direction, we can notice the initiative of the International Federation of Biosafety Associations, the Global Health Security Agenda, and the Global Biological Policy and Program of the Nuclear Threat Initiative, all of which are private, non-government associations.^{111–113}

The geographical distribution of such labs and personnel (biological, medical, veterinary and agricultural scientists, technicians, maintenance) should also be discussed at international level, as laboratories might be more useful at or near the places in which new diseases are likely to arise, and surveillance is more important.

The location of facilities, as mentioned in the second section, is another sensitive problem. The protests that have accompanied the construction of new facilities, when the relevant information reached the public, demonstrate that people are deeply concerned; in addition, no matter which arguments the government, universities or private sector engage with, strong opposition is likely to persist, especially as the other major problem of these facilities, *i.e.* full transparency, is not addressed.

Transparency and trust

At the Consultative Meeting of December 2017,²¹ practitioners devoted a session to remark on the benefits of research performed in high-containment labs, while carefully abstaining from mentioning dangerous and controversial research, some of which are linked to military interest and biological weapon-related research.¹⁶ Another session was devoted to ‘earning support and trust from the public’, indicating how support and trust are missing. The partial picture described in this article seems to justify fears, since at least some of the research performed in high-containment labs presents an extremely high potential risk. Furthermore, past performance^{76,78,105} is an indication that the chain of authorities that bear responsibility towards both their employees and society is not inclined to respond to society’s request for transparency.

The specific projects performed in high-containment laboratories worldwide are partially unknown, an issue that questions democracy and societal control, and potentially involves the military sector, as it is estimated that 20% of known BSL-4 facilities are defense-related.¹⁷ However, in case of accident, it is society that will pay the consequences, especially if the unavoidable accident happens in populated areas. A good understanding of the work performed in the laboratories, which organisms are used and their associated diseases, details of risk assessment, external auditing, and other measures, would be useful in mitigating the consequences of accidental release, thus limiting the danger to some extent. In case laboratories were accepted by (or forced on) local people, citizen awareness could also contribute to set limits to the kind of research being conducted.

Conclusions

Risk perception is subjective, depending on personal, cultural, and societal factors. Differing risk perceptions drive differing preferred policies. For example, if the risk of a bioterrorist or biological attack is perceived to be higher than the risks of accidental release from biological laboratories, it could make sense to undertake risky biological research for the purpose of preparing for or defending against an attack. The discussion about the opportunity to take one or more risks should involve those who would pay the consequences, *i.e.* society at large. Some discussions are very complex, and an understanding of biology and other aspects may be necessary: society has means of addressing complex problems, through trusted organizations (typically NGOs) that can mediate dialogue. The case of COVID-19 has shown that the majority of citizens are capable of understanding and willing to follow governmental indications. The minority of (vocal) anti-vaccination (anti-vaxxers) protesters, or their analogues in similar situations, could in part be convinced with a more transparent and open attitude.

A role for encouraging a wide discussion, already proposed,³¹ could be in the hands of the WHO, that is still the only worldwide agency that can organize such an admittedly difficult enterprise at a global level.

Matthew Meselson, a driving force in the development of the Biological and Toxin Weapon Convention, argued that “Every major technology—metallurgy, explosives, internal combustion, aviation, electronics, nuclear energy—has been intensively exploited, not only for peaceful purposes but also for hostile ones”.⁹⁵ Chemists have ‘paid their duty’ with the invention of dynamite, which was the reason behind the institution of the Nobel prize, as a form of penance. Physicists, after the production and use of the nuclear bombs, started a thorough reflection on the responsibility of science and scientists.¹¹⁴

Biologists must learn the lesson, and stop taking huge, useless risks before a major outbreak forces them (us) to spend some thoughts on the opportunity and the danger of our work.

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 **Javed Muhammad** 

Department of Microbiology, The University of Haripur, Haripur, Khyber Pakhtunkhwa, Pakistan

The author in this article has described different levels of laboratories working on pathogenic organisms. The author has highlighted the different types of research work conducted in these different levels of research labs and all possible risks arising from these labs and what should be the preventive measures.

In my opinion, the author is still using biosafety level 1, 2, 3 and 4 but the author needs to get updated with WHO latest edition of high containment and maximum containment levels. The article needs to review the language and grammar. Most of the sentences are very long and difficult to review.

1. Recognizing the possible dangers connected with this activity..... Rephrase the sentence structure and length.
2. In this article I briefly summarize the major features of these laboratories, exemplify some... The whole paragraph should not be in one sentence, suggest splitting it in 2-3 and make more logical/scientific.
3. BioSafety, Biosecurity, Biological risk,.... Keywords should be the same that are described in abstract. Also, BSL-4 and all levels are omitted so add updated information.
4. The study of pathogens is useful and important, as it helps... Very long sentence, difficult to keep tracking of information.
5. with exposure to pathological.... pathogenic not pathological
6. Unfortunately, we have always lived with accidents and mistakes in addition to.... Once the author is switched from diseases to their testing etc in labs, onwards discussion should be about labs as the title of article is concerned. switching again to diseases doesn't make any sense.

7. laboratories at low bio-safety level (BSL-2);... as mentioned earlier, all BSLs are abolished and replaced with 3 levels of labs (core, heightened and maximum) so whole article needs to be re written in context of updated information. Author is suggested to read latest literature about lab safety levels. BSLs can be used for previous reference but latest information needs to be added.
8. we can define risk as the product of the possible... use of appropriate definitions is recommended. Risk is defined elsewhere ISO 35001, WHO etc.
9. that can lead to disastrous consequences (see next section).... not recommended to mention. author needs to establish relationship between two ideas with logical reasoning and references. "see next section" is not a scientifically good term to use.
10. If they are not aware of the accident, or if the 'fix' does not work... what types of fixes? some examples just like the examples of accidents should be mentioned.
11. The discussion section should be renamed as solutions/ possible measures to manage lab accidents etc. Discussion is usually recommended in research articles.
12. Risks: Accidents happen on page 14... Repetition needs to be avoided.
13. WHO, that is still the only worldwide agency that can organize... reviewer does not agree, provide reference.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Partly

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Molecular Epidemiology of infectious diseases, Diseases surveillance and diagnosis, biorisk management.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 06 Oct 2025

Monica Zoppè

Noting that most of the comments and criticisms are of a linguistic nature, I have made slight modifications to the sentences that the reviewer found difficult.

In particular:

1. **Recognizing the possible dangers connected with this activity..... Rephrase the sentence structure and length.**

This activity, like working with pathogenic natural organisms is intrinsically dangerous. For this reason, countries have promoted the building of High Safety and High Containment Laboratories, classified as Biological Safety Levels 3 and 4.

2. In this article I briefly summarize the major features of these laboratories, exemplify some... **The whole paragraph should not be in one sentence, suggest splitting it in 2-3 and make more logical/scientific.**

While the reason why short phrase should be "more logical/scientific", I have split the sentence:

In this article, I briefly summarize the major features of these laboratories and exemplify some of the research that they host. I then highlight the possible dangers, and argue for the opportunity of a reduction of possibly dangerous research. I argue for more transparency and openness about activities that imply risks not only for those involved, but for human and environmental health as well.

3. **BioSafety, Biosecurity, Biological risk,.... Keywords should be the same that are described in abstract. Also, BSL-4 and all levels are omitted so add updated information.**

I am not aware of any 'rule' that keywords should be those used in the Abstract, but I have introduced BSL-3 and BSL-4 to the list of keywords.

4. **The study of pathogens is useful and important, as it helps... Very long sentence, difficult to keep tracking of information.**

I have split the phrase according to the reviewer's request.

The study of pathogens is useful and important, as it helps us prevent or cure many transmissible diseases through diagnostic, therapeutic and clinical research. However, studying pathogens is also intrinsically dangerous, as it poses the risk of contamination for laboratory workers (Laboratory Acquired Infections 1-4), possibly leading to community outbreaks. Furthermore, knowledge gained with the purpose of better understanding and managing disease may have the potential for malicious uses (known as dual-use research), which poses another layer of dilemma for scientists and science policy.

5. with exposure to pathological.... **pathogenic not pathological**

The reviewer is right: I change.

6. Unfortunately, we have always lived with accidents and mistakes in addition to....

Once the author is switched from diseases to their testing etc in labs, onwards discussion should be about labs as the title of article is concerned. **switching again to diseases doesn't make any sense.**

The author does not agree with the reviewer. Complex subjects sometimes require complex constructions. Competent readers should be able to follow the logic and understand the

meaning. Furthermore, the sentence does not 'switch again to diseases' but introduces the topics of accidents and mistakes.

7. laboratories at low bio-safety level (BSL-2);... as mentioned earlier, **all BSLs are abolished and replaced with 3 levels of labs (core, heightened and maximum)** so whole article needs to be re written in context of updated information. Author is suggested to read latest literature about lab safety levels. BSLs can be used for previous reference but latest information needs to be added.
All international sources (CDC, E-CDC, Wikipedia, NIH, and more) regularly use the BSL- 1 to 4 classification, which is the worldwide accepted standard.
8. we can define risk as the product of the possible... use of appropriate definitions is recommended. **Risk is defined elsewhere ISO 35001, WHO** etc.
"Risk" is a general term, used in many fields, and my reference is to the general meaning, not necessarily to bio-risk. Furthermore, neither ISO 35001 nor WHO provide a definition of risk.
The ISO 35001 document defines a process to identify, assess, control, and monitor the risks associated with hazardous biological materials ...
WHO describes the process of Risk assessment
If the reviewer is aware of other documents, the author would be grateful for precise indications.
9. that can lead to disastrous consequences (see next section).... not recommended to mention. author needs to establish relationship between two ideas with logical reasoning and references. **"see next section" is not a scientifically good term to use.**
This comment contradicts the previous one N. 6
10. If they are not aware of the accident, or if the 'fix' does not work... **what types of fixes?** some examples just likes the examples of accidents should be mentioned.
Added
... fix it, for example by mopping the spill, or drying the drops.
11. The discussion section should be renamed as solutions/ possible measures to manage lab accidents etc. **Discussion is usually recommended in research articles.**
I cannot see the reason for this request: a discussion can be about anything: research, results, opinions, proposals, and so on
12. Risks: Accidents happen on page 14... **Repetition needs to be avoided.**
Changed: Accident reports
13. WHO, that is still the only worldwide agency that can organize... **reviewer does not agree, provide reference.**
Which other body could take up such endeavor? I cannot think of any international institution with such capacity. If the reviewer has any suggestions, I would be glad to modify the manuscript.

Competing Interests: No competing interests were disclosed.

Reviewer Report 23 August 2022

<https://doi.org/10.5256/f1000research.122750.r145945>

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Jean Pascal Zanders

The Trench, Ferney-Voltaire, France

This manuscript provides a broad overview of the many aspects of biorisk management and issues related to research in high-level bio-containment laboratories. While each aspect could be the subject of more detailed analysis, the great contribution of this paper is that the contents are accessible to non-experts or people working on issues relating to illicit or unintended transfers of dual-use technologies to malevolent actors. As such, it can provide an excellent educational introduction to questions on technology governance, responsible science, risk management and non-proliferation.

Some comments (page references drawn from the PDF version of the manuscript):

pp 4-6 (just above header 'How many and where')

- The BTWC is briefly touched upon, but the issue is not further elaborated in the manuscript. The paragraph does not make clear why the treaty is important to the subject of the paper or how it contributes to the mitigation of the risks described in the paper.
- For instance, the next paragraph refers to ISO 35001 on biorisk management. It may be worth noting that the origins of this standard are in the 7th Review Conference of the BTWC (2001), when states parties recognised the possible contribution of biorisk management to to the objectives of the BTWC (e.g. [Increasing assurance under the BTWC through biorisk management standards](#)).

p 8 (above header 'Dangerous experiments')

- Discussion polio virus (top para): might benefit from update in view of detection in Europe and USA.
- Next para, perceptions of risk: it may also vary depending on culture or political system.
- Bottom page: Honk Kong (typo).

p. 9

(header 'Resurrecting extinguished influenza virus')

- Reference to number of deaths from the 1918 influenza pandemic: several recent authors place it at 50-100 million fatalities. (The sentence may require specific sourcing).

(header: 'If there is a gun in the scene ...')

- This reviewer would hesitate to name Bruce Ivins unless there is broader discussion of the anthrax letters. He committed suicide, as a consequence of which the FBI stopped the investigation into this person. In consequence, there is no final verdict or further review of available evidence.

(Header: 'The most dangerous', end of paragraph)

- How about mutations in related viruses, or possible re-emergence as a consequence of global warming (permafrost, etc.)?

p. 10 (para. above header: Once the accident has happened)

- 'the Annual Reports of the Federal Select Agent': add 'Program' at end.
- Fukushima: add some context. It is not clear this concerns a nuclear plant and what the consequences of the event were.

p. 12 (sub-header 'Basic knowledge')

- 3rd para, on smallpox: see earlier comment on why research might still be useful.

p. 13 (sub-header 'Defense', 2nd para.)

- It might be good to indicate that the Rajneesh cult spread salmonella bacteria (non-lethal), which made it easy to acquire and release.
- Concerning the anthrax letters: 5 fatalities and 17 infected persons, despite complex preparation.
- It may also be good to point out that Aum Shinrikyo failed across the board in its BW programmes, despite having large funds available.

p. 15, Conclusions

- Meselson: earlier (p. 4) the treaty was identified as Biological and Toxin Weapons Convention with as acronym BTWC.

Is the topic of the opinion article discussed accurately in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Are arguments sufficiently supported by evidence from the published literature?

Yes

Are the conclusions drawn balanced and justified on the basis of the presented arguments?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Chemical and biological weapons disarmament; education in support of disarmament

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard.

Author Response 31 Aug 2022

Monica Zoppè

To Jean pascal Zanders.

I thank the reviewer for the words of appreciation, and for the insightful and constructive criticism. I will address in the revised version (after receiving e second review) all the points raised, as detailed below:

BTWC will expand as suggested

Polio the article was written before the recent episodes; I will introduce a brief note about the Polio, the Monkey Pox and the West Nile virus, all of which have seen a surge in global cases. A thorough discussion would require another article, and this one is already quite long.

Influenza pandemic 1918 I have noticed that more recent estimates tend to provide higher number of victims: I am not sure how to interpret this trend, but a deeper search confirmed my impression.

'Global death toll estimates have been revised upwards in the decades since the pandemic. Initial assessments in the 1920s estimated deaths at around 21.5 million; this was subject to a recalculation in 1991 to between 24.7 and 39.3 million [24,25]. A 2002 estimate put deaths at around fifty million, with an upper limit as high as a hundred million deaths [23]. More recent estimates tend to fall in this broad range, with 40–50 million deaths being most commonly reported [2,13,22,26,27].' From: Saunders-Hastings PR, Krewski D. *Reviewing the History of Pandemic Influenza: Understanding Patterns of Emergence and Transmission*. Pathogens. 2016 Dec;5(4):66.

Bruce Ivins I had included a brief discussion about the FBI investigation and the doubts raised in the community, but removed it upon suggestion by another reviewer (who later rejected it anyways!). I thank this reviewer and will re-introduce the discussion.

Smallpox I really think that the possibility of permafrost releasing active virus is so small to be almost nonexistent. The idea seems to me a creative way to justify unjustifiable research: the danger of growing virus in the lab, spreading the know-how related to the virus and having people handling it poses a real danger in terms of both safety and security. Furthermore, in the remote case that new infections happen, whichever their origin, there will be new virus available, and of the specific strain.

My personal opinion is that ALL INFECTIOUS MATERIAL should be destroyed, and any activity linked with it (including sample storage) should be considered a crime against humanity.

If new strains ever appear (where from?) existing knowledge will certainly be sufficient to face the situation, as it has been sufficient to exterminate the old smallpox 40-50 years ago.

Fukushima the reviewer is right that some readers may not be familiar with the episode: I will add some context and reference

I will also address the remaining minor concerns of the reviewer, about the Rajneesh, the anthrax letters, and the Japanese cult.

Competing Interests: No competing interests were disclosed.

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