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Review Article

Biosafety and immunology: An interdisciplinary field for health priority

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ABSTRACT

Biosafety hazards can trigger a host immune response after infection, invasion, or contact with the host. Whether infection with a microorganism results in disease or biosafety concerns depends to a large extent on the immune status of the population. Therefore, it is essential to investigate the immunological characteristics of the host and the mechanisms of biological threats and agents to protect the host more effectively. Emerging and re-emerging infectious diseases, such as the current coronavirus disease 2019 (COVID-19) pandemic, have raised concerns regarding both biosafety and immunology worldwide. Interdisciplinary studies involved in biosafety and immunology are relevant in many fields, including the development of vaccines and other immune interventions such as monoclonal antibodies and T-cells, herd immunity (or population-level barrier immunity), immunopathology, and multispecies immunity, i.e., animals and even plants. Meanwhile, advances in immunological science and technology are occurring rapidly, resulting in important research achievements that may contribute to the recognition of emerging biosafety hazards, as well as early warning, prevention, and defense systems. This review provides an overview of the interdisciplinary field of biosafety and immunology. Close collaboration and innovative application of immunology in the field of biosafety is becoming essential for human health.

1. Introduction

Biosafety is the discipline that covers the safe handling and containment of biological materials to protect “One Health”, which includes humans, agriculture, the ecosystem, and the environment, from exposure to biosafety hazards. The primary biosafety hazards are infectious agents, which may cause disease or have other detrimental effects in humans, plants, or animals and are a focal point for biosafety studies. However, in addition to the surveillance and control of

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infectious agents, the targets of these agents, or the so-called hosts, also warrant attention, especially the host immune response [1]. Generally, host immune molecules and cells react to clear biosafety threats, such as pathogens, and eventually, the host recovers. If a biosafety threat cannot be effectively eliminated, it may become virulent or cause immune dysregulation, potentially leading to severe pathological changes and even death. Some biosafety hazards can also act as allergens, which can cause individuals to produce an excessive immune response (i.e., anaphylaxis) and lead to pathological damage [2]. Biosafety hazards may also target the immune system directly, inducing immune dysfunction-related diseases, including opportunistic infections, cancers, and severe anaphylaxis, or be toxic to other organs via inflammation, such as the mental health problems that arise with neuroinflammation [3,4].

However, the interaction between pathogens (one of the most common biosafety threats) and the host immune system is not simple [5]. Pathogens have been in conflict with their hosts for millions of years, and the evolution of various species has increased the complexity of this process [6,7]. First, some pathogens, including human immunodeficiency virus, influenza virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have developed immune escape mechanisms through evolutionary variation [8,9]. Second, some pathogens actively interfere with the host immune process via unique mechanisms to achieve immune escape, for example, the African swine fever virus and adenovirus [10,11]. Third, some pathogens can directly infect immune cells, destroy the immune process, and reduce the immune capacity of the host [12]. Fourth, some pathogens can shed into immune-exempt organs and survive in body fluids other than blood, achieving viral dormancy, and reinfection may occur under appropriate conditions [13,14].

Therefore, in addition to the assessment of the direct harm caused to the host, evaluation of the effects of biosafety hazards and biomaterials in humans and other organisms must focus on the interaction of these threats with the host's immune system (Fig. 1). Understanding the immunological characteristics of biosafety hazards important for prevention purposes, pre-exposure prophylaxis and monitoring, post-exposure diagnosis, and rehabilitation. In this review, we retrieved relevant references and provide an overview of the interdisciplinary field related to biosafety and immunology, involving the development of vaccines and other immune interventions such as monoclonal antibodies and T-cells, herd immunity, immunopathology, and multispecies immunity, i.e., animals and even plants. Meanwhile, advances in immunological technology that may contribute to the early warning and prevention of emerging biosafety hazards have also been described.

2. Immunology in surveillance, early warning, diagnosis, treatment, and prophylaxis against pathogens of high biosafety concern

The immune system, a sophisticated network mainly comprised of innate and adaptive defenses, serves as the body's shield against pathogens. Generally, innate immunity offers swift, generalized protection via physical barriers such as the skin and cellular defenders like phagocytes. On the other hand, adaptive immunity deploys specific T and B lymphocytes to accurately target and remember pathogens, enabling faster responses upon future encounters. A combination of immunological and microbiological technologies is critical for prediction and early warning of pathogens. The development of immunology is closely related to the scientific response to and basic research on pathogenic microorganisms [1]. One of the important applications is testing and diagnosis utilizing the host immune responses to biosafety hazards. Classical immunology tests are based on the specific binding reactions between antigens and antibodies and use specific antigens or antibodies to detect specific pathogen antibodies or antigens in body fluids, thereby indirectly determining the presence of pathogens or previous infections. In recent years, with the ongoing development of science and technology, immunological testing is also iterating rapidly, and some immunological techniques are already being used in the prevention and treatment of diseases.

2.1. Monoclonal antibody

Monoclonal antibody techniques have been developed and widely applied in recent years [15]. Progress in rapid and efficient screening, modification of antibodies, and their large-scale preparation and production *in vitro* have played an important role in the response to emerging and re-emerging viruses, particularly the Ebola virus, Rift Valley fever virus, and influenza virus [16–18]. Within the monoclonal antibodies, single-domain antibodies (sdAbs, or nano-antibodies) were discovered in the dromedary camel in the 1990s and have been rapidly developed and received considerable attention as a novel technology for diagnosis and treatment [19,20]. The sdAbs do not require synthetic assembly or binding of variable fragment heavy and light chain domains, so can avoid the complexities associated with the construction, screening, and expression of conventional antibody fragment antibody libraries. The small size of sdAbs confers the advantages of rapid penetration, deep tissue penetration, rapid clearance, and penetration of the immune barrier. The ability of sdAbs to penetrate the blood–brain barrier provides potential opportunities for the treatment of nervous and reproductive system infections, tumors, and autoimmune diseases [21]. The sdAbs may be particularly useful in the treatment of viral infections such as Zika virus and Ebola virus, which can penetrate the blood–brain barrier and blood-testis barrier [22]. Furthermore, sdAbs tend to target more rigid and conserved epitopes, which has important implications for developing broad-spectrum neutralizing antibodies against infectious disease targets that constantly mutate to escape the host immune system.

In addition, bi-specific and even tri-specific antibodies targeting multiple viral Env epitopes were developed recently to increase antibody breadth and potency [23]. A combination of two or more broadly neutralizing antibodies, and Fc-mediated inhibitory functions of antibodies such as antibody-dependent cellular cytotoxicity (ADCC) have a potential role in protection against wild-type or mutated viral infection [24].

Yolk antibodies, also known as IgY present in avian blood have several advantages over mammalian serum immunoglobulins in terms of production capacity, animal welfare, and immune specificity [25]. The major immunoglobulins present in the bird's blood accumulate in the egg yolk before being passed on to the offspring, enabling non-invasive collection of large amounts of antibodies. In view of the many functions and advantages of yolk antibodies in biological sample detection, anti-infection, and anti-toxicity, their potential role in preventing bioterrorism has also been attracting attention [26].

2.2. T-cell

T-cell immunity is an immune response to antigens as important as the antibody immunity of the host against pathogens. Techniques for detecting antigen-specific T-cells include the cytotoxicity assay, test of indicator molecule on T-cell surface, cytokine secretion assay, and cell proliferation assay. Although an antigen-specific T-cell immunoassay is already used in the diagnosis of tuberculosis, this method has not been widely used for serological detection in routine clinical diagnosis of many other infections [27]. With the development of novel techniques in recent years, diagnosis and treatment techniques based on antigen-specific T-cell immunity have improved markedly, especially in the treatment of hematological malignancies and solid tumors [28]. As the technology evolves, it is likely that T-cell-related techniques will play an important role in the diagnosis and treatment, in the development of vaccines against pathogen infection and in oncol-

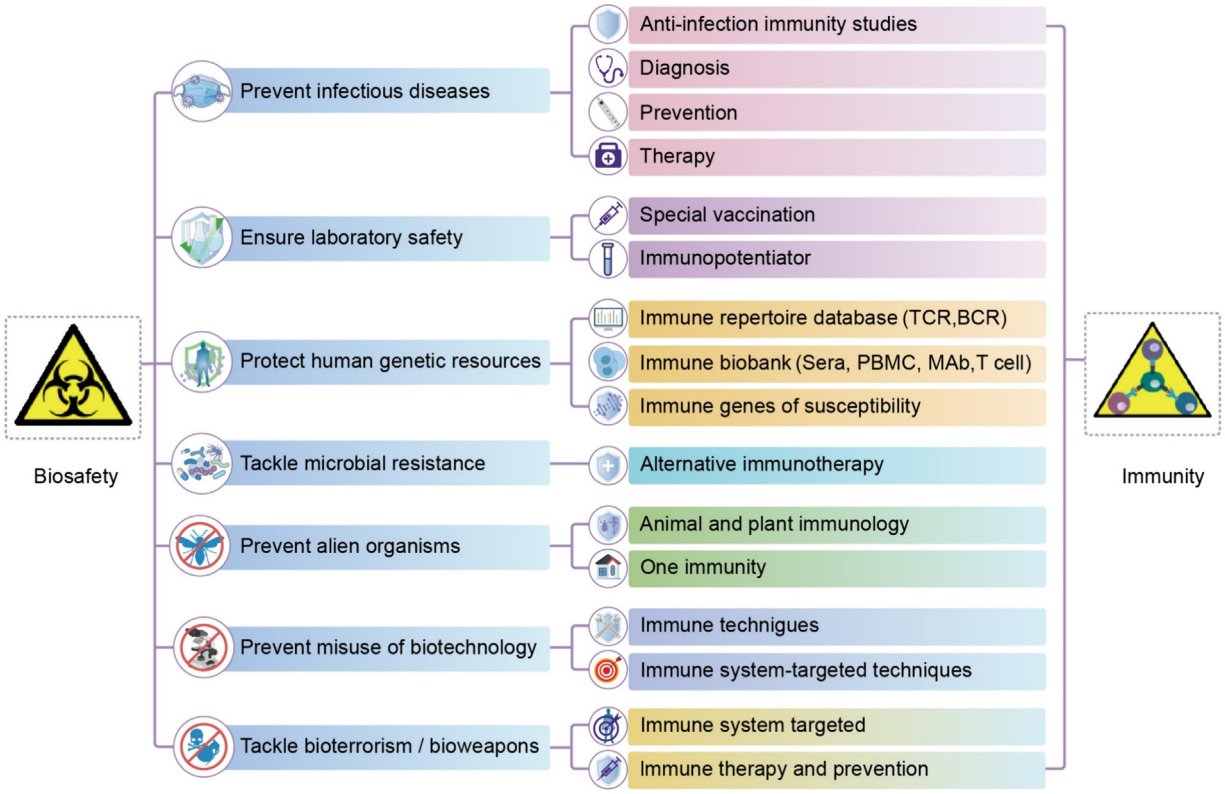

Fig. 1. Major interdisciplinary areas between biosafety and immunology. Abbreviations: TCR, T cell receptor; BCR, B cell receptor; PBMC, peripheral blood mononuclear cell; MAb, monoclonal antibody.

ogy, as well as in the identification of biological factors that pose a threat to humans [9]. T-cell immunoassays for emerging and re-emerging pathogens still have shortcomings, including a long detection time, high technical requirements, and need for standardization; however, the current T-cell immunoassays also provide a useful reference for clinical intervention and vaccine development [29,30]. Future trends include, but are not limited to, the detection of specific cellular immunity level of virus-infected individuals, the evaluation of T-cell immunity stimulated by vaccines, and the screening and discovery of novel antigen epitopes for potentially universal vaccines [31,32].

2.3. Mucosal immunity

Mucosal immunity is a specialized branch of the immune system guarding the body's mucosal surfaces, such as the gastrointestinal, respiratory, and genitourinary tracts. These surfaces are primary entry points for many pathogens. Respiratory viruses, such as influenza viruses, coronaviruses (including SARS-CoV-2), adenoviruses, and respiratory syncytial virus (RSV), infect humans via the mucosal surfaces of the respiratory tract, leading to diseases ranging from mild to severe. The mucosal immune response involves various cell types and molecular mechanisms, such as secretory IgA, interferon responses of mucosal epithelial cells, and the activation of innate immune cells like macrophages and dendritic cells [33].

The immune escape due to the quick mutations of pathogens entering the body via mucosal surfaces, such as influenza and SARS-CoV-2, may indicate the importance of mucosal vaccines [34,35]. As a significant stride in immunology, the development of mucosal vaccines is designed to be administered directly to the respiratory tract, primarily through nasal sprays, aiming to elicit local immune responses at the entry sites of pathogens and potentially providing more effective protection than traditional systemic vaccines [36,37]. Challenges in this area include developing safe and effective mucosal adjuvants, ensuring the stability and potency of the vaccine, and understanding the long-term durability of mucosal immune responses. Mucosal therapeutics offer unique advantages, including targeted delivery to specific mucosal sites and reduced systemic side effects [38]. One of the major challenges in the development of mucosal therapeutics is the effective delivery of drugs to mucosal surfaces. The mucosal environment is often hostile to foreign substances, which can lead to rapid degradation of therapeutics. Thus, significant efforts are being made to develop delivery systems that protect drugs from degradation while ensuring their effective absorption at the target site [39].

Future research in mucosal immunity is likely to focus on the interplay between the microbiome and the immune system, novel mucosal vaccine platforms, and innovative therapeutic approaches targeting mucosal surfaces. As our understanding of this complex system expands, it opens new avenues for prevention and treatment of a variety of diseases.

2.4. Vaccine

Vaccination is one of the most economical and effective ways of preventing and controlling infectious diseases [40,41]. With ongoing breakthroughs, vaccine technology has developed from the Pasteur principle of "isolation, inactivation, and injection" of pathogens to modern diverse vaccine strategies based on the integration of genetic engineering, immunology, structural biology, reverse vaccinology, systems biology, and artificial intelligence. A variety of strategies are now available for the development of vaccines against newly identified and re-emerging pathogens, including attenuated vaccines, inactivated vaccines, polysaccharide-protein binding vaccines, multivalent vaccines, virus-like particle vaccines, nanoparticle vaccines, viral vector vaccines, subunit vaccines, polypeptide vaccines, deoxyribonucleic acid (DNA) vaccines, and messenger ribonucleic acid (mRNA) vaccines [42].

Polypeptide vaccine is one of these vaccines and is prepared by identifying the amino acid sequence of important epitopes on infec-

tious pathogens and synthesizing polypeptides *in vitro* [9]. Polypeptide vaccine has the advantages of high safety and a broader spectrum, especially considering the involvement of conserved T-cell epitopes. However, independently used peptides often lead to insufficient immunogenicity and require multiple immunizations. Immunogenicity can be enhanced by various strategies, including fusion expression or chemical linkage of epitope peptides with carrier proteins, synthetic synthesis of interlinked peptide repeats, and certain specific adjuvants [43].

Vaccine development for infectious diseases, such as acquired immunodeficiency syndrome, dengue fever, and malaria, still faces many challenges due to pathogen mutation, multiple subtypes, the antibody-dependent enhancement effect infection, and immune escape [44]. During the coronavirus disease 2019 (COVID-19) pandemic, the application of innovative vaccine technology has accelerated the research and development, production, and application of vaccines. However, the emergence and prevalence of novel variant strains with immune escape characteristics have exceeded the speed of vaccine research and development, posing challenges to existing vaccines and highlighting the urgency of developing new vaccine technologies [45]. Furthermore, the immune parameters or combinations thereof and the modelling that correlates with vaccine protection, either mechanistically or non-mechanistically, are still unclear. This is important for vaccine development, especially in terms of estimation and prediction of protection after immunization.

2.5. Other immune techniques and interventions

Disruptive biotechnologies can be used in diagnosing, preventing, or treating diseases by acting on human immunity, such as gene editing, single-cell sequencing, extracellular vesicles, gene therapy, and regenerative medicine, etc., based on a logical relationship from idea to merchandise [28,46–59] (Table 1). A surprisingly sophisticated adaptive immune system that relies on small RNAs for sequence-specific targeting of foreign nucleic acids has been discovered in bacteria and archaea. Molecular vaccination in prokaryotes is achieved by integrating short fragments of foreign nucleic acids into a repetitive locus in the host chromosome known as a clustered regularly interspaced short palindromic repeat (CRISPR). The genome editing-related technique has become one of the most compelling topics in biotechnology. CRISPR-Cas-mediated diagnostics are portable and can detect various pathogens, cancer biomarkers, and single nucleotide polymorphisms with high specificity, speed, and low cost [46,47] (Table 1). The combination of Cas proteins with biosensors, biochips, biomagnetic beads, isothermal amplification, lateral flow, protein aptamers, and other technologies has resulted in the development of new diagnostic methods [48].

Including adaptive immunity, the immune system is composed of numerous heterogeneous immune cells that regulate physiological processes and protect organisms from disease. Single-cell sequencing technology has been used to evaluate immune cell responses at the single-cell level, which is crucial for identifying causes of disease and elucidating potential biological mechanisms that promote disease and might lead to the development of drug therapy and vaccines [49,50] (Table 1). Furthermore, sequencing technology based on the immune repertoire has provided a more in-depth understanding of infectious diseases, autoimmune diseases, and cancer [51]. Using high-throughput methods to sequence B-cell receptors (BCR) can screen for therapeutic antibodies with high specificity [52]. With the help of single-cell transcriptome sequencing and single-cell BCR sequencing technology, neutralizing antibodies have been isolated and identified in patients undergoing COVID-19 rehabilitation, which can be applied to research and development of therapeutic antibodies [53,54]. Meanwhile, high-throughput screening of T-cell receptors is also of considerable significance for T-cell-based adoptive therapy, which recognizes tumor antigens [28].

3. Immunological requirements and considerations for workers in biosafety laboratories and health care systems

Research on pathogens conducted at high-level biosafety laboratories often involves high concentrations of microorganisms, aerosol challenge experiments in laboratory animals, and pilot production of high-risk pathogens and toxins [60,61]. The conduct and management of these investigations place laboratory workers at substantial risk of exposure, which is increased further because of the unavailability of specific treatments for infections caused by some pathogens [62].

In recent decades, best practices have been designed, assessed, and applied to reduce the likelihood that laboratory or healthcare activities involving hazardous pathogens will cause harm to workers, the public, or the environment because of accidental releases or contacts (Fig. 2) [63,64]. This encompasses the adoption of sophisticated containment protocols, the deployment of laboratory facilities, laboratory equipment, personal protective equipment (PPE), consistent training sessions, and drills for staff, alongside rigorous waste management tactics to mitigate biohazard exposure [65]. Biosafety measures involve comprehensive risk assessments, the use of biosafety cabinets, and strict containment procedures to prevent accidental pathogen release. Continuous training and competency assessments are essential to maintaining high safety standards [66]. In addition to the protection by the consistent use of PPE, the immune system is the last gateway of biosecurity defense in humans (Fig. 2). Immunological requirements for personnel in high-risk environments include mandatory vaccinations and regular health monitoring. Advanced technologies, such as next-generation sequencing (NGS) and multiplex immunological testing, etc., enable rapid pathogen detection and immune response assessment [67]. Furthermore, throughout a series of biosafety guidelines and updated editions, quality laboratory science is reinforced by a common-sense approach to biosafety in day-to-day activities [68–70]. Thus, risks to laboratory workers have been mitigated markedly over time with improvements in biosafety procedures, primary biocontainment systems, personal protective equipment, and engineering facilities [71,72]. However, laboratory-acquired infections do continue to occur sporadically [73,74]. Therefore, additional protection in the form of vaccines, antibiotics, antiviral drugs, and antibodies remains an integral component in the protection of laboratory workers who work with highly hazardous pathogens.

Interventions regarding the immunization status of laboratory personnel may include special vaccinations to provide additional protection from highly hazardous pathogens [75], application of prophylactic agents or immunopotentiators, medical evaluation to ensure safety and well-being, and implementation of treatment after occupational exposure [76,77]. Serum is also routinely stored for biosafety workers so that their immune status can be tracked, and immunocompromised persons cannot enter high biocontainment laboratories for obvious biosafety reasons.

4. Concept of herd immunity against pathogens of biosafety concern

The concept of herd immunity first appeared in the 1920s [78] and was later developed in parallel with the use of smallpox, poliomyelitis, and measles vaccines [79]. However, there are still some controversies regarding this concept [80,81]. The current general understanding is that in the case of herd immunity, the chain of transmission of infectious diseases is interrupted and the susceptible population is protected. Herd immunity plays a crucial role in biosafety by indirectly protecting susceptible individuals within a population through a sufficient proportion of immune individuals. This effect reduces the risk of infection spread, offering collective protection and potentially improving biosafety outcomes by preventing the invasion of new infections [82].

Table 1
Innovative biotechniques in immunology and biomedicine.

Technique type	Description	Application	Advantage	References
CRISPR-Cas system	A sophisticated adaptive immune system in bacteria and archaea that relies on small RNAs for sequence-specific targeting of foreign nucleic acids.	Diagnostics for pathogens, cancer biomarkers, and single nucleotide polymorphisms, biotherapies, etc.	CRISPR-Cas-mediated diagnostics are portable, fast, low-cost, and highly specific. The combination with various technologies has led to new diagnostic and biotherapy methods.	[46–48]
Single-cell sequencing	Technique used to evaluate immune cell responses at the single-cell level, etc.	Screening of diagnostic and biotherapy targets of infectious diseases, autoimmune diseases, and cancer; development of drug therapy and vaccines.	In-depth understanding of immune responses and heterogeneity; Systematic screening of diagnostic and biotherapy targets.	[28,49–54]
Extracellular vesicles	Membrane-bound nanocarriers that can carry proteins, lipids, DNA, and different forms of RNA, etc.	An important delivery system for therapeutic agents, etc.	Used for intercellular communication and providing targeted bioactive molecules for disease treatment, etc.	[55]
Gene therapy	Medical intervention that transmits genetic material to humans, animals and/or plants.	Treatment of diseases by genetic modification at the DNA and RNA levels, and epigenetic level, etc.	Specifically targeting and modifying the genes responsible for a disease, potentially correcting the underlying causes rather than merely treating symptoms.	[56]
Regenerative medicine	Based on techniques that creates an environment for progenitor cells to develop into functional tissues to replace cells that die due to trauma, disease, or senescence.	Cell transplantation for reconstructing and promoting regeneration of tissues, etc.	Regulating immune responses and prevents transplant rejection, etc.	[57–59]

Abbreviations: DNA, deoxyribouucleic acid; RNA, ribonucleic acid; CRISPR, clustered regularly interspaced short palindromic repeat.

In the wake of COVID-19, some scientists have proposed building herd immunity by relying on natural viral infection. However, the SARS-CoV-2 variants continue to break through the immunity generated by natural infection and vaccination [83]. Furthermore, given the potential breakthrough of herd immunity by the influenza viruses with new evolutionary characteristics, some components of the influenza virus vaccine need to be administered every year. These considerations have given rise to the scientific question of how the virus evolves to break through the immune barrier at the population level. Notably, the rebound of common respiratory diseases in the 2022–2023 and 2023–2024 seasons showed a similar pattern in different countries and regions [45,84]. This is supposed to be attributed to reduced herd immunity following a prolonged period of exposure to minimal respiratory pathogens. However, the quantification of the decreased herd immunity of the so-called immune gap remains to be investigated, which is pivotal for the early-warning and biosafety assessment of future respiratory diseases.

Therefore, before intervention, it is essential to understand the key factors affecting herd immunity to a specific pathogen: first, the proportion of the population infected by the pathogen; second, the vaccination coverage; third, the duration of adaptive immunity established by the infection and vaccination, which can be determined by antigens from the pathogen itself; fourth, the speed at which pathogen variants emerge; and fifth, the composition of the population, including age, underlying diseases, and genetic susceptibility. Polymorphism of the human leucocyte antigen is thought to be related to herd immunity in terms of genetic susceptibility [51,85].

5. Animal immunity against pathogens in the “One Health” concept

Human immunity to pathogens, related vaccines, and diagnostic methods may play a central role in interdisciplinary research on immunology and biosafety [1,5]. Animal diseases, especially emerging and re-emerging pathogens and related immunological issues, are also important in this field of research. For example, emerging and re-emerging veterinary infectious diseases often cause a large number of animals being infected or even dying in a short period of time, leading to significant economic losses [86]. In recent years, African swine fever virus and avian influenza virus have been widespread in pigs and poultry on various continents, causing losses in the breeding industry [87]. Avian influenza viruses can be transmitted from chickens and ducks to humans, with documented cases in various settings such as live poultry markets and farms. Notably, clade 2.3.4.4b of highly pathogenic avian influenza (HPAI) A(H5N1) viruses have been detected in dairy cows in different states of the United States [88]. And recently a case of HPAI A (H5N1) virus infection in a dairy farm worker with conjunctivitis without respiratory symptoms was reported in Texas [89]. The virus carries a typical mammalian-signatured substitution PB2 E627K. This evidenceindicates that close contact with infected domestic animals is a primary risk factor for zoonotic infection. Meanwhile, these viruses also exist in wild boar and wild birds, posing an ongoing threat to animal health [90]. Therefore, immunization strategies, such as vaccination of livestock, poultry, pets, and other animals, are particularly important for animal-related biosecurity threats. Moreover, in recent years, a considerable proportion of emerging and re-emerging infectious diseases in humans have been confirmed to originate from animals as so-called zoonotic diseases. The prevalence of these diseases in humans can be reduced by prevention and control measures in animals.

Bats carry a variety of highly pathogenic viruses that can cause severe infection and even death in humans. However, the bats themselves do not become ill. In line with the concept of comparative immunology, research on the immune characteristics of bats and the mechanism of antiviral immunity is significant in terms of the prevention and control, diagnosis, and treatment of highly pathogenic viral infections in humans [91,92].

Immunological research in plants also has an important role in the prevention of biosafety threats [93]. Immunology covers the entire life cycle of plants, especially diseases of plants and their interactions with microbes, pests, and other species. Immunological studies also play a role in the recognition of alien species and intervention on their invasion.

In conclusion, research based on interactions between pathogens and the immune systems of the intended hosts (which may be human, animal, or plant) can help us to better understand the threats to humans and the environment and to explore countermeasures and protection strategies [94]. Furthermore, the inclusion of ecological, climatic, environmental, and other factors within the “One Health” framework will further broaden our vision of the application of immunology within biosafety.

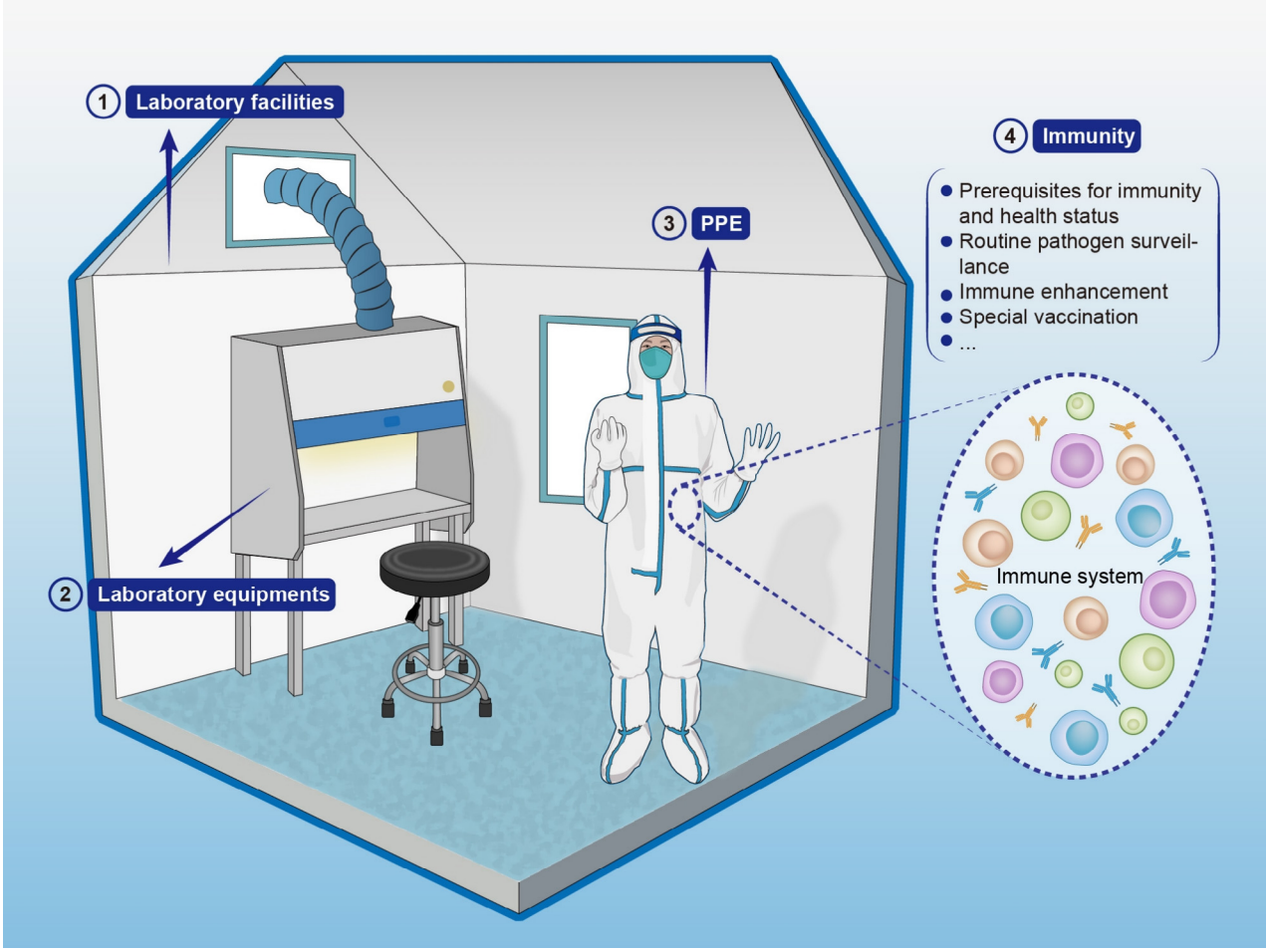

Fig. 2. The pivotal role of immunity for biosafety laboratory personnel. The diagram illustrates the critical components ensuring biosafety in a high-containment biosafety laboratory environment. The laboratory facilities, including the ventilation system, are crucial for ensuring safety and minimizing contamination risks. Essential laboratory equipment, such as the biosafety cabinet, forms the basis for safe and effective experimental operations. Laboratory personnel wear personal protective equipment (PPE) to prevent exposure to harmful substances. The immune system is the last gateway of biosecurity defense for laboratory staff, and the routine points of focus encompasses, but is not limited to, prerequisites for immunity and health status, routine pathogen surveillance, immune enhancement, and special vaccination, etc. These measures help maintain the health of laboratory personnel and the safe and smooth conduct of experiments.

6. Defense against bioterrorism and immunity

Bioterrorism involves the deliberate release of biological agents to cause illness, death, and fear among humans, animals, or plants, aiming at mass casualties, societal disruption, or economic loss [95]. Bioterrorism is a potentially significant threat to global security. The immune system is the last gateway of biosecurity defense in humans and is significant in terms of enhancing individual-level immunity and building a population-level immune barrier for defense against bioterrorism. Investigation of immune recognition mechanisms can benefit the detection and identification of biological agents that pose a threat to health. Bioterrorism-oriented defense technology mainly involves the fields of diagnosis, pre-exposure prophylaxis and vaccination, and post-exposure prophylaxis and treatment. Pre-exposure prophylaxis and vaccine research and development have been the specific focus of many biodefense research programs.

Innate immunity is the body's first line of defense and plays an essential role in eliminating foreign pathogens and guiding the body to produce an effective adaptive immune response [96]. Studies have shown that activation of innate immunity often provides preventive and post-exposure protection against multiple pathogens in cases where the pathogen in a bioterrorist attack is unknown. For example, CpG9 is a Toll-like receptor-9 agonist that can activate the innate and adaptive immune systems and has immunoprotective effects against a variety of pathogens, including *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularensis* [97]. Antimicrobial peptides can effectively control infection with multidrug-resistant pathogens by immune regulation or interruption of the invasion and replication of the pathogen [98]. However, owing to differences in species and human genetic polymorphisms, the timeliness, safety, and efficacy of innate immune stimulation require further investigation.

Activation of the adaptive immune system is important in the prevention of infection and post-exposure treatment of bioterrorism pathogens. Monoclonal antibodies have been used for pre-exposure prophylaxis and post-exposure treatment of many bioterrorism-related pathogens and are also required for rapid diagnosis of bioterrorism-related pathogens. Vaccines have always been a focus of research in the context of being an important means of protection against potential bioterrorism pathogens and can be used for pre-exposure and post-exposure prophylaxis against conditions. However, pathogen strains mutate rapidly and require continuous monitoring of their variability and vaccine effectiveness. A number of studies have shown that T-cells target the epitopes of the dominant immunogen of the virus. Furthermore, the target recognized by T-cells is relatively more conservative, and memory T-cells have a long lifespan, which means that they can provide lasting immunity [32]. For example, iden-

tification of multiple stable epitopes in COVID-19 as T-cell vaccine targets provides a direction for the development of more broadly protective COVID-19 vaccines [31].

7. Limitations

Biosafety and immunology themselves have a huge and systematic disciplinary system and involve multidisciplinary intersections, respectively. Here in our review, we only focus on several aspects of the interdisciplinary field related to biosafety and immunology with many regrettable omissions. And we are also regretted if some literature was not cited in the description. However, we believe that the interdisciplinary field of biosafety and immunology is an emerging field, which is of great significance to human health. The consensus on the contents and the future of biosafety and immunology requires the participation and discussion of more experts.

8. Perspectives

The development of biosafety to protect humans, agriculture, ecosystems, and the environment from exposure to biosafety hazards involves multidisciplinary collaboration. Immunology is one of the most important biosafety strategies, given that the host, as the subject of the biohazard, has a natural immune response. Studies of bionics pertaining to immunity can support the development of techniques for diagnosis, treatment, and prevention of biosafety hazards. The application of novel theories, methods, and products from the field of immunology will help eliminate biosafety threats and prevent biosafety hazards, especially with regard to infectious diseases.

The adoption of innovative immunological theories, techniques, and products promises significant strides in mitigating biosafety threats and neutralizing hazards, especially those related to infectious agents. By leveraging cutting-edge research in immune system functioning and pathogen resistance, we can enhance detection, refine therapeutic interventions, and strengthen preventive measures against a range of pathogens, ensuring a safer and healthier future in the face of evolving microbial challenges. Interdisciplinary studies in biosafety and immunology hold considerable promise for protecting human health and safety from the threat of emerging and re-emerging diseases and other biosafety hazards.

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Conflcit of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

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References

[1] W.J. Liu, J. Xu, The arms race in the war between virus and host: implications for anti-infection immunity, Infect. Dis. Immun. 2 (3) (2022) 129–131, https://doi.org/10.1097/id9.0000000000000062.
[2] S.B. Fritz, A.M. Singer, V.B. Revan, J.R. Baker Jr., Bioterrorism: relevance to allergy and immunology in clinical practice, J. Allergy Clin. Immunol. 109 (2) (2002) 214–228, https://doi.org/10.1067/mai.2002.121947.
[3] D. Li, S. Liu, Y. Ma, S. Liu, Y. Liu, J. Ding, Biomaterials that induce immunogenic cell death, Small Methods 7 (5) (2023) 2300204, https://doi.org/10.1002/smtd.202300204.
[4] C. Du, G. Li, G. Han, Biosafety and mental health: virus induced cognitive decline, Biosaf. Health 5 (3) (2023) 159–167, https://doi.org/10.1016/j.bsheal.2023.04.002.
[5] W.J. Liu, D. Liu, The triphibious warfare against viruses, Sci. China Life Sci. 60 (12) (2017) 1295–1298, https://doi.org/10.1007/s11427-017-9252-y.
[6] P. Wang, W.J. Liu, It's not just science: challenges for public health intervention in Ebola epidemics in the Democratic Republic of Congo, Sci. China Life Sci. 63 (7) (2020) 1079–1081, https://doi.org/10.1007/s11427-019-1670-6.
[7] P. Wang, C. Yue, K. Liu, D. Lu, S. Liu, S. Yao, X. Li, X. Su, K. Ren, Y. Chai, et al., Peptide presentations of marsupial MHC class I visualize immune features of lower mammals paralleled with bats, J. Immunol. 207 (8) (2021) 2167–2178, https://doi.org/10.4049/jimmunol.2100350.
[8] Y. Zhao, W. Xiao, Y. Wu, W. Fan, L. Li, C. Yue, Q. Zhang, D. Zhang, X. Yuan, S. Yao, et al., Parallel T cell immunogenic regions in influenza B and A viruses with distinct nuclear export signal functions: The balance between viral life cycle and immune escape, J. Immunol. 210 (8) (2023) 1074–1085, https://doi.org/10.4049/jimmunol.2200243.
[9] J. Liu, S. Zhang, S. Tan, B. Zheng, G.F. Gao, Revival of the identification of cytotoxic T-lymphocyte epitopes for immunological diagnosis, therapy and vaccine development, Exp. Biol. Med. (Maywood) 236 (3) (2011) 253–267, https://doi.org/10.1258/ebm.2010.010278.
[10] X. Zheng, S. Nie, W.H. Feng, Regulation of antiviral immune response by African swine fever virus (ASFV), Virol. Sin. 37 (2) (2022) 157–167, https://doi.org/10.1016/j.virs.2022.03.006.
[11] E.R.A. Oliveira, M. Bouvier, Immune evasion by adenoviruses: A window into host-virus adaptation, FEBS Lett. 593 (24) (2019) 3496–3503, https://doi.org/10.1002/1873-3468.13682.
[12] Y. Zheng, S. Li, S.H. Li, S. Yu, Q. Wang, K. Zhang, L. Qu, Y. Sun, Y. Bi, F. Tang, et al., Transcriptome profiling in swine macrophages infected with African swine fever virus at single-cell resolution, Proc. Natl. Acad. Sci. USA 119 (19) (2022) e2201288119, https://doi.org/10.1073/pnas.2201288119.
[13] J.G. Shantha, J.G. Mattia, A. Goba, K.G. Barnes, F.K. Ebrahim, C.S. Kraft, B.R. Hayek, J.N. Hartnett, J.G. Shaffer, J.S. Schieffelin, et al., Ebola virus persistence in ocular tissues and fluids (EVICT) study: Reverse transcription-polymerase chain reaction and cataract surgery outcomes of Ebola survivors in Sierra Leone, EBioMedicine 30 (2018) 217–224, https://doi.org/10.1016/j.ebiom.2018.03.020.
[14] A.E. Thorson, G.F. Deen, K.T. Bernstein, W.J. Liu, F. Yamba, N. Habib, F.R. Sesay, P. Gaillard, T.A. Massaquoi, S.L.R. McDonald, et al., Persistence of Ebola virus in semen among Ebola virus disease survivors in Sierra Leone: A cohort study of frequency, duration, and risk factors, PLoS Med. 18 (2) (2021) e1003273, https://doi.org/10.1371/journal.pmed.1003273.
[15] P. Nieri, E. Donadio, S. Rossi, B. Adinolfi, A. Podestà, Antibodies for therapeutic uses and the evolution of biotechniques, Curr. Med. Chem. 16 (6) (2009) 753–779, https://doi.org/10.2174/092986709787458380.
[16] Q. Wang, T. Ma, Y. Wu, Z. Chen, H. Zeng, Z. Tong, F. Gao, J. Qi, Z. Zhao, Y. Chai, et al., Neutralization mechanism of human monoclonal antibodies against Rift Valley fever virus, Nat. Microbiol. 4 (7) (2019) 1231–1241, https://doi.org/10.1038/s41564-019-0411-z.
[17] H. Xiao, T. Guo, M. Yang, J. Qi, C. Huang, Y. Hong, J. Gu, X. Pang, W.J. Liu, R. Peng, et al., Light chain modulates heavy chain conformation to change protection profile of monoclonal antibodies against influenza A viruses, Cell Discov. 5 (2019) 21, https://doi.org/10.1038/s41421-019-0086-x.
[18] Q. Zhang, M. Gui, X. Niu, S. He, R. Wang, Y. Feng, A. Kroeker, Y. Zuo, H. Wang, Y. Wang, et al., Potent neutralizing monoclonal antibodies against Ebola virus infection, Sci. Rep. 6 (2016) 25856, https://doi.org/10.1038/srep25856.
[19] H. Liu, L. Wu, B. Liu, K. Xu, W. Lei, J. Deng, X. Rong, P. Du, L. Wang, D. Wang, et al., Two pan-SARS-CoV-2 nanobodies and their multivalent derivatives effectively prevent Omicron infections in mice, Cell Rep. Med. 4 (2) (2023) 100918, https://doi.org/10.1016/j.xcrm.2023.100918.
[20] S. Muyldermans, Nanobodies: Natural single-domain antibodies, Annu. Rev. Biochem. 82 (2013) 775–797, https://doi.org/10.1146/annurev-biochem-063011-092449.
[21] C.G. Siontorou, Nanobodies as novel agents for disease diagnosis and therapy, Int. J. Nanomedicine 8 (2013) 4215–4227, https://doi.org/10.2147/ijn.S39428.
[22] M.E. Tsitokana, P.A. Lafon, L. Prézeau, J.P. Pin, P. Rondard, Targeting the brain with single-domain antibodies: Greater potential than stated so far? Int. J. Mol. Sci. 24 (3) (2023) 2632, https://doi.org/10.3390/ijms24032632.
[23] Z. Li, S. Li, G. Zhang, W. Peng, Z. Chang, X. Zhang, Z. Fan, Y. Chai, F. Wang, X. Zhao, et al., An engineered bispecific human monoclonal antibody against SARS-

CoV-2, Nat. Immunol. 23 (3) (2022) 423–430, https://doi.org/10.1038/s41590-022-01138-w.
[24] B. Su, S. Dispinseri, V. Iannone, T. Zhang, H. Wu, R. Carapito, S. Bahram, G. Scarlatti, C. Moog, Update on Fc-mediated antibody functions against HIV-1 beyond neutralization, Front. Immunol. 10 (2019) 2968, https://doi.org/10.3389/fimmu.2019.02968.
[25] B.L.B. Pacheco, C.P. Nogueira, E.J. Venancio, IgY antibodies from birds: A review on affinity and avidity, Animals 13 (19) (2023) 3130, https://doi.org/10.3390/ani13193130.
[26] A.T. Abbas, S.A. El-Kafrawy, S.S. Sohrab, E.I.A. Azhar, IgY antibodies for the immunoprophylaxis and therapy of respiratory infections, Hum. Vaccin. Immunother. 15 (1) (2019) 264–275, https://doi.org/10.1080/21645515.2018.1514224.
[27] S. Tan, N. Lin, M. Huang, Q. Wang, Y. Tan, B. Li, N. Zhang, T. Guo, Y. Cui, X. Chen, et al., CTL immunogenicity of Rv3615c antigen and diagnostic performances of an ESAT-6/CFP-10/Rv3615c antigen cocktail for Mycobacterium tuberculosis infection, Tuberculosis (Edinb.) 107 (2017) 5–12, https://doi.org/10.1016/j.tube.2017.07.011.
[28] D. Lu, Y. Chen, M. Jiang, J. Wang, Y. Li, K. Ma, W. Sun, X. Zheng, J. Qi, W. Jin, et al., KRAS G12V neoantigen specific T cell receptor for adoptive T cell therapy against tumors, Nat. Commun. 14 (1) (2023) 6389, https://doi.org/10.1038/s41467-023-42010-1.
[29] W.J. Liu, M. Zhao, K. Liu, K. Xu, G. Wong, W. Tan, G.F. Gao, T-cell immunity of SARS-CoV: Implications for vaccine development against MERS-CoV, Antiviral Res. 137 (2017) 82–92, https://doi.org/10.1016/j.antiviral.2016.11.006.
[30] H. Lin, J. Zhang, S. Dong, Y. Liu, P. Liu, G.F. Gao, W.J. Liu, G. Wu, An adjusted ELISpot-based immunoassay for evaluation of SARS-CoV-2-specific T-cell responses, Biosaf. Health 4 (3) (2022) 179–185, https://doi.org/10.1016/j.bsheal.2022.04.005.
[31] C. Yue, P. Wang, J. Tian, G.F. Gao, K. Liu, W.J. Liu, Seeing the T cell immunity of SARS-CoV-2 and SARS-CoV: Believing the epitope-oriented vaccines, Int. J. Biol. Sci. 19 (13) (2023) 4052–4060, https://doi.org/10.7150/ijbs.80468.
[32] M. Zhao, H. Zhang, K. Liu, G.F. Gao, W.J. Liu, Human T-cell immunity against the emerging and re-emerging viruses, Sci. China Life Sci. 60 (12) (2017) 1307–1316, https://doi.org/10.1007/s11427-017-9241-3.
[33] R.C. Mettelman, E.K. Allen, P.G. Thomas, Mucosal immune responses to infection and vaccination in the respiratory tract, Immunity 55 (5) (2022) 749–780, https://doi.org/10.1016/j.immuni.2022.04.013.
[34] M.A. Rose, S. Zielen, U. Baumann, Mucosal immunity and nasal influenza vaccination, Expert Rev. Vaccines 11 (5) (2012) 595–607, https://doi.org/10.1586/erv.12.31.
[35] J.M. Knisely, L.E. Buyon, R. Mandt, R. Farkas, S. Balasingam, K. Bok, U.J. Buchholz, M.P. D'souza, J.L. Gordon, D.F.L. King, et al., Mucosal vaccines for SARS-CoV-2: Scientific gaps and opportunities-workshop report, NPJ Vaccines 8 (1) (2023) 53, https://doi.org/10.1038/s41541-023-00654-6.
[36] K. Matsuda, S.A. Migueles, J. Huang, L. Bolkhovitinov, S. Stuccio, T. Griesman, A. A. Pullano, B.H. Kang, E. Ishida, M. Zimmerman, et al., A replication-competent adenovirus-vectored influenza vaccine induces durable systemic and mucosal immunity, J. Clin. Invest. 131 (5) (2021), https://doi.org/10.1172/jci140794.
[37] N. van Doremalen, J.N. Purushotham, J.E. Schulz, M.G. Holbrook, T. Bushmaker, A. Carmody, J.R. Port, C.K. Yinda, A. Okumura, G. Saturday, et al., Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces viral shedding after SARS-CoV-2 D614G challenge in preclinical models, Sci. Transl. Med. 13 (607) (2021) eabh0755, https://doi.org/10.1126/scitranslmed.abh0755.
[38] H. Zhang, J. Zhang, J.B. Streisand, Oral mucosal drug delivery: Clinical pharmacokinetics and therapeutic applications, Clin. Pharmacokinet. 41 (9) (2002) 661–680, https://doi.org/10.2165/00003088-200241090-00003.
[39] J.M. Wells, A. Mercenier, Mucosal delivery of therapeutic and prophylactic molecules using lactic acid bacteria, Nat. Rev. Microbiol. 6 (5) (2008) 349–362, https://doi.org/10.1038/nrmicro1840.
[40] K. Xu, C. Fan, Y. Han, L. Dai, G.F. Gao, Immunogenicity, efficacy and safety of COVID-19 vaccines: An update of data published by 31 December 2021, Int. Immunol. 34 (12) (2022) 595–607, https://doi.org/10.1093/intimm/dxac031.
[41] G.F. Gao, W.J. Liu, Let's get vaccinated for both flu and COVID-19: On the World Flu Day 2021, China CDC Wkly. 3 (44) (2021) 915–917, https://doi.org/10.46234/ccdcw2021.227.
[42] B.K. Nunnally, V.E. Turula, R.D. Sitrin, Vaccine analysis: Strategies, principles, and control, Springer, New York, 2015, https://link.springer.com/book/10.1007/978-3-662-45024-6.
[43] Y. Zhang, Y. Wu, M. Deng, D. Xu, X. Li, Z. Xu, J. Hu, H. Zhang, K. Liu, Y. Zhao, et al., CD8(+) T-cell response-associated evolution of hepatitis B virus core protein and disease progress, J. Virol. 92 (17) (2018) e02120-17, https://doi.org/10.1128/jvi.02120-17.
[44] J.G. Beeson, L. Kurtovic, C. Dobaño, D.H. Opi, J.-A. Chan, G. Feng, M.F. Good, L. Reiling, M.J. Boyle, Challenges and strategies for developing efficacious and long-lasting malaria vaccines, Sci. Transl. Med. 11 (474) (2019) eaau1458, https://doi.org/10.1126/scitranslmed.aau1458.
[45] W.J. Liu, S. Liu, A tale of two cities: From influenza HxNy to SARS-CoV-z, China CDC Wkly. 3 (49) (2021) 1052–1056, https://doi.org/10.46234/ccdcw2021.256.
[46] Y. He, S. Shao, J. Chen, High-fidelity identification of single nucleotide polymorphism by type V CRISPR systems, ACS Sens. 8 (12) (2023) 4478–4483, https://doi.org/10.1021/acssensors.3c02158.
[47] C.H. Huang, K.C. Lee, J.A. Doudna, Applications of CRISPR-Cas enzymes in cancer therapeutics and detection, Trends Cancer 4 (7) (2018) 499–512, https://doi.org/10.1016/j.trecan.2018.05.006.
[48] L. Li, G. Shen, M. Wu, J. Jiang, Q. Xia, P. Lin, CRISPR-Cas-mediated diagnostics, Trends Biotechnol. 40 (11) (2022) 1326–1345, https://doi.org/10.1016/j.tibtech.2022.04.006.
[49] L. Huang, F. Ma, A. Chapman, S. Lu, X.S. Xie, Single-cell whole-genome amplification and sequencing: Methodology and applications, Annu. Rev. Genomics Hum. Genet. 16 (1) (2015) 79–102, https://doi.org/10.1146/annurev-genom-090413-025352.
[50] L. Wen, F. Tang, Recent advances in single-cell sequencing technologies, Precis. Clin. Med. 5 (1) (2022) pbac002, https://doi.org/10.1093/pcmedi/pbac002.
[51] X. Wang, J. Zhang, P. Guo, Y. Guo, X. Yang, M. Liu, D. Zhang, Y. Guo, J. Zhan, K. Cai, et al., Rare peptide anchors of HLA class I alleles contribute to the COVID-19 disease severity and T cell memory, Biosaf. Health (2023) 355–362, https://doi.org/10.1016/j.bsheal.2023.09.002.
[52] M. Huang, Y. Ma, X. Gao, X. Li, Q. Ding, C. Liu, X. Liu, H. Zhang, N. Yang, Combining fluorescent cell sorting and single B cell amplification to screen the monoclonal antibody gene against human glypican-1 in pancreatic cancer, J. Oncol. 2021 (2021) 5646589, https://doi.org/10.1155/2021/5646589.
[53] H. Xiang, Y. Zhao, X. Li, P. Liu, L. Wang, M. Wang, L. Tian, H.X. Sun, W. Zhang, Z. Xu, et al., Landscapes and dynamic diversifications of B-cell receptor repertoires in COVID-19 patients, Hum. Immunol. 83 (2) (2022) 119–129, https://doi.org/10.1016/j.humimm.2021.10.007.
[54] Y. Cao, B. Su, X. Guo, W. Sun, Y. Deng, L. Bao, Q. Zhu, X. Zhang, Y. Zheng, C. Geng, et al., Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells, Cell 182 (1) (2020) 73–84.e16, https://doi.org/10.1016/j.cell.2020.05.025.
[55] R. Szatanek, M. Baj-Krzyworzeka, J. Zimoch, M. Lekka, M. Siedlar, J. Baran, The methods of choice for extracellular vesicles (EVs) characterization, Int. J. Mol. Sci. 18 (6) (2017) 1153, https://doi.org/10.3390/ijms18061153.
[56] C.C. Ma, Z.L. Wang, T. Xu, Z.Y. He, Y.Q. Wei, The approved gene therapy drugs worldwide: From 1998 to 2019, Biotechnol. Adv. 40 (2020) 107502, https://doi.org/10.1016/j.biotechadv.2019.107502.
[57] A.M. Brokesh, A.K. Gaharwar, Inorganic biomaterials for regenerative medicine, ACS Appl. Mater. Interfaces 12 (5) (2020) 5319–5344, https://doi.org/10.1021/acsami.9b17801.
[58] P. Ljungman, R. de la Camara, M. Mikulska, G. Tridello, B. Aguado, M.A. Zahrani, J. Apperley, A. Berceanu, R.M. Bofarull, M. Calbacho, et al., COVID-19 and stem cell transplantation: Results from an EBMT and GETH multicenter prospective survey, Leukemia 35 (10) (2021) 2885–2894, https://doi.org/10.1038/s41375-021-01302-5.
[59] M.S. Singh, S.S. Park, T.A. Albini, M.V. Canto-Soler, H. Klassen, R.E. MacLaren, M. Takahashi, A. Nagiel, S.D. Schwartz, K. Bharti, et al., Retinal stem cell transplantation: Balancing safety and potential, Prog. Retin. Eye Res. 75 (2020) 100779, https://doi.org/10.1016/j.preteyeres.2019.100779.
[60] P.B. Pedrosa, T.A. Cardoso, Viral infections in workers in hospital and research laboratory settings: A comparative review of infection modes and respective biosafety aspects, Int. J. Infect. Dis. 15 (6) (2011) e366–e376, https://doi.org/10.1016/j.ijid.2011.03.005.
[61] N. Li, L. Hu, A. Jin, J. Li, Biosafety laboratory risk assessment, J. Biosaf. Biosecurity 1 (2) (2019) 90–92, https://doi.org/10.1016/j.jobb.2019.01.011.
[62] S.N. Isaacs, Working safely with vaccinia virus: laboratory technique and review of published cases of accidental laboratory infections with poxviruses, in: J. Mercer (Ed.), Vaccinia virus: Methods and protocols, New York: Springer, 2019, pp. 1–27, https://doi.org/10.1007/978-1-4939-9593-6_1.
[63] A. MacNeil, M.G. Reynolds, I.K. Damon, Risks associated with vaccinia virus in the laboratory, Virology 385 (1) (2009) 1–4, https://doi.org/10.1016/j.virol.2008.11.045.
[64] G. Wu, Laboratory biosafety in China: Past, present, and future, Biosaf. Health 1 (2) (2019) 56–58, https://doi.org/10.1016/j.bsheal.2019.10.003.
[65] R.L. Mecklem, C.M. Neumann, Defining and managing biohazardous waste in U.S. research-oriented universities: a survey of environmental health and safety professionals, J. Environ. Health 66 (1) (2003) 17–22, https://doi.org/10.1016/j.bsheal.2019.10.003.
[66] E.V. Matosova, B.G. Andryukov, M.P. Bynina, E.I. Drobot, I.N. Lyapun, Biosafety of personnel of microbiological laboratories in the context of the federal law of the Russian Federation No 492-FZ of December 30, 2020, *On the biological safety of the Russian Federation*, Klin. Lab. Diagn. 67 (7) (2022) 414–422, https://doi.org/10.51620/0869-2084-2022-67-7-414-422.
[67] F.G. George, Active promotion of bio-industry technology development in China, Chinese Journal of Biotechnology 38 (11) (2022) 4012–4018, https://doi.org/10.13345/j.cjb.220861.
[68] A.K. Kintossou, S. Villar, Z. Kozlakidis, Immunological considerations for laboratory staff and COVID-19 biosafety, Biosaf. Health 5 (2) (2023) 108–111, https://doi.org/10.1016/j.bsheal.2023.03.001.
[69] C.Y. Ables, Soliciting stakeholder input for a revision of biosafety in microbiological and biomedical laboratories (BMBL): Proceedings of a workshop, Washington (DC): National Academies Press (US), 2016, https://doi.org/10.17226/23585.
[70] B. Ficociello, D. Giordano, F. Incoronato, A. Farinella, B. Pietrangeli, WHO laboratory biosafety manual: A new approach to security, Ann. Work Expo. Health 67 (4) (2023) 425–429, https://doi.org/10.1093/annweh/wxac086.
[71] J.E. Conte, Infection with human immunodeficiency virus in the hospital, Ann. Intern. Med. 105 (5) (1986) 730–736, https://doi.org/10.7326/0003-4819-105-5-730.

[72] F. Martina, C. Cecilia, L. Valentina, P. Lara, P. Paolo, N. Stefano, Protecting healthcare workers from SARS-CoV-2 infection: Practical indications, Eur. Respir. Rev. 29 (155) (2020) 200068, https://doi.org/10.1183/16000617.0068-2020.
[73] S.D. Blacksell, S. Dhawan, M. Kusumoto, K.K. Le, K. Summermatter, J. O'Keefe, J. Kozlovac, S.S. Almuhairi, I. Sendow, C.M. Scheel, et al., The biosafety research road map: The search for evidence to support practices in the laboratory-SARS-CoV-2, Appl. Biosaf. 28 (2) (2023) 87–95, https://doi.org/10.1089/apb.2022.0039.
[74] J. Siengsanan-Lamont, S.D. Blacksell, A review of laboratory-acquired infections in the Asia-Pacific: Understanding risk and the need for improved biosafety for veterinary and zoonotic diseases, Trop. Med. Infect. Dis. 3 (2) (2018) 36, https://doi.org/10.3390/tropicalmed3020036.
[75] National Research Council, Protecting the fFrontline in biodefense research: The special immunizations program, Washington (DC): The National Academies Press, 2011, https://doi.org/10.17226/13112.
[76] C.J. Hackett, Innate immune activation as a broad-spectrum biodefense strategy: Prospects and research challenges, J. Allergy Clin. Immunol. 112 (4) (2003) 686–694, https://doi.org/10.1016/S0091-6749(03)02025-6.
[77] J.A. Skyberg, Immunopotentiation for bacterial biodefense, Curr. Top. Med. Chem. 14 (18) (2014) 2115–2126, https://doi.org/10.2174/1568026614666141106162642.
[78] W.W. Topley, G.S. Wilson, The spread of bacterial infection: The problem of herd-immunity, J. Hyg. (Lond.) 21 (3) (1923) 243–249, https://doi.org/10.1017/s0022172400031478.
[79] J.C. Taube, E.C. Rest, J.O. Lloyd-Smith, S. Bansal, The global landscape of smallpox vaccination history and implications for current and future orthopoxvirus susceptibility: A modelling study, Lancet Infect. Dis. 23 (4) (2023) 454–462, https://doi.org/10.1016/s1473-3099(22)00664-8.
[80] Y. Xia, L. Zhong, J. Tan, Z. Zhang, J. Lyu, Y. Chen, A. Zhao, L. Huang, Z. Long, N.N. Liu, et al., How to understand "herd immunity" in COVID-19 pandemic, Front. Cell Dev. Biol. 8 (2020) 547314, https://doi.org/10.3389/fcell.2020.547314.
[81] A. McDermott, Core concept: Herd immunity is an important-and often misunderstood-public health phenomenon, Proc. Natl. Acad. Sci. USA 118 (21) (2021) e2107692118, https://doi.org/10.1073/pnas.2107692118.
[82] P. Fine, K. Eames, D.L. Heymann, "Herd immunity": A rough guide, Clin. Infect. Dis. 52 (7) (2011) 911–916, https://doi.org/10.1093/cid/cir007.
[83] D.M. Morens, G.K. Folkers, A.S. Fauci, The concept of classical herd immunity may not apply to COVID-19, J. Infect. Dis. 226 (2) (2022) 195–198, https://doi.org/10.1093/infdis/jiac109.
[84] M.N. Billard, L.J. Bont, Quantifying the RSV immunity debt following COVID-19: A public health matter, Lancet Infect. Dis. 23 (1) (2023) 3–5, https://doi.org/10.1016/s1473-3099(22)00544-8.
[85] K. Gulukota, C. DeLisi, HLA allele selection for designing peptide vaccines, Genet. Anal. 13 (3) (1996) 81–86, https://doi.org/10.1016/1050-3862(95)00156-5.
[86] W.J. Liu, H. Xiao, L. Dai, D. Liu, J. Chen, X. Qi, Y. Bi, Y. Shi, G.F. Gao, et al., Avian influenza A (H7N9) virus: From low pathogenic to highly pathogenic, Front. Med. 15 (4) (2021) 507–527, https://doi.org/10.1007/s11684-020-0814-5.
[87] J. Liu, H. Xiao, Y. Wu, D. Liu, X. Qi, Y. Shi, G.F. Gao, et al., H7N9: A low pathogenic avian influenza A virus infecting humans, Curr. Opin. Virol. 5 (2014) 91–97, https://doi.org/10.1016/j.coviro.2014.03.001.
[88] Centers for Disease Control and Prevention, H5N1 bird flu: Current situation summary. https://www.cdc.gov/flu/avianflu/index.htm, 2024 (accessed 15 January 2024).
[89] T.M. Uyeki, S. Milton, C. Abdul Hamid, C. Reinoso Webb, S.M. Presley, V. Shetty, S.N. Rollo, D.L. Martinez, S. Rai, E.R. Gonzales, et al., Highly pathogenic avian influenza A(H5N1) virus infection in a dairy farm worker, N. Engl. J. Med. (2024) 2028–2029, https://doi.org/10.1056/NEJMc2405371.
[90] W.J. Liu, Y. Wu, Y. Bi, W. Shi, D. Wang, Y. Shi, G.F. Gao, et al., Emerging HxNy influenza A viruses, Cold Spring Harb. Perspect. Med. 12 (2) (2022) a038406, https://doi.org/10.1101/cshperspect.a038406.
[91] D. Lu, K. Liu, D. Zhang, C. Yue, Q. Lu, H. Cheng, L. Wang, Y. Chai, J. Qi, L.F. Wang, et al., Peptide presentation by bat MHC class I provides new insight into the antiviral immunity of bats, PLoS Biol. 17 (9) (2019) e3000436, https://doi.org/10.1371/journal.pbio.3000436.
[92] D. Zhang, K. Liu, D. Lu, P. Wang, Q. Zhang, P. Liu, Y. Zhao, Y. Chai, J. Lyu, J. Qi, et al., Stability and structure of bat major histocompatibility complex class I with heterologous β2-microglobulin, J. Vis. Exp. 169 (2021) e61462, https://doi.org/10.3791/61462.
[93] Y. Wang, R.N. Pruitt, T. Nürnberger, Y. Wang, Evasion of plant immunity by microbial pathogens, Nat. Rev. Microbiol. 20 (8) (2022) 449–464, https://doi.org/10.1038/s41579-022-00710-3.
[94] G.F. Gao, For a better world: Biosafety strategies to protect global health, Biosaf. Health 1 (1) (2019) 1–3, https://doi.org/10.1016/j.bsheal.2019.03.001.
[95] H.J. Jansen, F.J. Breeveld, C. Stijnis, M.P. Grobusch, Biological warfare, bioterrorism, and biocrime, Clin. Microbiol. Infect. 20 (6) (2014) 488–496, https://doi.org/10.1111/1469-0691.12699.
[96] H. Ahmed-Hassan, B. Sisson, R.K. Shukla, Y. Wijewantha, N.T. Funderburg, Z. Li, D. Hayes, T. Demberg, N.P.M. Liyanage, Innate immune responses to highly pathogenic coronaviruses and other significant respiratory viral infections, Front. Immunol. 11 (2020) 1979, https://doi.org/10.3389/fimmu.2020.01979.
[97] C. Amlie-Lefond, D.A. Paz, M.P. Connelly, G.B. Huffnagle, K.S. Dunn, N.T. Whelan, H.T. Whelan, Innate immunity for biodefense: A strategy whose time has come, J. Allergy Clin. Immunol. 116 (6) (2005) 1334–1342, https://doi.org/10.1016/j.jaci.2005.08.048.
[98] L. Wu, A. Zheng, Y. Tang, Y. Chai, J. Chen, L. Cheng, Y. Hu, J. Qu, W. Lei, W.J. Liu, G. Wu, et al., A pan-coronavirus peptide inhibitor prevents SARS-CoV-2 infection in mice by intranasal delivery, Sci. China Life Sci. 66 (2023) 2201–2213, https://doi.org/10.1007/s11427-023-2410-5.