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Biorisk management, laboratory acquired infections and clinical containment

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Biorisk management, laboratory acquired infections and clinical containment

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Editorial: Biorisk management, laboratory acquired infections and clinical containment

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Editorial on the Research Topic
Biorisk management, laboratory acquired infections and clinical containment

The field of Biosafety is as old as Microbiology but gained significant attention when Arnold G. Wedum published articles on applied biosafety and risk assessments. Biorisk Management is a framework that encompasses both biosafety and biosecurity and enables an organization for the identification, assessment, mitigation, evaluation, and communication of the inherent biosafety and biosecurity risks. Biorisk management is gaining importance during the recent pandemic with the promise of mitigating laboratory acquired infections through multi-factoral approaches.

This Research Topic aims to cover promising, recent, and novel research trends in the domains of Biorisk Management, Laboratory Acquired Infections, Biosafety and Biosecurity. Specifically, it presents comprehensive reviews on new frontiers in biosafety and biosecurity, different approaches for the biorisk assessment, and biorisk management of genetic editing or microorganisms. The research articles included in the topic are mainly covering the areas of communication strategies, biocontainment in poultry industry, assessment and ways to improve the current biosafety and biosecurity situation in diagnostic and research laboratory, along with the importance to relevant training on these protocols.

In an interesting review article, Raybould present an overview on three new frontiers in biosafety and biosecurity and how biotechnology can be helpful in this regard. The author emphasized on the continuous improvement in policy and decision making to maximize the balance between opportunity and risk in applying biotechnology to solve societal challenges. He presented political leadership, innovative legislation, and responsible business and civil society participation as the new areas which should now be focused to achieve the overall objective of biosafety and biosecurity.

Bellati et al. advocate for the use integrated approach against the traditional approach of biosafety for the effective risk assessment in a laboratory, as the integrated approach contain multiple psychological and organizational factors. These factors should not be considered as secondary but recognized as fundamental for risk assessment.

Gene editing platforms have changed genetics in general and public health in particular. Despite its obvious benefits, it's widely debated for its hazards and uncertainty. Kalidasan and Theva Das highlight the problems raised by modern biotechnology in Malaysia concerning gene editing legislation, biosafety, and biosecurity. Although, in Malaysia, stem cell and cell-based therapies have standards and guidelines, appropriate legal framework for gene editing is still the need. In the same context, biosafety regulations are created to promote biotechnology while

minimizing environmental and health dangers. It is also important to address the potential use of GMOs as bioweapons. Multiple international frameworks can be helpful for Malaysia to successfully implement gene editing by developing thorough guidelines, legal policies, and standards.

Merrill et al. highlight the impact of communication strategy with the biosecurity. As the COVID-19 pandemic continues worldwide, it's become evident that good communication strategies regarding disease transmission risks and protective practices is vital but not universally understood. Illnesses resulted in animal fatalities cost hundreds of millions of dollars annually to the US hog industry. Biosecurity methods can lower these expenditures. Effective Biosecurity depends on constant execution and effected by human decision-making. Using an experimental game, Merrill et al. quantify how different messages of disease incursions affect the compliance of biosecurity procedures. The study shows that graphical communications mixed with linguistic terms denoting infection risk levels are more successful for guaranteeing biosecurity compliance than simple linguistic phrases or graphical messages with numeric risk levels.

Biosecurity techniques are extensively promoted to reduce the economic loss in poultry industry. In this article, Otte et al. employ a home economics viewpoint to examine village poultry keepers' biosecurity investments. The 2012/13 Tanzania National Panel Survey (TZ-NPS) covered 1,228 poultry-keeping households and in most which, disease caused more than half of bird losses. Given that chickens rarely contributed more than 10% of annual household income, 95% of households lost 10% of revenue due to disease. The value of poultry varies by gender, and the total amount may disguise intra-household differences. The "typical" village poultry-keeping household may not prioritize poultry investments, even if cost-effective. When disease risks touch the wider community and generate major externalities, poultry keepers must be supported by wider societal measures.

Campylobacter is the largest cause of bacterial diarrhea in humans, and chicken meat products are considered as a major source. Due to the prevalence of Campylobacter in poultry farms, biosecurity is the key area for intervention. A research study by Royden et al. examine farmers' biosecurity attitudes and found impediments to effective adoption. Staff members, farmers, managers, and workers with varying industry expertise were interviewed. Broiler farmers recognize the relevance of Campylobacter and the farm-to-fork chain's responsibility to reduce Campylobacter contamination of chicken meat for public health. This shows the improved status of participants' biosecurity awareness and the industry-wide focus on Campylobacter control. Participants questioned the efficiency of current biosecurity efforts in reducing Campylobacter. The study revealed that more farmer education is needed about biosecurity initiatives, including Campylobacter management.

Muhammad et al. study the current situation of diagnostic and research laboratories in Pakistan with respect to biosafety and biosecurity. They identified that diagnostic and research laboratories have made considerable gains in biosafety and biosecurity due to increased biorisk management knowledge. A total of 30 laboratories, 11 diagnostic, and 19 research labs, are surveyed and it is identified that research laboratories are better in personal protective equipment, biosafety behavior, waste management, biosafety and biosecurity measures, trainings, and safety and health services than diagnostic laboratories.

Miguita et al. suggest that with adequate control measures of biosafety, including patient telemonitoring, proper use of personal protection equipment, and sanitization of surfaces, cross infection of SARS-CoV-2 can be avoided and dental practice can be safely executed.

Vennis et al. provide a comprehensive overview of the worldwide legal biosecurity framework to biosecurity academics, policymakers, civil servants, and practitioners in order to provide a better understanding of the existing international instruments of biosecurity. The paper offers practical applications for and improves multidisciplinary capacity to prevent, identify, and respond to the spread of infectious disease.

Handwashing in Good Microbiological Practices & Procedures (GMPP) is considered as the most important risk control measure. In a simple but effective study, Sarwar et al. demonstrate that how to avoid the use of paper towel for closing the tap in a resource-limited settings. This paper describes a hand-washing procedure that not only doesn't require paper towels but also report easy execution and elevated handwashing compliance.

To emphasize the importance of relevant biosafety training, Qasmi et al. demonstrated that how an effective international virtual training can improve the awareness and knowledge of the laboratory professionals and students.

The Guest Editors would like to express their gratitude to all the authors and reviewers of this Research Topic and acknowledge their hard work and dedication toward the area of biosafety and biosecurity. The Guest Editors believe that the presented researches will encourage the generation of more knowledge and valuable research in the fields of biorisk management, laboratory acquired infection, and clinical containment.

Author contributions

This editorial is drafted by KA and FK and reviewed by EM. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Is Malaysia Ready for Human Gene Editing: A Regulatory, Biosafety and Biosecurity Perspective

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Gene editing platforms have revolutionized the field of genetics with a direct impact on the public health system. Although there are apparent benefits, it is often accompanied by public debates over its uncertainties and risks. In the Malaysian context, modern biotechnology has raised questions about how to best govern gene editing in regulations, biosafety, and biosecurity. Even though standards and guidelines on stem cell and cell-based therapies have been developed, there are no appropriate legal frameworks available for gene editing yet. Nevertheless, biosafety regulations were established to balance promoting biotechnology and protecting against their potential environmental and human health risks. There is also a need to address the potential of genetically modified organisms (GMOs) as bioweapons. Numerous frameworks from several international organizations may provide valuable input in formulating documents on gene editing. By establishing comprehensive guidelines, legal policies, and standards to tackle the challenges and risks associated with gene editing, Malaysia can successfully apply this modern technology in this country.

Keywords: Malaysia, gene editing, CRISPR, gene therapy, regulation, biosafety, biosecurity

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INTRODUCTION

Population health is widely recognized as a critical indicator of economic growth in a country (Lange and Vollmer, 2017). Malaysia's growth was substantial in 2019, whereby the gross domestic product (GDP) was RM1.51 trillion, and their gross national income (GNI) per capita increased from RM 43,307 to RM 45,131 that same year. Overall, the economy expanded by 4.3% in 2019, compared to 4.8% in the preceding year (Department of Statistics Malaysia, 2020). Under such circumstances, it is essential to ensure that health resources benefit the population, thereby enabling citizens to strengthen economic performance. Although the burden of disease in Malaysia is manageable by public and private healthcare systems (Quek, 2009; Thomas et al., 2011), the demand for treatment and disease prevention is still a significant challenge.

With the emergence of new medical technologies ranging from smart inhalers, robotic surgery, wireless brain sensors, 3-D printing, artificial organs, health wearables, virtual reality to precision medicine, and gene editing, Malaysia could have a tremendous breakthrough (Ellis, 2019). Precision medicine (also known as personalized medicine) is driven by genome sequencing technologies and data science, allowing clinicians to tailor treatments individually based on genes, environment, and

lifestyle factors (Academy of Sciences Malaysia, 2009; Jamal, 2017). Notably, precision medicine is already practiced in Malaysia with a high success rate, such as treating cancer through a tumor profiling approach that can identify various anti-cancer-therapies (Murugesan, 2019).

Another crucial advancement that has gained much attention worldwide is gene editing technology. Malaysia has made progress in medical genetics, with some researchers using genome editing to delete, insert, or modify DNA sequences to correct a particular disease (Hamid, 2018; Nithya et al., 2019). Despite its potential, there is a high demand for an ethics panel to develop guidelines for human genome editing in Malaysia, especially for germline editing (Fong, 2019). In such circumstances, governing the use of genome editing to improve healthcare, balancing potential benefits with unintended risks, and integrating societal values in the therapeutic application and decision-making is of utmost importance. Thus, this review aims to debate the regulatory, biosafety, and biosecurity aspects of gene editing in Malaysia.

GENOME EDITING: BASIC SCIENCES AND ITS THERAPEUTIC APPLICATIONS

Gene editing involves creating a specific double-stranded break (DSB) in the genome, followed by cellular repair mechanisms (Porteus, 2015; Mandip and Steer Clifford, 2019), either through non-homologous end-joining (NHEJ) where indels are created at the break site or homology-directed repair (HDR) where a specific nucleotide change takes place in the genome with the help of a donor sequence. Currently, four leading platforms exist for genome editing, namely engineered meganuclease, Zinc Finger Nuclease (ZFN), Transcription Activator Like Effector Nuclease (TALEN), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) (Ben-David, 2013; Ramalingam et al., 2013; Kim, 2016). The various generations of nucleases used for genome editing and their DNA repair mechanisms are illustrated in **Figure 1**, and a comparison of the different programmable nuclease platforms is shown in **Table 1**.

With the ease of genome editing, the pace of progress has increased exponentially. Many organisms have already been genetically modified, such as mice, rats, monkeys, pigs, cows, rabbits, frogs, zebrafish, fruit flies, worms, yeast, and bacteria (Gersbach, 2014). These species have contributed to the studies of genetics, genomics, gene function, and disease modeling. The most significant benefit of genome editing is undoubtedly applying these technologies to improve human health through gene therapy (Cox et al., 2015; Mandip and Steer Clifford, 2019). Numerous human diseases have already been targeted for gene therapy and have moved into preclinical phases such as viral infections, T-cell immunotherapy, hematological disorder, neuromuscular disorders, skin disorders, respiratory disorders, and many others.

In general, gene therapy can be broadly categorized into somatic and germline therapy. Somatic gene therapy involves changes to cells (i.e., bone marrow, blood, and skin) that are limited to the treated individual and would not be inherited by future generations (Smith, 2003). Broadly, alteration on somatic cells can be done either by *in vivo* modification targeting specific tissues with local delivery into the body or *ex vivo* modification targeting cells outside the body, followed by reinfusion of the edited cells. In terms of therapeutic delivery of genetic material (transgene), two approaches can be used: (i) viral delivery using a retrovirus, adenovirus, and adeno-associated viruses (AAV), or (ii) non-viral delivery using liposome, electroporation, tissue injection, and particle bombardment.

Before performing somatic cell genome editing, a few points should be considered (National Academies of Sciences Engineering and Medicine, 2017c), including which cells or tissue(s) are modified, where the editing takes place (*in vivo* or *ex vivo*), specific goal(s) of the modification (treatment or prevention of disease or introduction of new traits), and the precise nature of the modification (changing disease-causing mutation, disruption or overexpression of an endogenous gene, or addition of a novel function). Notably, several additional features must be considered with both *in vivo* and *ex vivo* editing, such as the ability to isolate the relevant cell type (i.e., *ex vivo*), the ability to control biodistribution of the genome-editing tool (i.e., *in vivo*), the ability to limit immune response to delivery vectors that could lead to rapid and complete clearance of cells that have received the editing complex, and the ability to edit the genome in non-dividing cells (i.e., dividing cells such stem cells versus non-dividing cells such as neurons). Regardless of the application, each strategy needs to be evaluated in terms of safety, efficacy, risk, cost, and feasibility.

On the other hand, germline gene therapy involves modifying genes that will be passed to the next generation, thus not being widely attempted in humans. Germline therapy must be performed during the early stages of development on egg cells, embryonic stem cells, sperm cells using pronuclear microinjection or nuclear transfer (Smith, 2003). Liang et al. (2015) who published the first report of human embryo genetic engineering utilized tripronuclear (3PN) zygotes and edited a portion of the human β-globin gene using CRISPR/Cas9. Since the 3PN zygote would develop naturally into an embryo but does not result in birth (non-viable human zygotes), that embryo was used to avoid ethical concerns. The findings showed several off-target mutations resulting in mosaic embryos, highlighting the need for further investigation before clinical application. Another researcher from China, He Jiankui, performed germline gene therapy on twins babies Lulu and Nana (Ryder, 2018) where he injected the embryos with CRISPR/Cas9 to knock out CCR5 co-receptor to prevent HIV binding. Unfortunately, his findings revealed that only Nana would be resistant to HIV (the edits removed both copies of her CCR5 gene), while Lulu would still be susceptible to infection (she still had one functional copy of CCR5) (Cyranoski, 2018).

It is crucial to ensure that only embryos with correctly targeted alleles would be returned to the uterus to complete pregnancy (National Academies of Sciences Engineering and Medicine, 2017a) as some of the cells would not have the desired edits (mosaicism), and there may be unwanted effects of the removal of disease-causing variant on the human gene pool. Alternative

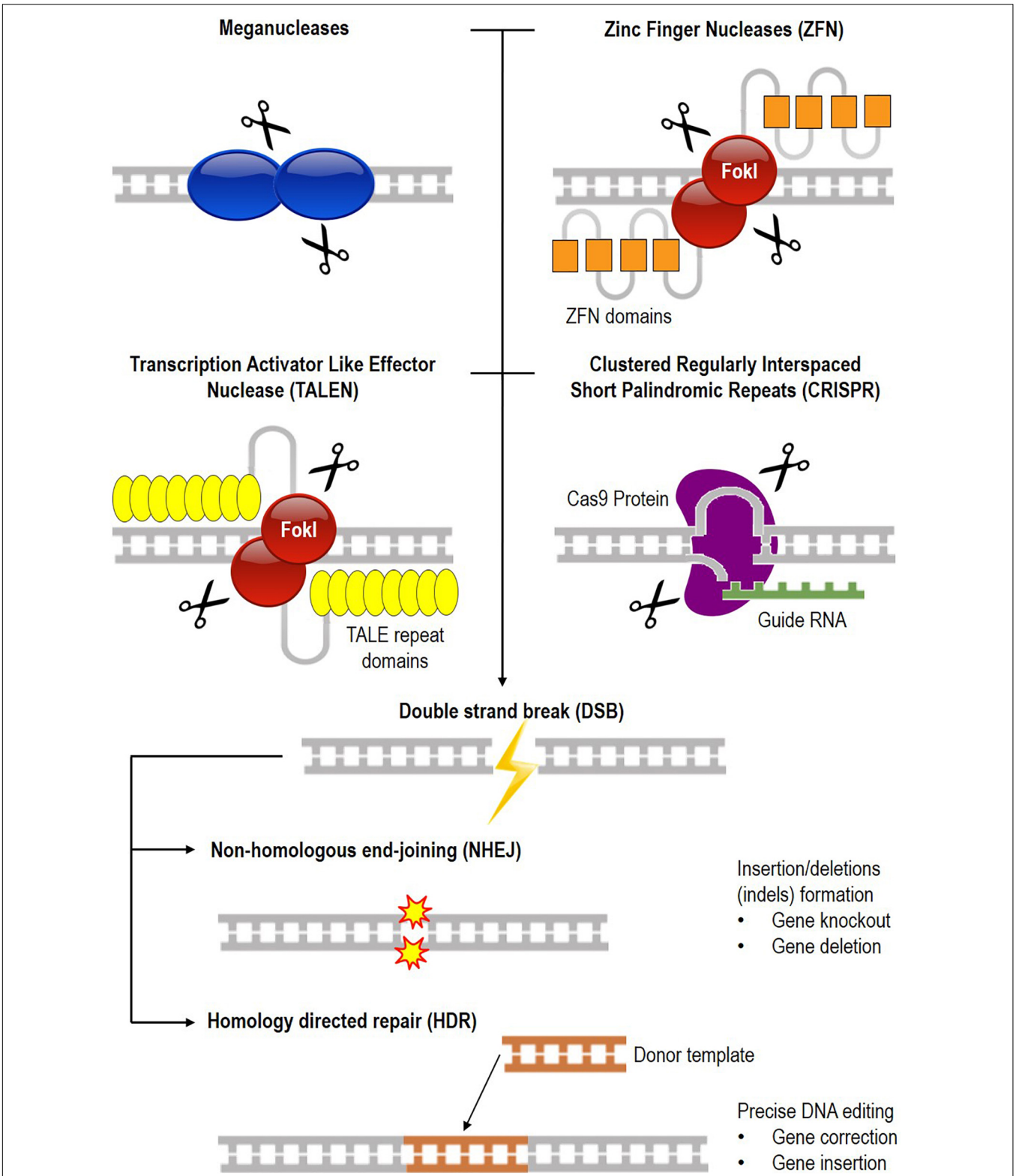

FIGURE 1 | Common DNA targeting platform for genome editing. There are currently four different nucleases available for gene editing which are meganuclease, Zinc Finger Nuclease (ZFN), Transcription Activator Like Effector Nuclease (TALEN), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR). DNA is cleaved (scissors symbol), resulting in a double-stranded break (DSB) that is repaired by either non-homologous end-joining (NHEJ) or homology-directed repair (HDR). NHEJ results in the formation of insertions or deletions (indels) for gene knock-out or deletion, while in HDR, a donor DNA repairs the broken ends of the chromosome for gene correction or insertion.

TABLE 1 | Systematic comparison of meganuclease, Zinc Finger Nuclease (ZFN), Transcription Activator Like Effector Nuclease (TALEN), and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) genome editing platforms.

Features	Meganuclease	ZFN	TALEN	CRISPR/Cas9
Source	Organellar DNA, bacteria, phage	Bacteria, eukaryotes	Bacteria (*Xanthomonas* sp.)	Bacteria (*S. pyogenes*)
Polymeric state	Dimers (two identical subunits)	Dimers (two FokI domains)	Dimers (two FokI domains)	Monomer (only sgRNA-Cas9 complex)
Type of recognition	Protein-DNA	Protein-DNA	Protein-DNA	RNA-DNA
Recognition site	Between 18 and 44 bp	Between 18 and 36 bp	Between 24 and 40 bp	Between 17 and 23 bp
DSB pattern	Staggered (3′ overhang)	Staggered (5′ overhang)	Staggered (heterogenous overhang)	Staggered (5′ overhang, Cpf1 system); blunt (SpCas9)
Specificity	High	Low to moderate	Moderate	Low to moderate
Ease of design and engineering	Difficult	Difficult	Moderate	Easy
Immunogenicity	Unknown	Low	Unknown	Unknown
Ex vivo delivery	Easy using electroporation and viral vector	Easy using electroporation, viral vector and lipofection	Easy using electroporation, viral vector and lipofection	Easy using electroporation, viral vector and lipofection
In vivo delivery	Easy to difficult (depending on size of nuclease)	Easy to difficult (depending on size of nuclease)	Difficult (large size of TALEN)	Moderate (*S. pyogenes* is large)
Multiplexing	Low	Low	Moderate to high	High
Cost (USD)	4,000–5,000	5–10,000	Less than 1,000	Less than 100
Success rate	Low	Low (∼24%)	High (>99%)	High (∼90%)
Targeting constraints	Targeting novel sequencing	Targeting non-G-rich sequence	5′ targeted base must be a T for each TALEN monomer	Targeted sequence must precede a PAM sequence
Advantages	Possible to edit various types of genome editing (knockout, reporter, specific alleles)	Designed to target any DNA sequence; targeting of biallelic genes	Designed to target any DNA sequence; targeting of biallelic genes	Targeting of biallelic genes and multiplexing
Disadvantages	Lacks DNA-binding domains; inefficient for inadequate knowledge on designing construct; time-consuming	Binding capacity of ZFN depends on neighboring ZFs; decreased specificity can lead to off-target cleavage	Cloning of TALE repeats is troublesome and error prone	Target sites limited for PAM motif; higher chance of off-target cleavage

routes should also be considered over heritable edits (i.e., using edited sperms to fertilize donor eggs) as it is inconclusive whether germline editing can be performed safely. All these factors must be evaluated carefully based on scientific and ethical grounds before considering germline therapy.

Debate 1: What Are the Risks and Benefits of Modifying Human DNA? What Are the Arising Controversies of Gene Editing?

Jesse Gelsinger's tragic death during his clinical trials turned gene therapy into a significant debate (Sibbald, 2001; Gelsinger, 2016). The 18-year-old American had a condition called ornithine transcarbamylase deficiency (OTC), where he lacked a functional enzyme that breaks down ammonia, and becomes toxic in higher concentrations. On 13th September 1999, he received an adenoviral vector injection (3.8×10^{13} particles) to introduce a normal gene for the enzyme directly into his liver (Savulescu, 2001). Unfortunately, he experienced a severe immune reaction to the vector and died 4 days after receiving the treatment.

His death highlighted a few ethical and legal issues (Savulescu, 2001; Sibbald, 2001). Firstly, he was not informed about the preclinical evidence of patients with dangerous side effects from the therapy or that three monkeys had died of a clotting disorder and severe liver inflammation after being injected. Secondly, the research team was careless, negligent, and reckless as they failed to evaluate Jesse's condition adequately. Thirdly, prolonged storage of the vector for 25 months led researchers to underestimate its potency. Fourthly, there was a conflict of interest between the researchers and a private sector biotechnology collaborator in the project that prevented reporting any adverse effect to the Food and Drug Administration (FDA). Consequently, the U.S. Department of Justice directed all guilty parties to pay a sum of fines (Couzin and Kaiser, 2005). The court declared that a toxic reaction in humans should have halted the trial as early as possible, and the investigators misrepresented the clinical findings to the study's regulators.

Moving forward, the First International Summit on Human Gene Editing (2015) recommended that all research must be subjected to appropriate legal and ethical rules and oversight (National Academies of Sciences Engineering and Medicine, 2015) and "rigorously evaluated existing and evolving regulatory frameworks for gene therapy clinical trials." As of November 2017, 2597 trials were approved and undertaken in 38 countries, with most gene therapy clinical trials addressing cancer (i.e., gynecological, nervous, gastrointestinal, genitourinary, skin, lung, hematological), and inherited monogenic diseases (i.e., primary immunodeficiency disorders, cystic fibrosis) (Ginn et al., 2018). These gene therapy trials offered clear proof-of-concept, demonstrating safety, and emphasized critical issues for therapy advancement.

However, somatic modification could exert conflict of interest, particularly in behavioral genetics, physical traits, and sports science. Low levels of monoamine oxidase A (MAOA) have been reported among people who experienced maltreatment during childhood, resulting in violent behavior and increased crime rate as they age (Polcz and Lewis, 2016). In such a phenomenon, should gene therapy be initiated to lower the risk of violent outbursts? Should these offenders be regarded as lesser criminals due to their genetic predisposition? Another speculative issue on gene manipulation is gene doping among athletes to increase their performance, maximize bodily function, and alter muscle endurance (Battery et al., 2011). Considering gene editing would most likely not be detected during testing, the World Anti-Doping Agency (WADA) banned it in 2003. It is crucial to draw the line between therapeutic uses and gene editing enhancement (Cwik, 2019). The latter poses major ethical, societal, and regulatory issues that need to be acknowledged before allowing genetic enhancement to become a reality.

In terms of germline gene therapy, He Jiankui's experiment caused much controversy in biomedical research (Normile, 2018; Ryder, 2018). The announcement of He's heritable genome editing during the Second International Summit of Human Genome Editing (2018) caused scrutiny on inadequate oversight and transparency, lack of parental informed consent, the existence of alternative care for preventing infection, the likelihood that gene editing will cause other medical problems, and the source of research funding (National Academies of Sciences Engineering and Medicine, 2019). The scientific community believed that the risks and benefits of germline editing were unclear to allow it to proceed and called for a moratorium until there was broad consensus on the clinical use of genome editing, and an extensive regulatory framework, ethical framework, religious viewpoint, public and societal engagement prior to this technology moving forward (Porteus and Dann, 2015).

In general, germline genome editing's ethical issues can be classified into those arising from its potential failure and success (Ormond et al., 2017; Coller, 2019). Firstly, the potential harm is perceived as a risk that does not outweigh the potential benefits. In germline editing, the unintended consequences are not well understood. In such circumstances, adopting national and international policies (i.e., legislation, regulation, and professional guidance), document enforcement (i.e., legally binding or self-compliances), and oversight mechanisms (i.e., licensing) would be the standard framework to addressing germline genome editing. Secondly, if the technology works as intended, the individual, family, and society would be largely impacted. The technique affects the person's future, whose genes are altered without their consent. Even though parents hold the decision-making capacity, there may be individuals who did not wish to remove their medical conditions and disagree with the decision made by their parents. On the other hand, parents may believe that such interventions are intended to reduce potential harm to the child. In this scenario, there is an evident conflict between informed consent and non-maleficence.

There are significant concerns about eugenics, social justice, and equal access to therapy (Coller, 2019). Eugenics is a concept that retains positive traits and removes negative characteristics. In such a context, germline modification may result in the loss of genetic diversity in the future generation and create children with the best traits (designer babies). Many consider this as 'playing God,' while some believe that it is merely altering genes rather than selecting against individuals. These issues raise an argument related to genetic enhancement where the manipulation for physical and mental abilities, and knowledge may most likely result in professional success. Since human germline therapy would probably only be affordable to people from a specific socioeconomic class, the central dilemma is that individuals who have the resources would obtain unfair success.

Despite these ethical and social concerns, the National Academies of Sciences, Engineering, and Medicine (NASEM) recommended that clinical trials on heritable human genome editing proceed for limited purposes, under these following conditions (National Academies of Sciences Engineering and Medicine, 2017a): (i) the absence of reasonable alternatives, (ii) limited to editing genes that have been demonstrated to strongly cause or to predispose to a disease, (iii) restricted to converting genes to versions that are prevalent in the population and are known to be associated with ordinary health with little or no evidence of adverse effects, (iv) the availability of credible preclinical and/or clinical data on risks and potential health benefits of the procedures, (v) ongoing, rigorous oversight during clinical trials on the effects of the procedure on the health and safety of the research participants, (vi) comprehensive plans for long-term, multigenerational follow-up that respects personal rights, (vii) maximum transparency consistent with patient privacy, (viii) continued assessment of health and societal benefits and risks, with broad ongoing participation and input by the public, and (ix) reliable oversight mechanisms to prevent extension to uses other than preventing a severe disease. In short, the development and application of somatic and germline therapy should consider conducting careful scientific research to build an evidence-based study, evaluating ethical, legal, and social issues (ELSI), and conducting meaningful stakeholder engagement, education, and dialogue (SEED) (Howard et al., 2018). The adapted questions that should be discussed for each of the mentioned aspects are tabulated in **Table 2**.

MODERN BIOTECHNOLOGY IN MALAYSIA

With the launching of the National Biotechnology Policy (NBP) by the former Prime Minister of Malaysia, Datuk Seri Abdullah Ahmad Badawi, in 2005, Malaysia expressed its intention to engage in the biotechnology arena on par with the advancement of the 21st century (Ahmad Badawi, 2005; Quah and Arujanan, 2005). Malaysia offers a conducive environment for biotechnology investors due to numerous favorable factors such as being rich with various flora and fauna that can be developed into natural and medicinal/therapeutic products, having skilled human resources with a trained pool of talent for the biotechnology industry, and having good infrastructure

TABLE 2 | Example of questions for conducting careful scientific research, ethical, legal, and social issues (ELSI) research, and meaningful stakeholder engagement, education, and dialogue (SEED) in context of gene editing.

Aspects	Example of questions
Building a scientific evidence base for gene editing	
Carry out ongoing responsible scientific research to create a solid foundation of facts, especially with regard to risks and benefits	• Is the current standards and practices of sharing academic and commercial research results, in particular with regard to risks and benefits, adequate for the current and future gene editing field? • Should there be a common framework developed for tracking (systematically) all forms of basic and (pre) clinical research? • If so, which kind of work does it take to adhere to this? All research, or just work done in human cells? • Who should/will be taking responsibility for tracking or reporting this? where does the funds come from to coordinate and support those efforts? • How would a long-term medical monitoring of human patients be coordinated informatively? • Will the patients be expected to agree to lifelong follow up after treatment? How should this be achieved while preserving individual autonomy? • For each of the above questions, who should decide the answers to these questions? Based on what criteria?
Ethical, legal, and social issues research (ELSI) of gene editing	
Somatic cell gene Therapy	• Do we require any changes to the existing legal structure to tackle somatic gene therapy? If so, who would form the legal structure any further? • Are the principles and procedures present in clinical trials sufficient? • How can somatic gene therapy trials be performed and assessed? • Do we require specific patient protection or status in these trials? • What are the protocols to be established for patients undergoing these treatments (i.e.: consent, genetic counseling, follow-up monitoring)? • To what degree will commercial companies be willing, or be allowed to offer, potentially upon consumer request, treatments based on therapies, where so much vagueness regarding likely harm? • Which healthcare practitioners should engage in the implementation of somatic gene therapy and the care of patients receiving these treatments? • How are we going to ensure equal access to the technology? • How do we ensure the need drives the usage and not the technical imperative? • Who will determine on roles and obligations in this novel context? • What criteria will be used to select the eligible diseases/populations to be treated? • How do we ensure that research funding is distributed proportionally to the amount of gene editing work being carried out?
Germline gene therapy	• Will gene editing of human germ line cells, gametes and embryos be permitted in basic science, for better knowledge of human biology (i.e.: human development) and without planning to be used to establish modified human life? • Should gene editing of germ line cells, gametes, or embryos or any other cell resulting in heritable modification be allowed in a clinical setting for humans? • Would any principles or reasoning justify the use of germline gene editing in humans in a clinical context, given the existing ban on such techniques in many jurisdictions? • Why should we consider using germline gene editing in the clinic when there are alternative ways in which couples can have healthy (biologically related) children? Who will decide? Based on what criteria? • Before considering germline gene editing, would we first understand the risks and benefits of somatic gene editing? • What are the functions and duties of the various parties involved in those decisions? • How do commercial incentives and the technological imperative play a role in these decisions? • If we entertain gene editing for reproductive use, what criteria would be considered safe according to various stakeholders (scientist, ethicists, clinicians, policy makers, patients, lay public)? Who will set this safety threshold and based on what risk/benefit calculations? • If germline gene editing was allowed, how would the fact that for the first time, a human would be directly editing the nuclear DNA of another human in an inherited manner cause some form of segregation of types of humans? • If ever permitted, should germline gene editing be limited only for specific medical purposes with a particular high probability of developing a disease, and if so, does it matter if the risk is not 100%, but much lesser? • How do we define/demarcate medical reasons from enhancement? And, as was posed above for the use in somatic cells, for what medical conditions will gene editing be deemed suitable for use? What will the criteria be and who will decide?
Stakeholder, engagement, education and dialogue (SEED) for gene editing	
Planting SEEDs for gene editing	• What are the roles and obligations do various stakeholders have in developing and sustaining engagement, education and dialogue? • What will, and what should be the role of scientists and other academics in this type of popular media communications, and engagement activities? • As public engagement can have multiple goals, before each activity, we must consider: What are our objectives? And, what strategy of engagement will best meet these objectives? • How will the mass of voices we want to include in public engagement be weighed against each other? How are we to make sure every voice is heard? • What position will feedback and preferences of various stakeholders play in the discussion and decision-making process? How will those opinions be balanced and treated in policy making? • How can we ensure that public education is not limited to a token work package in science grants and/or to campaigns that try to persuade for or against gene editing? • How can we ensure that such public education and engagement is available to everyone, including in countries that currently may not have the resources to take on such SEED activities?

Adapted and modified from Howard et al. (2018).

for research and development (R&D) with modern facilities and state-of-the-art equipment for biotechnology research.

The Malaysian NBP, through its nine thrusts, would provide a comprehensive roadmap that would accelerate growth in the biotechnology industry (Arujanan and Singaram, 2018). The nine thrusts and its aim include: (i) agriculture biotechnology development to enhance the value of the agricultural sector, (ii) healthcare biotechnology development to strengthen the discoveries of natural products, (iii) industrial biotechnology development for the advancement of bioprocessing and biomanufacturing technologies, (iv) R&D and technology acquisition to foster multidisciplinary teams in research and commercialization initiatives, (v) human capital development in line with market needs through special schemes, programs and training, (vi) financial infrastructure development to provide funding and incentives to academia, private sector and government-linked companies, (vii) legislative and regulatory framework development to enable continuous reviews of the country's regulatory framework and procedures in line with global standards and best practices, (viii) strategic positioning to build brand recognition for Malaysian biotechnology products, and (ix) government commitment to establish a professional implementation agency to oversee the development of the biotechnology industry.

The Malaysian Biotechnology Corporation (currently known as Malaysian Bioeconomy Development Corporation Sdn. Bhd.) was founded to serve as a one-stop organization to facilitate the involvement of companies in the biotechnology industry, implement government policies and initiatives, encourage research and development as well as commercialization, and create a robust investor ecosystem (Quah and Arujanan, 2005; Quah, 2007; Arujanan and Singaram, 2018). Meanwhile, to stimulate bio-entrepreneurship, BioNexus special status was awarded to qualified foreign and Malaysian biotechnology companies that provided incentives, grants, and capacity building programs to assist growth. Moreover, to complement the NBP, the Bioeconomy Transformation Programme (BTP) was launched in 2012 to accelerate its bioeconomy development.

Despite such initiatives, Malaysia's biotechnology innovation faced critical and challenging implications (Mokhtar and Mahalingam, 2010; Arujanan and Singaram, 2018). Some of the stumbling blocks in Malaysian biotechnology include an imbalance between talent development and market needs, primarily due to the lack of skilled human capital and industrial bases, insufficient funding for biotechnology R&D, project duplication, absence of collaboration between research institutes and universities, lack of commercialization from research output, political appointments for top positions at government agencies and research institutes, and pursuing university ranking (i.e., QS World University Rankings, Times World University Rankings) through publications that dilute industrial engagement. In such circumstances, Malaysia should adopt a sectoral industrial policy by which the state directs resources to targeted industries identified as crucial for their future competitiveness. Furthermore, the biotechnology industry requires mobilization and efficient utilization of scientific expertise through training, education, and collaboration to build a competent and competitive industry. Interestingly, as Malaysia is a collectivist society, the development, commercialization, and success of modern biotechnology are primarily linked to public acceptance.

Debate 2: What Is the Public's Acceptance of Various Applications of Modern Biotechnology in the Malaysian Context?

A series of studies were conducted in the Klang Valley region among several stakeholders on acceptance of biotechnology in Malaysia. The respondents comprised of both genders, aged 18 years and above, had various educational levels and diverse racial and religious beliefs. The preliminary studies among this group showed a high level of awareness among biotechnologists and policymakers as they were directly involved in R&D or policy matters (Amin et al., 2007a; Amin and Ibrahim, 2011). On the other hand, the NGOs, media, politicians, and the general public exhibited a moderate level of awareness due to the limited exposure to modern biotechnology issues. The knowledge level of Buddhists and Christians was significantly higher than Muslims. The difference in educational exposure and deeply rooted religious beliefs may have contributed to these findings.

Following that, a re-evaluation study revealed an increase in overall awareness level compared to the previous assessment (Amin et al., 2011b). Once again, Muslim scholars displayed the lowest level of awareness. This suggests the importance of instilling more knowledge as Islam is the major religion in the country, and their permissibility of various modern biotechnology applications is often needed. Taken together, the level of awareness and knowledge is considered moderate in Malaysia, which calls for more effort and dissemination of information.

Acceptance toward modern biotechnology is predicted mainly by several categories of perception (i.e., general promise and concern of biotechnology, technology optimism, nature/materialistic value, predisposition toward Science and Technology (S&T), attachment to religion and custom), and attitude (i.e., familiarity, moral concerns, risks, risk acceptance, benefits, and encouragement) (Amin et al., 2007b, 2011d). The factors affecting public attitude toward modern technology are shown in **Table 3**. To evaluate GM soybean's risk/benefit in Malaysia, a study was undertaken to analyze the perception and attitude parameters (Amin et al., 2006). The study concluded that factors predicting genetically modified (GM) soybean encouragement were linked to perception about the benefits, acceptance of risk, and moral concern. Overall, if the application offered clear benefits to consumers and were of low moral concern, the application would be highly encouraged (i.e., most respondents considered GM palm oil which was modified to reduce its saturated fat content with no gene transfer, highly acceptable) (Amin et al., 2008).

As mentioned previously, public acceptance is crucial to driving modern biotechnology forward, and one of the strategies would be using the influential role of media to disseminate

TABLE 3 | Factors related to public perceptions, understanding, acceptance and ethical principles of modern biotechnology.

Factors	Explanation
Attitude dimensions[a]	
Perceived benefit	• Usefulness or benefit was found to be a prerequisite for support. • If the applications were perceived to have significant benefits such as in health care, the applications were supported despite having some risks. • If the application was perceived to have only modest benefits, it was not supported even though the risks were perceived to be minor.
Perceived risk	• Perceived risk is also a substantial variable of encouragement. • If the perception of risks related to biotechnology is sufficiently high, no amount of benefits is likely to make it acceptable.
Risk acceptance	• Modern technologies that benefits are always accompanied by risks which posed serious dilemmas for societies. • 'Revealed preference' approach is based on the assumption that by trial and error, society has arrived at an "essentially optimum" balance between the associated risks and benefits. • 'Expressed preferences' approach measure public attitudes towards the risks and benefits from many activities and use the concept risk adjustment factor to establish levels of acceptable risks.
Moral concerns	• Societal and individual risk perceptions are proportional to moral values. • Individual who is willing to accept some level of risk, if the product was considered worthy and was not morally objectionable. • Fall into two classes: intrinsic (the process of modern biotechnology is objectionable in itself) and extrinsic (possible risks of different application of biotechnology).
Familiarity	• Whether a product contains a risky substance, whether the risk is known to science, and whether a person has control over consuming a certain product. • Five characteristics correlated highly with each other which reflected familiarity: observability, knowledge (known to those exposed), immediacy consequences, familiarity (not new) and known to science.
Encouragement	• Support or acceptability of a biotechnology application.
General attitudinal classes[a]	
Knowledge and awareness	• More knowledgeable makes people more considerate to genetic engineering. • Perception of risk is higher amongst those with greater objective knowledge, and those who have discussed biotechnology over recent months, but such perception is low amongst those with little knowledge. • Acceptance of biotechnology by the public may not be related to awareness at all, in which regardless of whether individuals were aware of biotechnology, respondents were able to make a judgment about how useful or risky it was. • Those with more education may be better able to assess both risks and benefits of biotechnology critically.
Engagement	• Greater scientific knowledge is moderately associated with support for science. • 'Attentive public' approach: combine responses to the questions on awareness and talking to others about the subject of biotechnology. • 'Informed citizen' approach: people who have minimally heard of biotechnology and have a vocabulary of biological terms and concepts that is adequate for reading the science section of a major paper.
General value orientations (worldviews)	• Risk perception is defined by the norms, value systems, and cultural mannerisms of societies. • Those who are more concerned about nature are less optimistic about biotechnology, while those who embrace materialistic values are more optimistic.
General promises and concerns	• The general promise includes a set of items reflecting the promise of biotechnology to improve the quality of life. • The general concerns referred to the general reservations or concerns about the possible consequences of biotechnology. • People firstly form attitudes towards the overall risk and usefulness of the technology, and then only infer from these general attitudes how risky or beneficial a particular application of the technology is.
Confidence in key actors	• People come to know about new scientific discoveries and technological developments from the mass media such as television, radio, newspapers and books. • People often judge risk according to their perception of its controlling agents: if these controlling agents have a track record of secrecy, or they dominate supposedly independent regulatory bodies and the public policy process, then people magnify the perceived risks. • Without confidence in key players such as scientists, regulators, people are likely to have excessive perceptions of risks, as the assurances provided by the experts that the risks are low or manageable are treated with uncertainty.
Attitude toward Science and Technology/ technology optimism	• Technology optimism refers to what the public feel about current technologies, whether they will improve his/her way of life in the next 20 years. • Those who are optimistic about one technology tend to be confident towards others. • Attitude toward Science and Technology or the impact of technology was found to influence risk magnitude and benefit of technological hazards.
Societal values (nature versus materialist)	• Ecological attitudes (which comprised of an aggregate of attitude towards environmental issues, impact of technology and post-material values) have shown considerable influence on both perceived risk magnitude and risk acceptance of technological risks. • Enthusiasts of biotechnology were found to believe in free-market economic (materialist), while the rejectors were more concerned about nature and the environment.
Demographic factors	• Demographic characteristics such as age and gender must be included because some researchers have argued that the continuing process of scientific discovery leaves older people behind and because men and women are known to differ on several science-related and technology-related topics. • Education needs to be included because of its strong connections with knowing and learning. • Peoples' occupation and religious belief are also enduring characteristics that shape many social and political opinions on a wide range of topics.
Ethical dimension[b]	
Rights theory	• Always act so that you treat human beings as autonomous individuals, and not as a mere means to an end. • Right of an individual to make choices about their own life, and not to be subjected to the imposition of others.

(Continued)

TABLE 3 | Continued

Factors	Explanation
Theories of justice	• The society has to operate with such principles of justice that cater to the well-being of the less fortunate members of the society.
Consequentialism and utilitarianism	• Consequentialism argues that one knows what the appropriate action is, not based on universal duty, but rather based on the outcomes of one's actions. • Discussions those around risk and benefit whereby it is the consequences of the use of biotechnology that are seen as important, rather than any pre-existing understanding of one's duty or the appropriateness of maintaining a given set of relationships.
Precautionary principle	• Given the unknown and unpredictable consequences and risks of biotechnology, opposers argue that regulatory policy should approach biotechnology from the stance of the precautionary principle. • With the precautionary principle as the default mode of regulation, the regulatory policy should evaluate biotechnology for its human health, animal health, environmental, social, economic, cultural, ethical, and reciprocal impacts.
Environmental ethics	• 'Human-centered' approach: the environment is valued for what it can provide for humans, and we protect it so that the resources will be there for our use and that of future generations. • 'Ecocentric' approach: the environment is valued not for what it can give us, but because it has intrinsic value, separate from any value that we may provide it.
Religion	• The spiritual division refers to religion or the belief of individual or people. • Acceptance and success of biotechnology will be based on the ideological beliefs and the cultural values adopted by individual human beings, who, in turn, will shape societal beliefs and values. • There are principles or guidelines on how we should live, and what is the right thing to do in most religions.

[a]*Adapted and modified from Amin et al. (2007).*
[b]*Adapted and modified from Amin (2009).*

information to the lay public. A study was performed to analyze the coverage of biotechnology issues in four mainstream Malaysian newspapers (i.e., Utusan Malaysia, Berita Harian, New Straits Times, and The Star) and correlated it to the Malaysian public awareness (Amin et al., 2011e). There was limited coverage in the newspapers, as within the span of ten years (2001–2010), only 729 news items on biotechnology were retrieved. Among the four mainstream newspapers, biotechnology issues were mostly covered by Malay newspapers, with Utusan Malaysia having the highest number of articles. As these newspaper companies are government-owned, government policies, the success of a research project, and the commercialization of products that promoted economic development or improved the standard of living in Malaysia were portrayed positively. Notably, Malaysia's media failed to provide any room for discussion and debate, substantially reducing public education in the subject matter. It is also important to point out that these newspapers only covered policies and their implementation, thus minimizing exposure to modern biotechnology's real content. Likewise, another study was undertaken to analyze the coverage of ethical issues of biotechnology in the mentioned Malaysian newspapers (Amin et al., 2011f). From the study, it was discovered that government ministers served as the primary source of information. Malaysians were exposed to various biotechnology ethical issues, whereby applications such as human cloning (a baby girl named Eve) were painted in a negative light. From a religious context, Islamic law forbids human cloning, while stem cells for medical or research purposes are widely accepted.

In such circumstances, the ethical dimension of modern biotechnology in Malaysia needs an immediate assessment. A study revealed that there were seven factors related to ethical aspects (Amin et al., 2009, 2011c), including labeling, risks to human health, whether biotechnology threatens the natural order of things, monopoly of the field, patenting rights, human rights to modify living things, and confidence in regulation. When confronted with these aspects, Malaysians were unsure whether a human has the right to modify living things and whether modern biotechnology threatens the natural order. The technology was perceived as having moderate risks to human health, and the public was moderately concerned about the monopoly of the modern biotechnology market by companies in developed countries. The respondents also had moderate confidence in government regulations and expected the authorities to play a larger role in regulation and providing safety. The respondents expressed a high level of need for labeling products to indicate product safety and acknowledged patenting rights of scientists and industries. There is a greater need to set the direction and pace of development in such circumstances to prevent questionable or premature commercialization of biotechnology products.

Another research was undertaken to assess five ethical aspects (familiarity, perceived risk, denying benefits if it is not developed, religious and ethical acceptance) of GM rice, which contained a synthetic mouse gene to enrich vitamin C (Amin et al., 2011a). Shockingly, unfamiliarity was observed among policymakers, although they were responsible for regulating current biotechnology issues. There were concerns regarding the extinction of the original species, potential risks to health, and long-term harmful effects of consuming the rice. The respondents with tertiary education considered GM rice more acceptable from their religious viewpoints than those with a lower level of education. In summary, the Malaysian public was doubtful about the transfer of a synthetic animal gene to plants. There is a need for clear guidelines on the permissible status of gene transfer to guide the Malaysian biotechnology industries in such a scenario.

Overall, Malaysian stakeholders in the Klang Valley region were perceptive on modern biotechnology applications and products (Amin et al., 2011d). Malaysian policymakers were reasonably optimistic about the development of modern biotechnology in Malaysia. Biotechnology knowledge differed across religions, races, ages, and education levels, but not gender. In contrast, awareness levels differed across ages,

education levels, and gender, but not across religions and races. Religious attachment played a significant influence on the public's perception toward modern biotechnology applications, with the Malays being most positively influenced by religion, followed by Indians and Chinese. Finally, all biotechnology applications were moderately accepted by respondents from all races, ages, and educational backgrounds. Public perception, understanding, and awareness can influence commercial introduction and adoption of the new technologies. The acceptance of genetic modification in different areas of application was linked to attitude, which is influenced by socio-demographic variables, knowledge about genetics and biotechnology, and the perception of personal health risks.

Focusing on health biotechnology (HB) in Malaysia, there are numerous challenges to successful innovation (Abuduxike and Aljunid, 2017). Firstly, there is a lack of a conducive innovation system for sustainable HB due to insufficient expertise in universities, and limited communication between universities, research institutions, health biotech firms, and government agencies. Secondly, inadequate funding due to bureaucracy and lack of transparency in funding allocation, especially for commercialization and long-term R&D and HB product development. Thirdly, shortage of local human capital and a wrong mindset of new graduates, where the training curriculum does not cater to the practical skills needed in the industry. Fourthly, the research areas are extensive, unfocused, and do not reflect the strengths of Malaysia. Finally, there are too many government policies and regulations, such as lack of a clear framework, lack of an effective commercialization chain, trouble registering, patenting products locally, and poor implementation. In such instances, Malaysia must be proactive to improve the current situation before embarking on its journey toward developing a successful, innovative, and sustainable HB.

REGULATIONS AND GUIDELINES IN MALAYSIA

To further strengthen the efforts of NBP, the National Institutes of Biotechnology Malaysia (NIBM) was established to administer three national biotechnology institutes, namely the Malaysian Institute of Pharmaceuticals & Nutraceuticals (IPHARM), Agro-Biotechnology Institute Malaysia (ABI), and Malaysia Genome Institute (MGI). Biomedical product and clinical translation regulations such as human cell- and tissue-based products are governed by the Ministry of Health (MOH) (Idrus et al., 2015). Thus, the Medical Development Division of MOH formulated four standards, including the Guideline of Cell and Gene Therapy Products (CGTPs) to regulate all industrial players in the field.

Guidelines for Stem Cell Research and Therapy (2009)

In Malaysia, stem cell research is developed mainly in MOH facilities and university hospitals (Ministry of Health Malaysia, 2012). MOH is actively involved in stem cell regulations and provides numerous frameworks to guide researchers, clinicians, and companies in research, clinical trials, and manufacturing. A Guidelines on Stem Cell Research and Therapy was established, which highlighted that (Ministry of Health Malaysia, 2009b): (i) all experiments and clinical trials must be driven by a solid foundation of essential scientific and animal experimentation and must adhere to the highest medical and ethical standards, (ii) research on human adult stem cells, non-human stem cells and embryonic stem cell lines are allowed, and (iii) research on stem cells derived from fetal tissues of legally performed termination of pregnancy is permitted. On the other hand, the following are not permitted under the guidelines: (i) an *in vitro* culture of any intact human embryo, development from the fusion of human stem cell or any pluripotent cells with non-human cells, for more than 14 days or until the formation of the primitive streak begins, (ii) the introduction of human embryonic stem cells (hESC) into non-human primate blastocysts or in which any embryonic stem cells (ESC) are introduced into human blastocysts, and (iii) breeding of animal into which hESC have been introduced at any developmental stage.

The guideline only considers interventions at the *in vitro* level, animal studies, or clinical trials to sufficiently show safety, quality, and efficacy. Nevertheless, the currently accepted clinical application of stem cell- or/and cell-based therapies such as bone marrow or peripheral blood stem cell transplantation are limited to leukemia, lymphomas, and certain malignancies. The implementation of other clinical cases, including heart failure, stroke, spinal cord injuries, and organ failures, is still experimental. Nevertheless, in 2016, a pilot clinical trial, led by a team of orthopedic surgeons and stem cell scientists from Universiti Kebangsaan Malaysia (UKM), succeeded in treating a group of patients for knee articular cartilage defects using unmatched donor umbilical cord-derived mesenchymal stem cells (Rahim, 2019).

National Standards for Stem Cell Transplantation (2009)

Stem cell therapy showed promising medical intervention for the treatment of malignancies in Malaysia. For example, the survival rate improved significantly for acute leukemia, with more than 50% fully cured because of bone marrow transplants (Murugappan, 2019). Thus, MOH increased its efforts in framing standards and guidelines to keep up with this technology. The National Standards for Stem Cell Transplantation was published to cater to the collection, processing, storage, and infusion of hemopoietic stem cells (HSC) and other therapeutic cells (Ministry of Health Malaysia, 2009e). The standards aimed to ensure the safety and efficacy of the product to be infused into the recipient. At present, the rules allow minimal manipulation of the cells/tissues whereby: (i) the processing of structural tissue should not change the original relevant tissue's characteristics through reconstruction, repair, or replacement, and (ii) the processing for cells or non-structural tissue should not alter related tissue's biological properties. In such circumstances, the processes of cutting, grinding, shaping, centrifugation, soaking in antibiotic

or antimicrobial solutions, sterilization, irradiation, cell separation/concentration/purification, filtering, lyophilization, freezing, cryopreservation, vitrification is considered minimal manipulation, and any other alteration is subjected to scientific consideration and would have to be evaluated by experts. Notably, specialized processing procedures such as gene manipulation and insertion of new genetic material are only allowed after approval from an institutional review board or human ethics committee.

National Guidelines for Hemopoietic Stem Cell Therapy (2009)

The advancement of stem cell therapy drove Malaysia to set up the National Stem Cell Coordinating Centre, a database of all registered donors for peripheral blood, bone marrow, and umbilical cord blood (Aruna, 2014). Moreover, the National Guidelines for Hemopoietic Stem Cell Therapy was released by MOH to provide standards for any medical facility in performing hemopoietic stem cell transplantation (HSCT) (Ministry of Health Malaysia, 2009c). HSCT is routinely performed for patients with malignant and non-malignant hematological conditions, solid organ tumors, inherited metabolic, and primary immunodeficiency diseases. Moreover, experimental procedures must be performed as clinical trials, and ethics approval should be obtained and adhere to National Guidelines for Stem Cell Research and Therapy.

At this juncture, evidence-based outcomes from all stages of clinical trials are needed to ensure the intervention will be safe and effective (Fiona, 2016). In the future, health and regulatory bodies such as the Medical Research and Ethics Committee (MREC), Medical Service Development Division of the Health Ministry, Clinical Research Centre (CRC), Clinical Research Malaysia (CRM), National Pharmaceutical Regulatory Agency (NPRA), National Stem Cell Research and Ethics Sub-committee (NSCERT), Institute for Medical Research (IMR), Malaysian Stem Cell Registry, the various ethics committees at higher learning institutions and medical centers, the BioMedical Division of Biotech Corporation, investors, fund providers, and other stakeholders, can engage with the public to provide more awareness on the progress of cell therapy and the funding mechanisms involved in the clinical trials.

National Standards for Cord Blood Banking and Transplantation (2009)

Cord blood banking is gaining popularity among Malaysian parents, especially with the emergence of many private cords blood banking facilities in local settings such as StemLife and CryoCord (Goh, 2013). By preserving and storing blood taken from a baby's umbilical cord right after birth, these companies state that they can treat blood disorders, including thalassemia, leukemia, and bone marrow failures. Thus, The National Standards for Cord Blood Banking and Transplantation was developed to guide cord blood collection facilities to process, test, bank, select, release, and uphold quality medical and laboratory practices in cord blood banking (Ministry of Health Malaysia, 2009d).

Checklist for Research on Stem Cell and Cell-Based Therapies (NSCERT 2009)

The National Stem Cell Research and Ethics Sub-committee (NSCERT) developed a standard checklist for any application related to research on stem cell and cell-based therapies (Ministry of Health Malaysia, 2009a). The following procedures should be followed during submission: (i) all applications from MOH and the private sector must be submitted to MREC and registered under National Medical Research Register (NMRR); meanwhile, applications from universities must obtain approval from respective Institutional Review Board (IRB) or Independent Ethics Committee (IEC), (ii) upon review, a complete application will be forwarded to NSCERT for recommendation, (iii) NSCERT will make recommendations based on the proposed scientific evidence, (iv) NSCERT's recommendations will be submitted to MREC/IRB/IEC, and applicants will be informed about the final decision.

Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia (2016)

In general, CGTPs are categorized for "treating or preventing diseases in human beings, or administered to human beings with a view of restoring, correcting or modifying physiological functions by exerting pharmacological, immunological or metabolic action" (Ministry of Health Malaysia, 2016). In such circumstances, they are classified as medicinal products under the Sale of Drugs Act 1952: Control of Drugs and Cosmetic Regulations 1984 [P.U.(A) 223/84] (Laws of Malaysia, 1984). Under Part III: Registration and Licensing, Clause 7 (1), "no person shall manufacture, sell, supply, import, possess or administer any products unless the product is a registered product, and the product holds the appropriate license required and issued under these regulations." Moreover, due to the increase of CGTPs, the ministry divided the control and regulation into three approaches where: (i) the clinical use/medical procedure of the product will be under the ambit of Medical Development Division, and Medical Practice Division of the MOH, (ii) the device element of such products must comply with the Medical Device Act and regulations under the ambit of Medical Device Authority (MDA), and (iii) the National Pharmaceutical Control Bureau (NPCB) [currently known as National Pharmaceutical Regulatory Agency (NPRA)] will ensure the medicinal product's quality, efficacy, and safety.

This guideline covers cell therapy, xenotransplantation, and gene therapy, predominantly focusing on human stem cells, human tissue therapy products (e.g., skin, cardiovascular, ocular, musculoskeletal tissues), human cellular therapy products (e.g., cartilage cells, pancreatic islet cells, cultured skin cells, hematopoietic stem/progenitor cells derived from peripheral and cord blood), genetically modified cellular products, cell-based cancer vaccines, cell-based immunotherapies, and dendritic cells, lymphocyte-based therapies, cell-based therapies for cancer, peptides, and proteins. For gene therapy, the products may include recombinant nucleic acid sequences of biological origin, genetically modified viruses, genetically modified

microorganisms, and cells altered by one or more of these substances. These products are widely classified based on the delivery method, such as viral vectors, nucleic acids in a simple formulation (naked DNA), and nucleic acids formulated with agents such as liposomes. Furthermore, the regulation also outlines the quality of biotechnological products, starting materials used to manufacture the active substance, materials used in culture, and preservation of the cells. The development of CGTPs guidelines in Malaysia is crucial to increase safety and control, promote sound science and its practical application in cell therapy.

The risk of cell-based therapy must be assessed through stringent regulation and oversight, and currently, there are two classes of products that have been identified. Firstly, the lower risk cell therapy products must be minimally manipulated, intended for homologous use only as determined by labeling, does not involve combination with another drug/article/device, and does not have a systemic effect. The product is regulated by the Medical Practice Division, donor screening and testing, and Good Tissue Practices. Secondly, the higher risk cell therapy products are used for other than normal function, is combined with non-tissue components, or is used for metabolic purposes and regulated as a biologic product. The quality and scientific evaluation must be adequately addressed to evaluate the product's effectiveness and safety.

Debate 3: Are the Current Standards and Guidelines Sufficient to Govern Gene Editing?

The activities related to the stem cells are predominately guided by the documents discussed above, which suggests good practices and guidelines, and are not legally binding regulations. In the absence of such regulations, there are no legal consequences when a person violates the practices recommended in the instruction (Gopalan et al., 2019). Besides a lack of legal framework, there are also overlapping guidance documents (i.e., Guidelines for Stem Cell Research and Therapy, National Standards for Stem Cell Transplantation, National Guidelines for Hemopoietic Stem Cell Therapy), thereby causing confusion among researchers and clinicians. Even though MOH released a 'Checklist for Research on Stem Cell and Cell-Based Therapies,' the document fails to address the issue of non-compliance and accountability (Gopalan et al., 2017). As the guidelines are deemed adequate and updated, MOH decided against establishing any legal document specifically for stem cells (i.e., Stem Cell Act) to govern the activities (Ministry of Health Malaysia, 2012). However, the absence of regulatory policies or any legal documentation may enable exploitation to generate profit in stem cell research and technologies, with unknown consequences. Nevertheless, the former Deputy Health Minister, Dr. Lee Boon Chye, announced that the CGTPs guidelines would be enforced from 2021 to safeguard public health (Bernama, 2018; Chung, 2018).

Respondents in a survey compared the jurisdiction between the current Malaysian stem cell research to other national regulatory agencies such as the US FDA and the UK's Human Fertilization and Embryology Authority (Abdul Aziz et al., 2018). They believed that active engagement with regulators was crucial to guide what can be done in research and therapy. The respondents felt that the existing Malaysian guidelines were variable and limited, and there was a disconnect between written regulations and the day-to-day encounter by the clinical laboratory and scientists. There were mixed responses regarding the current regulatory regimen, wherein some regarded the framework as overly restrictive and hindered research advancement. Simultaneously, some claimed it was excessively facilitative due to the lack of monitoring and enforcement. This tug-of-war between regulation and scientific development in trying to stay abreast with neighboring countries while preventing irresponsible experimentation is undoubtedly challenging. In such circumstances, inspection and regular personnel training would play an essential role in maintaining quality and reducing incidences (Idrus et al., 2015). Even though there are no reports of misconduct, fraud, or deaths involving stem cell research in Malaysia, one cannot rule out the possibilities (Abdul Aziz et al., 2018; Gopalan et al., 2019). Without any formal complaints, no action can be taken. At present, the regulatory policy contains numerous loopholes such as overlapping of contents and is non-legally binding. Therefore, the solution lies in improving current guidelines, including a practical legislation framework.

Although there are many dilemmas about stem cell research in Malaysia, it is unclear whether gene editing is captured under any standards and guidelines. Given the current international proposals, Malaysia could adopt some of the elements in formulating policies addressing gene editing while adding its own historical, economic, social, and cultural perspective. It was perceived that public consultation would be an alternative option to direct governance of research and clinical applications using human gene editing (Alta Charo, 2016). Moreover, voluntary self-regulation and/or self-imposed rules could potentially restrict aspects of tissue donation, donor recruitment, and experimental procedures. A notable example of voluntary self-regulation is the Asilomar 1975: International Congress on Recombinant DNA Molecules, which declared a voluntary moratorium on recombinant DNA experiments by reviewing its potential hazards before pushing it forward (Barinaga, 2000; Berg, 2008). The experts agreed that research should be continued, but with stringent restrictions that estimate recombinant DNA technology risks and formulated ways of minimizing them. At the time, even without legislative restrictions, this moratorium proved that research could be undertaken as some scientists could self-govern. Notably, the congress community comprised primarily of academicians who may not have had a financial conflict of interest. Since then, the scientific era has changed drastically, genetic engineering has gone commercial, and a number of academics have shifted to biotechnology companies. In such a scenario, self-moratorium may not be feasible as many would have to adhere to company policies and the profit margin.

Regulation and legislation are crucial to manage emerging technologies for the public's benefit. For instance, Japan has a regulative pathway that classifies risks as high, medium, or low (Alta Charo, 2016; National Academies of Sciences Engineering and Medicine, 2017b). United States (US) regulates its medical

devices similar to Japan; however, in drug products, the US treats them as equally dangerous and utilizes safety and efficacy rules. Likewise, Singapore follows a risk-based approach for cell therapy and determines whether the modifications are major or minor, homologous or non-homologous, and in combination with other products. On the other hand, Brazil established laws governing genetically engineered food, stem cell research, and cell therapy, including constitutional prohibitions on human tissue sale. Remarkably, the Biosafety Law in Brazil tackles gene editing issues, allowing somatic gene editing in human subjects. Ecuador's constitution bans the use of genetic material for scientific research that violates human integrity. In Panama and Mexico, genetic modification for reasons other than severe disease treatment is punishable by a 2-to-6-year prison sentence. Similarly, Colombia also imposes a 1-to-5-year prison sentence for applications other than treatment, diagnosis, and research to alleviate suffering.

China has a formulated regulatory framework governing gene and cell therapy, and the State Food and Drug Administration plays a role in approving gene therapy products for commercialization. Additionally, legal guidelines for human embryo research and *in vitro* fertilization (IVF) procedures have been published by authorities of the People's Republic of China (Ministry of Health China, 2001, 2003). At this point, it is worth visiting the issue of He Jiankui, who created gene-edited babies using the CRISPR/Cas9 system (Cohen and Normille, 2020; Dyer, 2020). Jiankui was sentenced to 3 years prison sentence and fined 3m yuan (£329 000; €386 000; $430 000) by the Chinese court for fabricating an ethics review certificate. Jiankui and his team were also convicted of practicing medicine without a license, deliberately violating national regulations in scientific research and medical treatment. This implies that China has no strict regulations specific to gene editing and calls for rules relating to the genome to be included in the civil code (Cyranoski, 2019a,b).

Comparing the regulatory framework to a Western context such as the US or European Union (EU) could serve as a potential model to strengthen regulations and legal policies for gene editing in Malaysia, as summarized in **Table 4** (Grant, 2016; Samori and Rahman, 2016; Halioua-Haubold et al., 2017). In the US, the FDA controls numerous products ranging from food, tobacco, vaccines to therapeutics. Gene therapy products are strictly regulated under Section 351 of the Public Health Service Act (PHSA), which covers "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic products, or analogous products, . . . applicable to the prevention, treatment, or cure of a disease of human beings." European Medicines Agency (EMA) is the centralized regulatory authority in the EU. Gene therapy products are classified as Advanced Therapeutic Medicinal Products (ATMP) and are governed under the ATMP regulation that covers Gene Therapy Medicinal Products (GTMP), Somatic Cell Therapy Medicinal Products (CTMP), Tissue Engineered Products (TEP), and Combined ATMPs. The US FDA and the EU EMA released resources relevant to gene editing (Shim et al., 2017), as summarized in **Table 5**.

Although Malaysia has made some progress in CRISPR technology, it requires more initiatives to strengthen its growth to be par with other developed countries (Hamid, 2018). Thus, it is the scientific community's responsibility to engage with political leaders to further highlight the potential of gene editing (i.e., funding, law, and public engagement). The government needs to develop and implement a comprehensive national framework that guides genetic resources and biotechnology applications (Komen, 2012). International guidelines must be translated into federal laws and regulations, and a coordinated framework for biosafety should also be established. In such circumstances, governance on genetic products through gazetting the Biosafety Act 2007 is a practical effort in regulating the technology (Hafis Aliaziz and Ab Rahma, 2018).

BIOSAFETY AND BIOSECURITY IN MALAYSIA

A biosafety measure was drafted following acceptance of the Cartagena Protocol in 2003, led by the Ministry of Science, Technology, and Environment (Darsan Singh et al., 2019). In the following year, the ministry was reorganized as Ministry of Science, Technology and Innovation (MOSTI) and the Ministry of Natural Resources and Environment (currently known as the Ministry of Energy and Natural Resources). Since then, the Ministry of Energy and Natural Resources has taken the lead role in monitoring and enforcing the Biosafety Act 2007, under the regulation of four authorities, namely Department of Biosafety (DOB), National Biosafety Board (NBB), Genetic Modification Advisory Committee (GMAC), and Institutional Biosafety Committee (IBC) (Arujanan and Singaram, 2018).

Biosafety Act (2007) and Biosafety (Approval and Notification) Regulation (2010)

The aim of Act 678: Biosafety Act 2007 is to "regulate the release, importation, exportation and contained use of living modified organisms (LMOs), and the release of products of such organisms, with the objectives of protecting human, plant and animal health, the environment and biological diversity" (Laws of Malaysia, 2007; Darsan Singh et al., 2019). Modern biotechnology (Part I, Section 3) is defined as "*in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of the nucleic acid into cells or organelles, or fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection." In this context, LMOs means "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology." In Malaysia, the term LMOs and genetically modified organisms (GMOs) are used interchangeably. There are five categories (i.e., release, contained use, importation for release, importation for contained use, exportation) of activities involving LMOs regulated by the Act (Ministry of Natural Resources and Environment Malaysia, 2007).

The Act consists of seven parts (Laws of Malaysia, 2007; Zainol et al., 2011; Idris, 2013): (i) Part I touches on preliminary aspects such as citation, commencement, non-application,

TABLE 4 | Comparison between the gene therapy regulatory framework in United States (US), European Union (EU), and Japan.

	Malaysia	US	EU	Japan
Key regulatory structures	• Ministry of Health (MOH) • National Pharmaceutical Regulatory Agency (NPRA) • National Stem Cell Research and Ethics Sub-committee (NSCERT) • Medical Research and Ethics Committee (MREC) • Institutional Review Board (IRB) or Institutional Ethical Board (IEB)	• Food and Drug Administration (FDA) • Center for Biologics Evaluation and Research (CBER) • 351 Product • Office of Tissues and Advanced Therapies (OTAT)	• European Medicines Agency (EMA) • Committee for Medicinal Products for Human Use (CHMP) • Advanced Therapeutic Medicinal Products (ATMP) • Committee for Advanced Therapies (CAT)	• Pharmaceuticals and Medical Devices Agency (PMDA) • Center for Product Evaluation • Regenerative Medicine Product • Office of Cellular and Tissue-based Products
Name of product	Cell and Gene Therapy Products (CGTPs)	Gene Therapy Product	Gene Therapy Medicinal Product (GTMP)	Gene Therapy Product
Definition of gene therapy	• Contains an active substance which consists of a recombinant nucleic acid administered to human beings with a view to regulate, repair, replace, add or delete a genetic sequence. • Its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of gene expression of this sequence.	• Mediate effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms. • The products may be used to modify cells *in vivo* or transferred to cells *ex vivo* before being administrated to the recipient.	• Contains an active substance which consists of a recombinant nucleic acid administered to human beings to regulate, repair, replace, add or delete a genetic sequence. • Its therapeutic, prophylactic, or diagnostic effect relates directly to the product of genetic expression of this sequence.	• Articles which are intended to be used in the treatment of disease in humans or animals, and are transgened to express in human or animal cells.
Some main guidelines	• Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPS) in Malaysia (2016) • Checklist for Research on Stem Cell and Cell-based Therapies (NSCERT 2009)	• Long Term Follow-up After Administration of Human Gene Therapy Products; Guidance for Industry (2020) • Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (2013) • Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (1998)	• Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials (2019) • Quality, preclinical and clinical aspects of gene therapy medicinal products (2018) • Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (2012)	• Regenerative Medicine Promotion Law (2013) • Act of Safety of Regenerative Medicine (2013) • Act on Pharmaceuticals and Medical Devices (2013)

interpretation, and fees on activities that will be carried out, (ii) Part II covers the establishment and functions of NBB, GMAC, the appointment of Director General and other officers, (iii) Part III deals with release and importation activities which necessitate application for approval, (iv) Part IV discusses the notification of specific events of LMOs such as export, contained use and import, (v) Part V focuses on the risk assessment, risk management report and emergency response plan, (vi) Part VI and Part VII cater to the issue of enforcement, appeal, and other miscellaneous aspects.

The Biosafety (Approval and Notification) Regulation 2010 was released to cater to two major issues (Laws of Malaysia, 2010). Firstly, on the environment and human safety of LMOs and giving the public confidence in LMO products through the IBC that operates at the institutional level. The establishment of IBC is aimed to "provide guidance for safe use of modern biotechnology, to monitor activities dealing with modern biotechnology, establishing and monitoring the implementation of policies and procedures for the purpose of handling LMOs and determining the classes of Biosafety Levels for contained use activity for the purpose of modern biotechnology research and development undertaken within a facility." Secondly, the regulation governs the approval, certification, and notification of any release and importation of LMOs and LMO products. Notably, the provision (Part VII, Section 25) includes socio-economic considerations such as "the changes in the existing social and economic patterns and means of livelihood of the communities that are likely to be affected by the introduction of the LMOs, and the effects to the religious, social, cultural and ethical values of communities arising from the use or release of the LMOs."

Biosafety Guidelines for Contained Use Activity of Living Modified Organism (2010)

It was reported that many protested against the application for a confined genetically modified (GM) rice field trial at the Malaysian Agricultural Research and Development

TABLE 5 | Relevant regulatory guidelines applicable for gene editing technologies adapted from the Food and Drug Administration (FDA), US and the European Medicines Agency (EMA), EU.

Guidance titles	Year published
Food and Drug Administration (FDA), US[a]	
Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency; Guidance for Industry	2021
Human Gene Therapy for Neurodegenerative Diseases; Draft Guidance for Industry	2021
Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations; Draft Guidance for Industry	2020
Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Guidance for Industry	2020
Long Term Follow-up After Administration of Human Gene Therapy Products; Guidance for Industry	2020
Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry	2020
Human Gene Therapy for Hemophilia; Guidance for Industry	2020
Human Gene Therapy for Rare Diseases; Guidance for Industry	2020
Human Gene Therapy for Retinal Disorders; Guidance for Industry	2020
Evaluation of Devices Used with Regenerative Medicine Advanced Therapies; Guidance for Industry	2019
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions; Guidance for Industry	2019
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use; Guidance for Industry and Food and Drug Administration Staff	2017
Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception; Guidance for Industry	2017
Deviation Reporting for Human Cells, Tissues, and Cellular and Tissue-Based Products Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR Part 1271; Guidance for Industry	2017
Recommendations for Microbial Vectors Used for Gene Therapy; Guidance for Industry	2016
Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products; Guidance for Industry	2015
Considerations for the Design of Early Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry	2015
Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry	2015
Guidance for Industry: BLA for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System	2014
IND Applications for Minimally Manipulated, Unrelated Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic and Immunologic Reconstitution in Patients with Disorders Affecting the Hematopoietic System – Guidance for Industry and FDA Staff	2014
Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products	2013
Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage	2011
Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines	2011
Guidance for Industry: Potency Tests for Cellular and Gene Therapy Products	2011
Guidance for Industry: Cellular Therapy for Cardiac Disease	2010
Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products	2009
Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)	2008
Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry	2007
Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy	1998
European Medicines Agency (EMA), EU[b]	
Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP)	2019
Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials	2019
Quality, preclinical and clinical aspects of gene therapy medicinal products	2018
Management of clinical risks deriving from insertional mutagenesis	2013
Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products	2013
Design modifications of gene therapy medicinal products during development	2012
Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells	2012
Creutzfeldt-Jakob disease and advanced therapy medicinal products	2011
Questions and answers on gene therapy	2010
Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors	2010
ICH Considerations: oncolytic viruses	2009
ICH Considerations: general principles to address virus and vector shedding	2009
Follow-up of patients administered with gene therapy medicinal products	2009
Scientific requirements for the environmental risk assessment of gene-therapy medicinal products	2008
Non-clinical studies required before first clinical use of gene therapy medicinal products	2008
Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products	2008
Non-clinical testing for inadvertent germline transmission of gene transfer vectors	2006
Development and manufacture of lentiviral vectors	2005

[a]*Adapted from FDA Cellular and Gene Therapy Guidances: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances.*
[b]*Adapted from EMA Multidisciplinary: gene therapy: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-gene-therapy.*

Institute (MARDI) at Tambun Tulang, Perlis, claiming "genetic engineering is an inherently unpredictable process associated with unintended effects" (Goh, 2019; Sira, 2020). In reality, GM crops are evaluated using extremely stringent research protocols that ensure their safety (Arujanan, 2017). In such circumstances, a guideline to regulate the handling, storing, and transferring LMO without endangering humans, plants, animal health, the environment, and biological diversity was published.

In general, the Biosafety Guidelines for Contained Use Activity of LMOs divides the containment facility into five categories based on organisms, including genetic modification of microorganisms (GM-BSL), plants (GP-BSL), animals (GA-BSL), arthropods (GI-BSL), and aquatic organisms (GF-BSL). Under various containment facilities and levels (i.e., BSL-1, BSL-2, BSL-3, and BSL-4), a comprehensive description of the work practices, the minimum requirements for setting up facilities, and the required equipment under the different containment levels for contained use activities of LMO are provided. Moreover, the document also guides the disposal methods for biohazardous waste, as well as waste segregation and handling, whereby irresponsible disposal is prohibited and tightly governed by the Environmental Quality Act 1974, Environmental Quality (Scheduled Wastes) Regulations 1989, and Biosafety Act 2007.

A notification form must be submitted to IBC and NBB for any importation and exportation of LMOs. The LMOs must be clearly labeled and packaged in a tight container to avoid any material loss during transportation. The shipping of the LMOs starting from the research facility, storage facility, and field trial site should be recorded by IBC to ensure tracking. The LMO's storage areas must be cleaned and clearly labeled, and access should only be permitted to trained authorized personnel. Furthermore, an inventory should be maintained to avoid unintentional release of LMO into the environment, and inspections should be recorded.

Guidelines for Institutional Biosafety Committees (2010)

Institutional Biosafety Committee in any organization should be registered with the NBB and adhere to the Biosafety Act 2007 and Part II of the Biosafety (Approval and Notification) Regulations 2010. The Guidelines for Institutional Biosafety Committees: Use of LMOs and Related Materials was established to describe the setting up of the IBCs, its role, and scope, and processes that must be followed when obtaining, using, storing, transferring, or destroying LMO/recombinant DNA molecule (rDNA) (Ministry of Natural Resources and Environment Malaysia, 2010b).

Institutional Biosafety Committee plays a significant role to: (i) guide the principal investigator (PI) on biosafety policies for the use of LMO/rDNA research, the safety of laboratory personnel and other members of the organization, (ii) recommend and regularly review LMO/rDNA research that complies with Biosafety Act 2007 and Biosafety (Approval and Notification) Regulations 2010, (iii) monitor the facilities, procedures, practices, training and expertise of personnel involved in LMO/rDNA research, (iv) inform the PI of the results of the IBC's review of all activities involving the use of LMO/rDNA, (v) evaluate and set containment levels for LMO/rDNA research, (vi) assess field experiments to make sure that the proposed risk assessment, risk management and emergency response plan are adequate, (vii) execute emergency response plan covering accidental spills and personnel contamination resulting from LMO/rDNA work, (viii) review and report to the head of the organization and to the NBB any notable problems with non-compliance of the Biosafety Act 2007 and Biosafety (Approval and Notification) Regulations 2010 and any significant research-related accidents or illnesses, and (ix) ensure that the information provided in the application form (Approval/Notification) is correct and complete.

In terms of modern biotechnology, the following activities must obtain IBC approval: (i) deliberate transfer of a drug resistance trait to microorganisms, (ii) intentional transfer of rDNA or DNA/RNA derived from rDNA into human research participants, (iii) deliberate formation of rDNA containing genes for the biosynthesis of toxin molecules lethal for vertebrates, (iv) use of Risk Group 2, Risk Group 3 or Risk Group 4 agents as host-vector systems, (v) cloning of DNA from Risk Group 2 or higher agents into non-pathogenic prokaryotes or lower eukaryotic host-vector systems, (vi) utilizing infectious or defective Risk Group 2 or higher agents, (vii) using whole animals in which the animal's genome has been altered by the stable introduction of rDNA or DNA/RNA derived from rDNA into a germ-line, (viii) viable rDNA-modified microorganism tested on whole animals, (xi) genetically engineered plants by rDNA procedures, and (x) formation of rDNA material containing two-thirds or more of the genome of a eukaryotic virus.

Malaysia Laboratory Biosafety and Biosecurity Policy and Guideline (2015)

In 2013, the Biosafety and Biosecurity Subcommittee of the National Technical Advisory Committee of Public Health Laboratory gathered local personnel's input and expertise to implement effective biosafety practices and establish a Malaysia Laboratory Biosafety and Biosecurity Policy and Guideline. The document comprises basic concepts and approaches to regulate all activities involving handling, manipulation, working, using, storing, and disposing of infectious and potentially infectious agents/materials and microbial toxins in all laboratories in the country (Ministry of Health Malaysia, 2015). Furthermore, the guide is a useful reference for establishing good microbiological techniques (GMT), biosafety, and biosecurity in the laboratory and defined containment zones.

This document provides a comprehensive guide on basic administrative controls, engineering controls, standard operating procedures, and personal protection controls. In terms of administrative controls, the Institutional Biosafety and Biosecurity Committee (IBBC) is solely responsible for ensuring the policy and guidelines are implemented. The IBBC serves as the custodian for all the biosafety and biosecurity administrative controls for the organization. Meanwhile, the engineering personnel handles the physical containment facility (i.e., BSL-1, BSL-2, BSL-3, and BSL-4), infrastructure, design, safety, and security requirements.

Standard operating procedures (SOPs) are produced to ensure all routine laboratory activities and specific methods for handling particular microorganisms, pathogens, and toxins are reproducible when performed by any individual following the instruction. The IBBC establishes all SOPs related to infectious and potentially infectious agents/materials and microbial toxins. Besides that, personnel protective equipment (PPE) minimizes exposure to infectious agents and microbial toxins. PPE must be made available along with proper SOP. Laboratory biosafety checklist is also included in the document, covering three levels of containment (i.e., BSL-1, BSL-2, and BSL-3) facilities, including laboratory and its design, gas cylinders and chemicals handling/storage, refrigerators/freezers/cold rooms, electrical equipment, personal protective equipment, waste management, occupational health, and safety program, general engineering controls, general practices and procedures, general laboratory housekeeping, fire protection, biological safety cabinet (BSC), administrative controls, decontamination, handling of contaminated waste, and laboratory biosecurity.

Draft Code of Conduct for Biosecurity in the Framework of Biological Weapons Convention (2015)

In considering the need for immediate action on biosecurity, a workshop was held in 2015 as a platform to discuss and present Malaysia's draft of the National Code of Conduct for Biosecurity (Science and Technology Research Institute for Defence, 2015). This initiative aimed to create awareness on codes of conduct, define professional and ethical behavior, and come up with a mutual agreement on the code of conduct among the broader scientific community. Thus, a draft of code of conducts was established to raise awareness on potential dual-use and prevent malicious misuse, to assist research organizations avoiding any direct or indirect contributions to the development and production of potential biological weapons, to demonstrate that research organization are fully compliant with national and international legislation, and support the Biological and Toxin Weapons Convention (BTWC) as an international norm prohibiting biological weapons. The 10 significant elements of the draft are related to: (i) biorisk assessment and risk management, (ii) raising awareness, (iii) safety and security, (iv) education and information, (v) accountability and oversight, (vi) reporting misuse, (vii) internal and external communication, (viii) research and sharing knowledge, (ix) accessibility, and (x) supply, shipment and transport.

Biorisk assessment (BRA) and biorisk management (BRM) highlights the misuse of biological substances in hazardous applications either intentionally or due to a lack of risk assessment and management. It is crucial to restrict access of biological products to authorized personnel only, and the activities must be reviewed regularly by the organization in terms of resources, responsibilities, compliance, and communication for reliable BRA and BRM. All staff must be educated and regularly trained in dual-use aspects of biological products and biosecurity regulation, as well as be aware of the potential harm of product misuse. Scientists working with pathogenic organisms or dangerous toxins must adhere to safe and good laboratory practices. Moreover, scientists must take the initiative to disseminate information, convey national and international regulations, and establish policies to prevent the misuse of biological products.

Other than that, any scientist that becomes aware of activities that breach the BTWC or other international law must report the suspicion of the biological product, information, or technology directly to the appropriate authorities and agencies. Personnel involved in reporting would be protected from any unwanted consequences. In such a phenomenon, the scientist must fully observe principles and be responsible for overseeing research projects or publications. Access by unauthorized personnel to any internal and external data about potential dual use must undergo serious consideration. In terms of supply, shipment, and transport, all dual-use biological products should be screened by the relevant authorities and must be transported or exported carefully following applicable regulations. Implementing these elements of code of conduct for biosecurity will ensure safety and enable a secure environment to conduct responsible medical and life sciences work.

Debate 4: Are the Current Biosafety and Biosecurity Guidelines Sufficient to Regulate Gene Editing?

The impact of biotechnology activities on environmental sustainability and biodiversity is a global biosafety concern. In such circumstances, the precautionary principle approach is crucial to ensure the safe use of GMOs. This principle seeks to predict the consequences of biotechnology and its application that may increase threats to human health or the environment and the precautionary actions that must be undertaken. Furthermore, the precautionary approach must also consider the bioethics principle in decision-making, as it is closely related to how technology may influence humans' well-being, animals, and nature. In this case, a project on a field release of engineered mosquitoes [OX513A(My1)] into an uninhabited forested area of Bentong, Pahang, and Alor Gajah, Melaka was approved by NBB on 5 October 2010 [reference number NRE(S)609-2/1/3] (Lacroix et al., 2012). The application was approved based on recommendations by the GMAC and had successfully addressed concerns raised through public consultation (conducted for 30 days) (Ministry of Natural Resources and Environment Malaysia, 2010c; National Biosafety Board, 2010). Furthermore, information on the project was made available on the Biosafety Department website and published twice in a local newspaper (with a gap of 2 weeks).

Despite implementing a well-planned trial, some community groups were still dissatisfied with the public engagement process (Hamin and Idris, 2011; Idris et al., 2012, 2013; Subramaniam et al., 2012). It is uncertain whether the local communities in Bentong and Alor Gajah were included in the mandatory consultation before the board's approval. Notably, individual informed consent was not obtained regarding the field trial as it was not feasible. Moreover, there was also a negative perception of the trial on the use of GMO technology. Indeed, the degree of

communication explaining the risks and benefits of the field trial to public health was unclear. Revisiting the Biosafety Act (Part IV, Section 35), the word 'may' indicate that it is the discretionary power of the Board of Minister to consider socioeconomic values in evaluating GMOs. This provision conflicts with Part III, Section 15: "Advisory Committee shall assess such application for the purpose of making recommendations to the Board," which is purely based on scientific evidence and not ethical ones. There is also vagueness in terms of public participation in decision making (Part VI, Section 60): "subject to the discretion of the Board, the public may have access to such information relating to any application for approval, approval granted or notification, which has not been granted confidentiality under subsection 59(2) in such manner as the Board thinks fit." The word 'manner' could simply mean to preserve the commercial benefit if requested by the applicant. At this point, there is a lack of clarity on incorporating public and socio-economic considerations in the actual decision making. The Act seems overshadowed by diplomacy in accessing information by the public and the controlled manner related to its release.

In Denmark, the Danish Board of Technology encourages society's active involvement in biosafety issues (Glover et al., 2003; Idris et al., 2012). In the United Kingdom, due to a lack of trust in science officials, it is crucial to provide as much information as possible to the public for biosafety approval. In Brazil, there is an attempt to broaden the public's participation in biosafety evaluation, while in India, intensive media coverage and NGO demonstration have reflected a sense of insufficient engagement with the issue. There are collective attempts to engage civil society in developing the biosafety framework in Kenya and Zimbabwe despite constraints in resources and capacity. China has also sought to address biosafety issues within its governmental context, rather than a civil society where public participation has been widely incorporated into the decision-making. There are numerous existing international biosafety and biosecurity standards developed by World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) that can be applied to any institution globally (Bielecka and Mohammadi, 2014), as shown in **Table 6**.

It needs to be noted that it was not easy to get industries to accept the provision on "may also take into account socio-economic considerations," which demands more transparency (Hamin and Idris, 2011; Ramatha and Andrew, 2012). In general, socioeconomic values can be considered during the development of a domestic biosafety regulatory regime, during the risk assessment for GMOs, after a risk assessment, and during the appeal, review, or renewal of a permit. The evaluations are based purely on the economic impacts such as the distribution of benefits, research and development efforts, social and cultural issues that include public opinion, and ethical considerations. It is indeed tricky, time-consuming, and cost-ineffective to have socioeconomic views in decision making.

Moving forward, the application of viral vectors for gene therapy plays a vital role in achieving therapeutic efficacy (Ghosh et al., 2020). Nevertheless, these methods pose a risk and are still being studied to safeguard safety and effectiveness. There are limited resources available at the national or institutional level in the Malaysian context to assess and minimize the risk of viral vectors in research or clinical areas. Viral vectors are permitted to be used in experiments provided that the DNA (Ministry of Natural Resources and Environment Malaysia, 2010a) introduced is fully characterized and will not increase the virulence of the host or vector, and does not comprise or represent more than two-thirds of the genome of a virus.

TABLE 6 | Relevant biosafety and biosecurity documents applicable for gene editing technologies adapted from the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), US.

Guidance titles	Year published
World Health Organization (WHO)[a]	
Guidance on regulations for the transport of infectious substances 2019–2020	2019
Biosafety video series	2019
WHO Global Consultative Meeting on the Safe Shipment of Infectious Substances: 15–16 March 2018	2018
WHO consultative meeting high/maximum containment (biosafety level 4) laboratories networking: 13-15 December 2017	2018
Report of an extended meeting of the biosafety advisory group: 13–15 December 2016	2018
Extended Biosafety Advisory Group meeting, 24–26 November 2014	2015
Laboratory Biorisk Management: Strategic Framework for Action 2012–2016	2012
Responsible life sciences research for global health security	2010
Biorisk management: Laboratory biosecurity guidance	2006
Public health response to biological and chemical weapons: WHO guidance	2004
Laboratory biosafety manual: 3rd Edition	2004
Centers for Disease Control and Prevention (CDC), US[b]	
Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition	2009

[a]*Adapted from WHO Biorisk management: core documents: https://www.who.int/ihr/publications/bioriskmanagement_1/en/.*
[b]*Adapted from CDC Biosafety in Microbiological and Biomedical Laboratories (BMBL) 5th Edition: https://www.cdc.gov/labs/BMBL.html.*

Biosafety caters to "containment principles, technologies, and practices that are implemented to prevent unintentional exposure to pathogens and toxins, or their accidental release," while biosecurity refers to the "institutional and personal security measures designed to prevent the loss, theft, misuse, diversion or intentional release of pathogens and toxins," and both require special attention (World Health Organization, 2018). It is widely acknowledged that Malaysia's initiatives to promote modern biotechnology has encouraged the scientific community to explore genetic engineering. However, this may trigger the malicious use of technology for terrorist activities (Berns, 2014; Gronvall, 2014). The provision of the Biosafety Act 2007 and the Biosafety (Approval and Notification) 2010 regulations would have been inadequate to address biosecurity in Malaysia.

Considering those circumstances, Malaysian's BTWC bill which was drafted in 2012 and Science and Technology Research Institute for Defence (STRIDE) under the Ministry of Defence (MINDEF) addressed the deliberate use of biological agents or toxins as a weapon (Science and Technology Research Institute for Defence, 2018). Nevertheless, ensuring compliance with the BTWC by all institutions in Malaysia, such as the personnel

TABLE 7 | Summary of key ministry, regulatory bodies, and their publications to safeguard modern biotechnology in term of regulations and guidelines, biosafety and biosecurity in Malaysia.

	Description	Objective(s) and focus
Regulations and guidelines		
Key ministry	Ministry of Health (MOH)	• Facilitate and support the people to attain their potential fully in health, appreciate health as a valuable asset, take individual responsibility and positive action for their health. • Ensure a high-quality health system that is customer centered, equitable, affordable, efficient, technologically appropriate, environmentally adaptable, and innovative. • Emphasize professionalism, caring and teamwork value, respect for human dignity, and community participation.
Regulatory bodies	Medical Development Division	Develop medical services in the MOH's hospital, in particular, the speciality and sub-speciality services.
	Medical Practice Division	Ensure safe, efficient and quality health care standards through monitoring, legislation, regulation and regulation.
	Medical Device Authority	Provide regulatory control of the medical device industry in Malaysia, through compliance of act by ensuring safety and performance to protect public towards excellent customer satisfaction.
	National Pharmaceutical Regulatory Agency (NPRA)	Safeguard the nation's health through scientific excellence in the regulatory control of medicinal products and cosmetics.
Publications	Sale of Drugs Act 1952: Control of Drugs and Cosmetic Regulations (1984)	All drugs in pharmaceutical dosage forms and cosmetics must be registered before sales and marketing are permitted in the country.
	Guidelines for Stem Cell Research and Therapy (2009)	Facilitate researchers and clinicians from MOH, universities and private sector that are involved in stem cell research and therapy (adult stem cells and human embryonic stem cells)
	National Standards for Stem Cell Transplantation (2009)	• Laboratory framework to support stem cell therapy from the point of collection, processing, storage, handling and infusion of the products to ensure patients' safety. • Standards apply to sources of cells currently used for transplantation and cell therapy (bone marrow, peripheral blood and umbilical/placental blood).
	National Guidelines for Hemopoietic Stem Cell Therapy (2009)	Standards for any clinical facility in Malaysia performing hemopoietic stem cell transplants.
	National Standards for Cord Blood Banking and Transplantation (2009)	Standards on cord blood banking for transplantation in both private and public cord blood banks in Malaysia
	Checklist for Research on Stem Cell and Cell-based Therapies (2009)	Describes some of the procedures to be followed in making applications for stem cell and cell-based research involving human subjects, prepared by National Stem Cell Research and Ethics Sub-committee (NSCERT).
	Guidance Document and Guidelines for Registration of Cell and Gene Therapy Products (CGTPs) in Malaysia (2016)	• Outline the concept and basic principles of CGTPs. • Introduce the registration framework and guidelines to be applied. • Provide applicants with a "user guide" for the relevant scientific data and information, to substantiate the claimed quality, safety and efficacy of the product.
Biosafety and biosecurity		
Key ministry	Ministry of Energy and Natural Resources	Provide exceptional services in the management of natural resources and conservation of the environment in line with the national vision.
	Ministry of Health (MOH)	*same as above*
	Ministry of Defence (MINDEF)	Protect and defend the national interest which is the cornerstone of the sovereignty, territorial integrity and economic prosperity of the nation
Regulatory bodies	National Biosafety Board (NBB)	The regulatory body for making a decision pertaining to the release, importation, exportation and contained use of any living modified organism (LMOs) derived from modern biotechnology.
	Department of Biosafety (DOB)	• Evaluate the applications for the release, importation, exportation and contained use of living modified organism, and the release of products of such organisms. • Carry out the monitoring and enforcement activities under the Biosafety Act 2007 • Provide technical advisory on the handling of living modified organisms. • Raise public awareness regarding the role of biosafety in human, plant and animal health, the environment and biological diversity. • Promote research, development, educational and training activities relating to biosafety.
	Genetic Modification Advisory Committee (GMAC)	• Makes decisions on LMOs use in Malaysia and to provide scientific, technical and other relevant advice to the NBB. • Identification and safety management of risks associated with the use of genetically modified organisms (GMOs) and products containing or consisting of GMOs.
	Institutional Biosafety Committee (IBC)	Monitor any work which involves the use of any LMOs, or recombinant DNA (rDNA) molecule materials conducted at or sponsored by the organization, irrespective of the source of funding.
Publications	Biosafety Act (2007)	Regulate the release, importation, exportation and contained use of LMOs, and the release of products of such organisms, with the objectives of protecting human, plant and animal health, the environment and biological diversity.

(Continued)

TABLE 7 | Continued

	Description	Objective(s) and focus
	Biosafety (Approval and Notification) Regulation (2010)	• Ensuring the environmental and human safety of LMOs and giving the public confidence in LMO products by established the IBC. • The activities covered include the approval, certification and notification of any release and importation of LMOs and LMO products.
	Biosafety Guidelines for Contained Use Activity of Living Modified Organism (2010)	• Identify the Biosafety Levels (BSL) for containment of any LMO activity. • Describe work practices under the various containment levels. • Outline the minimum requirements for setting up facilities for contained use activities of LMO. • Identify equipment requirements under the different containment levels.
	Guidelines for Institutional Biosafety Committees (2010)	Describes the setting up of the IBCs, its role and functions and also processes that must be followed when obtaining, using, storing, transferring, or destroying LMO/rDNA materials.
	Malaysia Laboratory Biosafety and Biosecurity Policy and Guideline (2015)	• Basic concepts and approaches in the form of policy and guidelines that govern all activities involving the handling, manipulation working, using, storing and disposing of infectious and potentially infectious agents/materials and microbial toxins in all forms and sizes of laboratories in Malaysia. • Reference for the development and establishment of the respective institutional code of practice for good microbiological technique (GMT), biosafety and biosecurity in a laboratory and defined containment zone.
	Draft Code of Conduct for Biosecurity in the Framework of Biological Weapons	• Raise awareness of potential dual-use and the need to prevent malicious misuse. • Help research institutions to avoid any direct or indirect contributions to the development and production of potential biological weapons. • Demonstrate that research institutions in the country are fully compliant with national and international legislation and support the Biological and Toxin Weapons Convention Nucleus (BTWC) as an international norm prohibiting biological weapons.

working with pathogens and toxins, engineered controls, and biocontainment facilities, remains a conflict (Subramaniam, 2014). The personnel must be qualified and well-trained to understand the biological agent's containment conditions and how it can be safely manipulated and accessed. In such situations, the biorisk management committee (BMC) should be knowledgeable about biosafety and biosecurity legislation and its management. Currently, the appointment of a biosafety officer is predominately based on work experience and is responsible for implementing regulations in individual institutions or laboratories. Hence, the primary goal is to build a suitable 'biorisk culture' that comprises of proper biosafety and biosecurity practices and demonstrates responsible conduct at all levels in an organization.

Based on the discussion above, Malaysia's biosafety law is somewhat ambiguous in addressing bioethical concerns (Idris et al., 2013). It is recommended that the acts find a balance between promoting the advancement of modern biotechnology, ensuring environmental and public health safety, and considering public engagement in decision-making. For effective engagement, the following may be practical (Quinlan et al., 2016): (i) employing a wide range of resources to promote public education on the latest technologies, (ii) defining the objectives before seeking input, (iii) interacting with public groups from which information is needed, (iv) employing a clearly defined approach in making biosafety decisions, and (v) avoiding technical jargon. Stakeholders, policymakers, and the research community must work closely to assess risks and benefits. The government should also take initiatives to regain public confidence to enable them to understand the regulations (Zainol et al., 2011). Specifically, Malaysian authorities should be diligent in addressing the misuse of genetic engineering as bioweapons/bioterrorism (Majid, 2012). The scientific community and policymakers must collaborate and take responsibility to prevent the accidental or deliberate release of biological agents.

CONCLUSION AND FUTURE DIRECTIONS

Emerging technologies being developed over the next 5–10 years would significantly impact the economy and society (Academy of Sciences Malaysia, 2017a,b). Notably, technologies such as gene editing will drastically change the way we think about healthcare and will likely eliminate hereditary diseases. Malaysia is expected to embark on various emerging science and technology areas, especially concerning the following initiatives: (i) genetic testing of inherited diseases, (ii) gene therapy, (iii) genetic profiling, (iv) gene editing, (v) gene-manipulated gamete, and (vi) gene therapy and stem cell treatment for degenerative diseases. Even though gene editing has much to offer, it is crucial to evaluate the implementation of this tool in medicine. In such a context, three giants influence the application of gene editing (Capps et al., 2017): (i) individuals involved in the development of the technology, (ii) institutions where research is housed, and applications transpire, and (iii) the prevailing cultures that exert influence in this area of study.

Firstly, individuals refer to researchers and policymakers, politicians, and administrators who create regulatory conditions in which gene editing occurs. The discovery is relevant if it translates into useful products; in this respect, the gene editing platform should be a public resource. Scientists and

their institution depend on the public who volunteer their time, bodies and experiences for clinical trials through data and biosamples. The procedures use huge public time and resources, capital flow, and specific oversight and regulation. Thus, scientists are accountable to the public and should refocus their progress and investment in biomedical research based on public needs. Secondly, the contributing institutions, namely education, research and training, and security and stability, are the major research players. A broad partnership is necessary among institutions, researchers, participants, and the public. From this perspective, most public benefits from open science where researchers gather and share data, rather than conceal and withhold data. Thirdly, the value of trustworthiness is crucial, so the public expects their interest to be respected and considered in the pursuit of commercialization by the holding institution. Researchers may be hesitant about the concept of shared benefit and solidarity. Nonetheless, they should learn to prioritize the interest of the public without being critical of the process. Secrecy and hype-oriented misinformation may otherwise result in discouraging participation. Thus, by creating a safe space for engagement, information dissemination, honesty, and upholding research integrity, technology can be accelerated confidently.

At this juncture, it is essential to refocus gene editing laws and ethics toward clinical applications (Nicol et al., 2017). Notably, an overly rigid legislative response may prevent the researcher from undertaking gene editing work irrespective of the potential benefits. Mechanisms for periodic review need to be established to ensure responsiveness and re-evaluation of risks and benefits. Moreover, regulations must be adequately adopted to address new technological advances and applications as they arise. It is crucial to set different thresholds for acceptable risk-benefit ratios legitimately. By engaging a more comprehensive range of stakeholders (i.e., patients and families), the acceptable threshold for risks and benefits would be more apparent. Besides that, human research's ethical evaluation may provide an opportunity for public participation, such as having diverse membership in the IBC.

Moving ahead, biosafety and bioethics are of vital concern. In Malaysia, there remains a substantial lack of awareness on the issue (Zainol et al., 2011). There is a need for greater exposure to biosafety concerns, and relevant information must be provided through appropriate education. Education also has to be conducted at all levels, including schools, universities, and the public (Rusly et al., 2011; Ndolo et al., 2018). For instance, classes on biosafety can be included as a minor subject at schools and universities. For the public, practical strategies can be utilized, such as workshops, seminars, forums, small discussion groups, and the dissemination of biosafety issues in the newspapers, radio, and television. The public needs to be informed of the facts to bring modern biotechnology forward (Idris et al., 2012; Ramatha and Andrew, 2012). These initiatives may explore the possibilities of including socio-economic aspects in decision making. Policymakers must also address the potential misuse of biological agents as bioweapons (Majid, 2012). Alongside GMAC reviews, STRIDE/MINDEF can provide input on whether genetic engineering research would potentially pose a danger to national security. Furthermore, to safeguard the application of modern biotechnology in Malaysia, it is vital to produce and train more experts in legal issues associated with gene editing.

Malaysia has many standards, guidelines, and policies to cater to modern biotechnology, as summarized in **Table 7**. Its future role can be enhanced by creating a balance between promoting the development of the biotechnology industry and ensuring environmental and public health safety. Based on our discussion, the outlook on gene editing is not transparent, and it is unclear whether the existing regime suffices to address the technology. Malaysia is still new to this technology and needs to address several areas before embarking on this modern technology in the current situation. In such a phenomenon, several international organizations have issued frameworks and guidelines that offer different approaches to safeguard the regulation, biosafety, and biosecurity aspects of gene editing. All responsible parties such as MOH personnel, policymakers, bioethics, legal researchers, and physicians should create a forum to discuss such recommendations to formulate a document for gene editing in Malaysia explicitly. The guidance must be authoritative and enforceable and should be up to international standards for human research.

AUTHOR CONTRIBUTIONS

VK contributed to the conception and wrote the manuscript. KT participated in drafting the review and revising it critically for important intellectual content. All the authors reviewed the final manuscript to be submitted.

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Biosecurity in Village and Other Free-Range Poultry—Trying to Square the Circle?

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Village poultry commonly suffer significant disease related losses and a plethora of biosecurity measures is widely advocated as a means to reduce morbidity and mortality. This paper uses a household economy perspective to assess some "economic" considerations determining biosecurity investments of village poultry keepers. It draws on the 2012/13 Tanzania National Panel Survey (TZ-NPS), which covered 1,228 poultry-keeping households. Disease was the most frequently reported cause of bird losses and, in the majority of households, accounted for more than half of reported bird losses. However, given that poultry rarely contributed more than 10% to total annual household income, for 95% of households the value of birds lost to disease represented <10% of annual income. The value placed on poultry within households may vary by gender and the overall figure may mask differential intra-household impacts. The break-even cost for various levels of reduction of disease losses is estimated using a partial budget analysis. Even if achieved at no cost, a 75% reduction in disease-associated mortality would only result in a one percent increase of annual household income. Thus, to the "average" village poultry-keeping household, investments in poultry may not be of high priority, even when cost-effective. Where risks of disease spread impact on the wider community and generate significant externalities, poultry keepers must be supported by wider societal actions rather than being expected to invest in biosecurity for purely personal gain.

Keywords: poultry, village, biosecurity, risk, economics, household

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INTRODUCTION

Domesticated animals[1] deliver significant monetary and non-monetary products and services to society. These benefits can be put at risk by infectious and parasitic diseases, which can have a dramatic impact on productivity through morbidity and mortality and hence directly and indirectly affect the associated human communities. The generic recommendation that livestock keepers "enhance biosecurity" is a widely proposed solution to the threat of animal disease in the livestock development literature. FAO (1) defines biosecurity as "*the implementation of measures that reduce*

[1]Livestock – animals kept for production, investment and sale, companion animals for pleasure and sporting animals.

the risk of the introduction and spread of disease agents," comprising three principal elements: (i) segregation, (ii) cleaning, and (iii) disinfection.

"Improved biosecurity" is said to increase productivity, enhance income and food security, protect human health, and reduce antimicrobial use [e.g., (2–4)]. The recommendation to enhance biosecurity is not only leveled at market-oriented/commercial livestock producers but also at low-input low-output livestock keepers, many of which keep small flocks of free-range/scavenging poultry [see (5) for a review of pertinent literature].

Rural, extensive poultry raising ("village poultry") is extremely popular in low- and middle-income countries (LMICs), because it does not need a large investment, poultry reproduce rapidly, and birds can scavenge for feed. They thrive on kitchen waste, broken grains, earthworms, snails, insects and vegetation. Village poultry make a significant contribution to poverty alleviation and household food and nutrition security by providing scarce animal protein and bioavailable micronutrients in the form of meat and eggs and income to meet essential family needs (6, 7). In many LMICs village poultry remain by far the most numerous type of poultry raised and, despite small flock sizes, in aggregate account for 60–90% of the poultry population (8). In Indonesia for instance, 22 million households raise village chickens of which only 1 million (<5%) have more than 30 birds (9).

A wide array of recommended biosecurity measures can be found in the literature, yet no standardized classification exists. **Table 1** lists the main biosecurity recommendations for backyard/village poultry compiled by Conan et al. (5) in their systematic review of biosecurity measures for backyard poultry.

The principles of biosecurity are well-defined and practical measures have been devised, yet, with the exception of vaccination against selected diseases, the authors have been unable to find scientific evaluations of the "protective" effect for specific measures in commercial, let alone backyard poultry. Even less information on the benefit-cost ratio of specific biosecurity measures for individual poultry keepers has been generated. In fact, Conan et al. (5) conclude: "*We are left with the impression that the proposed lists of recommendations were made without weighing biosecurity measures according to prioritization criteria, efficiency or financial and technical feasibility*."

The technocratic view of many development practitioners is, that farmers "do what they do, because they do not know better," i.e., lack technical knowledge. However, farmers operate in economic, social and ecological contexts and their behavior may well be "rational" if these contexts are better taken into account. In order to address the gap in information identified, the paper presents a generic assessment of the "economic" aspects determining biosecurity investments of village poultry keepers by adopting a household economy perspective. It draws on the 2012/13 Tanzania National Panel Survey covering 1,228 poultry keeping households and is structured as follows (i) a description of village poultry keeping in Tanzania (ii) an analysis of poultry losses, the role of diseases, and the magnitude of losses in relation to total household income, (iii) a partial budget analysis of break-even cost of theoretical biosecurity investments leading to reduction of (observed) disease losses by 10, 25, 50, and 75%, and (iv) discussion and conclusions.

KEY CHARACTERISTICS OF VILLAGE POULTRY AND THEIR ROLE IN THE HOUSEHOLD ECONOMY IN RURAL TANZANIA

The following description of village poultry keeping in Tanzania is based on data collected by the Tanzania National Bureau of Statistics (TZ-NBS) as part of the implementation of the 2012/13 Tanzania National Panel Survey (TZ-NPS) (10). The TZ-NPS includes an expanded livestock module, with between 80 and 100 questions. In comparison, traditional living standards measurement surveys (LSMSs) include between 5 and 20 questions on livestock. In addition to LSMS information items, the TZ-NPSs collect information on (i) livestock ownership and herd/flock dynamics (e.g., sales, thefts, gifts, etc.), breeds kept, differentiated as local/indigenous vs. improved/exotic; (ii) use of inputs, including feed, water, labor, vaccines and drugs; (iii) production and use of livestock products and services, such as meat, milk and eggs, but also dung and traction; and (iv) sale and home-consumption of animal source foods.

The 2012/13 TZ-NPS collected data from 3,154 randomly selected rural households. Of these, 1,751 (56%) owned livestock, 1,228 (39%) owned poultry and 495 (16%) owned poultry as their sole type of livestock. Mean and median flock size of poultry owning households was 13.1 and 10.0 birds, respectively. Fifty-six percent of flocks consisted of 10 birds or less, 43% of flocks fell into the range of 11–50 birds and only 13 flocks (≈1%) had more than 50 birds (excluded from further analysis).

The vast majority of birds were of indigenous breed (15,036 vs. 27 "exotic") and flocks were self-replacing. Over the recall period of 1 year, 95% (19,743/20,780) of recorded "entries" were hatched within the flock. Seventy percent of flocks did not have a bird added from "outside" and the 30% of flocks that introduced birds, either through purchase, as gift or payment, introduced a median number of three birds.

Birds from 22% of the households scavenged exclusively while those from 73% of the households were supplemented with some household "waste." Only 5% of households provided small amounts of other feed (not further specified). None of the flocks were housed during daytime while 80% of households kept their birds indoors at night, either in chicken coop (46%) or in the family house (34%). Annual expenditure on poultry was low, with 77% of households having spent nothing on their poultry over 12 months.

Seventy-three percent of households had slaughtered (for home consumption) and 40% had sold birds over the past year. The average number of birds consumed (across all households) was 2.9 (median 2) and the average number of birds sold was 2.2 (median 0). Only 8% of households had sold eggs in the past 12 months and, overall, around 95% of eggs produced remained in the household. The dataset does not provide information on the numbers/proportions of eggs used for hatching and home consumption.

TABLE 1 | Recommended biosecurity measures for backyard/village poultry [elaborated from Conan et al. (5)], rationale, cost and comment.

Measure	Rationale	Cost	Comment
Structural			
Indoor raising	Limits contacts with wild birds, other flocks and people outside the household	Building, feed, litter and additional labor, possibly different disease profile leading to requirement of additional medicines and skills	Defeats the entire rationale of backyard poultry keeping. If sheds are open (likely to be the case in tropical climates) there will still be contact with wild birds.
Fences to limit free-ranging	Limits contacts with flocks and people outside the household	Cost of fencing plus required extra feed	Contact with wild birds and pests may be reduced, but may increase as feed can attract wild birds and pests
Structural and/or operational			
Separation by age (and poultry species)	Reduces passing on of infection from older to younger birds or between poultry species	Requires some form of "fencing"/physical barrier and restricting access to the area	If birds scavenge, they will still be exposed to wild animals and pests. Single age flocks are more susceptible to morbidity during outbreaks of diseases such as infectious bursal disease.
Quarantine of introduced birds for 14 days	Reduces risk of exposure to pathogens possibly carried by introduced birds	Requires "quarantine pen/area" and probably additional feed and labor	May facilitate theft of birds quarantined away from homesteads.
Separation of sick birds	Reduces exposure to pathogen responsible for disease	Requires "quarantine pen/area" and probably additional feed and labor	Birds can be infective before showing signs of disease and measure should be accompanied by cleaning and disinfection
Operational with additional expense (incl. family labor)			
Cleaning and disinfection	Reduces pathogen load in the house/pen and on equipment	Cost of detergent/disinfectant and (family) labor	Reduces within-flock spread but not introduction
Cleaning of food and water containers	Reduces pathogen load in feed and water	Cost of sanitizers and (family) labor	Reduces within-flock spread but not introduction
Secure safe water	A number of poultry diseases can be transmitted by drinking water.	Cost of disinfectant and (family) labor	No specific advice on how. Even tap water may not be safe in many LMIC locations
Composting manure outside flock area	Inactivates pathogens that are excreted with poultry feces.	Compost bin, labor required to collect manure (and bedding) and to manage composting process	Only feasible where/when birds are kept in a circumscribed area, e.g., night pen. Reduces within-flock spread but not introduction.
Early removal and adequate disposal of dead birds	Reduces exposure to pathogen responsible for disease	Labor required to regularly check the flock; disposal can be perceived by vulnerable households as a loss of scarce food	Reduces within-flock spread but not introduction.
Vaccination[1] against endemic diseases of importance	Reduces poultry morbidity/mortality and replication and spread of infectious agents	Vaccine, vaccinator fee	Does not reduce risk of pathogen introduction, is pathogen specific, may not protect against infection, may give false sense of security
Operational, no apparent additional expenses (but opportunity costs)			
Source poultry from trusted/disease-free flocks	Reduces likelihood of introducing pathogen via incubating or healthy carrier		Actually quite frequently practiced (possibly even the norm) as markets are often distant and birds can easily be sourced from "trusted" neighbors. Disease freedom is difficult to ensure given the limited testing capacity in LMIC.
Avoidance of live bird markets and other farms	Reduces risk of introducing pathogen on shoes, clothes, hands of poultry keeper		Given small number of birds sold/bought (possibly mostly at farm gate), visits to live bird markets may not be particularly frequent.
Visitor restriction	Reduces risk of introducing pathogen on shoes, clothes, hands of visitor		

[1] *Not included in Conan et al. (5).*

The average annual household income of all rural households keeping poultry was 2.3 million (median 1.6 million, IQR 0.9–3.0 million) TZ Sh. (app. USD 1,480) (**Table 2**). Crop production contributed the largest average within-household share of income (52%) followed by non-agricultural activities (34%) while income from livestock (poultry and other species) contributed an average share of 14%. Compared with households keeping poultry and other types of livestock, households with poultry as their only type of livestock averaged a slightly lower annual income of 2.0 million TZ Sh. (median 1.3 million, IQR 0.7–2.4 million), with crops, non-agricultural activities and poultry contributing 52, 40, and 8%, respectively.

TABLE 2 | Mean and median annual income (thousand TZ Sh.[1]) of rural poultry-keeping households (hhs) in Tanzania in 2012/2013 by income source.

	All poultry keeping hhs (1,214[2])			Poultry only livestock hhs (495)		
	Mean	Median	Ratio[3]	Mean	Median	Ratio[3]
Total	2,319	1,619	1.43	1,976	1,330	1.49
Crops	984	758	1.30	765	614	1.25
Livestock	314	52	6.03	119	12	9.56
Non-ag.	1,019	255	3.99	1,092	282	3.87

[1] *1 USD ≈ 1,570 TZ Sh.*
[2] *No income data for one household.*
[3] *Mean/median.*

As indicated by the high mean-to-median ratio, income from livestock/poultry was extremely skewed (11) with a small number of households obtaining a relatively high income from livestock. Given total income is much more evenly distributed than livestock income, it follows that some households receive a large share of their income from livestock/poultry. **Table 3** presents the distribution of share of household income from livestock/poultry of rural poultry-keeping households. Distribution of the control of household income could not be disaggregated by gender.

POULTRY DISEASE RISK AND LOSSES

The "group" (herd/flock)-level disease prevalence tends to increase as size of the group increases, whereas within the "group" (herd/flock) prevalence of disease tends to decrease as group size increases [e.g., (12–14)]. The disease risk and losses were assessed separately for flocks of 1 to 20 birds (n = 1,037) and flocks of 21–50 birds (n = 178) at the time of data collection.

Table 4 displays the number and proportion of households reporting bird losses over the past year by cause for the two flock size groups. Disease was the most frequently reported cause of bird losses in both groups, having caused losses in around 60% of households. "Accident/injury," including predation, was the second most frequent cause of bird losses (36 and 43%), followed by theft, which was experienced by around 20% of households. In both groups, the number of birds lost due to disease, accident or theft was markedly higher than the number of birds consumed, sold or gifted out, 10,512 vs. 5,133 and 2,370 vs. 1,435 in the smaller and larger flock-size groups, respectively.

Disease was not only the most frequently experienced cause of bird losses, but with a median of 9 and 10 birds lost in flocks experiencing disease, disease was also responsible for the largest number and share of birds lost. Disease accounted for 66.0 and 59.4% of bird losses in the smaller and larger flocks size groups, respectively. The average value of birds lost to disease was intermediate between the value of stolen birds, which had the highest average value, and birds lost to accident/injury, and amounted to ∼55% of the average value of birds sold.

Over a year, households with flocks of 1 to 20 birds on average lost 22% of their birds to disease (deaths/initial flock plus entries) with disease losses ranging from 0 to 93%. In the larger flock size group, average disease losses amounted to 13% of birds with a range of 0–59%. **Table 5** displays the frequency distribution of the proportion of birds lost to disease for the two flock size groups.

Larger flocks had a higher likelihood of sustaining a "small loss" (74 vs. 53% chance of losing <20% of the flock) but a lower risk of sustaining high loss, e.g., 1 vs. 15% risk of losing > 50% of the birds (Flock size itself apparently acts as "insurance" against "total loss" as it increases the likelihood of survivors.).

Newcastle disease was by far the disease most frequently mentioned to have affected poultry in both groups (53 and 55% of smaller and larger flocks) followed by fowl pox, reported by 3% of households with smaller flocks and 6% of households with larger flocks. Reported Newcastle disease vaccination (which did not take the frequency of vaccination into account), however, did not affect the proportion of birds lost to disease with average losses of 24% in flocks that had vaccinated and 21% in non-vaccinated flocks. Introduction of birds through purchase or gifts also did not affect the magnitude of disease losses, with average disease losses of 17% in flocks, which had introduced birds vs. average losses of 22% in flocks that had not introduced birds.

The value of birds lost to disease as proportion of total annual household income (**Table 6**) can serve as crude measure of economic impact on affected households. For more than half of all households, the value of birds lost to disease represented <1% of annual household income and for 95% of households it represented <10% of annual income. For a mere 2% of households, bird losses from disease represented more than 20% of annual household income.

Figure 1 depicts the relationship between the proportion of birds lost to disease and the value of lost birds as proportion of annual household income. Clearly, the proportion of birds lost to disease is only a moderate predictor of the impact on total annual household income. A relatively small proportional loss of birds can translate into a relatively large loss in household income while conversely, a relatively high bird loss does not necessarily equate with a high loss in household income.

BREAK-EVEN COST OF BIOSECURITY INVESTMENTS

A partial budget analysis of the break-even cost of biosecurity investments leading to a reduction of disease losses by 10, 25, 70, and 75% was carried out for flocks of 1–20 and 21–50 birds. Average parameter values (e.g., initial and final inventory, number of birds lost to disease, number of eggs produced, etc.) and prices of the flock size groups of 1–20 and 21–50 birds were used for the analysis. The number of avoided egg losses from reduced disease mortality was estimated as the product of the number of deaths avoided and half of the average number of eggs produced per bird per year. The analysis does not assign a salvage value to diseased/dying birds, although these are often consumed. Details of the calculations are provided in the **Annex**.

TABLE 3 | Distribution of share (%) of household income from livestock/poultry of rural poultry-keeping households (hhs) in Tanzania in 2012/2013.

	All poultry keeping hhs (1,214[1])		Poultry only livestock hhs (495)	
	n	%	*n*	%
<10%	746	61	381	77
10 to <20%	165	14	46	9
20 to <30%	91	7	24	5
30 to <40%	76	6	20	4
40 to <50%	43	4	11	2
≥50%	93	8	13	3

[1]*No income data for one household.*

TABLE 4 | Number and proportion of households (hhs) experiencing bird losses and number of birds lost by cause in flocks of 1–20 and 21–50 birds (upper panel), and number, proportion and median value of birds lost by cause in flocks of 1–20 and 21–50 birds (lower panel).

	1–20 birds (*n* = 1,037 hhs)			21–50 birds (*n* = 178 hhs)		
Households	***n***	**%**	**Birds lost[1]**	***n***	**%**	**Birds lost[1]**
Disease	626	60.4	11.1/9	111	62.4	12.7/10
Accident/injury	373	36.0	7.3/5	76	42.7	9.7/6
Theft	174	16.8	4.9/3	32	18.0	7.1/6
Birds	***n***	**%**	**Mean bird value**	***n***	**%**	**Mean bird value**
Disease	6,940	66.0	3,533	1,408	59.4	3,866
Accident/injury	2,717	25.8	2,407	735	31.0	3,003
Theft	855	8.1	4,275	227	9.6	5,176
Total	10,512			2,370		

[1]*Mean/median number of birds lost by households with losses.*

TABLE 5 | Frequency distribution of the proportion of birds lost to disease for flocks of 1–20 and of 21–50 birds.

Share[1] of birds lost to disease	1–20 birds			21–50 birds		
	n	**%**	**Cumulative %**	***n***	**%**	**Cumulative %**
<10%	444	42.8	42.8	87	48.9	48.9
10 to <20%	105	10.1	52.9	44	24.7	73.6
20 to <30%	124	12.0	64.9	22	12.4	86.0
30 to <40%	124	12.0	76.9	15	8.4	94.4
40 to <50%	87	8.4	85.2	8	4.5	98.9
50 to <60%	62	6.0	91.2	2	1.1	100.0
60 to <70%	47	4.5	95.8	0	0.0	100.0
70 to <80%	31	3.0	98.7	0	0.0	100.0
80 to <90%	9	0.9	99.6	0	0.0	100.0
≥90%	4	0.4	100.0	0	0.0	100.0

[1]*Number lost to disease over initial inventory plus entries.*

TABLE 6 | Frequency distribution of value of birds lost to disease as proportion of annual household income for flocks of 1–20 and of 21–50 birds.

Value of birds lost as share of household income	1–20 birds			21–50 birds		
	n	**%**	**Cumulative %**	***n***	**%**	**Cumulative %**
<1%	640	61.7	61.7	101	56.7	56.7
1 to <2%	131	12.6	74.3	26	14.6	71.3
2 to <3%	67	6.5	80.8	13	7.3	78.7
3 to <4%	52	5.0	85.8	8	4.5	83.1
4 to <5%	28	2.7	88.5	11	6.2	89.3
5 to <10%	69	6.7	95.2	10	5.6	94.9
10 to <20%	32	3.1	98.3	5	2.8	97.8
20 to <50%	14	1.4	99.6	2	1.1	98.9
≥50%	4	0.4	100.0	2	1.1	100.0

The annual value of avoided bird and egg losses resulting from the maximum assessed disease reduction of 75% amounts to 24,682 TZ Sh. (app. USD 15.7) and 29,025 TZ Sh. (USD 18.5) for the smaller larger flock size groups, respectively (**Table 7**). These values thus represent the breakeven costs of biosecurity measures above which their cost would be higher than the returns. For both flock size groups, this reduction in disease-associated mortality would, if achieved at no cost, result in a one percent increase of annual household income.

Reducing disease associated mortality by 25%, a figure, which might be more realistic, would pay for itself if it could be achieved at a cost of around 8,000–10,000 TZ Sh. (USD 5.0–6.5) per year (around 0.5 USD/month).

DISCUSSION

In Tanzania, as elsewhere, the majority of rural poultry-keeping households have diversified income sources with cropping being the source of slightly over 50% of income, followed by non-agricultural activities contributing 35–40%. Poultry are generally managed as a low-input, low-output activity with minimal investments. More than three out of four households with poultry as their sole type of livestock obtain <10% of their annual income from poultry and are thus relatively resilient to shocks affecting their birds; although it is acknowledged that the loss of poultry may impact some household members more than others. However, around 10% of households with poultry as their sole type of livestock obtain 30% or more of their income from poultry, which makes them highly vulnerable to poultry disease and other events that decimate their flock.

Infectious disease is the most frequently reported cause of poultry losses (>60% of birds lost), resulting in an average loss of 22 and 13% of birds in smaller (1–20 birds) and larger (21–50 birds) flocks, respectively. In both flock size groups, disease

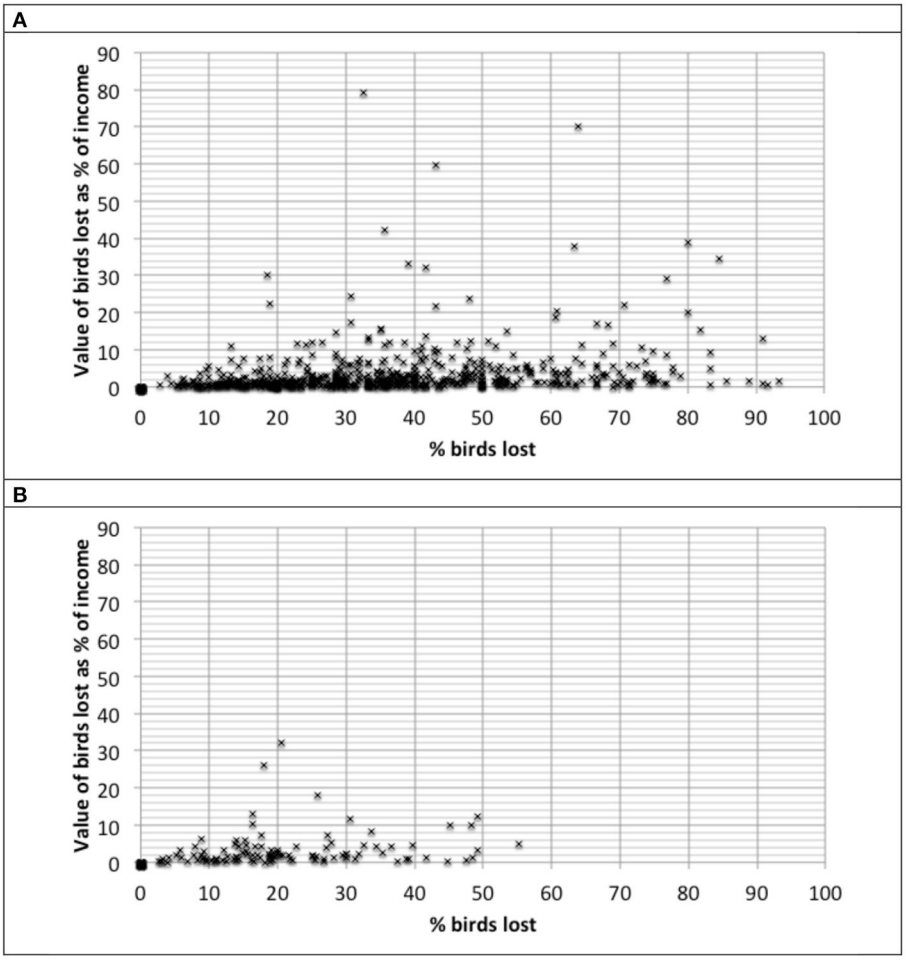

FIGURE 1 | Relationship between the proportion of birds lost to disease and the value of lost birds as proportion of annual household income. **(A)** Flocks of 1–20 birds. **(B)** Flocks of 21–50 birds.

attributable mortality translates into the loss of 7–8 birds per year per flock, more than the number of birds consumed and sold. Given this high toll of disease losses, efforts to reduce disease incidence appear highly warranted. However, considering the resource limitations (including labor) and diversified livelihoods strategies of village poultry keeping households, interventions need to be low-cost, highly effective and simple to implement.

No estimate of the reduction in disease risk is available for any of the biosecurity recommendations compiled by Conan et al. (5), either as stand-alone or as part of a combination of measures. Of the biosecurity recommendations, only indoor raising reduces (but does not necessarily eliminate) contact with wild birds, probably an important source of pathogen introduction. Indoor raising, however, comes at a high cost as it requires investment in a chicken house, additional expenses for chicken feed and additional labor to feed chicken and maintain cleanliness of the chicken house. In Cambodia for instance, the cost of building a poultry house is USD 25 when monthly family income is USD 75 (15). Using computer simulation to assess the cost and benefits of various forms of backyard poultry keeping, Gyeltshen et al. (16) found that housing had the maximum positive effect on flock size but resulted in net loss to the farmers. In addition to the cost of infrastructure, any biosecurity measure that restricts scavenging activities is associated with extra costs (and labor) of feeding the birds.

As scavenging is an essential element of village poultry keeping, the ceiling of achievable biosecurity through means other than housing may be low. In fact, in a cluster randomized trial of the impact of biosecurity measures (cleaning yards and equipment, quarantine of newly introduced and sick animals and burning dead birds) on poultry health in backyard flocks, Conan et al. (15) find that "*despite good compliance among poultry owners, the biosecurity intervention implemented in this study was not associated with improvements in poultry mortality rates. These findings suggest that basic biosecurity measures may not suffice to limit the spread of infectious diseases in backyard poultry flocks*

TABLE 7 | Household-level impacts of biosecurity interventions reducing the proportion of birds lost to disease by 10, 25, 50, and 75% in flocks of 1–20 and 21–50 birds.

	Proportion of disease losses prevented			
Impact at household level	**10%**	**25%**	**50%**	**75%**
Flocks of 1–20 birds				
Number of deaths avoided	0.67	1.67	3.35	5.02
Number of egg losses avoided	4.12	10.30	20.61	30.91
Value of avoided losses in TZ Sh.	3,291	8,227	16,455	24,682
Value of avoided losses in number of birds[1]	0.50	1.25	2.50	3.76
Increase in household income (%)	0.15	0.37	0.75	1.12
Flocks of 21–50 birds				
Number of deaths avoided	0.79	1.98	3.96	5.93
Number of egg losses avoided	3.31	8.28	16.55	24.83
Value of avoided losses in TZ Sh.	3,870	9,675	19,350	29,025
Value of avoided losses in number of birds[1]	0.56	1.40	2.80	4.19
Increase in household income (%)	0.13	0.32	0.64	0.96

[1]*Having reached average age/weight for sale.*

in Cambodia." Even for small-scale intensified poultry producers with housed poultry, the biosecurity "ceiling" is low as for most producers closed housing is prohibitively expensive (a closed house, which requires forced ventilation, costs about seven times as much as the prevailing "open" house) while open houses are not particularly biosecure.

Although improving biosecurity is likely to enhance flock productivity, a significant proportion of poultry keepers continue their "risky" production practices despite receiving advice on risk-reducing measures (17). Aini (18) attributed the low adoption of biosecurity measures by backyard farmers to their low cost-effectiveness.

Cost-effective measures to improve productivity of village poultry do exist, but these do not necessarily (exclusively) focus on disease risk. Predation of young chicks can be a significant cause of bird losses, exceeding the number of birds lost to disease [e.g., (19, 20)]. Henning et al. (21) assessed the impact of two interventions to improve backyard poultry production in Myanmar, namely (1) vaccination of individual birds against Newcastle disease (ND) and (2) improved management of chick rearing by providing coops for the protection of chicks from predation and chick starter feed. The benefit:cost ratio (BCR) for ND vaccination was very high (28.8) while the BCR for improved chick management was lower (4.7) but still high. Discounted Net Present Values for ND vaccination and improved chick management over a 10-year period were 30,791 and 167,825 Kyat (around 31 and 168 USD), respectively. Thus, despite high BCRs, the absolute benefits accruing from cost-effective improvements in backyard poultry production under Southeast Asian conditions appear rather moderate (0.26 and 1.4 USD/month). Research investments in the effective control of ND in village chickens via vaccination in sub-Saharan Africa has been calculated to yield a high BCR (22) with ongoing benefits where cost-sharing with farmers supports regular vaccination of village chickens against ND (23, 24).

Investments in poultry production with a high benefit:cost ratio may still prove to be unattractive to the average village poultry keeper as the additional return only results in a very modest increase in total household income and returns to investments in activities more central to their livelihood are possibly larger. Given the "livelihoods" impact of poultry disease losses is to a large extent determined by the share of household income derived from poultry, households relying heavily on poultry should be the ones most likely to adopt measures to mitigate poultry disease risks to improve production. Many of these households will be among the poorer in their respective communities and proposed interventions to improve poultry production need to be tailored to their specific circumstances, needs and capabilities rather than dwell on generic principles. The value placed on poultry within households may vary by gender (25) and unfortunately much of the data available to date does not allow analyses to be disaggregated by gender. It should also not be assumed, that disease is the most pressing problem and a more holistic, participatory and gender-sensitive approach to poultry production appears warranted. To appropriately tailor biosecurity and husbandry interventions to local conditions, it is essential that the various members (i.e., men, women and those of differing socio-economic and language groupings) of communities and households knowledgeable about poultry production be involved from the outset (26).

Disease risks to extensive rural poultry production have increased in many LMICs over the past two decades in association with the increased movement of intensively raised commercial poultry into rural areas. For example, the sale of spent hens in South Africa has been documented to contribute to the spread of ND in rural areas (27). Commercial birds that have been vaccinated against diseases such as ND, may display no clinical disease while shedding ND virus that can infect susceptible birds.

Developing biosecurity improvements for village poultry, considered worthwhile from a private farmer perspective, requires time for trust to be built and positive impacts achieved, including improved food safety and reduced zoonotic disease risks (28). Therefore, projects and programs must build in appropriate time and resources to support participatory approaches. Where risks of disease spread impact on the wider community and generate significant externalities, action should be taken, but efforts must be carefully targeted and poultry keepers supported by wider societal actions rather than being expected to invest in biosecurity for purely personal gain.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://microdata.worldbank.org/index.php/catalog/2252/related-materials.

ETHICS STATEMENT

Ethical review and approval was not required for the animal study because the data used for the analysis were secondary data.

AUTHOR CONTRIBUTIONS

JO has led the conceptual development, the data analysis, and the drafting of the initial manuscript. JR, RA, and ER contributed to the conceptual development and the drafting of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.678419/full#supplementary-material

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frontiers in Veterinary Science

BRIEF RESEARCH REPORT
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Message Delivery Strategy Influences Willingness to Comply With Biosecurity

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As the Covid-19 pandemic continues worldwide, it has become increasingly clear that effective communication of disease transmission risks associated with protective behaviors is essential, and that communication tactics are not ubiquitously and homogenously understood. Analogous to Covid-19, communicable diseases in the hog industry result in millions of animal deaths and in the United States costs hundreds of millions of dollars annually. Protective behaviors such as preventative biosecurity practices are implemented to reduce these costs. Yet even with the knowledge of the importance of biosecurity, these practices are not employed consistently. The efficacy of biosecurity practices relies on consistent implementation and is influenced by a variety of behavioral factors under the umbrella of human decision-making. Using an experimental game, we collected data to quantify how different messages that described the likelihood of a disease incursion would influence willingness to follow biosecurity practices. Here we show that graphical messages combined with linguistic phrases demarking infection risk levels are more effective for ensuring compliance with biosecurity practices, as contrasted with either simple linguistic phrases or graphical messages with numeric demarcation of risk levels. All three of these delivery methods appear to be more effective than using a simple numeric value to describe probability of infection. Situationally, we saw greater than a 3-fold increase in compliance by shifting message strategy without changing the infection risk, highlighting the importance of situational awareness and context when designing messages.

Keywords: message efficacy, experimental game, compliance, numeric message, linguistic message, graphical message, risk, uncertainty

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INTRODUCTION

As the current Covid-19 pandemic sweeps across the globe, a second pandemic is raging through hogs: African swine fever is devastating swine industries, evidenced by the millions of hogs killed in Asia and Africa in 2019–2020. Endemic diseases such as Porcine Reproductive and Respiratory Syndrome (PRRS) and Porcine Epidemic Diarrhea virus (PEDV) cost over a billion dollars annually in the U.S., with PRRS alone estimated at over $600 million (1). Biosecurity, defined here as

management practices designed to reduce the spread of disease, can be used preventively to reduce the likelihood of disease incidence. Preventative biosecurity generates private and public benefits. Yet, biosecurity practices come with both upfront costs, such as building a facility to clean trucks after hog transport, or opportunity costs (e.g., time required to properly sanitize boots). Waiting to develop biosecurity until the risk of a disease is imminent increases costs based on the old adage "Good, fast and cheap: Pick two." Costs may be associated with development of biosecurity capacity, or could be associated with consistent adherence or compliance with existing biosecurity practices. In either case, one key, understudied component of biosecurity efficacy is the human component. Biosecurity is carried out by humans, both in planning and in day-to-day operations, and thus carries very real complexity and risks associated with behavior and decision-making.

Human behavior and decision-making dictate the likelihood of biosecurity lapses that can lead to disease outbreaks. Simple mistakes are difficult to completely prevent, but may be limited with training. Breaks in compliance associated with intentional decisions can be reduced using a variety of strategies such as behavioral nudges (2). Yet there are challenges to shifting behavior because factors motivating behavior are varied and complex. For example, workers at production facilities may be less willing to wash their hands for the appropriate length of time as they are leaving after a long shift. Many opportunities exist for decisions detrimental to herd health and opposing good biosecurity practices.

Human decision-making is influenced by a variety of socio-psychological factors (3, 4), including how the risk of animal infection is communicated (5, 6). Moreover, decision-making is decidedly heterogeneous and responses to the same information may differ dramatically between individuals (7).

Here, risk communication is intended to motivate changes in behavior by disseminating disease information. Within the risk communication literature, the advantages and shortcomings of different messaging styles relate to how a message is framed and presented (e.g., numeric, linguistic, and graphical or visual messages) as well as the context in which it is delivered (8–12). Numeric messages employ precision, but are likely to be poorly understood given that around 50% of our population has minimal quantitative literacy (13) and individuals with low numeracy frequently rely on numerical context (e.g., framing) to direct their behavior (14). Linguistic messaging formats can be more easily grasped in certain contexts, but lack the precision inherent in a numerical message. Graphical or visual formats have been identified as increasing salience in certain contexts, due to their ability to convey patterns and relationships (15). Despite the lack of a unifying solution, it is evident that the type of message has an effect on individual risk perception and consequent behavior (9, 10, 16).

To test how risk information may influence behavior, we created an online experimental game simulating a worker's day in a hog production facility. At one point during each day, participants are asked to exit the facility to perform a task. To exit, participants must decide to either comply with a shower-in, shower-out biosecurity practice, or leave through the emergency exit. Leaving through the emergency exit has the potential for increased earnings, but also the risk of a costly disease incursion. In essence, this choice boils down to either accepting less money by choosing the safe, biosecure option or taking a chance to get more money but with the possibility of monetary loss. This simple binary choice is influenced by the risk information provided to the participant about the chance of infection if they decide to gamble when they exit the building. Participants in this experiment are told in advance that they will make actual U.S. dollars based on their performance during the experiment. Incentive compatible, performance-based incentives such as these have been found to increase engagement and salience in experiments (15, 17).

Here we sought to understand the influence of the format of the risk information presented to the participant about their decision to comply with the biosecurity practice. We tested four risk communication message formats: (1) Numerical, (2) Linguistic, (3) a threat gauge demarked with numeric increments (Hereafter referred to as Numerical Threat Gauge), and (4) a threat gauge demarked with linguistic increments (Hereafter referred to as the Linguistic Threat Gauge) (**Figure 1**). We refer to these four formats as "treatments." Additionally, we sought to understand how depicting infection risk as a fixed estimate or value (Certain) might alter behavior, as contrasted with describing infection risk as a best estimate with a range of possible values (Uncertain).

Building off previous research (5), we hypothesized that compliance with the shower-in, shower-out biosecurity practice would progressively increase from a relatively low compliance with risk communicated using a Numerical format, then higher frequencies of compliance with the Linguistic format and the most frequent compliance observed with the two threat gauge message formats. Of the threat gauge formats, we hypothesized that a Linguistic Threat Gauge format would generate a higher frequency of compliance than information delivered using a Numeric Threat Gauge.

METHODS

Recruitment, Experimental Design, Development, and Economics

Participants were recruited using Amazon Mechanical Turk (mTurk), an online survey recruitment platform (18). mTurk has been validated as a source for high quality data for conducting research (19). Institutional Review Board-accepted protocols were followed for an experiment using human participants (University of Vermont IRB # CHRBSS-16-232-IRB).

Data were gathered using a serious game methodology. Game design matches that used in Merrill et al. (5) but with differences in risk communication format treatments. Here, participants completed an experimental game in which they were instructed that their performance would dictate the amount of money they would earn converted from experimental dollars to real U.S. dollars at a rate of $350 to $1 U.S. Participants interacted with the simulation by using a keyboard to move their character around a hog production facility. In the beginning

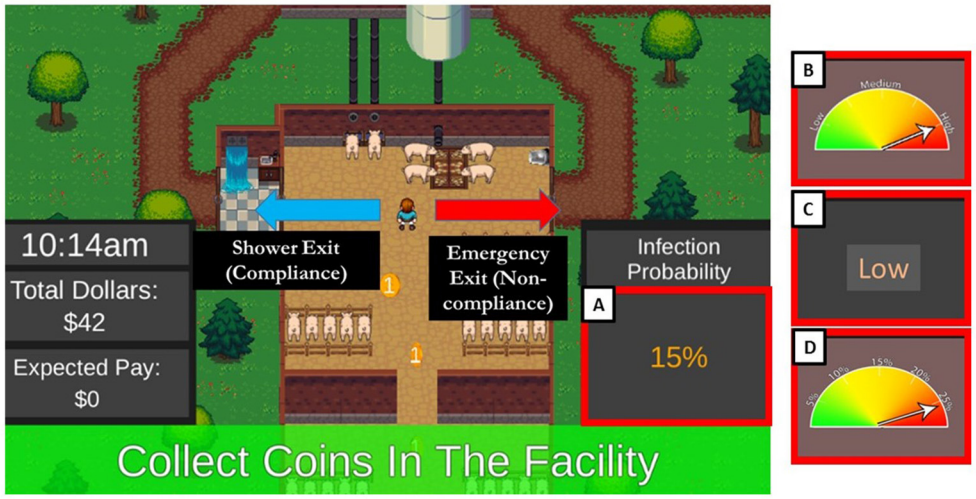

FIGURE 1 | Depicted is the decision point during the experiment. This screen grab shows **(A)** the Numeric risk message format as the current treatment. Additional treatment formats used to depict risk are displayed on the right: **(B)** Linguistic Threat Gauge, **(C)** Linguistic phrase, and **(D)** Numeric Threat Gauge message format.

of each round, participants completed tasks within the facility. Once per round, a truck would arrive outside the facility, prompting a binary decision by the participant. Participants were provided information about the likelihood that their animals would become sick, thus incurring an associated cost, if they were to bypass the biosecurity practice by using the emergency exit (**Figure 1**). Participants would then decide to either: (1) Quickly get to the truck by avoiding the time-expensive shower biosecurity practice but risk their animals becoming sick which resulted in a loss of $50 plus potential earnings collected during the round; or (2) Choose the safe option by adhering to the shower-in, shower-out biosecurity practice, incurring the monetary costs associated with the time required to shower, but removing the risk of a disease-related loss. Given the associated costs, the choice to bypass the shower-in, shower-out biosecurity exit carried a potential benefit of approximately $9.20 experimental dollars, and a potential cost of $82.48 dollars ($50 plus the average they would have made if they used the biosecurity practice). This means that the optimal economic decision was to skip biosecurity when the risk was 1% (Very Low) or 5% (Low) but to use biosecurity when the infection risk was 15% (Medium) or 25% (High). Associated costs for each of these when skipping biosecurity are as follows: (1) when infection risk was 1% or Very Low, expected cost for skipping biosecurity was -$7.96 (i.e., the negative cost indicates that participants were likely to make money by bypassing the biosecurity practice), (2) when infection risk was 5% or Low the expected cost was -$2.99, (3) when infection risk was 15% or Medium the expected cost was $9.42, and (4) when infection risk was 25% or High the expected cost was $21.84.

Data analyzed included the dependent variable, the binary decision of whether or not to comply with biosecurity, and the independent variables associated with the infection risk information.

The compliance game platform used to administer the experiment was developed using Unity software (Unity Technologies, Version 5.3.5f1), hosted online using WebGL (20)as described in detail in Merrill et al. (5).

Treatments

Four treatments were tested. Each treatment was designed to provide information about the risk that participants could face if they chose to exit the building without complying with the shower-in, shower-out biosecurity practice (**Figure 1**). The four risk information treatments were:

1) Numeric: Risk information displayed numerically: 1, 5, 15 or 25%
2) Linguistic: Risk information displayed linguistically: "Very Low," "Low," "Medium" or "High"
3) Numeric Threat Gauge: Risk information displayed using a threat gauge with an arrow pointing to a number: 1, 5, 15 or 25%
4) Graphical Threat Gauge: Risk information displayed using a threat gauge with an arrow pointing to a linguistic phrase: "Very Low," "Low," "Medium" or "High."

Covariates

All four treatments were implemented with four risk levels denoting the probability of infection: 1%/Very Low, 5%/Low, 15%/Medium, and 25%/High. Additionally, each treatment and infection risk level grouping was played using two levels of certainty: (1) certain risk–a single, fixed risk value, and (2) uncertain risk–an estimate with a range of risk values. This generated 32 combinations of the treatments and covariates. Because of the length of time required to complete each of these combinations in a single sitting, and concerns of experimental fatigue, we decided to have each participant play 24 of the 32 (75%) combinations, acquiring samples across all treatments using an incomplete block design.

TABLE 1 | Frequency of observed use of the shower-in, shower-out biosecurity practice (compliance) by treatment and covariate interaction.

Treatment: infection risk message	Infection risk	Infection certainty	Observed frequency
Numeric	1	Certainty	0.133††
Numeric	1	Uncertainty	0.181
Linguistic	1	Certainty	0.248
Linguistic	1	Uncertainty	0.200
Num. Threat Gauge	1	Certainty	0.238
Num. Threat Gauge	1	Uncertainty	0.391
Lin. Threat Gauge	1	Certainty	0.276
Lin. Threat Gauge	1	Uncertainty	0.438†
Numeric	5	Certainty	0.419
Numeric	5	Uncertainty	0.476
Linguistic	5	Certainty	0.524
Linguistic	5	Uncertainty	0.686
Num. Threat Gauge	5	Certainty	0.381††
Num. Threat Gauge	5	Uncertainty	0.667
Lin. Threat Gauge	5	Certainty	0.457
Lin. Threat Gauge	5	Uncertainty	0.724†
Numeric	15	Certainty	0.819†
Numeric	15	Uncertainty	0.848
Linguistic	15	Certainty	0.924
Linguistic	15	Uncertainty	0.933
Num. Threat Gauge	15	Certainty	0.848
Num. Threat Gauge	15	Uncertainty	0.905
Lin. Threat Gauge	15	Certainty	0.952††
Lin. Threat Gauge	15	Uncertainty	0.952††
Numeric	25	Certainty	0.895
Numeric	25	Uncertainty	0.876†
Linguistic	25	Certainty	0.943
Linguistic	25	Uncertainty	0.943
Num. Threat Gauge	25	Certainty	0.981††
Num. Threat Gauge	25	Uncertainty	0.971
Lin. Threat Gauge	25	Certainty	0.971
Lin. Threat Gauge	25	Uncertainty	0.962

†*Indicates lowest observed frequency per infection probability category.*
††*Indicates highest observed frequency per infection probability category.*

Analysis: Logistic Regression Mixed Effects Model

All analyses were completed using R (21). We used a mixed effects logistic regression model. The decision whether or not to use the biosecurity practice was quantified as a binary variable and was regressed against the message delivery treatment, the uncertainty covariate, the infection risk covariate as well as two-way interactions. Participant was treated as a random variable.

RESULTS

Recruitment

Similar to recruiting efforts from Merrill et al. (5), we recruited 140 individuals from mTurk to participate. The experiment used four blocks, each with 35 individuals. Each participant completed 75% of the scenario set, resulting in 105 decisions for each of the 32 treatment combinations, totaling 3,360 binary compliance decisions. On average, a decision to use the shower-in, shower-out practice made $32.48 experimental dollars, whereas, a decision to skip the biosecurity practice made $41.68 experimental dollars when their animals did not become infected. If their animals became infected, they lost all accrued experimental dollars from that scenario plus an additional $50 experimental dollars. Eighteen of the 140 individuals indicated that they lived or worked on a farm or were a farmer.

Treatments: Risk Communication Message Format

The Numeric message format had the lowest compliance with 58.1% compliance, followed by the Numeric threat gauge (67.2%) and the Linguistic phrase (67.5%). Information displayed using the Linguistic Threat Gauge resulted in the highest overall frequency of compliance (71.7%). We found some evidence for a difference between Numeric and Linguistic message formats ($p = 0.0587$, z-value $= 1.891$). Good evidence exists for differences between Numeric format and the Numeric Threat Gauge format ($p = 0.003$, z-value $= 2.931$), Numeric format and the Linguistic Threat Gauge ($p < 0.001$, z-value $= 3.871$), Linguistic message format and the Linguistic Threat Gauge ($p = 0.037$, z-value $= 2.081$). Evidence does not support other differences between treatments. High variability in decision making was observed for the Numeric Threat Gauge, indicating an inconsistent response to that message format.

Covariates and Interactions

Unsurprisingly, infection risk level was a strong predictor of behavior with significantly increasing levels of compliance as risk increased from 1% (1% infection risk observed compliance = 26.3%. Five percent infection risk observed compliance = 54.2%, odds ratio = 9.38, p-values < 0.001. Fifteen percent risk observed compliance = 89.8%, odds ratio = 272.45, p-values < 0.001 and 25% risk observed compliance = 94.3%, odds ratio = 768.68, p-values < 0.001). Here odds ratios describe the odds of choosing the shower practice compared to the intercept (1% Certain Numeric message). An odds ratio of 1 (or 1/1) indicates that it was equally probable that the participant would skip or select the biosecurity practice. An odds ratio of 10 (or 10/1) indicates that the participant was 10 times more likely to choose the shower practice under those conditions. Compliance tended to increase when treatments were presented with Uncertainty (an estimate plus a range of possible values) compared to Certain estimated values of risk; Contrasted with the intercept (Certain Numeric message), messages delivered with Uncertainty resulted in the Linguistic phrase odds ratio = 1.08, p-value = 0.821: Numeric Threat Gauge odds ratio = 2.64, p-value = 0.004 and Linguistic Threat Gauge odds ratio = 2.42, p-value = 0.012. Uncertainty against the Certain Numeric message carried an odds ratio = 1.21 and a p-value = 5.39. Thus, the overall signal is that uncertainty seems to increase the willingness to forgo potential extra profits by using the shower-in, shower-out biosecurity practice. Further details regarding overall compliance with the biosecurity practice are found in **Table 1** and **Supplementary Table 1**.

DISCUSSION

Our contribution to the literature may be to help understand how to best communicate risk, thus increasing behavior that could reduce the spread of disease. When facing the Covid-19 pandemic it is apparent that improving the efficacy of risk communication will help save lives and reduce the impact of disease outbreaks. Our experiment, which tests message formats for delivery of disease risk information, reveals compelling insights especially with the swine production industry facing the threat of African swine fever, and our society coming to terms with a global pandemic. The results from our experiments can benefit stakeholders who seek to foster a biosecure culture in their production facilities, and may highlight communication tactics that could help broader risk communication strategy.

Treatments: Risk Communication Message Format

Behavioral responses to the four risk communication formats were somewhat surprising. We hypothesized that information displayed using either of the threat gauge treatments would result in increased willingness to comply with the shower-in, shower-out biosecurity practice. Merrill et al. (5) found that compliance was highest with the use of a linguistic threat gauge, over a linguistic phrase or a numeric value. Those results were replicated. However, compliance when risk was displayed using the Numeric Threat Gauge was not significantly higher than the compliance observed when risk was displayed using a Linguistic phrase. Risk communication using a Linguistic Threat Gauge was associated with the highest compliance–at ∼72%–across all scenarios. In contrast, risk communicated numerically was correlated with the lowest frequency of compliance with the shower-in, shower-out biosecurity practice at approximately 58%. An intermediate level of compliance was seen with the Linguistic treatment and Numeric Threat Gauge at 67.5 and 67.3%, respectively, and were not significantly different from each other. Differences between risk communication treatments become more distinct when we look at interactions with the infection risk covariate (**Figure 2**) (22).

Covariates: Infection Risk and Infection Risk Uncertainty

Supporting previous research, infection risk was confirmed as a dominant driver of decision-making strategy (5, 6). Most individuals, regardless of risk communication message format, complied with the biosecurity practice when the risk of infection was 15% with an average of 89.8% compliance and when the infection risk was 25% with an average compliance of 94.3% (**Table 1**). Substantial variability in compliance with biosecurity was observed in the lower risk infection categories. When risk was "low" or 5%, we observed a mean frequency value of 54.2%, ranging between 38.1% (Numeric Threat Gauge with Certainty) to 72.4% (Linguistic Threat Gauge with Uncertainty). The lowest infection risk tested was 1%, and, as expected, correlated with the lowest frequency of biosecurity compliance (mean frequency of 25.6%). Similar to the 5% infection risk category, high variability was observed when infection risk was very low or 1% with compliance frequency values ranging from 13.3% (Numeric format with Certainty) to 43.8% (Linguistic Threat Gauge with Uncertainty).

Supporting previous research (5, 6), uncertainty in the infection risk tended to increase willingness to use the biosecurity practice. This uncertainty effect was typically more pronounced at the 1 and 5% infection risks where high variability in responses was noted by treatment and covariate combination (**Table 1**).

Translating findings to suggested best management practice policies should proceed, but with understanding of some of the limitations. Participants were recruited using mTurk. In a similar experimental game, detailed by Clark et al. (23), biosecurity investment behavior when confronted with disease and biosecurity information was compared between a sample of mTurk participants and a cohort of industry professionals at the 2018 World Pork Expo. While Clark and others' study was analogous, it examined willingness to directly invest in biosecurity as contrasted with foregoing opportunity for gain by using biosecurity. Data from this study was not found to differ significantly between industry professionals and mTurk participants. This surprising lack of an observed difference may stem from the broad array of potential motivating factors that influence individual behavior. In other words, while there are likely differences in behavior between industry professionals and mTurk participants, teasing those differences out may be challenging, especially given the potential overlap in the communities (i.e., ∼13% of mTurk participants identified as farmers, lived on a farm or worked on a farm).

Given that behavior is complex, we sought to reduce complexity by design. Here we reduced the possible motivating factors for participant decisions to a minimum, in order to observe differences in response to risk messages. Motivating factors influencing real world decisions are much more complex and nuanced. However, we suggest that there may be underlying consistencies in message interpretation that may be leveraged. Further, our research confronts only one aspect of effective message design for on-farm workers: risk information description. To design effective messaging, other aspects need to be considered, such as providing action steps (e.g., how to use the shower-in, shower-out facility) and insuring perceived relevancy of the message to the farm worker (24).

Poor biosecurity if examined cumulatively or industry-wide, can lead to widespread disease outbreaks (25). For example, the authors showed that disease outbreaks have high likelihood to turn into pandemics in a system where the producer population is largely willing to accept risk. In contrast, in risk averse populations, disease outbreaks tend to be small in magnitude and more easily suppressed. Our results demonstrate that simple changes in the communication strategy can drive substantial behavioral shifts; in one case, we increased compliance from under 40% to over 70% of participants with no change to the actual risk of infection. In a different situation, we observed over a 3-fold increase in biosecurity compliance. Such shifts could alter the state of a system from one where outbreaks

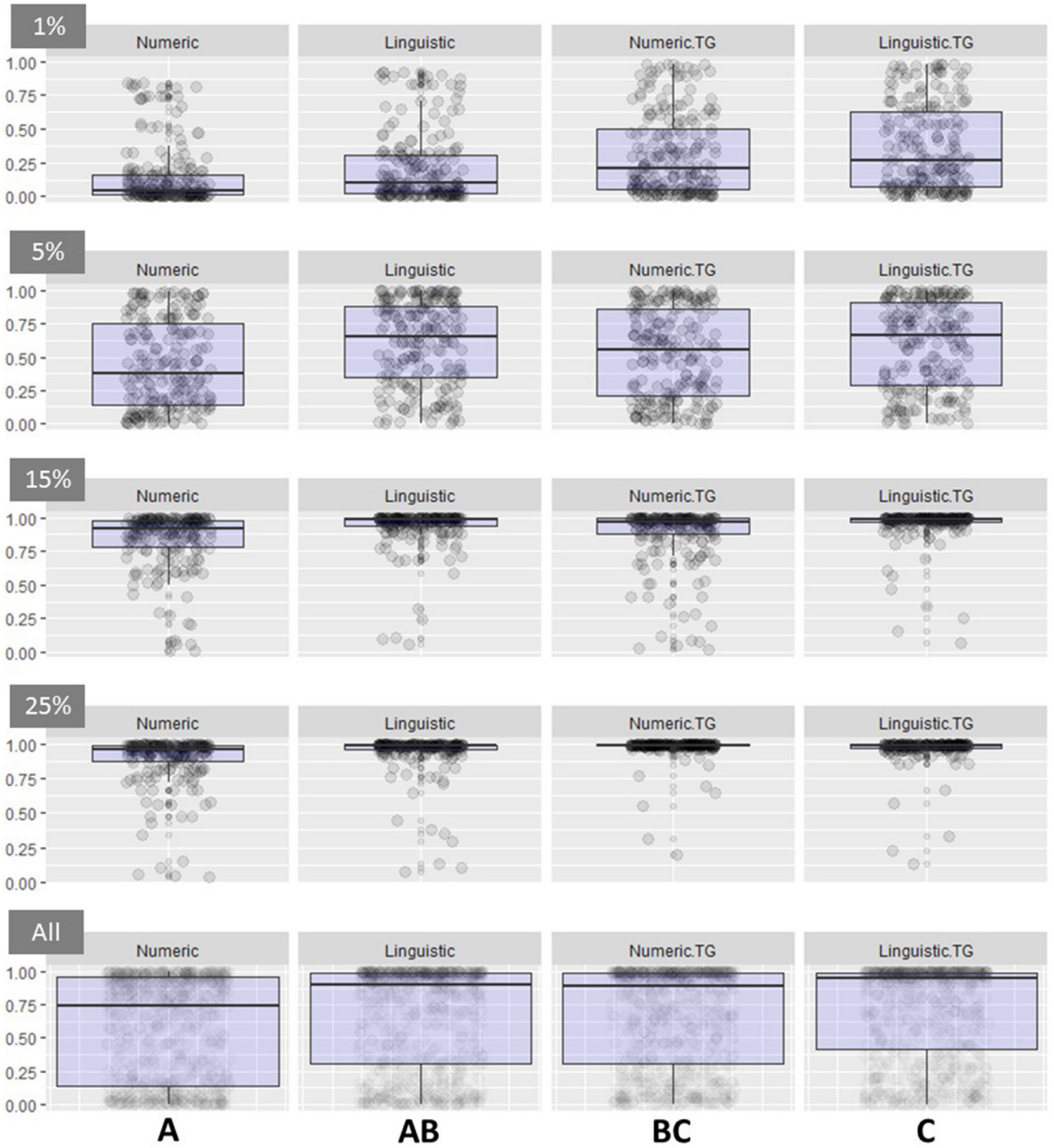

FIGURE 2 | Box plot depicting results from the Mixed Effect Logistic Regression model for each of four levels of Infection Risk and the combination of all infection risk categories (Rows: 1, 5, 15, and 25%, All infection risk categories combined). The y-axis reports the probability of compliance with the biosecurity practice. Columns depict treatments (Left to Right: Numeric, Linguistic, Numeric Threat Gauge, and the Linguistic Threat Gauge. Significance between treatment categories is noted by bold letters on the bottom of the figure.

were common and widespread to a system where outbreaks are quickly suppressed.

Risk communication and message efficacy under the threat of disease is at the forefront of many of our minds. To describe the threat of contracting Covid-19, the City of Los Angeles, California has recently adopted a threat gauge display that mimics our threat gauge (26). Adopting this messaging tactic over a numeric estimate of the risk likely resulted in the reduce spread of Covid-19 and fewer resultant deaths.

CONCLUSION

Here we partially confirm our hypothesis that risk information delivered using a graphical message has higher efficacy for ensuring compliance with biosecurity practices, with the significant caveat that the use of numbers in risk messages, even graphically depicted messages, appears to reduce efficacy. Overall, we suggest that message formats that include numbers are likely to be relatively ineffective in communicating risk or

improving biosecurity and should be used with care during message design. Moving to the use of a graphical display, instead of a numerical display, has the potential to positively nudge behavior. As noted by Bucini et al. (25), relatively small improvements in biosecurity behavior can result in substantial economic and social benefits to livestock industries. Real-world messaging strategies may substantially impact outbreak severity, which is well-worth the comparatively limited cost of implementation. In a true outbreak situation, when the threat is imminent, message design may make a difference measured not only in economic impact but in the lives of animals and people.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board University of Vermont IRB # CHRBSS-16-232-IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SM, CK, AZ, LT, JS, EC, TLS, and DS assisted with design and conceptualization of the experiment and underlying experimental game. LT, EC, and SM helped with data curation. SM worked on data analysis and Initial manuscript drafts were created. Project funding was generated with the help of JS, SM, CK, AZ, and TLS. Experiments were conducted by SM, LT, and EC. Software development was primarily led by LT and EC. Subsequent manuscript editing and retooling was completed by all authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.667265/full#supplementary-material

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New Frontiers in Biosafety and Biosecurity

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Keywords: sustainable development, regulation, innovation, biotechnology, decision-making

INTRODUCTION

Biotechnology has great potential to contribute to sustainable development. Over the past 18 months, it has enabled rapid deployment of methods to detect, treat and protect people against infection by SARS-CoV-2 (Baek et al., 2020; Beigel et al., 2020; Voysey et al., 2021). In addition, gene editing is promising to revolutionize medicine, public health, agriculture and manufacturing through, among other things, the treatment of hereditary diseases, the control of agricultural pests and vectors of dangerous human pathogens, the breeding of crops for healthier diets and livestock for greater animal welfare, and the production of organisms for industrial biotechnology that produce raw materials that may replace fossil fuels in the manufacture of numerous products (Barrangou and Doudna, 2016; Collins, 2018; Ricroch, 2019; Clarke and Kitney, 2020).

Nevertheless, application of biotechnology could cause severe harm if the associated risks are not well managed. Gain-of-function research may increase our knowledge of pathogen evolution; however, it may also cause catastrophic effects if laboratory containment fails or if the new knowledge is used to develop biological weapons (Duprex et al., 2015). Treatment of disease using gene editing, particularly through heritable modifications, raises numerous questions about the bearing of inter-generational risks and the possible exacerbation of health inequalities (Vasiliou et al., 2016). And the use of biotechnology in agriculture remains controversial over 25 years after genetically modified (GM) crops were first grown commercially. Supporters point to reduced pesticide use, greater carbon sequestration and increased yield and profitability for farmers who grow GM crops (Brookes and Barfoot, 2018). By contrast, critics claim that the use of GM crops perpetuates harmful environmental and social consequences of industrial agriculture (Wilson et al., 2021).

To realize the potential of biotechnology, society must envisage biosafety and biosecurity as more than simply containment of organisms that have been bioengineered. Biosafety and biosecurity should seek to enable continuous improvement in policy- and decision-making to optimize the balance between opportunity and risk in using biotechnology to find sustainable solutions to societal problems. I discuss three new frontiers that must be opened to achieve this aim: political leadership in making and justifying choices about the use of biotechnology for sustainable development; regulations that encourage innovation; and responsible innovation by businesses and responsible engagement by civil society.

FRONTIER 1: POLICY LEADERSHIP

"Following the science" is a phrase commonly used by governments during their responses to the spread of SARS-CoV-2 (Stevens, 2020). It implies that "correct" decisions are reached solely by rigorous scientific analysis and reliable data. However, good decision-making "depends above all on

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sound ethical reasoning that ascribes value and normative judgement to empirical facts" (Cristina de Campos-Rudinsky and Undurraga, 2021). Data on the reliability of tests for a virus and the efficacy and safety of a vaccine alone cannot determine whether particular people ought be tested or vaccinated. Such decisions require ethical and political evaluation of what these procedures are intended to achieve in circumstances where choices must be made. Once a trade-off has been identified–for example, between cancer diagnoses and treatment for COVID-19 during the SARS-CoV-2 pandemic (Dinmohamed et al., 2020)—data on the performance of tests and vaccines can contribute to the design of options for achieving the best outcome. However, the definition of "best outcome" remains a political and ethical choice, not a scientific discovery.

"Following the science" is convenient for decision-makers who wish to avoid controversy over the reasoning behind the choices they have made. Prioritizing COVID-19 treatment over cancer diagnoses is one example. Another is decision-making about whether to permit cultivation of GM crops in the EU. Here decisions are regularly postponed to wait for new studies that ostensibly aim to reduce scientific uncertainty about the properties of a crop to a level where the correct decision becomes clear (Mastroeni et al., 2021). However, repeated failure to reach decisions seems to be more about the unwillingness or inability of decision-makers to formulate clear policy aims for GM crops; hence, they request more data as a delaying tactic rather than as an aid to decision-making (Devos et al., 2014; Mastroeni et al., 2021). Attempts to contract out decision-making to "the science" are bad for public policy as the values underlying choices are not debated, decisions appear arbitrary, and scientific advisors may be able to make policy decisions that are not theirs to make (Pielke, 2007; Raybould and Macdonald, 2018).

Opening the first new frontier for biosafety and biosecurity requires political leadership to stop hiding behind scientific advice and clearly define the trade-offs and justify the inevitable choices that must be made to maximize the sustainable development opportunities provided by biotechnology. There will be trade-offs between objectives; for example, reducing greenhouse gas emissions may be incompatible with increasing dietary choices. There will also be trade-offs in delivery of the objectives. Banning all biotechnology research may maximize short-term human safety but endanger it in the long term because medicine, agriculture and manufacturing are unable to innovate. Conversely, placing no restrictions on research may hasten the development of life-saving products but also increase the probability of existential damage to human civilization (Sears, 2020).

In such circumstances, political leadership must choose the balance between divergent objectives so that policy is co-ordinated and businesses know what kinds of product are required. Scientists should encourage political discussion of the role of biotechnology in enabling these choices and discourage attempts to avoid debate about choices through "following the science." A corollary is that scientists should refrain from using scientific advice as "stealth advocacy" for their preferred policy choices (Pielke, 2007). Scientific advisors should provide options, including the use of biotechnology where suitable, for accomplishing agreed policy choices; they should not seek to close down debate by implying that certain policy choices are scientifically valid or invalid.

FRONTIER 2: REGULATION AND INNOVATION

Active political leadership provides top-down setting of general objectives for biotechnology in sustainable development. By contrast, delivering these objectives requires bottom-up innovation in the application of biotechnology. Crucial to this task is whether the principal aim of biotechnology regulatory policy is elimination of risk or willingness to take acceptable risk based on the value of the opportunity. The former is sometimes described as the precautionary principle and the latter as the innovation principle (Bogner and Torgersen, 2018).

Figure 1 shows different conceptual approaches to regulation of technology and how the innovation and precautionary principles differ. Regulation of medical ("red") biotechnology seems to apply the innovation principle. While problems in implementation remain (Syrett, 2020), regulatory authorities for medicines recognize that regulations must encourage innovation as well as control risk (Nagai, 2019). To maintain a suitable balance between innovation and risk, regulation of medical biotechnology seeks timely adaptation to general trends, such as the increasing expectations of patients, rapid scientific developments, and changes in healthcare systems and the pharmaceutical industry (Eichler et al., 2015). In addition, decision-making is flexible, with authorities able to issue emergency use authorizations for products, such as SARS-CoV-2 vaccines and treatments, that provide countermeasures to public health crises (Eastman et al., 2020).

Regulation of applications of biotechnology to agriculture, public health and environmental protection ("green biotechnology") seems to apply the precautionary principle or even technophobia. Evaluation of green biotechnology products focuses on detecting the potential to cause harm rather than deliver benefit. Indeed in EU regulatory evaluations, consideration of the potential benefits of GM crops is explicitly excluded (Bartsch, 2014). Decision-making is inflexible, with data requirements being slow adapt to advances in knowledge about the process of genetic modification (Herman et al., 2009) and familiarity with the types of product being evaluated (Raybould and Poppy, 2012; Bachman et al., 2021).

A precautionary approach to regulation of green biotechnology has stifled innovation. The product range is limited, comprising mainly herbicide-tolerant and insect-resistant GM commodity crops produced by a few large multinational companies (Bonny, 2017). Innovation is encouraged when a different regulatory approach is adopted. Argentina regulates gene-edited (GE) crops similarly to conventionally bred crops and the range of products and product developers is markedly greater than for GM crops

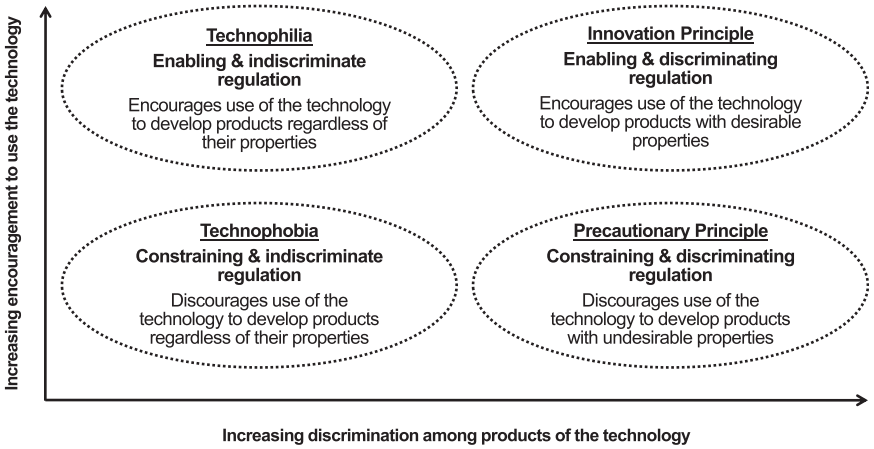

FIGURE 1 | A conceptual classification of approaches to regulation developed from Chataway et al. (2006) and Raybould (2019).

(Whelan et al., 2020). Exempting GE crops from GM regulations is a good start in changing the focus of regulations for green biotechnology from precaution to innovation. Making the regulation of all green biotechnology more like that of red biotechnology would be even better and represents a second new frontier for biosafety and biosecurity.

FRONTIER 3: RESPONSIBLE INNOVATION AND ENGAGEMENT

A third new frontier for biosafety and biosecurity is enthusing civil society about the potential for biotechnology, particularly green biotechnology, to deliver sustainable development. If large sections of society are hostile to biotechnology, political leaders may be unwilling to make the case for its role in sustainable development, and regulatory systems are likely to become even more focused on precaution than innovation, thereby undermining progress on the other new frontiers.

Eliminating hunger is a vital sustainable development goal. However, GM crops as a solution to mass starvation may have been oversold, conveying a rather threatening and pessimistic tone; in effect, product developers have been saying allow us to use biotechnology or millions of people will starve (Raybould, 2019). Such messages of "doom and gloom" tend to create apathy, not inspiration (Knowlton, 2017). It is unsurprising, therefore, that people are sceptical or even cynical about the motives of GM product developers and the opportunities for green biotechnology to contribute to environmental, social and economic sustainability, even if they accept that it may make existing systems more productive in the short term.

Creating optimistic messages that green biotechnology can reduce hunger while also changing aspects of current production systems that people dislike is crucial. An interesting example is a paper by Kwon et al. (2020) who used gene editing to make tomato plants more compact and earlier yielding. Rather than presenting the crop as a potential improvement for existing tomato production, they discussed how it could be used in hydroponic vertical farms. Industrial ("white") biotechnology may similarly contribute to changing the societal perception of biotechnology by developing products that replace meat from livestock (Rischer et al., 2020).

Certification and standards are useful for product developers wanting to go beyond regulatory compliance as a way to back up claims about sustainability. The recently launched British Standards Institution Responsible Innovation (RI) Guide provides a structured process for product developers to demonstrate that they have taken action to minimize the potential harmful effects and maximize the potential benefits of their products (Tait et al., 2021). One can envisage compliance with sustainability standards becoming a part of such RI exercises. However, current sustainability schemes, particularly in agriculture, tend to exclude products of biotechnology (Williams et al., 2018). The lost opportunities caused by prejudice against biotechnology in the "sustainability certification industry" emphasizes that everyone, not just product developers but also NGOs and other elements of civil society, has a duty to behave responsibly in debates about the use of biotechnology (Raybould, 2019).

CONCLUSION

Achieving sustainable development will be extraordinarily difficult, hence all the different colours of biotechnology should be evaluated for potential to contribute to its realization. Regarding biosafety and biosecurity as being more than the minimization of risk from potentially dangerous organisms will be key to this enterprise. Biosafety and biosecurity should be reimagined as techniques for optimizing the balance between opportunity and risk in the application of biotechnology to sustainable development. Achieving this objective requires co-ordinated change on several fronts: political leadership to make and justify policy choices that maximize opportunities for biotechnology to find

sustainable solutions to societal problems; regulations that consider the need to innovate as being at least as important as the need to be precautionary; and civil society that is prepared to engage responsibly in policy debates about the potential contribution of biotechnology to sustainable development. The final element may be the most difficult to achieve as there is considerable vested interest in defining sustainability as being fundamentally incompatible with the use of biotechnology.

AUTHOR CONTRIBUTIONS

AR conceived and wrote the article.

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A Cross-Sectional Survey to Assess Biorisk Management System in Research and Diagnostic Laboratories in Khyber Pakhtunkhwa, Pakistan

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Financial, cultural, and managerial hurdles have made biosafety and biosecurity measures difficult in resource-constrained countries like Pakistan. Because of increasing awareness of biorisk management, diagnostic and research laboratories have made major advances in biosafety and biosecurity in the recent decade. As a result, identifying and addressing gaps in biorisk management has never been more critical. The purpose of this study was to assess the current situation of personal protective equipment (PPE), biosafety behavior, waste management, biosafety and biosecurity measures, training and safety, and health services in diagnostic and research laboratories across Pakistan's Khyber Pakhtunkhwa (KP) province. We adapted the WHO Laboratory Assessment tool (2012) and CWA 15793 (Biorisk management guidelines) for conducting a cross-sectional survey, which was distributed among various laboratories in KP. The survey included 30 laboratories, including 11 diagnostic and 19 research laboratories. In comparison to diagnostic laboratories, biorisk management practices in research laboratories were better in terms of PPE, biosafety behavior, waste management, biosafety measures, biosecurity measures, trainings, and safety and health services. KP laboratories' biorisk management practices have improved over time, according to our findings. However, we were able to identify inadequacies that would require considerable improvements to the current setups based on the WHO and CWA 15793 recommendations. Organizations can tailor their biosafety measures and training to address identified gaps using the presented KP snapshot.

Keywords: biosafety, laboratories, Khyber Pakhtunkhwa, Pakistan, biorisk management

INTRODUCTION

To avoid laboratory-acquired infections and control the spread of potentially hazardous agents in the environment, diagnostic and research laboratories must maintain a safe and secure environment (1). For safe and secure practices, laboratories must have a complete Biorisk Management (BRM) system that complies with the Global Health Security Agenda (GHSA) and bioethical guidelines (1–3).

Laboratory BRM has been given a high priority, especially among scientific circles, throughout the world for the past few decades (4). Numerous advancements in biosafety and biosecurity practices and procedures have emerged from this level of prioritization. Furthermore, through systematic awareness and capacity building, this has led to progress in the use of equipment and administrative controls, particularly in developed regions of the world (5). Despite the increased number of laboratory research and diagnostic settings in low and middle-income countries (LMICs), progress has been gradual (4–6).

Despite limited and inadequate funding allocated to BRM, Pakistan has made significant progress as a result of national and international organizations' efforts to raise awareness and build capacity. In Pakistan, however, public health, scientific research, veterinary medicine, and diagnostic laboratories face administrative and financial challenges. Pakistan currently has a number of challenges, including a strain on the health-care system due to its large population, a scarcity of health-care professionals, particularly in rural areas, a lack of oversight mechanisms, and limited resources allocated to improving or maintaining safe healthcare practices (7). Leadership and administration in many clinical and research settings in Pakistan are struggling to prioritize BRM due to an already overburdened healthcare system.

KP is Pakistan's third most populous province with a population of 30.52 million (8). KP hosts 11 private and 30 public universities and research institutes, 277 hospitals, and a number of diagnostic and biomedical facilities (9). In comparison to other provinces, a study conducted in KP in 2012 found that improper use of personal protective equipment (PPE), lack of proper sharps disposal mechanism, lack of standard operating procedure for laboratories, and accident reporting systems were the highest (9). Since 2012, a number of national and international organizations, as well as the Pakistani government, have been striving to build BRM capability and raise awareness in compliance with the GHSA and International Health Regulations (IHR) (8–11). These efforts have sensitized many stakeholders, including diagnostic laboratories, research institutions, and academics in taking responsibility and prioritizing BRM at their laboratory settings in Pakistan.

Since 2012, no survey for evaluating BRM systems in KP laboratories has been conducted. Furthermore, the 2012 study only examined only diagnostic or hospital settings (9). As a result, the purpose of this survey was to assess BRM systems in diagnostic and research laboratories in KP province in order to better identify the gaps and opportunities for future research and capacity-building efforts (9).

MATERIALS AND METHODS

For assessing and appraising laboratory BRM systems, a variety of tools and guidelines are available (12, 13). The questionnaire was developed in accordance with CWA 15793 (Biorisk management guidelines) and the WHO Laboratory Assessment Tool (2012) for evaluating BRM systems in KP laboratories for this study (14, 15). Both approaches have been utilized in a variety of settings. They cover a wide range of biosafety and biosecurity indicators, as well as practices and procedures, behaviors, safety and health services, waste disposal, and the use of personal protective equipment (PPE). The cross-sectional survey was conducted using an online questionnaire (12–15). The survey was conducted from September through November of 2016. Laboratory technicians, technologists, supervisors, quality control managers, postgraduate students, research officers, and faculty from universities, diagnostic, and research laboratories were the target respondents. Since we aimed to include institutes rather than individuals, convenience-based sampling was used to identify and recruit respondents for the survey. There were two components to the survey questionnaire. The first section of the questionnaire inquired about the type of laboratory and the respondents' titles and affiliations. The second section included questions about compliance and resource availability in the domains of PPE, safety and security procedures, behaviors, training, waste disposal protocol implementation, and health service information. **Table 1** includes all the categories, variables, and questions included in the survey. All aspects assessed in these laboratories were given codes from Variable 1 (V1) to Variable 54 (V54).

Ethics Statement

According to approval from the Departmental Bioethics Committee, Department of Microbiology, Hazara University, Mansehra, Pakistan with letter number F.No.HU/MB/BEC/2016/10-05, informed consent was acquired from study participants, and respondents were informed that their participation in the survey was voluntary. No personal information was linked to the data acquired during analysis, and all responses were kept anonymous and confidential.

Statistical Analysis

SPSS 20.0 was used to analyze the data, and Microsoft Excel was used to generate the graphs. Depending on whether the laboratory was diagnostic or research-based, we segregated our results. PPE, biosafety behaviors, waste management, biosafety measures, biosecurity measures, training, and safety and health services were divided into seven groups for further stratification (**Table 1**).

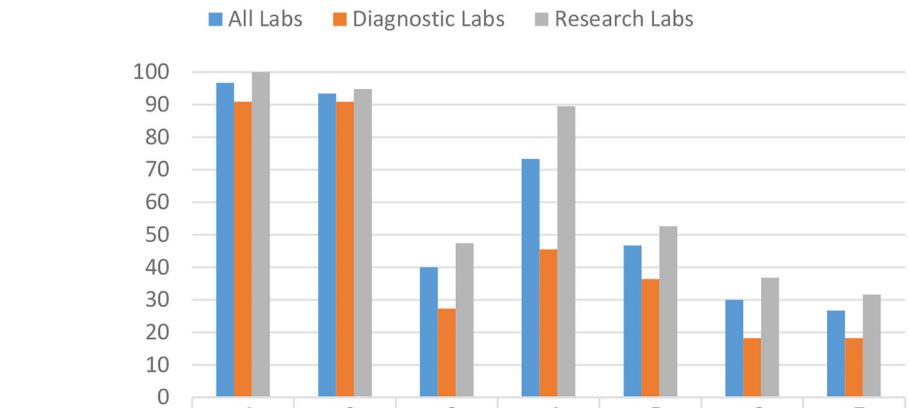
RESULTS

Participant Details

A total of 30 laboratories from KP responded to the online survey, including 11 diagnostic and 19 research laboratories.

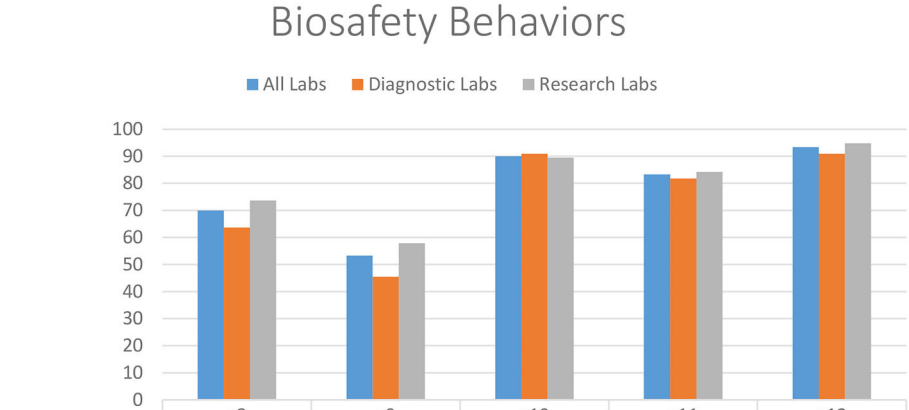
TABLE 1 | The list of variables (V) used for the cross-sectional survey to assess biorisk management system in research and diagnostic laboratories in Khyber Pakhtunkhwa, Pakistan.

Indicator	V	Indicator	V	Indicator	Variable
Lab coat	v1	Use of liquid disinfection	v21	Eyewash station	v41
Gloves	v2	Implementation status of liquid disinfection	v22	Emergency Shower	v42
Goggles	v3	Methods to ensure the efficacy of disinfection	v23	Does your staff/students have access to workers health services?	v43
Where are coats and lab linens washed?	v4	Are procedures for safe and secure transport of culture, specimens, samples, and other contaminated materials effectively?	v24	Does your staff/students follow a regular yearly visit to workers health services?	v44
Is protective clothing of approved design and fabric provided for all staff/students for everyday work?	v5	Are the biosafety procedures available at the bench level?	v25	Are individuals considered unfit for work on health grounds identified and prevented from accessing areas where there are risks of exposure?	v45
PPE for Chemical and radiation	v6	Do you use biosafety cabinets to manipulate samples producing potentially dangerous aerosols?	v26	Are conditions that could impact personnel associated with the facility addressed? These may include medical conditions affecting work, the ability to use appropriate PPE safely, or factors affecting general well-being	v46
Face Shield	v7	Do you have a biohazard sign indicated on the doors of the rooms where microorganisms are handled?	v27	Have the vaccination needs been identified?	v47
Are staff prohibited from wearing the protective clothing outside of the lab?	v8	Are warning and accident prevention signs used to minimize work hazards?	v28	Is there an immunization program for the lab?	v48
Are staff prohibited from wearing open-toed footwear?	v9	Are areas requiring vaccinations to enter indicated?	v29	Are women of childbearing age warned of the consequences of working with certain microorganisms, carcinogens, mutagens, and teratogens?	v49
Are staff prohibited from eating, drinking, smoke, or apply cosmetics in the lab working areas?	v10	Are controls in place to ensure that demand originates from legitimate facilities and individuals?	v30	Are women of childbearing age told that if they are, or suspect that they are, pregnant, they should inform the appropriate medical/scientific staff member so that alternative working arrangements may be made for them if necessary?	v50
Is it prohibited to store food or drinks in the lab working areas?	v11	Is access to lab areas restricted to authorized personnel?	v31	Are first-aid boxes provided at strategic locations?	v51
Is mouth pipetting forbidden?	v12	Is the whole building securely locked when unoccupied?	v32	Are qualified first-aiders available?	v52
Do you have separate disposals for infectious and non-infectious wastes?	v13	Are rooms containing hazardous materials and expensive equipment locked when unoccupied?	v33	Are such first-aiders trained to deal with emergencies peculiar to the lab, e.g., contact with corrosive chemicals, accidental ingestion of poisons and infectious materials?	v53
Do you have covered waste disposal containers?	v14	Is access to such rooms, equipment and materials appropriately controlled and documented?	v34	Are notices prominently posted giving clear information about first-aiders' location, telephone numbers of emergency services, etc.?	v54
Do you have safe and adapted waste containers?	v15	Have the staff/students been presented with a biosafety manual?	v35		
Do you have special sharps containers?	v16	Is training on "Biosafety while sampling" required for your lab staff/students before work?	v36		
Do you have dedicated waste for used solvents?	v17	Is training on "Using disinfectants and procedures in disinfection" required for your lab staff/student before work?	v37		
Have all potential waste streams and other sources of contamination been identified and documented?	v18	Is training on "Proper waste management" required for your lab staff/students before work?	v38		
Is there an adequate organization for the collection and disposal of general household rubbish?	v19	Are refresher training on these topics organized at least every 3 years?	v39		
Are discarded infectious materials removed daily or more often and disposed of safely?	v20	Were lab workers, e.g., domestic and clerical staff, instructed on the lab's potential hazards and the material it handles?	v40		



	v1	v2	v3	v4	v5	v6	v7
All Labs	96.67	93.33	40	73.33	46.67	30	26.67
Diagnostic Labs	90.91	90.91	27.27	45.45	36.36	18.18	18.18
Research Labs	100	94.74	47.37	89.47	52.63	36.84	31.58

FIGURE 1 | Availability and appropriate usage of PPE in diagnostic and research laboratories in Khyber Pakhtunkhwa (KP), Pakistan.



	v8	v9	v10	v11	v12
All Labs	70	53.33	90	83.33	93.33
Diagnostic Labs	63.64	45.45	90.91	81.82	90.91
Research Labs	73.68	57.89	89.47	84.21	94.74

FIGURE 2 | Biosafety behaviors in diagnostic and research laboratories in Khyber Pakhtunkhwa (KP), Pakistan.

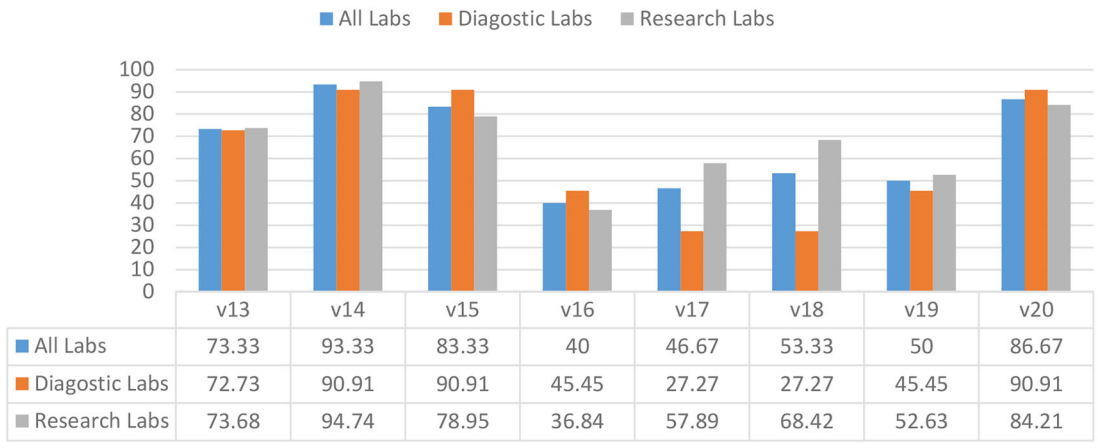
The respondents belonged to Swabi, Peshawar, Haripur, Mardan, Nowshehra, Mansehra, Kohat, Bannu, Swat, DI Khan, Dir regions of KP.

Personal Protective Equipment

The majority of laboratories used gloves (93.33%) (V2) and lab coats (96.67%) (V1), although diagnostic laboratories demonstrated reduced compliance with the guideline that lab coats should not be washed at home (73.33%) (V4) (**Figure 1**). Face shields (26.67%) (V7), goggles (40.00%) (V3), clothing of approved design and fabric (46.67%) (V5), and PPE for chemical and radiation protection (30.00%) (V6) were used and available in limited laboratories in KP (**Figure 1**).

Biosafety Behaviors

In the restrictions on food storage inside the laboratory (83.33%) (V11), eating and drinking in the working area (90.00%) (V10), and mouth pipetting (93.33%) (V12), laboratories demonstrated substantial compliance (**Figure 2**). Almost half of diagnostic and research laboratories did not have a protocol in place to reduce or



	v13	v14	v15	v16	v17	v18	v19	v20
All Labs	73.33	93.33	83.33	40	46.67	53.33	50	86.67
Diagostic Labs	72.73	90.91	90.91	45.45	27.27	27.27	45.45	90.91
Research Labs	73.68	94.74	78.95	36.84	57.89	68.42	52.63	84.21

FIGURE 3 | Waste management practices in diagnostic and research laboratories in Khyber Pakhtunkhwa (KP), Pakistan.

limit the use of open footwear (53.33%) (V9) in the lab (**Figure 2**). In addition, there was significantly less compliance with the restriction on wearing protective clothing outside of laboratories (70.00%) (V8) (**Figure 2**).

Waste Management

Most of the diagnostic and research laboratories had separate disposal containers for infectious and non-infectious waste (73.33%) (V13), excluding sharp containers (93.33%) (V14) and biological waste containers available (83.33%) (V15) (**Figure 3**). Almost half of the diagnostic (45.45%) and research (36.84%) labs did not have a dedicated sharps container available (V16). Discarded infectious materials were removed daily or more often in most laboratories (86.67%) (V20). Diagnostic laboratories were struggling with having dedicated waste for used solvents (27.27%) (V17) and identifying all potential waste streams (27.27%) (V18). Most of the diagnostic and research laboratories also did not have an adequate organization for collecting and disposing of household rubbish (50.00%) (V19).

Biosafety Measures

According to the survey results, the majority of diagnostic and research laboratories in KP were compliant in the use of liquid disinfectants (90.00%) (V21), implementation of liquid disinfection (90.00%) (V22), written biosafety procedures available at the bench (86.67%) (V25), use of biosafety cabinets for aerosol-generating procedures (80.00%) (V26), and display of accident prevention signs (73.33%) (V28) (**Figure 4**). Several laboratories lacked indications of areas requiring vaccination (26.67%) (V29), implementation of safe and secure sample transport (66.67%) (V24), and display of biohazard signs on the doors of rooms where microorganisms are handled (60.00%) (V27) (**Figure 4**).

Biosecurity Measures

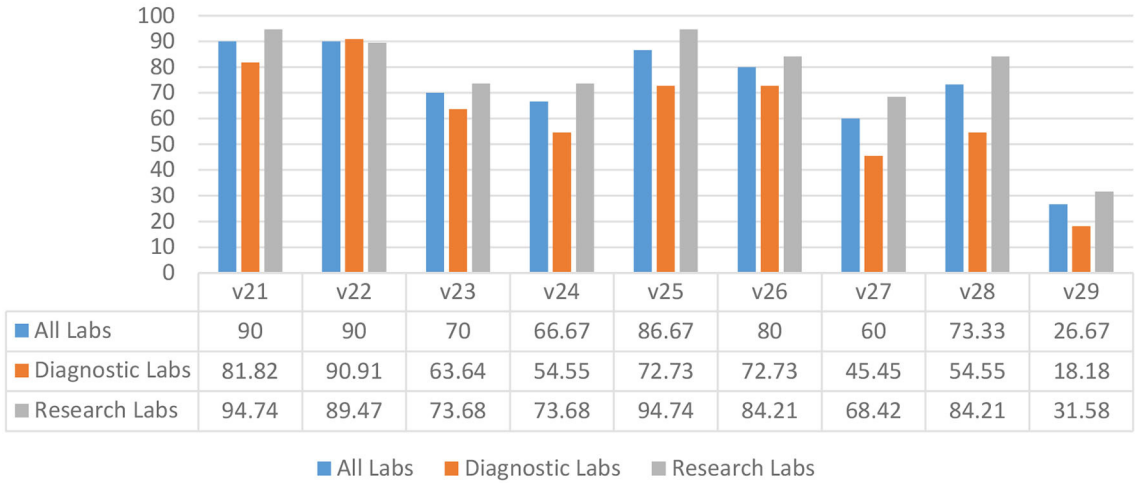
Overall, the results showed that biosecurity measures were being followed in laboratories throughout the KP province (**Figure 5**). In most laboratories, access and security of laboratory settings (V31–34) were deemed adequate. "Controls in place to ensure demand originates from legitimate facilities or individuals" (60.00%) (V30) was the most undermined biosecurity practice. The overall percentage of biosecurity controls and measures compliance (80.67%) in KP province shows a positive picture in both research and diagnostic settings (**Figure 5**).

Training

Most laboratories required biosafety training for students and staff prior to sampling (83.33%) (V36), the use of disinfectants (86.67%) (V37), and proper waste management (86.67%) (V38) (**Figure 6**). Fewer laboratories had mandatory 3-year refresher training (53.33%) (V39) and training for auxiliary staff (56.67%) (V40) (**Figure 6**). A biosafety manual was not available to 60.00% of the laboratory staff and students (V35) (**Figure 6**).

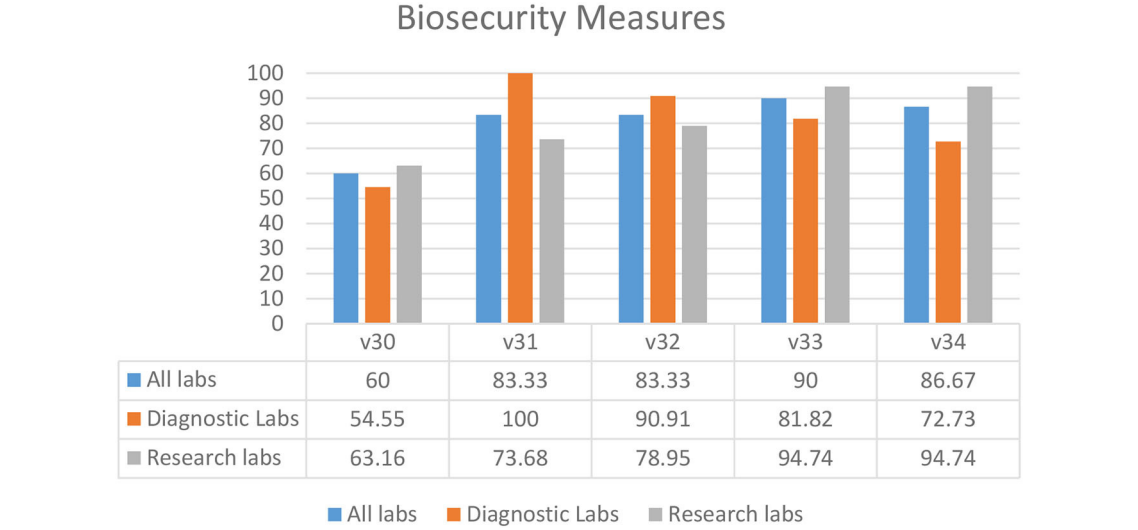
Safety and Health Services

Survey results indicated that laboratories had an ineffective immunization program (30.00%) (V48) in their facilities (**Figure 7**). Diagnostic laboratories had better compliance for identifying the needs for vaccination (81.82%) (V47) and an annual visit to health services by staff members (63.64%) (V44), as compared to the research laboratories (**Figure 7**). This compliance might be due to the affiliation of most diagnostic laboratories with hospital settings. In almost half of the laboratories, access to first aid boxes (63.33%) (V51) and qualified first aiders were missing (V52–53). A similar pattern was seen for safety and health variables relevant to pregnancy and childbearing age while working in a laboratory (V49–50) (**Figure 7**). Most of the laboratories did not have an eyewash station (16.67%) (V41).



	v21	v22	v23	v24	v25	v26	v27	v28	v29
All Labs	90	90	70	66.67	86.67	80	60	73.33	26.67
Diagnostic Labs	81.82	90.91	63.64	54.55	72.73	72.73	45.45	54.55	18.18
Research Labs	94.74	89.47	73.68	73.68	94.74	84.21	68.42	84.21	31.58

FIGURE 4 | Biosafety measures in diagnostic and research laboratories in Khyber Pakhtunkhwa (KP), Pakistan.



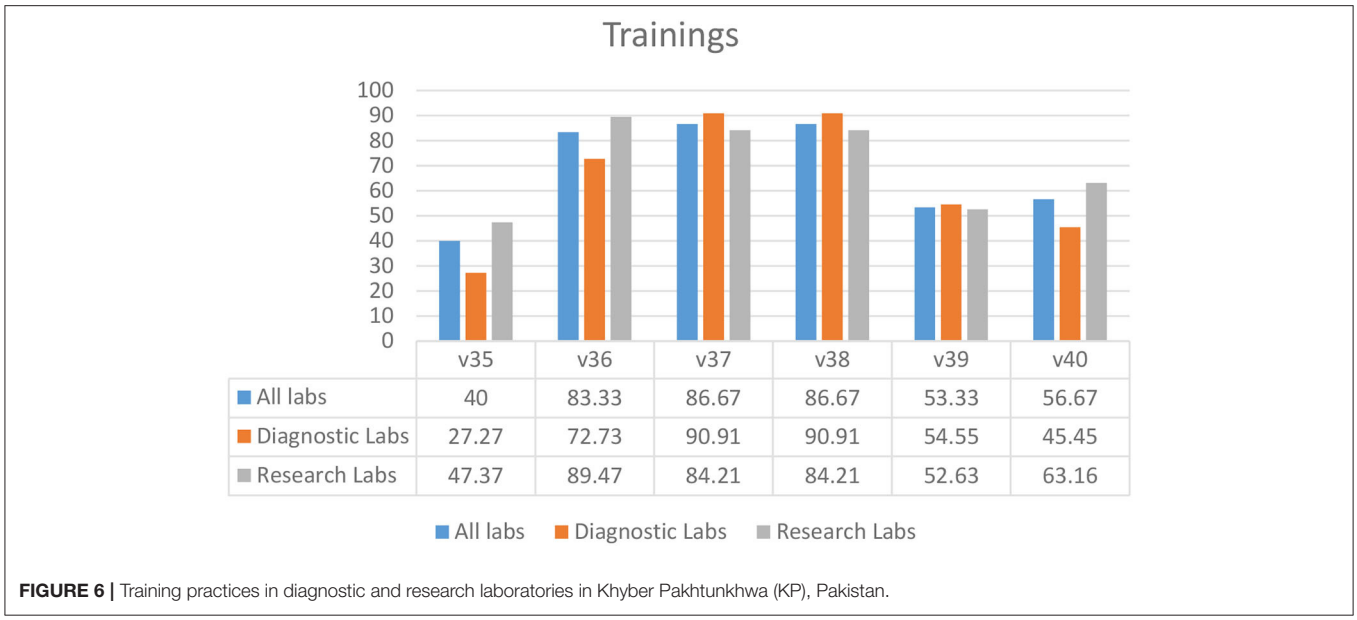
	v30	v31	v32	v33	v34
All labs	60	83.33	83.33	90	86.67
Diagnostic Labs	54.55	100	90.91	81.82	72.73
Research labs	63.16	73.68	78.95	94.74	94.74

FIGURE 5 | Biosecurity measures in diagnostic and research laboratories in Khyber Pakhtunkhwa (KP), Pakistan.

DISCUSSION

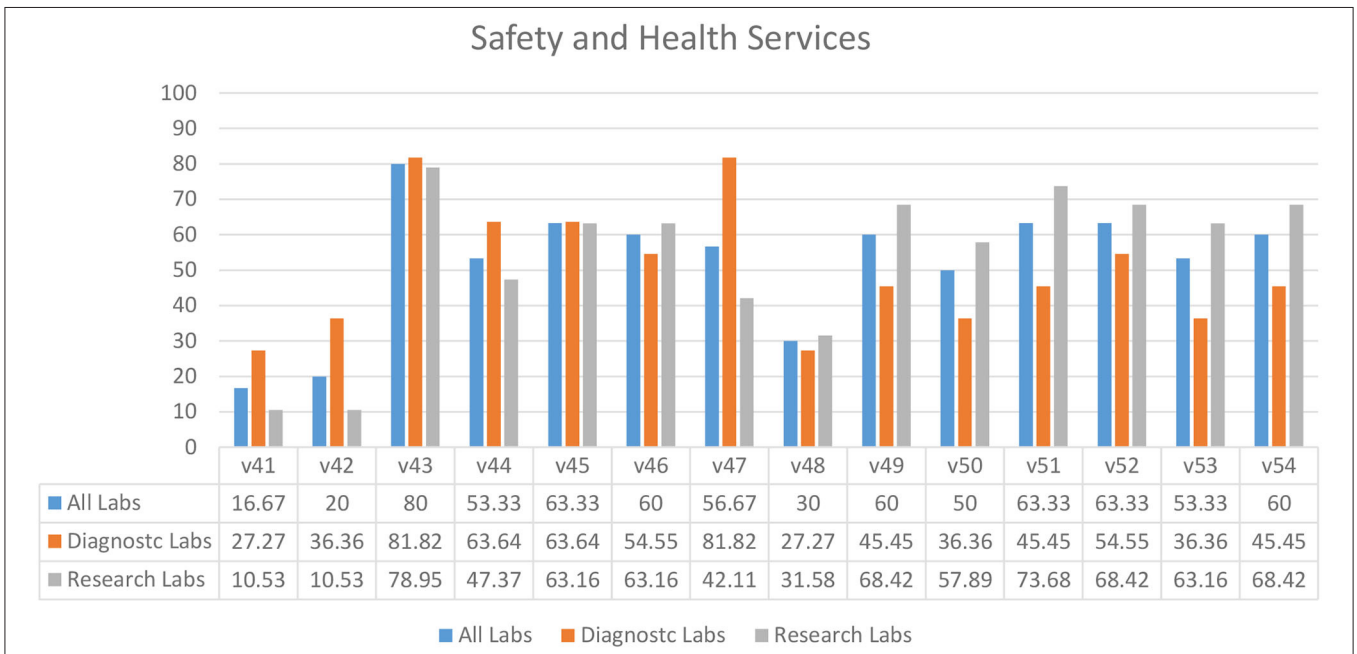
Diagnostic Laboratories Comparison: 2012 and 2016

In 2012, a cross-sectional survey in Pakistan evaluated BRM systems in diagnostic settings (9). Nasim et al. created a diagnostic laboratory questionnaire that included questions about routine laboratory practices, mouth pipetting, PPE, disinfection methods, and specimen handling and collection. We compared our 2016 data to the results of the survey conducted in 2012 (9) to assess the current state of BRM systems in diagnostic laboratories and any progress made over time (**Figure 8**). We found eight standard variables in both data sets. When the data was compared, all eight variables show significant improvements (9). Despite the low level of sharps container compliance in KP (45.4%) in 2016, there has been a significant improvement from 11.2 percent of diagnostic laboratories in 2012. Since 2012, the use of biosafety cabinets, the absence of food and drink in the work area, the availability of gloves and lab coats, and biosafety and security training have all improved significantly. Many national and international organizations have been working with Pakistani laboratories to improve BRM systems in recent years, and this significant improvement can be attributed to them.



	v35	v36	v37	v38	v39	v40
All labs	40	83.33	86.67	86.67	53.33	56.67
Diagnostic Labs	27.27	72.73	90.91	90.91	54.55	45.45
Research Labs	47.37	89.47	84.21	84.21	52.63	63.16

FIGURE 6 | Training practices in diagnostic and research laboratories in Khyber Pakhtunkhwa (KP), Pakistan.



	v41	v42	v43	v44	v45	v46	v47	v48	v49	v50	v51	v52	v53	v54
All Labs	16.67	20	80	53.33	63.33	60	56.67	30	60	50	63.33	63.33	53.33	60
Diagnostc Labs	27.27	36.36	81.82	63.64	63.64	54.55	81.82	27.27	45.45	36.36	45.45	54.55	36.36	45.45
Research Labs	10.53	10.53	78.95	47.37	63.16	63.16	42.11	31.58	68.42	57.89	73.68	68.42	63.16	68.42

FIGURE 7 | Safety and health services in diagnostic and research laboratories in Khyber Pakhtunkhwa (KP), Pakistan.

In 2018, another study looked at the impact of training on BRM practices at five universities in one of KP's districts (16). According to Rashid and colleagues, 82 percent of the students had received BRM training and were found to have the knowledge and skills to properly use PPE, manage waste, and respond to emergencies (15). Rashid et al., on the other hand, found a significantly lower compliance rate in some universities, indicating the need for additional interventions to put the knowledge and skills learned during these trainings into practice. Further research into the reasons for resource constraints and low leadership engagement and priority toward BRM should be investigated to identify specific factors impeding implementation (15, 16).

A 2017 study in KP assessed compliance with hospital waste management rules in 44 public and private hospitals, uncovering serious shortcomings in the hospital waste management systems (1). However, when compared to the previous study, our findings revealed significant improvements in the waste management system in KP laboratories (9). This disparity could be explained by the sample investigated, as we were looking at waste management in laboratories rather than hospitals. Some significant deficiencies in the laboratories' health and

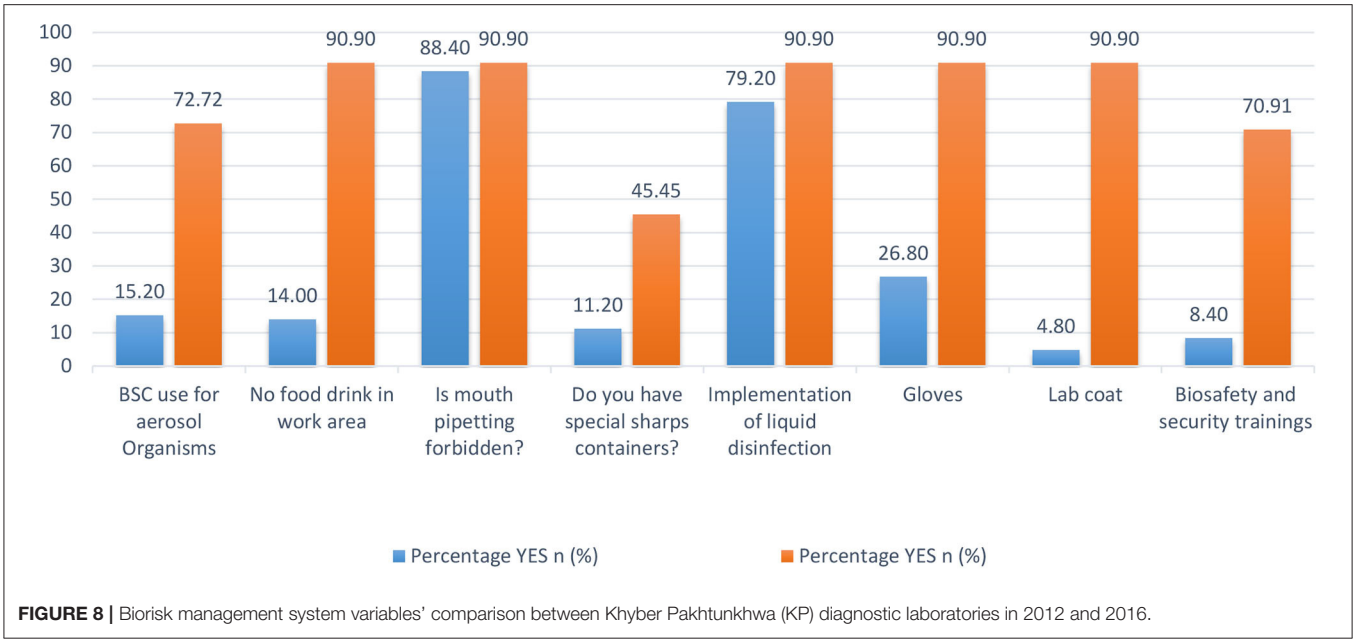


FIGURE 8 | Biorisk management system variables' comparison between Khyber Pakhtunkhwa (KP) diagnostic laboratories in 2012 and 2016.

safety services were found during our investigation. In these laboratories, a robust occupational health and medical/incident surveillance program should be prioritized for long-term improvement and evaluation (9).

Follow-Up Activities and Progress Related to the Improvement of Biorisk Management System Across Institutions

Since 2014, the Pakistan Biological Safety Association (PBSA) has collaborated with the Fogarty International Center on the BioPrism flagship program to develop biosafety practices in Pakistan. The program employed a three-tiered training-of-trainers approach. Sixty professionals are being taught the fundamentals of biosafety from all over the country. Pre- and post-tests are used to assess their understanding of the concepts as well as the training's effectiveness. At the end of training, each participant is asked to demonstrate the skills they gained. Top achievers were selected to participate in a 5-day "master trainer" course to improve their presentation and communication skills. Verbal exams were conducted after the master trainer course to assess the trainers' comprehension of the subject, delivery, and communication skills. Each trainer is assigned a topic to present, and their skills were assessed depending on how successfully they do so. High scorers were then selected for a third, more intensive "wet workshop." At the completion of the session, the high achievers were given the title of master trainer. All participants, including master trainers, should first train at least seven individuals and report to PBSA. These trainings were successful in establishing a network of dedicated and well-trained biosafety professionals. PBSA has launched a new series of workshops in Pakistan called Responsible Conduct in the Life Sciences. Participants should train at least seven people and report to the PBSA, including master trainers. In the same way that the BioPrism program prepares participants to become trainers, these seminars do as well (17). Multiple workshops on high-reliability organization, influence without authority, and waste management were held at the national and regional levels by PBSA and FIC/NIH in conjunction with biorisk management experts. In addition, the program's trainers have been offered support in conducting training in their individual institutions to promote biorisk management principles (17).

CONCLUSION

The laboratories in KP are evidently working hard to improve their BRM systems and practices, as indicated by this study. These efforts must be reinforced, with a focus on continuous improvement, which is critical for successful BRM systems. Continual improvement necessitates thorough inspections and audits of BRM systems to identify non-conformities. This study provides an overview of the current BRM systems' strengths and areas for improvement. Despite the fact that leadership engagement has become so vital in this process, more research is needed to determine how to gain public sector leadership to invest and prioritize BRM for continued improvement.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Departmental Bioethics Committee, Department of Microbiology, Hazara University, Mansehra, Pakistan

with letter number F.No.HU/MB/BEC/2016/10-05. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JM: conceptualization, methodology, writing, and review and editing. SS: conceptualization, methodology, project administration, and review and editing. SQ, AI, and TK: critical review. GA: statistical analysis and interpretation. MZ and RD: writing the first draft of results and discussion. FA: writing of the original draft, statistical analysis and interpretation of the data, and supervision. All authors contributed to the article and approved the submitted version.

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The Role of Biosecurity in the Control of *Campylobacter*: A Qualitative Study of the Attitudes and Perceptions of UK Broiler Farm Workers

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Campylobacter is the leading cause of human bacterial diarrhoeal disease worldwide, with poultry meat products contributing to a large proportion of cases. Due to the ubiquitous presence of *Campylobacter* in the poultry farm environment, biosecurity is the main area for intervention to prevent colonisation of commercial broiler chicken flocks. However, research has repeatedly demonstrated that farmers' uptake of biosecurity recommendations is often poor. This study explored farmers' attitudes towards biosecurity and identified barriers to effective implementation of biosecurity protocols. Semi-structured interviews were conducted with 1–3 members of staff on each of 16 broiler farms; 6 owned by, and 10 contracted to, 3 different UK poultry integrators. In total, 28 interviewees participated, including farm owners, managers, and workers, with a range of industry experience. Thematic analysis of the interviews revealed high levels of recognition amongst broiler farmers of the importance of *Campylobacter* and the responsibility of the whole farm-to-fork chain within the poultry industry to reduce *Campylobacter* contamination of chicken meat for the benefit of public health. Participants' self-reported awareness and implementation of biosecurity has improved significantly following the industry-wide focus on *Campylobacter* control. However, there are frustrations with the industry's approach to tackling *Campylobacter* and the heavy burden of responsibility that has been put on interventions at the farm-level. There was also scepticism amongst participants as to the effectiveness of current biosecurity measures in the reduction of *Campylobacter.* Nevertheless, the interviewees' recognition of the benefit of improved biosecurity on broiler health and welfare and other important targets, such as reducing antimicrobial usage, leaves a legacy of which the UK broiler industry can be proud. There is scope for further farmer education about the evidence supporting biosecurity interventions, particularly in the control of *Campylobacter*, and

a need to establish more effective channels of communication. Furthermore, to give all players within the industry agency and investment in industry targets, contributions from all levels should be permitted in the design of future biosecurity interventions. Biosecurity compliance may be improved through collaborative efforts, such as participatory and co-design practises, to facilitate knowledge co-creation and exchange.

Keywords: *Campylobacter*, biosecurity, food safety, broiler chicken, interview, compliance, qualitative

INTRODUCTION

Campylobacter is the leading cause of human bacterial diarrhoeal disease worldwide. Poultry meat and products are estimated to account for ∼70% of human campylobacteriosis cases in the UK, due to the consumption of undercooked meat or cross-contamination of raw meat within the kitchen (1). Due to the ubiquitous presence of *Campylobacter* spp. in the poultry farm environment, biosecurity practises have been highlighted as the main area for intervention to prevent the spread of *Campylobacter* into and between broiler houses and the subsequent colonisation of commercial broiler chicken flocks (2–5). "Biosecurity" encompasses all hygiene practises that are put in place to ensure the risk of a disease occurring or spreading is minimised (6). Biosecurity measures are designed to prevent the introduction and spread of disease-causing organisms into a flock or herd (7, 8) and have been shown to be key in the prevention of disease in poultry units (9, 10). Controlling *Campylobacter* at the farm-level is crucial to reduce the level of *Campylobacter* entering processing plants and the public health risk to consumers (11). The consistent application of biosecurity measures is essential for the success of all types of animal production, including to prevent disease introduction and reduce production and financial losses that may occur following infection of a herd or flock (7, 8). However, research has repeatedly demonstrated that compliance with biosecurity protocols is poor, despite serious and potentially economically devastating consequences (8). Moreover, there has been little research regarding attitudes and perceptions of biosecurity measures with people working on broiler farms, particularly within the UK poultry industry.

In 2010, the Food Standards Agency (FSA) and the UK poultry industry set a joint target to reduce *Campylobacter* in chicken meat at retail; aiming to reduce the prevalence of the most contaminated chickens (>1,000 cfu/g) to below 10% at the end of the slaughter process, initially by the end of 2015 (12). From 2014 to 2018, the FSA conducted UK-wide surveys of *Campylobacter* contamination on fresh chickens at retail. Over this period, overall prevalence reduced from 73.2 to 40.9%, and the percentage of chickens contaminated with >1,000 cfu/g reduced from 19.7 to 3.8% (13, 14). This focus on the reduction of *Campylobacter* followed the introduction of the UK National Control Programme (NCP) for *Salmonella* in meat chickens. This resulted in the introduction and enforcement of biosecurity measures on broiler farms to ensure that the percentage of meat chicken flocks remaining positive for *Salmonella enterica* serotype Enteritidis and *S.* Typhimurium was <1% by the end of 2011, as set out in Regulation (EC) No 646/2007 (15). The Red Tractor Assurance Scheme (16), which represents 1,097 UK broiler chicken assured members and 90% of UK broiler production (17), amended their standards in 2011 to improve biosecurity requirements amongst their members (18). This included the implementation of a designated hygiene area, either demarcated with a physical barrier or a clearly marked area, and footwear change and hand sanitisation at shed entry (18). In 2014, Red Tractor further increased focus on farm biosecurity in response to concerns over *Campylobacter* (17, 18). Requirements introduced included defined biosecure areas for farm and shed entry and equipment cleansing, disinfection of vehicle wheels and equipment at farm entry, footdips, physical barriers, and footwear changes at entry to each biosecure area, inclusion of biosecurity requirements during flock depopulation events and the requirement of all staff to hold a "Poultry Passport," which includes a biosecurity training module. Further auditing and penalty measures were also introduced to ensure compliance (18). In the same year, the FSA first "named and shamed" supermarkets over the levels of *Campylobacter* in their chicken meat (19), increasing the visibility of the high levels of *Campylobacter* contamination of UK-produced chicken meat and the progress of industry reduction targets. One outcome of these targets has been a rapid evolution in on farm biosecurity measures enforced by poultry assurance schemes and integrators, changing the working practises of farm workers throughout the UK broiler industry in a short period of time.

This research aims to explore how broiler farm workers are responding to these recent industry targets and culture changes. The success of new control initiatives depends upon compliance on-farm, and it is crucial to understand the motivations of people working on broiler farms to enable the development of achievable strategies and suitable biosecurity measures appropriate for the UK poultry industry. Previous studies of both agricultural and domestic animal sectors have found co-design and participatory approaches to be fundamental in encouraging biosecurity compliance (20–22) and the relevance of these strategies to the UK poultry industry will be explored in more depth throughout this study.

This study aims to elicit farmers' attitudes and perceptions to biosecurity, identify barriers for maintaining biosecurity protocols, and to investigate risky behaviours associated with biosecurity breaches and the introduction of *Campylobacter* into poultry houses. These topics will be explored both in relation to general biosecurity measures and in the context of controlling *Campylobacter* on broiler chicken farms.

MATERIALS AND METHODS

Selection of Interview Participants

Farms were recruited from one major poultry integrator (Integrator 1), who nominated six company-owned and eight independent-contracted farms, representing a range of internal biosecurity audit scores and *Campylobacter* testing results. A further two independent farms contracted to two other poultry integrators (Integrators 2 and 3) were recruited by word-of-mouth. All participants were approached directly by telephone or email to request participation and arrange a suitable time and location for the interview. All farms were commercial, intensive, indoor broiler chicken farms in mainland UK. Farms rearing slow-growing broiler chicken breeds and/or with free-range farming practises were excluded from the study. These farms were excluded as they represent a small minority of UK broiler chicken production. There is also a significant difference in biosecurity practises between housed and free-range broiler flocks meaning it would not be possible to explore similar experiences with biosecurity practises with staff on these differing sites.

Ethics

The study protocol was reviewed and approved by The University of Liverpool Veterinary Research Ethics Committee (Reference VREC478). All participants were informed that participation would be anonymous with all data anonymised prior to publication, so that farms and farmers could not be identified in any published results. Permission to record the interview was sought at project outset with the integrator and prior to the interview with the participant as it was considered a vital component of the qualitative interview process to facilitate subsequent data analysis.

Interview Design

The interviews were undertaken by a single interviewer. Interviews were semi-structured and used a topic guide (**Table 1**) to ensure key areas were covered in each interview. However, the interview was participant-led, with the order of the interview determined by the participant(s) and additional relevant topics pursued as they arose. Questions were non-leading and phrased to encourage participants to communicate their personal views and anecdotes. The interview guide was reviewed and revised following an initial pilot interview.

Thematic Data Analysis

All interviews were transcribed verbatim by a commercial transcribing firm, except the pilot interview which was transcribed by the interviewer. Transcripts were then checked for accuracy and anonymised by the interviewer. Thematic analysis (23) was used to assess the transcripts to highlight minor and major themes. Analysis was inductive with themes developed from the data collected. Initial line-by-line coding of transcripts revealed recurring opinions and subject areas which were assigned as minor themes. Minor themes were linked together and common subject areas exposed and categorised as major themes. Interviews were continued until "sampling-to-saturation," where there were no new ideas emerging from the interviews and there was little or no change to the codebook (**Supplementary Material**). All analysis was undertaken using the qualitative data management tool NVivo 12.1.0. Further analysis was carried out looking at how commonly themes occurred and examining minority and majority opinion.

RESULTS

Study Population

Sixteen interviews were conducted with between one to three members of staff on 16 broiler farms, six owned by and 10 contracted to three different UK poultry integrators (Integrator 1, 2, or 3). A total of 28 participants, three females and 25 males, took part, including farm owners, managers, and workers, with a range of experience in the broiler industry. Further details of the interviewees and farms involved in the interviews are included in **Table 2**. The length of the interviews ranged in time from 33 min to 1 h 44 min (Mean = 48 min; Median = 44 min). A pilot interview took place in May 2016, with the rest conducted between June 2017 and January 2018. The transcript from the pilot interview was reviewed in detail and considered to be of acceptable quality to be included in the overall analysis.

Themes Identified

Through thematic analysis of the transcripts, minor themes were found to link to overarching major themes. Six major themes and seven minor themes were identified and will be discussed in more detail below:

1. *Campylobacter* in Vogue
2. The Importance of Biosecurity
    a. The Legacy of *Campylobacter* Control
3. Scepticism and Controversy
    a. About *Campylobacter*
    b. About *Campylobacter* Control
4. Biosecurity Compliance
    a. Requirement and Enforcement
    b. Other Contributing Factors
5. Biosecurity Issues and Improvements
    a. Specific Biosecurity Issues
        i. Control Room Barriers
        ii. External Site Visitors
        iii. Partial Flock Depopulation ("Thinning")
    b. Potential Improvements
6. Power and Responsibility

Campylobacter in Vogue and the Legacy of *Campylobacter* Control

Since the industry introduced targets to reduce *Campylobacter* in broiler chickens, participants believed that there had been an improvement in on-farm biosecurity practises and farmers' understanding of their importance:

"Obviously, as farms, by doing things like the [. . .] barriers and other biosecurity measures, we are improving the health of the chickens, generally, anyway. So, therefore, how can you knock the biosecurity? Obviously, it's had a benefit on the health of the chickens so far. Even if you totally forget the Campylobacter side of it, there are definite improvements that we have done so that hasn't been a bad exercise." – Independent-Contracted Farm Owner and Manager

Interviewees described *"a definite knock-on effect,"* whereby the increase in biosecurity and the drive to reduce *Campylobacter* had improved other aspects of broiler chicken production, including overall flock health and performance. There was repeated emphasis that biosecurity was important for the overall health and performance of the flock:

"Listen. Biosecurity is just as important as performance. If you haven't got biosecurity, you haven't got performance. They go hand-in-hand, and they really do." – Company-Owned Farm Manager

There was a prevalent opinion that the focus on *Campylobacter* was "in Vogue" and a fashion and would pass in time:

"It's very much the thing at the moment. Without a doubt, in a period of time, it won't be highlighted. There might be something else that comes on the- You know, there might be another thing that is highlighted, and we'll have to concentrate on that. Salmonella, that's a strange one. . . A few years ago, that was the thing they were concentrating on." – Independent-Contracted Farm Owner and Manager

The focus on the reduction of *Campylobacter* was said by interviewees to be a recent development. Interviewees commented that they had not heard of *Campylobacter* until recently and called it a *"new problem."* Others believed that, until recently, either *"there wasn't an issue with Campy"* or felt that it had been *"kept quite quiet."* The tightening of biosecurity measures was described as *"a big sea-change"* within the broiler chicken industry and a current prominent focus of the integrators. Interviewees cited the public "naming and shaming" in the media of the prevalence of *Campylobacter* in individual supermarkets' retail chicken as the event that kick-started industry attention towards *Campylobacter*.

The time frame for the introduction of increased biosecurity measures on farms was estimated by many to have been within the last 2 to 5 years, with many citing the lack of specific biosecurity measures prior to this as evidence of how quickly the focus on biosecurity to reduce *Campylobacter* has spread through the industry. On-farm biosecurity was framed as "before-*Campylobacter*" and "after-*Campylobacter*." Interviewees mentioned that "before," farms only had foot dips at the entrance to each shed, which were *"virtually optional,"* and there was no requirement for extensive personal-protective equipment (PPE) or shed-specific clothing and equipment. Whereas "after," strict requirements to follow enforced biosecurity protocols were introduced. An improvement in biosecurity around "thinning and catching" ("partial and final flock depopulation"—discussed in more detail below) was also cited to have been introduced in this period.

TABLE 1 | Interview topic guide.

Topic headings	Areas explored
Profile of individual	- Education, length of service and motivation
Training and feedback on biosecurity	- Training (and type of) in biosecurity - Feedback on biosecurity
Perceptions and Implementation of Biosecurity	- Definition and importance of biosecurity - Current biosecurity measures - Perceptions of biosecurity standards - Difficulties in practising biosecurity - Improvements to make biosecurity easier - Incentivisation to follow biosecurity
Responsibility for biosecurity and control of *Campylobacter*	- Responsibility for biosecurity and *Campylobacter*-status of flocks - Trusted sources of information
Future options and challenges	- Opinions on the future of biosecurity and the control of *Campylobacter* in the UK broiler chicken industry

Participants highlighted that *Campylobacter* control was a multifactorial problem, with many factors that need to be controlled to minimise risk and reduce levels of colonisation. It was commented that this is why *Campylobacter* is a more frustrating pathogen to control than *Salmonella*:

"[Campylobacter]'s not going to be like Salmonella where there's a silver bullet, you can just- you can solve it." – Independent-Contracted Farm Manager

Comparisons were drawn with recent efforts in the poultry industry to tackle *Salmonella* and how the focus on *Salmonella* was replaced by *Campylobacter*. Interviewees believed that a solution would be found to reduce Campylobacter to acceptable levels, with some adding that there would then be another problem to tackle as "it does seem to be a never-ending battle with something".

There was a feeling amongst participants that even if *Campylobacter* could not be eradicated from broiler farms, this focus within the industry had left a legacy and had a positive impact on broiler production. Furthermore, improved biosecurity was argued to be facilitating the poultry industry's ongoing targets to reduce antibiotic usage, which was understood to be a positive change. All participants understood how important biosecurity was in the prevention and control of all infectious pathogens, including *Campylobacter*. Participants felt that the presence of *Campylobacter* in a flock was an indicator of poor biosecurity and believed that farms with poor biosecurity were more likely to have *Campylobacter*-positive flocks.

TABLE 2 | Details of 28 interviewees and 16 farms participating in 16 interviews in May 2016 and between June 2017 and January 2018.

Farm no.	Integrator 1, 2 or 3 [Independent Farm (I)/Company-Owned Farm (C)]	No. of houses on site (approximate total no. of broilers per flock cycle)	No. of participants in interview [male (M)/female (F)]	Role [Owner (O), manager (M), assistant manager (AM), general worker (W), spouse (S)]
1	1 (C)	12 (310,000)	2 (M)	M and AM
2	1 (I)	11 (400,000)	3 (M)	M, AM, and W
3	1 (I)	4 (170,000)	1 (M)	O (also M)
4	1 (I)	6 (210,000)	2 (M+F)	M and AM
5	1(C)	9 (290,000)	2 (M)	M and AM
6	1 (I)	4 (130,000)	2 (M)	O and M
7	1 (I)	4 (210,000)	2 (M)	O and M
8	1 (I)	4 (130,000)	2 (M)	O and W
9	1 (C)	8 (210,000)	2 (M)	M and AM
10	1 (I)	8 (320,000)	1 (M)	M
11	1 (C)	8 (300,000)	2 (M)	M and AM
12	1 (C)	8 (290,000)	1 (M)	M
13	1 (C)	8 (280,000)	2 (M)	M and AM
14	1 (I)	4 (200,000)	1 (F)	M
15	2 (I)	4 (130,000)	2 (M+F)	O (also M) and W (also S)
16	3 (I)	3 (80,000)	1 (M)	O (also M)

Power and Responsibility

Participants believed that the whole poultry industry, from farm to fork, had a responsibility for the reduction of *Campylobacter,* with some framing this as a moral obligation:

> *"I think as an industry we have an ethical responsibility to provide a food safe product to the consumers." – Independent-Contracted Farm Manager*

None of the interviewees suggested that farms did not have a role to play in reducing *Campylobacter* in chicken meat and, as previously explained, believed that the recent improvement in biosecurity was beneficial to the industry as a whole. However, interviewees did not believe that *Campylobacter* negatively affects broilers but is only of concern to human health. A small number of participants expressed the opinion that if *Campylobacter* did have a detrimental effect on chicken health and welfare then it would have been eradicated from broiler farms:

> *"I think I probably shouldn't say this, but when somebody says, "If Campylobacter affected chickens, it would have been sorted out years ago." It's true, it would have been, but the fact that it has no detrimental effects to the chicken, is why…I was going to say, we don't have to worry about it, but our job is to grow the chickens as well as we can, to the best standard and welfare as possible." – Independent-Contracted Farm Owner*

There was a common view that farms have been unfairly targeted and more could be done in other areas of production. Many participants did not believe that *Campylobacter* could be eradicated from broiler chicken flocks. It was felt that improvements could be made during processing to reduce the levels of *Campylobacter* on broiler carcasses and that by introducing more interventions in slaughterhouses, this would reduce the burden of responsibility on farms and may even eliminate *Campylobacter* from retail chicken.

There were several controversies and frustrations expressed by participants surrounding the biology of *Campylobacter* and their understanding of its transmission. Each farm had specific issues which they believed were the cause of *Campylobacter* on their farm, for example the ventilation, the weather or climatic factors, pests and public/vehicular access routes. Often blame was passed onto others, such as the breeder flocks, hatcheries, feed mills or catchers. Whether or not it was scientifically plausible, blame was largely shifted onto something that was out of the individual's control.

Whilst many of the interviewees thought increased biosecurity was important, some were sceptical as to its effectiveness in the reduction of *Campylobacter* and others did not believe that biosecurity was the solution to controlling *Campylobacter*. Participants explained how they consistently applied the correct biosecurity measures and flocks would test positive or the results of testing differed between flocks. Participants discussed their frustrations with trying to predict when flocks would be *Campylobacter* positive and that this *"appears to follow no patterns."* Many felt that flocks that "should be" negative would test positive, and those that had suffered biosecurity breaches, either necessary or accidental, would test negative. This participant explained this phenomenon:

> *"When you've got good biosecurity, it's got to lower the risk of getting Campylobacter. Then you go to some places, their biosecurity is top notch, new sheds, all very clean everywhere and they've still got very bad Campylobacter." – Company-Owned Farm Manager*

Some participants believed that the farmers were often ignored in the decision-making process that would ultimately affect their daily lives, as explained by this participant:

> *"The conversation we've had now is ten times longer than any- is the only conversation where anybody has asked me any questions about what we do…And, just a point of view. They don't want to know about the little guys. The little guys, the farmers are the guys that actually keep them going. So, for instance, we went to a meeting not long ago and had 50 farmers in the room. Average experience – 10 years each. I'm a bit of an 'old in the tooth' one now. So that's 500 years of growing chickens experience in that room and not once in a four-hour meeting did the integrator representatives actually ask for anyone's opinion. They told us, and these guys are people who have never actually grown a chicken in their life. So rather than saying, "We've got this problem, this is what we think, has anybody got any ideas?", [they said,] "This is the problem, this is what we're going to do about it." They were wrong on so many levels." – Independent-Contracted Farm Owner and Manager*

Participants expressed a desire for feedback and communication from the integrator about current events and developments in the production chain, including welfare and biosecurity requirements. The integrators were reported to hold considerable power over their farms, particularly financial influence with regards to contracted farms, where they were described as *"the paymaster."* Interviewees described the increasing pressure put on them by integrators to comply with biosecurity regulations. One contracted farm explained they had considered stopping broiler farming due to the requirement to comply with increasing regulations. Other interviewees from contracted farms commented that they had switched contracts due to the *"dictatorial"* nature of integrators and the high level of supervision and oversight.

Biosecurity Issues, Compliance, and Improvements

Interviewees were asked to describe the biosecurity measures employed on site and to discuss any specific compliance issues that had arisen in the implementation of these and also suggestions for improvement. All participating farms were part of the Red Tractor assurance scheme which requires adherence to a minimum biosecurity standard. The common biosecurity measures employed across all farms interviewed included, but were not limited to, restricted and monitored access of the farm perimeter, an anteroom at the entrance to the broiler house containing a physical barrier delineating a biosecure area, widespread use of disinfectant footbaths, farm and broiler house-specific clothing and footwear, and rigorous policies preventing the introduction and spread of disease. Of the common biosecurity measures implemented on-farm, issues with specific biosecurity measures and flock events repeatedly arose during interviews: the control room barriers, external site visitors, and partial flock depopulation.

Control Room Barriers

Commercial poultry houses frequently separate the flock from the outside world with an "anteroom" or "control room," a room within the house that must be entered by staff and visitors before entering the main area housing the flock. Anterooms are frequently split into two areas by a barrier; a defined demarcation zone to change boots, with the area closest to the door giving access to the birds being considered "clean." Under current Red Tractor standards, the type of separation between the contaminated and the clean areas must be a permanent or removable (for cleaning purposes) physical barrier, such as low wall (16, 18, 24, 25).

The usefulness of such barriers was questioned by participants. There was a great deal of frustration amongst participants that the type of barrier within the control room had changed multiple times in a short period of time, which fueled a common belief that the industry did not know how to control *Campylobacter* but needed to be seen to be doing something. Participants sometimes used lay understandings, often at odds with current scientific "facts," to explain their attitudes to, and behaviour regarding, recommended biosecurity practises. For example, not observing control room barriers was due to a perception that barriers fail to prevent *Campylobacter* colonisation and a lack of evidence to the contrary. Interviewees also commented on the practicality and usefulness of some of the required biosecurity measures and were scornful of the people, "*sat in an office somewhere,*" who introduced them. In addition, the cost of having to change the barriers multiple times to comply with regulations was a source of frustration for the independent farms. The barrier was described as a health and safety risk and expected to eventually be removed from sheds for this reason.

External Site Visitors

Many participants felt that external site visitors, such as relief staff and external maintenance staff, did not comply with biosecurity protocols or use site-specific clothing and equipment and had to be *"babysitted."* Participants felt that visitors did not understand the importance of biosecurity and that because *"they haven't got the ownership thing,"* they did not feel that it was important to follow the protocols in place. Participants felt that larger sites with more staff were more difficult to keep *Campylobacter*-free. Vehicular access was a major issue for many participants; compliance with and the effectiveness of wheel washing was questioned, and participants believed that drivers were a biosecurity risk.

Partial Flock Depopulation (Thinning)

During intensive broiler chicken production, a process called "partial depopulation," also known as "thinning," takes place. At the beginning of each flock cycle, sheds are stocked with extra birds, some of which are then removed during thinning. This ensures the correct stocking densities are maintained whilst the remaining chickens grow to the desired final slaughter weight before the flock goes for final processing. Thinning is common practise throughout the UK poultry industry; allowing farmers to maximise productivity by utilising available space, whilst ensuring that the birds are kept at the correct stocking density to meet necessary welfare requirements. Poultry "catchers" are employed to collect ("catch") chickens from farms during flock depopulation events. Catchers are either contracted by farms

and poultry companies or employed by an integrated poultry company. Catchers work in groups of 4–6, catching 5,000–6,000 birds per hour during 15 h days of very physical work in tough conditions (26, 27).

Participants mentioned that flocks were stocked at lower densities and thinned less (only once as opposed to two or three times) than they used to be, which was seen to have been introduced primarily as another anti-*Campylobacter* measure. A ban on thinning to help control *Campylobacter* was felt to be a very political issue within the broiler industry, with some integrators keener to implement a ban than others.

> *"It doesn't matter what you do, you've got to take the forklift in the shed, you've got to take the modules in the shed and the catcher's got to go in the shed. So, the way around it is simple. Don't thin. The answer to not thinning though, is expensive, because it puts 10p a bird on price on the shelf. And it means we need 20% more growing space in the UK." – Independent-Contracted Farm Owner and Manager*

There was very little appetite to stop thinning amongst interviewees; the economic impact this would have on broiler production and the need for decreased stocking densities was thought to be too financially devastating. Integrators with lower stocking densities were said to be more in favour of a ban because it would put their competitors at a commercial disadvantage.

On farms testing for *Campylobacter* before and after thinning, many participants commented that flocks often tested positive after thinning. There were very mixed views on the catchers themselves.

> *"There are some catchers that don't really care about their own personal hygiene, let alone my biosecurity." – Company-Owned Farm Manager*

Participants expressed frustration that they follow biosecurity protocols diligently, only to have the catchers enter the sheds during thinning whilst not observing biosecurity restrictions. Some interviewees felt that because catchers are not invested in the farms, they are not invested in upholding the required standards of biosecurity. However, it was understood that catching is highly pressurised and time sensitive and very little can be done to change this process:

> *"They try their best, they wash their wellies, they do everything that's feasibly possible. I can't think of anything else that they could do." – Independent-Contracted Farm Owner*

It was recognised by many that catchers supplied by a company were better at following biosecurity than those on contracts. This was often felt to be because contracted catchers were paid by the bird. Company catchers had more oversight and were easier to hold to account. Some interviewees did not believe that there was any difference between company and contract catchers but just between catching teams. The relationships between the catching team-leader, the catching team and the farm staff were recognised as important parts of whether the team adhered to biosecurity measures and best catching practise.

Participants discussed the impact of stress on broiler health, including gut health. One interviewee described the stressors that can affect a flock during thinning:

> *"They're not used to it, they're plodding along having a laugh, and then one day the lights get turned off, they've been taken off feed. Then you've got this big forklift coming in making a racket, all the catchers, put the mods in the sheds, they're not used to that." – Company-Owned Farm Manager*

Participants believed that increased stress increased susceptibility to *Campylobacter* infection. Although participants discussed other sources of stress that occurred throughout the flock cycle, such as weather and feed changes, the most stressful period was described as thinning. Sources of stress during thinning included feed withdrawal prior to and during thinning and changes in lighting and high and/or unusual noise levels during thinning. Heat was also regarded as a major source of stress, either from the weather or generated by thinning. Some participants felt that if the birds became stressed there was very little that could be done to prevent *Campylobacter* infection and that they were able to predict *Campylobacter*-positive flocks from the occurrence of certain stressors during the flock cycle.

Biosecurity Compliance and Improvements

A considerable proportion of the interviews was spent discussing the main motivators, which encourage farmers to follow biosecurity, and barriers, which discourage them from implementing the required standards. Broadly these fell into two categories: (i) biosecurity compliance due to requirements and enforcement and (ii) biosecurity compliance, or non-compliance, due to other factors such as time pressures, financial (dis)incentives and personality traits.

There was a high level of acceptance amongst interviewees of the requirement to carry out biosecurity measures. Whether or not the interviewee understood why they were being asked to carry out the biosecurity practise or believed in the effectiveness of the measure, many carried it out simply because it was required:

> *"What we're doing at the moment, it doesn't motivate me to be stricter, because what we're doing is what we've been told to do anyway. There's no more that we can do, it's like, if they tell us, "We want you to do it this way." We'll do it this way, we'll just do what they tell us to do." – Company-Owned Farm Manager*

Many participants commented that the biosecurity requirements had become a habit and that over time they had got into a routine of practising certain measures, despite the extra time it took to complete some tasks compared to in the past. The additional time-cost to follow biosecurity protocols was mentioned by participants to have added pressure to broiler farming:

> *"There's time. When you think we go in the shed and we've got to change wellies, put these overalls on, gloves on, so you're there five, ten minutes in the shed, times that by [no. of sheds]. It just takes a ridiculous amount of time. We've seen like, it takes us a hell of lot longer to walk the birds now, just from all of this coming in.*

Whatever you've got to do I suppose." – Independent-Contracted Farm Assistant Manager

Others admitted that they are less compliant with biosecurity when they enter the shed for a non-routine matter, particularly when addressing issues that might affect welfare:

"When you've got a breakdown, biosecurity goes out the window. It's the birds' welfare at the end of the day." – Independent-Contracted Farm Manager

Participants also confessed that they were worse at adhering to biosecurity protocols if they enter a broiler shed at night in the event of an alarm. Shed-specific PPE and overalls were commonly cited as measures that participants were likely to ignore, notably at night or if the sheds were very hot, for example during chick placement and the first few days of the flock cycle.

Company farms were said by some to be better at biosecurity compliance than independent farms because there was greater oversight and enforcement by integrators.

"Yeah, the independent sector is probably the worst, because we can just do our own thing." – Independent-Contracted Farm Owner and Manager

Interviewees commented that the length of time a person had spent in the industry influenced biosecurity compliance, with those new to the industry more likely to comply than those who had witnessed the evolution of biosecurity within the industry. Personality was also said to influence adherence to biosecurity protocols. Some participants told anecdotes in which one individual was credited with a farm's good or bad record with *Campylobacter*. This was used as an example of how personality and individual differences in behaviour were crucial in *Campylobacter* control. Participants felt that certain stressors, such as staff shortages and lack of time-off, may demotivate some farmers and result in poor biosecurity compliance.

Participants recognised the labour required in policing compliance and the difficulty in ensuring that everyone was consistently adhering to the required measures. Interviewees admitted that they ignored certain biosecurity protocols unless they were being visited or audited. Audits were viewed by interviewees as a way to satisfy management and minimise the level of oversight from their managers. Other participants expressed the view that complying with biosecurity practises was a *"tick box exercise"* to fulfil for auditing purposes. Some felt that there was too much auditing within the industry and described the biosecurity audits as *"a hassle,"* which acted as a drain on time and resources and an unwelcome distraction from necessary farm work.

Participants commented that financial incentives or penalties related to *Campylobacter* testing results may result in more effective and quicker uptake of desired biosecurity measures.

"It depends on what they're trying to achieve with the biosecurity I suppose. If they're just being told to improve their standards because of Campylobacter, there's no financial penalty at all or risk to their business, they might not see the bigger picture of, "That actually also protects you against all the other diseases as well"." – Independent-Contracted Farm Manager

Financial considerations were cited as both a pro and a con with regards to biosecurity compliance. One participant remarked that *"with farmers, most things are financial."* Independent farms were said to be more resistant to change *"if there's a price tag attached to it."* The lack of financial incentive to reduce *Campylobacter* and the fact that *Campylobacter* is not seen to detrimentally affect the chickens were cited as reasons for poor biosecurity compliance. This was contrasted to the effort to eliminate *Salmonella* from flocks, where there are financial implications for *Salmonella*-positive flocks, which was said to better motivate farmers to produce negative flocks. However, independent farms were also said to be more likely to comply with biosecurity for the control of *Campylobacter* because they are financially and emotionally invested in their farm and the benefits of compliance include better flock performance and therefore profit. Those who felt that financial incentives would improve biosecurity compliance considered that testing would have to be done by an impartial external party and that considerable manpower would be required to do this.

Many of the interviewed farms undertook routine *Campylobacter* testing. The results of this were seen as a reliable indicator of on-site biosecurity compliance. In addition, some interviewees were part of a *Campylobacter* league table where theirs and other farms' *Campylobacter* results were published every crop. Participants' opinions on public league tables were mixed and largely dependent upon whether farms scored highly or not. Participants who were scoring poorly admitted that this was why they did not like the system, but that if they performed well, they were happy to have their results shared. Some participants were embarrassed by the results of their flocks' *Campylobacter* testing and exhibited a sense of pride that they did not want to be seen near the bottom of the league table. Participants did not like it when their farms slipped down the league table, but this encouraged them to better future results. Those participants who found the league table motivating felt that it improved their job satisfaction and encouraged healthy competition between farms. Others felt it improved collaboration and knowledge exchange between farms:

"It makes you see where you are from other people, it makes you think what other people are doing and that's where the chatting starts. You talk to other people and find out what they're doing differently." – Independent-Contracted Farm Manager

Participants explained that a public results table encouraged some people to cheat the system by not sampling correctly or trying different methods to ensure that the submitted swabs would be negative. Participants did not feel that there was a benefit to scoring well but felt that scoring poorly resulted in forms of punishment with the results framed as *"who has been a good boy and who has been a bad boy."* Participants scoring poorly felt demotivated by their results, especially where they felt they were doing everything that had been asked of them.

Some at the lower end of the league table wanted to improve but felt that they were fighting a losing battle. Participants reiterated that *Campylobacter* was very difficult to control and that they were being punished for something that was not their fault.

Interviewees described meetings and training events they had attended on *Campylobacter* and biosecurity measures. These were cited as an important method to improve compliance by helping farmers understand why certain measures had to be implemented.

> *"Some people say it's down to whether you're lazy or not, but I think it's down to whether you personally think it makes a difference."* – *Independent-Contracted Farm Manager*

Participants felt that training would be beneficial to ensure that people did not only see biosecurity as a measure to reduce *Campylobacter* but as a method to improve the welfare, health and performance of the birds, to reduce the economic impact of an infection and, for contract growers, to protect their business, as explained by this participant:

> *"Training? If people actually realised that they're actually helping themselves. Yes, it is a hassle…you shouldn't be looking at it as a Campy benefit, but it might help you reduce the risk of your birds getting infected with something else which will impact on you."* – *Independent-Contracted Farm Owner*

There was a general belief that the easier and more practical something was to implement in a broiler farm setting then the more likely people were to follow it.

> *"I think the key to improving standards on farms is to make sure it's workable and easy for the people that have to use it every day. There was a discussion around showering in and out of every shed and it just wouldn't be done. I mean, if you got an alarm call at three o'clock in the morning, there's no way the farmer's going to go for a shower and go in and sort it out. It has to be workable."* – *Independent-Contracted Farm Manager*

Participants felt that there were very few measures left that could be introduced on farms. Showering was commented upon as the only measure left to be introduced on farms. However, this was not a popular idea, with many believing it to be impractical. It was suggested that as older sheds were replaced, biosecurity would improve across the industry and that new builds should be encouraged or required to comply with gold standard biosecurity practises to improve compliance and achieve industry uniformity. However, there was a prevalent sense of fatalism and defeat that *Campylobacter* was largely out of farmers' control. There was a common view that as *Campylobacter* is a ubiquitous bacterium present in the farm environment it is very difficult to tackle.

DISCUSSION

This study used semi-structured interviews to elicit the attitudes and perceptions to biosecurity of people working on broiler farms in the context of *Campylobacter*-control. Whilst studies have demonstrated that there is poor correlation between self-reported and observed compliance (24, 28), the main aim of this study was not to quantify biosecurity compliance but to investigate the incentives and barriers to compliance with biosecurity measures. A qualitative approach was thus appropriate for this broad exploratory context and has provided a method for understanding farmers' beliefs regarding the relative importance of biosecurity in different situations, the contexts in which their behaviour might differ, and their perceptions of their role in the control of *Campylobacter*. This qualitative approach revealed that the main barriers to biosecurity compliance included a lack of training and education on biosecurity and scepticism that *Campylobacter* control could be achieved through current biosecurity measures. There was a belief that these biosecurity measures lacked practicality and were difficult to implement due to financial implications and time constraints. Participants wanted to be more involved in the design of interventions and this should be embraced to give farmers agency and investment in industry targets. These issues will be explored in more depth below.

The UK poultry industry is highly integrated, with the top five integrator companies, who supply major supermarket retailers, accounting for ∼80% of total UK production (29). Following the poultry industry's 2010 target to reduce *Campylobacter* in chicken meat at retail, the integration of the UK poultry meat supply chain has been effective in rolling out widespread biosecurity measures across broiler farms to achieve these goals (30). Participants commented upon the velocity of change and were frustrated by continual changes to these biosecurity requirements, such as control room barriers. The perceived rate of change in biosecurity practises within the industry and difficulty in controlling and predicting *Campylobacter* infection may have fuelled some of the scepticism and frustrations expressed by participants regarding *Campylobacter* and biosecurity measures. Participants were frustrated with not being able to reliably produce *Campylobacter*-free flocks compared with *Salmonella*-free ones. Industry *Salmonella* targets were easier to achieve as vaccination of broiler breeders is believed to have played a role in reducing *Salmonella*-positive broiler flocks (31, 32). Lapses in biosecurity are also more likely to result in the introduction of *Campylobacter* than *Salmonella* to broiler flocks (32). Allen and Lavau (30) conducted interviews across the UK poultry supply chain and encountered similar frustrations with predicting and controlling *Campylobacter* and the apparent randomness in whether a biosecurity intervention proves successful in preventing flock colonisation. Participants commented that the results of routine *Campylobacter* testing and a published league table could be both a positive and negative experience, depending on the nature of the results. However, these results also motivated them to open discourse with other farms, to increase collaboration and knowledge exchange, and to reflect on their own practises, leading to self-directed improvement. Stress, caused by thinning and other flock cycle events, was highlighted by participants as a risk factor for *Campylobacter* colonisation and major barrier to *Campylobacter* control.

Many studies have demonstrated that partial flock depopulation, or thinning, is a risk factor for a broiler chicken flock to become colonised with *Campylobacter* (33–36). It is not yet clear if the relationship between thinning and *Campylobacter* colonisation results from associated stressors, bird age, or the breach in biosecurity that occurs during catching. Despite the threat to biosecurity that catchers posed during thinning, there was little demand to stop this process amongst interviewees due to the associated negative financial effect. Previous studies have identified the widespread practise of thinning in the UK, and the lack of enthusiasm to stop thinning due to the economic impact (37, 38). Particularly on independent farms, other financial considerations, such as the cost of biosecurity measures, were described by participants to be a barrier to biosecurity compliance. Fraser et al. (37) found a clear inverse relationship between the willingness of farmers to adopt a biosecurity measure and its estimated cost. Furthermore, participants discussed the benefits of financial inducements or penalties for *Campylobacter* results. Fraser et al. (37) concluded that this, or possibly a policy decision with legal ramifications, may be necessary to facilitate adoption of and ensure farmer compliance with biosecurity measures.

Audits and official enforcement of biosecurity measures (either conducted internally by an integrator company or externally by supermarkets and assurance schemes) were not framed positively by interviewees. Participants felt that there was too much auditing within broiler farming and admitted to only complying with certain biosecurity measures during audits. As previous studies have found, auditing, enforcement and direct observation only increase compliance in the short-term or create a tick-box exercise where people only comply when being observed and audited. The presence of visible CCTV cameras in broiler house control rooms have only been shown to improve biosecurity compliance in the short-term, with behaviour reverting to type within 6 months after installation (24). This study concurred with others that methods other than auditing are required to improve biosecurity compliance. There is a need to improve understanding of biosecurity measures by demonstrating why and how to apply them (24, 25, 39–41). Additionally, there needs to be an educational focus directed at explaining how diseases are introduced to a farm and the significance of each measure in terms of risk reduction, placing special emphasis on measures that are not applied despite their importance and effectiveness. Furthermore, current research on *Campylobacter* must be better communicated with all tiers of the broiler industry, including farm workers. Participants did not believe that *Campylobacter* has a detrimental effect on the health or welfare of chickens and felt that if *Campylobacter* did have a negative effect on broilers, then it would have been eradicated. *Campylobacter* has long been considered a commensal organism of broiler chickens. However, recent research has indicated that *Campylobacter* may cause disease in birds, negatively impacting upon their health and welfare and increasing the risk of hock burn and pododermatitis (42, 43). Arguably, biosecurity compliance may increase if broiler farm workers understood that *Campylobacter*-colonisation of flocks may have negative impacts on health, welfare, and performance.

Training and education were advocated by this study's participants, who believed that for farmers to comply with biosecurity measures it was necessary for them to "buy-in" and believe that the interventions will have an impact. It was clear from this study that education and knowledge exchange was crucially important to improve biosecurity compliance. These findings concur with a recent survey of the United States' broiler industry's understanding of *Campylobacter* interventions (40), which concluded that education and training programs were needed to improve the understanding of *Campylobacter* in broiler production, including the importance of on-farm biosecurity. However, training alone cannot be expected to solve the industry's issues with compliance. Millman et al. (27) investigated poultry catchers' understanding and experience of key biosecurity threats posed by poor compliance and the barriers to good biosecurity practise during thinning. The authors concluded that emphasising the importance of training was unlikely to result in gold standard biosecurity practise and reduction or removal of the barriers to implementing the required measure, such as through provision of extra time or equipment, may be a better aid to success. Catchers were described as in a *"Catch-22,"* where the time pressures of the job prevented them from complying with biosecurity protocols. What outsiders may have perceived to be the result of ignorance was seen by the catchers to be a necessary and conscious decision to adjust biosecurity protocols to complete the current job. In this study, time pressures were also a factor which affected reported biosecurity compliance. Participants admitted that during an emergency and the night-time, they were more likely to ignore biosecurity protocols, particularly with regards to wearing the correct PPE. Racicot et al. (25) found issues with biosecurity compliance regarding wearing PPE and handwashing, finding that these measures were often neglected, particularly for short visits (<17 min) and for those occurring during the afternoon. Previous studies have shown that farm design has been shown to play a role in compliance with biosecurity measures. For example, adequately positioned equipment (for example provisions for hand washing or PPE) is thought to contribute to enhancing and maintaining compliance (24). In this study, interviewees commented upon the importance of the practicality of biosecurity measures and the ease of their implementation to ensure compliance.

Conversely, Racicot et al. (24, 25) noted that some individuals simply seemed to willingly disregard the rules. This indicates that psychological characteristics may also be part of the problem and the authors advocated future investigation of personality traits, attitudes, and motivations (24). The effect of personality on a person's willingness to comply with biosecurity measures was discussed by interviewees. For example, participants felt that there were differences between different catching teams and that the personal interactions between the farm staff and the catching team influenced biosecurity compliance. Interestingly, Siekkinen et al. (44) found that female producers invest more financially in biosecurity than their male counterparts. Unfortunately, we were not able to investigate the role of gender on biosecurity compliance as only two women were interviewed in this study, which reflects the gender balance of the UK broiler farm

workforce. There were differing views from participants as to the differences in biosecurity compliance between company-owned and contracted farms, with participants stating that compliance by company farms was better than on independently owned farms due to higher levels of oversight and enforcement. Hinchliffe et al. (45) describe a perception with the UK poultry industry that biosecurity is more effectively implemented within integrated production processes due to an ability to easily exercise control over the entire farm-to-fork chain. Similarly, East et al. (46) surveyed the level of adoption of a range of biosecurity procedures on Australian poultry farms and found a lower rate of adoption in independently owned farms, which was concluded to be due to the absence of guidelines imposed by a head office.

Ultimately, this study agreed with others that reasons for lack of compliance could not be boiled down to a lack of information or communication with personnel on biosecurity (24, 25, 27). Whilst lack of knowledge and training is an aspect of the problem, personal and farm characteristics are also determinants of compliance. Moreover, participants expressed a lack of autonomy and believed that their views and experience were often ignored in the design and implementation of interventions, which must be addressed. Interviewees expressed frustration with the lack of involvement they had in all decision-making processes, both on company and contract farms, and commented that before this study they had never been asked for their views on biosecurity interventions. Farmers possess tacit knowledge and experience that could be harnessed in the co-design and improvement of future interventions that may have positive and far-reaching effects on all aspects of the broiler industry. Allowing farmer contributions in this process will provide the "buy-in" required and give them agency to increase compliance and help the industry maintain its *Campylobacter* reduction targets. Biosecurity compliance may be improved by seeking to establish effective methods of communication, educating broiler farm workers about the importance of practises rated as too time-consuming, and by allowing more farmer input into the co-design of interventions.

This study suffered from some potential for bias during participant selection. Purposive sampling was used; two farms were selected through word-of-mouth and the other 14 farms were nominated by a major UK poultry integrator. The poultry integrator was asked to select farms with a range of internal biosecurity audit scores and *Campylobacter* results to ensure that a range of experiences and views were represented. Whilst 14 of the 16 participating farms were owned or contracted to one major UK poultry integrator, the main UK integrators require very similar on-farm standards and adhere to Red Tractor standards. Furthermore, ten participating farms were also independent, contract growers rather than company-owned farms, who may choose to contract grow for other poultry integrators. Thus, the views expressed are expected to be representative of the UK broiler industry. The results are also applicable to other intensively reared poultry species in the UK and similar rearing systems worldwide. Future work would benefit from exploring the views of broiler farm owners, managers and workers supplying other parts of the broiler chicken market and specific consumer demographics, such as the wholesale and Halal markets. Farms supplying the wholesale and Halal markets are less likely to be part of an integrated system that has undergone the recent overhaul to biosecurity measures, including reducing the number of thinning events to no more than one per flock, and Halal chicken meat has been demonstrated to have a higher *Campylobacter* prevalence than non-halal (47).

CONCLUSION

In this study, we have shown there is a high level of recognition amongst broiler farmers of the importance of *Campylobacter* and other disease threats. All participants understood their responsibility in the reduction of *Campylobacter* colonisation of commercial broiler flocks. Participants' self-reported awareness and implementation of biosecurity measures has greatly improved following the industry-wide focus on *Campylobacter* control in broilers. There are frustrations with the industry's approach to tackling *Campylobacter* and the heavy burden of responsibility that has been put on interventions at the farm-level, particularly for a disease that is difficult to control and is not widely seen to detrimentally affect the health and welfare of broiler chickens. Compliance may be improved by establishing effective channels of communication with farmers to share current scientific research on *Campylobacter*. Additionally, more can be done to educate farmers with regards to the evidence-base supporting current biosecurity interventions. It is imperative that all players within the industry are asked to contribute to any decision-making process and are involved in the co-design of biosecurity interventions. Farmers are responsible for the implementation of biosecurity interventions and opportunities to develop and improve biosecurity measures and overall compliance may be achieved by utilising co-design approaches with farmer input. It is crucial to harness farmers' valuable on-farm experience and to give them agency and investment in the industry's *Campylobacter* reduction targets. However, the emphasis within the interviews that the target to reduce *Campylobacter* has had a noticeable positive knock-on effect on the implementation of biosecurity within the broiler industry is very positive. The universal recognition of the benefit of this with regards to broiler health and welfare and other important targets, such as reducing antimicrobial usage, leaves a legacy of which the UK broiler industry can be proud.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Liverpool Veterinary Research Ethics Committee, University of Liverpool (Reference VREC478). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NW conceived and designed the study and advised on all aspects of the analysis. AR contributed to study design, performed the data collection and analysis, and wrote the paper. RC advised on study design and data collection, analysis, and interpretation. All authors contributed to manuscript revision and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.751699/full#supplementary-material

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Biosafety in Dental Health Care During the COVID-19 Pandemic: A Longitudinal Study

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Background: The coronavirus disease 2019 (COVID-19) pandemic had quite an impact on dental health care. Concerns about the risk of SARS-CoV-2 transmission through contaminant fluids and droplet formation during several dental procedures highly impacted dental health care, drastically reducing the number of dental practices worldwide. To monitor SARS-CoV-2 contamination in dental clinics, a longitudinal study was carried out during the return of dental practice at university.

Methods: Dental health care professionals [(DHCPs); teachers, undergraduate dental students, and dental assistants] and patients were screened for SARS-CoV-2 RNA in a dental school clinic environment from 11th January to 12th March 2021 (9 weeks). Serological testing was performed on DHCPs in two-time points. Additionally, samples with low *Ct* values were sequenced to identify the circulating SARS-CoV-2 variant and possible transmission clusters.

Results: We found a low number of dental staff (5.8%), patients (0.9%), and environment sites (0.8%) positive for SARS-CoV-2. Most positive cases had asymptomatic to mild symptoms, and two asymptomatic DHCPs presented prolonged infection. In the first week after previous exposure to COVID-19, 16.2% of DHCPs had IgM or IgG antibodies against SARS-CoV-2, and 1/3 of them had undetected antibodies in the last weeks. The variant zeta (P.2) could be detected. No cross-infection was observed between participants.

Conclusion: Our study suggests that dental practice can be safely executed when adequate control measures and biosafety protocols are applied. DHCP and patient testing, patient telemonitoring, proper use of personal protection equipment, and sanitization of surfaces are essential to avoid SARS-CoV-2 cross-infection in dental practice.

Keywords: COVID-19, SARS-CoV-2, RT-PCR, antibodies, variant, dental public health

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak resulted from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which triggers a systemic disease with heterogeneous clinical manifestations, from asymptomatic to multiorgan failure [1], causing substantial health impacts in several countries, negatively affecting dental care.

As dentists work in close contact with patients, initial studies have shown potential increasing risks related to dental practice, both for dental staff and patients [2, 3]. The transmission of SARS-CoV-2 is mainly due to inhalation or direct contact with contaminated fluids, including saliva droplets. This pathogen can also survive on solid surfaces exposed to contaminated fluids [4–7].

To reduce the risk of contamination in dental practice, in April 2020, the American Dental Association (ADA) and the Center for Disease Control and Prevention (CDC) recommended that dental healthcare professionals (DHCPs) conduct only urgent and emergency procedures, avoiding any routine dental care that could generate aerosols [8].

Since then, many private and public dental clinics have stopped or reduced the number of appointments due to scarce personal protective equipment (PPE) availability and adapted to the facilities and protocols [9–11], increasing the number of dental emergencies [12] and affecting dental education [13, 14]. The changes suggested by health and professional agencies are significant. However, it is necessary to assess their effectiveness as preventive and protective measures against COVID-19 in the return of clinical dental practice.

In this present study, to monitor contamination of SARSCoV-2 in dental clinics during the return of students to university, a longitudinal study was carried out evaluating the efficacy of constant testing in environment, teachers, dental students, dental assistants, and biosafety protocols implementation to prevent SARS-CoV-2 transmission during the return of dental practice at university.

MATERIALS AND METHODS

Ethical Approval and Consent of Participants

The present study was approved by the Ethics Committee of Universidade Federal de Minas Gerais (Protocol CAAE n°31041720.3.0000.5149). All participants enrolled in this study were volunteers, and their samples and clinical data were collected only *via* signed consent forms.

Study Design

A longitudinal study with convenience sampling was performed at the Clinic of Emergence at the School of Dentistry of UFMG, from 11th January to 12th March 2021 (9 weeks) (**Figure 1**). All DHCPs ($n = 103$) were trained before following new dental care protocols by ADA/CDC/ANVISA for COVID-19 [8, 15] and presented a knowledge test with a minimum passing score of 80% or more. All patients ($n = 105$) were previously telemonitored and only participants presenting body temperature measured below 37°C have access to the dental clinic, according to ADA/CDC/ANVISA recommendations [8, 15], and filled a metadata form (**Supplementary Figure 1**).

In the first and last week of the study, whole blood samples were collected from the DHCPs (teachers, dental students, and dental assistants) to detect anti-SARS-CoV-2 IgM and IgG antibodies using serological tests (732-10, *Labtest Diagnóstica*). Virus RNA was weekly investigated by real-time PCR (RT-PCR) in nasopharyngeal samples from DHCPs and saliva samples from patients attending the clinic.

The environmental sampling was tested by RT-PCR and performed on day one, before the first day of activities, and once a week after dental procedures.

The personnel who collected the samples were also monitored weekly using nasopharyngeal swabs and RT-PCR. Only those who tested negative participated in sample collection (data not shown).

Sample Collection From Dental Health Care Professionals, Patients, and Environment

Nasopharyngeal swabs were collected by trained investigators and maintained in a 0.8-ml viral transport medium (VTM). Up to 3.2-ml volume of non-stimulated saliva samples were collected in 50 ml sterile tubes before analysis. Up to 10 nasopharyngeal samples and 3–5 saliva samples were pooled and analyzed by RT-PCR [16].

The environmental sampling was collected in 6 main areas (**Supplementary Figures 2–4**), totaling 100 sites from frequently touched surfaces, surfaces near 1–2 m distance from dental chair, and air. A sterile swab embedded in VTM was used to collect samples from a minimum of 25 cm^2 area of each surface. Sampling from the internal part of the dental suction system was performed with swab introduction (approximately 20 cm in length). A tube containing the VTM was kept open during the whole procedure of environmental sampling.

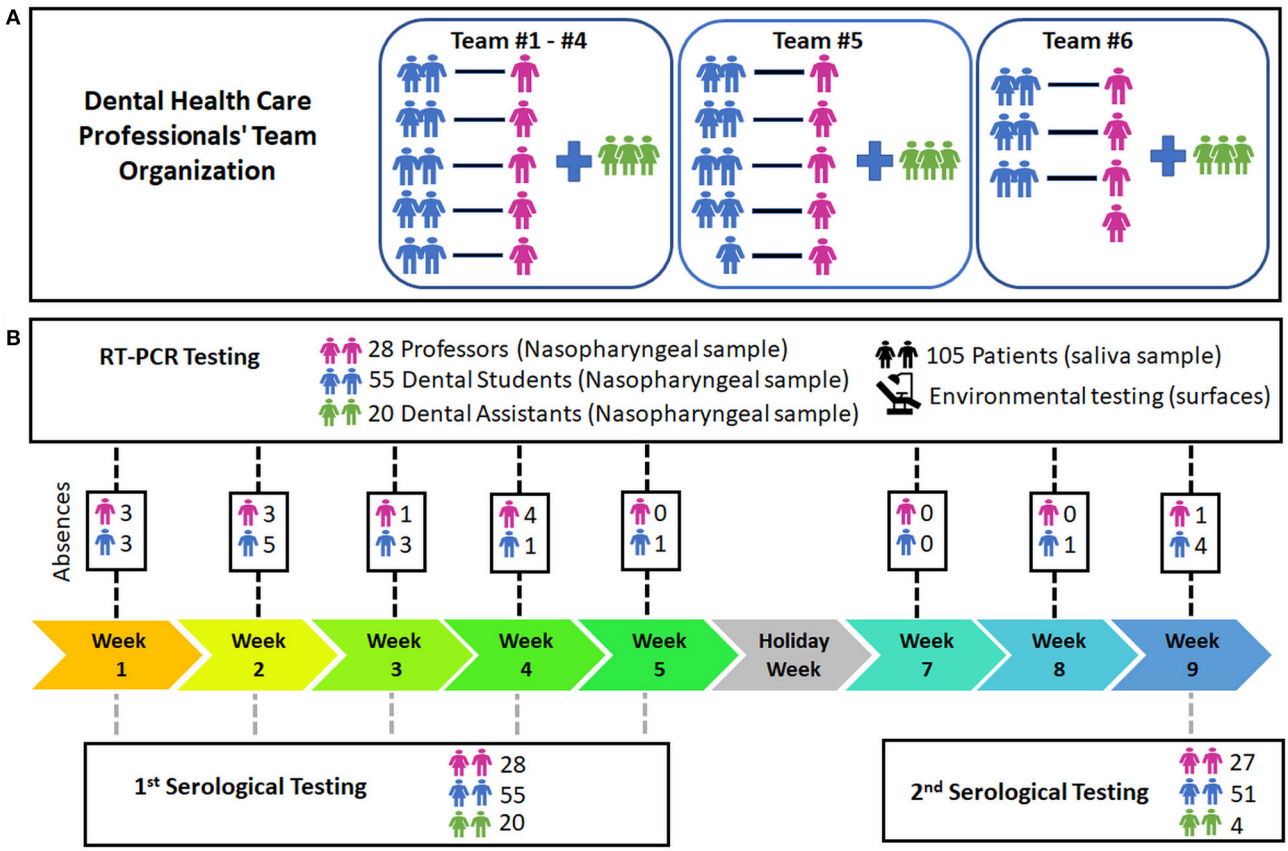

FIGURE 1 | Study workflow and dental healthcare professionals' team. **(A)** Teams of dental healthcare professionals. **(B)** Testing workflow of the study. The presence and absence of each dental healthcare professional per week are demonstrated on **Supplementary Figure 5**.

RNA Extraction and RT-PCR

Molecular diagnosis was performed in accordance with the CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel. Viral RNA extraction was performed using the Quick-RNA™ Viral Kit (R1035, ZYMO Research) and amplified using the Multiplex Luna® Universal Probe One-Step RT-PCR Kit (New England Biolabs, Bioscience) and 2019-nCoV RUO kit (10006713, IDT) for *N1*, *N2*, and *RNase P* gene regions. Reactions were performed using an Applied ABI 7500 (Applied Biosystems). Positive and negative controls were used in each run to validate the method, including standard curves. When pooled sample amplified SARS CoV-2 *N1* and/or *N2* genes with cycling threshold (Ct) values minor 40, the pooled samples were individually diagnosed.

Whole Virus Genome Sequencing

All positive samples (*N1* or *N2* targets, $Ct < 30$) were sequenced using the QIAseq FX DNA Library Prep kit (QIAGEN, Germany) and the Illumina MiSeq (Illumina, USA). Negative control was included, and a custom pipeline for data quality control and consensus genome reconstruction was used [17]. All mutations detected in the novel consensus genome were manually verified. The viral genomes were classified into Pango lineages (pangolin tool v2.4.2). To corroborate the classification, a dataset ($n = 103$) containing only lineages identified in Belo Horizonte during January and February 2020 was created using public genomes (GISAID EpiCoV database). The dataset was aligned (Minimap2 [18] and a maximum likelihood phylogeny was inferred (Q-tree v2.0.3 [19] - GTR+F+I+G4 model [20, 21].

Data Analysis

Categorical data were presented using absolute and relative frequencies. Numerical data were presented using mean and standard deviation. All estimates were calculated using Microsoft Excel.

RESULTS

SARS-CoV-2 Infection Prevalence in Dental Health Care Professionals Using RT-PCR

Before the study period, 48.5% (50/103) of the participants reported being tested by different types of COVID-19 test, and 12.6% (13/103) of them tested positive. Among these 13 DHCP reporting previous positive tests, there were nine students, three dental assistants, and one teacher (**Tables 1**, **2**).

During the study, 5.8% (6/103) of the DHCP tested positive for SARS-CoV-2 (one teacher, three students, and two dental assistants).

TABLE 1 | Demographic and clinical data of participants.

	Teachers	Dental students	Dental assistant	Patients
Total (n)	28	55	20	105
Age				
Mean (±PD)	43.4 (±7.2)	25.6 (±2.8)	50.2 (±10.5)	44.8(±17.1)
Sex				
Female (%)	14 (50.0%)	43 (78.2%)	20 (71.4%)	75 (71.4%)
Male (%)	14 (50.0%)	12 (21.8%)	8 (28.6%)	30 (28.6%)
Comorbidities/conditions				
Pregnant or breastfeeding	–	1	1	2
Hypertension	1	–	4	29
Diabetes	–	–	1	9
Immunodepression	–	–	–	1
Lung disease	1	4	1	6
Heart disease	–	–	–	4
Kidney disease	–	—	-	1
Liver disease	-	-	-	-
Other	–	1	–	16
Symptoms in recent days				
Fever	–	1	1	–
Shortness of breath	1	3	1	4
Chills	1	2	2	1
Diarrhea	2	9	1	–
Loss of taste	–	4	4	4
Tiredness or fatigue	2	8	2	3
Cough	5	4	3	5
Headache	6	17	12	9
Sore throat	1	4	5	4
Decreased smell	–	2	4	2
Muscle or body aches	1	8	4	4
Other	–	–	–	2
Time of onset of symptoms				
Less than 7 days	–	8	3	6
Between 7 and 14 days	–	3	2	4
Between 15 and 21 days	1	1	2	–
More than 21 days	8	12	6	12
Previous COVID-19 testing				
Yes	17	26	6	17
No	11	27	21	88
Exam type				
Immunochromatography serological test	2	4	–	–
Chemiluminescence serological test	–	2	–	1
Fluorescence serological test	1	–	–	1
ELISA serological test	3	1	3	1
Molecular test (RT-PCR)	15	22	4	9
Did not know how to inform			1	4
Test result for COVID-19				
Positive	1	9	3	5
Inconclusive	–	–	–	–
Negative	16	18	3	11
Another vírus	–	–	–	–

n, number. PD, Pattern Deviation. %, percentage.

TABLE 2 | History of travel and previous contact with a COVID-19 positive person.

	Teachers	Dental students	Dental assistant	Patients
Total (*n*)	28	55	20	105
Contact with confirmed or suspected COVID-19 case				
Yes	12	30	13	11
No	16	25	15	94
Contact period				
Less than 7 days	–	7	5	1
Between 7 and 14 days	2	2	2	2
Between 15 and 21 days	1	2	–	–
More than 21 days	9	19	5	7
Contact with symptomatic case?				
Yes	5	21	9	7
No	4	6	1	2
Did not know how to inform				
Contact with confirmed case?				
Yes	10	22	9	7
No	2	3	2	1
Did not know how to inform	–	–	–	–
Exam type (Contact)				
Immunochromatography serological test	2	1	1	–
Chemiluminescence serological test	1	1	–	1
Fluorescence serological test	–	–	1	–
ELISA serological test	–	–	3	–
Molecular test (RT-PCR)	6	23	3	4
Did not know how to inform	1	5	5	5
Have you traveled anywhere in the past few days?				
Yes, to other City in MG State	5	12	3	7
Yes, to other Brazilian State	8	7	2	3
Yes, to other Country	1	2	–	–
No	14	34	23	95
If you answered yes to the previous question, what is the return time for the trip?				
Less than 7 days	6	8	1	1
Between 7 and 14 days	5	10	4	1
Between 15 and 21 days	1	1	-	2
More than 21 days	1	-	-	5
Have you been vaccinated recently?				
Yes	3	6	4	7
No	25	48	24	98
Recent vaccination type				
Flu Vaccine	1	1	2	6
Pneumonia Vaccine (Pneumococcal vaccine polyvalent)	–	–	–	–
Other	2	5	2	1
Period of vaccination				
Less than 7 days	–	–	–	–
Between 7 and 14 days	–	1	–	1
Between 15 and 21 days	–	1	1	–
More than 21 days	3	4	3	6

n, number.

Timelines with the number of RT-PCR tests and positive results per DHCP are illustrated in **Figures 2A,B**, respectively. According to the presence and week, all DHCPs' results are shown in **Supplementary Figure 5**.

Indeterminate results (i.e., *Ct* <40 for *N1* or *N2* genes) are indicative of lower viral load during the beginning or end of viral peak and represented a total of 16.5% in our study (**Supplementary Figure 5**). These individuals were retested the

following week and found to be negative. Only one student with an indeterminate test was symptomatic and tested negative 14 days later, indicating that the infection had been resolved.

Asymptomatic Prolonged Infection Cases

Asymptomatic prolonged infections were identified in two individuals. A teacher (L#10) tested positive three times (on weeks 3, 5, and 9), after the first RT-PCR positive result in the study, with an interval of 15 and 43 days. A student (S#52) tested positive two times (weeks 1 and 7), with a 49-day interval between each positive result. Both were female, IgG positive in the second serological tests, and reported no symptomatology when RT-PCR results were positive.

Prevalence of Antibodies Against SARS-CoV-2 in Dental Health Care Professionals

On the first serological testing, 99 DHCPs were analyzed and 16.2% (16/99) presented positive results. Of those, 3.0% (3/99) were IgM+ only, 8.1% (8/99) were IgG+ only, and 5.1% (5/99) were IgM+/IgG+. Only one participant was immunized for COVID-19 during the study.

At the final antibody testing, a reduced number of dental assistants and students (totaling 76/99; 76.8%) were present in the clinic due to work schedule and graduation course completion, respectively and 15.8% (12/76) of the participants tested positive (4 IgM+, 4 IgG+, and four positive for both IgM and IgG).

Considering the two time-points of serological testing, 7.9% (6/76) remained positive results in both tests. Out of this, four of them maintained the same serology (2 IgM+, 1 IgG+, and 1 IgM+/IgG+). The other two presented IgM antibodies in the beginning and IgM+/IgG+ in the second test; one reported to have contact with a confirmed COVID-19 case and the other received the COVID-19 vaccine before the serological test. All six participants were negative for the RT-PCR tests during the whole study, suggesting previous exposure to SARS-CoV-2 and COVID-19 vaccine.

In total, 5.3% (4/76) DHCPs had antibodies detected at the beginning of the study but no longer showed positivity after 2 months, presenting the second serological result negative for both antibodies. These four individuals tested negative in all RT-PCR tests.

During the study, seroconversion was observed in the two prolonged infection cases. They were negative for antibodies at the beginning of the study and presented IgG antibodies at the end, confirming the exposure to COVID-19 during the study.

Figures 2C,D show the absolute number of serological tests performed in each group of dental staff and positive results. **Supplementary Figure 6** shows the number of positive IgG and IgM antibody positive cases and cumulative cases are represented by the black line.

Co-worker Infection Assessment

In order to evaluate whether the measures to control COVID-19 transmission implemented in this study were efficient, we analyzed possible co-worker infections. We evaluated teams composed of teachers that individually monitored work pairs of dental students (**Figure 1A**). Each team was present in one fixed period of a weekday in the dental clinic and 12.9±3.1 RT-PCR tests were performed weekly per team (**Figure 3A**). The number of positive cases per week is presented in **Figure 3B**.

The students worked with the same partner throughout the study, and 27 students' work pairs were evaluated. No cross-infection was detected in either partner, neither simultaneously nor one following another, in the subsequent weeks (**Figure 3C** and **Supplementary Figure 5**).

Prevalence of SARS-CoV-2 in Asymptomatic Patients

A total of 105 patients participated in the study (**Tables 1**, **2**). Only one patient (1/105; 0.9%) was positive for SARS-CoV-2 on the 8th week and was an asymptomatic boy.

Most patients were only tested once because they did not have to return for dental procedure follow-up. Therefore, 18.1% (19/105) of the patients could be retested (for 2–3 weeks), and all retested negative, reinforcing that all the control procedures prevented the infection of patients during the dental practice.

Environmental Testing

A total of 898 samples were collected (**Figure 4A**). Positive samples (0.7%, 6/898) were found only in the 9th week (**Figure 4B**) and indeterminate samples (2%, 21/898) were found on the 8th week and 9th weeks (**Supplementary Figure 7**).

Comparing the 2 weeks, the positive and indeterminate surfaces were different each week. The supporting and purge areas were negative in all the weeks tested (**Supplementary Figure 7**).

SARS-CoV-2 Variants Identified

To evaluate whether the control protocols prevent cross-infection among the participants, we sequenced the whole genome of SARS-CoV-2 from two positive samples presenting *Ct* values compatible with whole genome sequencing. Both participants (student and dental assistant) never worked at the same work team over the entire study and became positive in different stages of the study: the dental assistant (LBI_279) became positive at the first week and the student (LBI_283) at the 7th week, suggesting no possible cross-infection at the clinics. The phylogenetic reconstruction ruled out the possibility of virus spillover during the clinics and cross-infection between the two participants (**Supplementary Figure 8**). Both viral genomes are classified as zeta variant (previous P.2), the most prevalent SARS-CoV-2 lineage present in the city during the study. However, each sample was grouped in different branches compared to other virus references sequences from the Belo Horizonte city at the same time of the study reinforcing that both cases came from two independent events of infection unrelated to the dental clinical practice.

DISCUSSION

The study was conducted at the beginning of a big wave of COVID-19 in Belo Horizonte City and the vaccination distribution was limited to a few health care workers at hospitals.

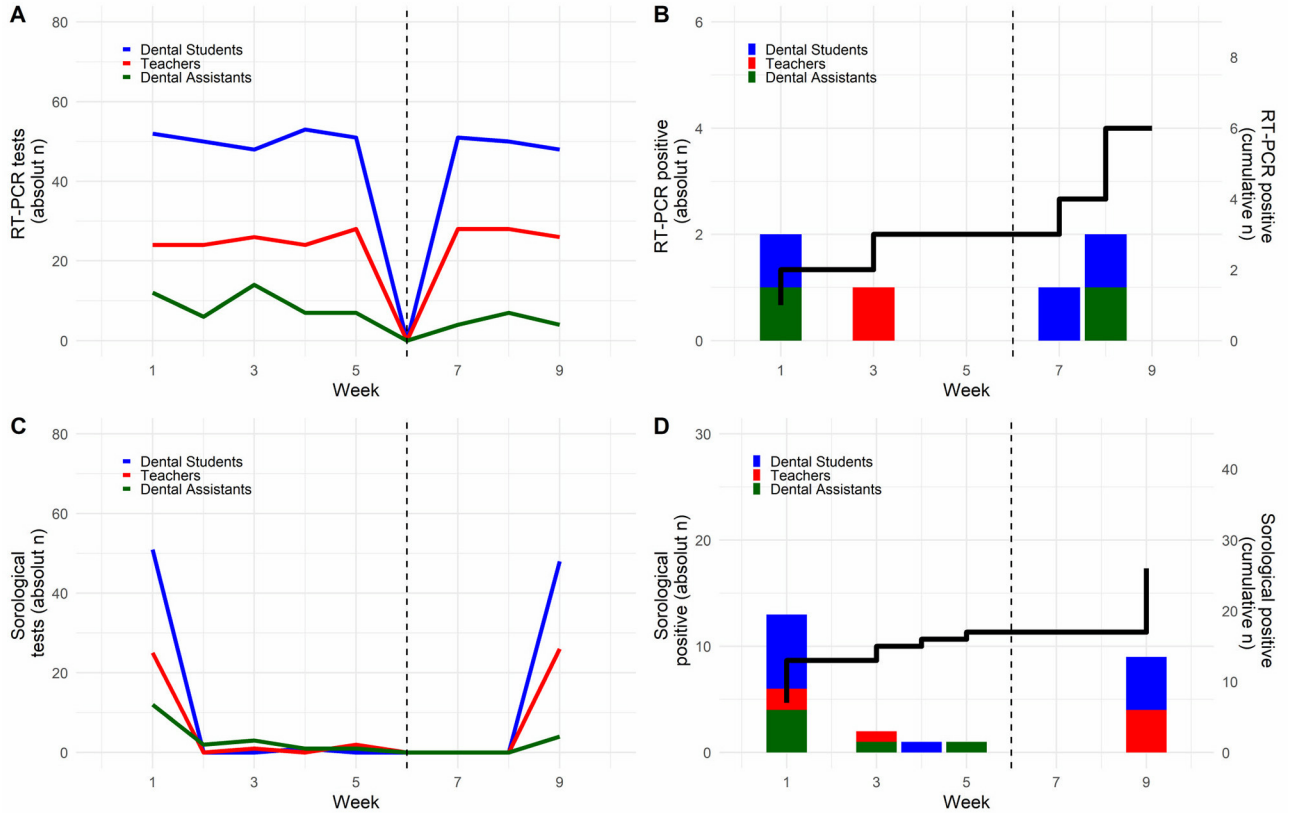

FIGURE 2 | RT-PCR and serological tests in dental healthcare professionals. **(A,B)** Shows the number of RT-PCR tests and positive results, respectively. The black line shows cumulative cases **(C,D)** present the number of serological tests and the positive results of each week of the study. The black line shows cumulative cases.

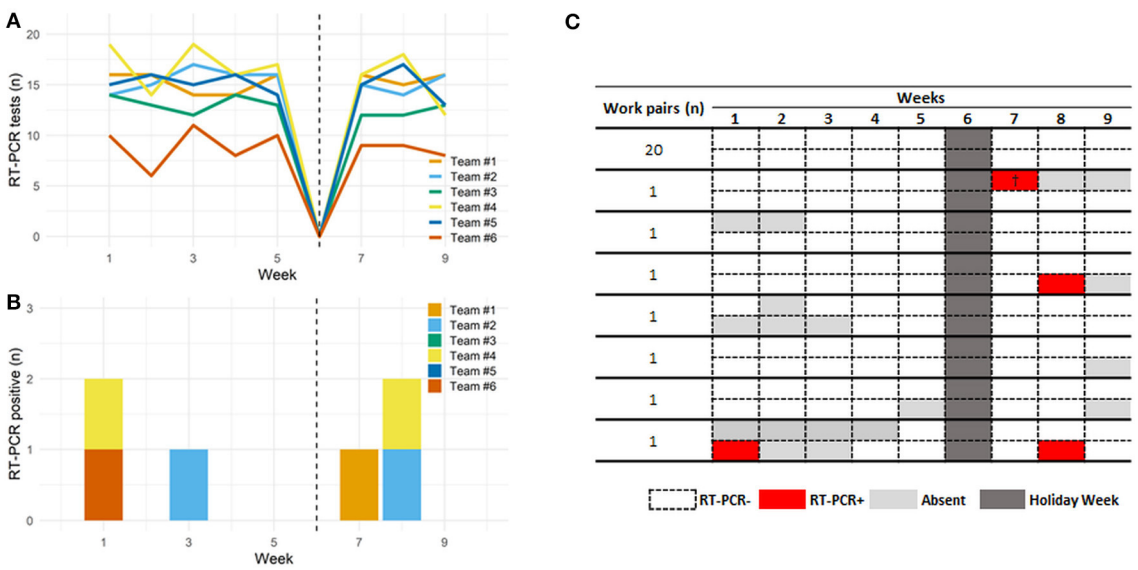

FIGURE 3 | RT-PCR tests and results for SARS-CoV-2 in dental healthcare professionals. **(A)** Shows the number of RT-PCR tests during study timeline per team composed by teachers, dental students and dental assistants. The number varied between teams due to the absence of some participants, either because of COVID-19 diagnostic or personal reasons. **(B)** Shows the number of RT-PCR positive cases by team during the 9 weeks. **(C)** Shows the presence and results found in work pairs of dental students. (†), shows the sequenced samples of the SARS-CoV-2 zeta variant.

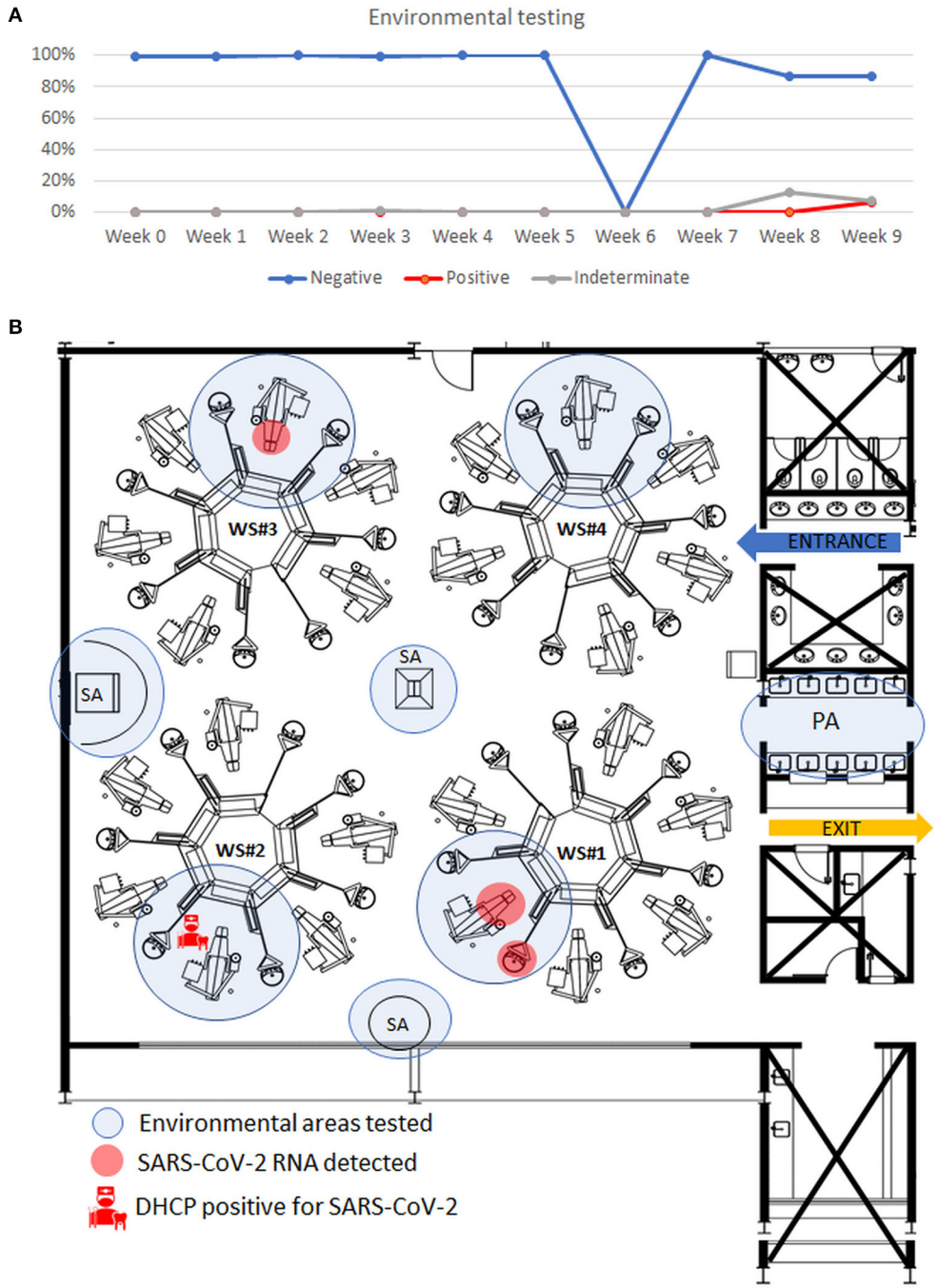

FIGURE 4 | Results of environmental samples collected from the dental clinic and tested by RT-qPCR. **(A)** Graphic representation of the results of environmental samples per week. Values in percentage. **(B)** Representative figure, on week 9, showing the spatial distribution of areas positive for SARS-CoV-2 RNA, detached in red, and position of the detected positive dental health professional in the workstation#2 in the clinic. Workstation #1 presented detected (the sink bench, detergent dispenser, dental chair upholstery, light handle, and light arm) and indeterminate results (non-hazardous waste disposal, air sample, and saliva ejector hose–external part). The workstation #3 presented one sample positive in the light arm and presented indeterminate results in the other three spots. WS, workstation. DHCP, dental health care professional. PA, Purge area. SA, supporting area.

In this period, only 1.3% of the Brazilian population was vaccinated. This scenario made it possible to realize the study in a convenience sample of DHCPs and patients of a public dental health care University from Brazil. The presence of the COVID-19 virus has been demonstrated in oral tissues and saliva [4, 6]. This triggered concerns about biosafety in dental practice, how

to detect and manage patients with COVID-19 when they need dental and oral lesion assistance, and controlling and minimizing the virus cross-infection.

To analyze the biosafety of dental treatment during the COVID-19 pandemic period, a longitudinal screening for SARS-CoV-2 was conducted on DHCPs, patients, and the environment by RT-PCR test during 9 weeks of follow-up. Additionally, two time-points of serological testing and identification of SARS-CoV-2 variants were also performed. To the best of our knowledge, this is the first study in dental health care that experimentally addresses all these points.

During the study, detection of antibody levels for SARS-CoV-2 was present in 16.2% DHCPs; this number was similar to the seroconversion rate (16.3%) found in dental healthcare workers reported by Shields et al. in 2021 [22]. Half of the DHCPs sustained the positive serology results during the 2 months of our research. IgM and IgG levels are known to decrease over time significantly. While IgM decreased by 53%, IgG decreased by 32%, and the number of the receptor-binding domain (RBD)-specific memory B cells could be detected 6.2 months after infection [23].

The RT-PCR and serological tests were suitable methods to detect and alert patients and DHCPs about the need to implement preventive measures during the daily life of participants. We observed a low number of DHCPs who tested positive for SARS-CoV-2 by RT-PCR during the study (6%). Notably, most of the positive and indeterminate results were observed in the week following the *carnival* holiday. It is known that secondary infection by household contacts occurs around 16.3–52.4% [24, 25] when quarantine measures are not respected between individuals [24] and immediately after symptom onset in the first case [25]. In our study, some of these DHCPs reported to have traveled to their family's home cities, and others confirmed contact with someone positive, which is highly suggestive of COVID-19 contamination outside the dental clinic. This fact was also established by the phylogenetic inference of whole genome sequencing from SARS-CoV-2 positive samples. Despite the crescent COVID-19 vaccination and its efficacy in reducing disease severity [26, 27], it is important to monitor asymptomatic individuals and encourage the continued use of preventive measures not only in the dental clinic but also in the social environment to avoid the spread of the disease until total population immunization. In addition, until the end of the study, only 1.3% of the Brazilian population was immunized, demonstrating the efficacy of control measures applied.

The continuous testing allowed the detection of 2 cases of prolonged infection with positive RT-PCR results for 43 and 49 days. Although rare cases of prolonged infection or reinfection, it seems to be related to SARS-CoV-2 intra-host evolution and viral replication that can generate quasi-species diversity [28]. This prolonged infection varies according to host capacity to control infection and may present low transmissibility after the first week of the disease, which is the time when the number of viable virus titles in the upper respiratory tract is at its peak [29, 30].

We found no cross-infection between co-workers or patients, nor a positive environmental area for SARS-CoV-2 RNA where the DHCPs tested positive. This is probably due to the adequate use of PPE to reduce the risk of COVID-19 transmission significantly [31]. It is important to remember that in the present study, all DHCPs were trained for biosafety protocols before the study following the CDC/ADA/ANVISA recommendations [8, 15]. It states the proper use of complete PPE included wearing a disposable isolation gown, N95 respirator, face shield, goggles, disposable cap, gloves, safety glasses, and shoes. All metal, plastic, and marble surfaces were sanitized with 70% ethanol and dental chair upholstery with quaternary ammonium detergent before and after patient assistance; the same workstation was used with an interval of 24 h between each patient. One particular detail of the present dental clinic was the natural ventilation of the environment and the significant distance between workstations (approximately 10 m from each other), which could reduce cross-infection between participants.

Environmental contamination was mainly present during the last 2 weeks of the study. Such positivity was probably due to the secretion of patients who tested positive for COVID-19 during dental treatment. The workstation where the positive patient was assisted presented indeterminate results in some surfaces and air. In the following week, there were positive areas, but not all patients could be tested, and the unique DHCP who tested positive for SARS-CoV-2 in this week worked in a workstation area that tested negative, reinforcing the environmental contamination most probably resulting from the patients' fluids. In the last 2 weeks of the study, the Belo Horizonte City population presented an increasing number of positive COVID-19 individuals, and sanitary measures were more restrictive at this moment due to the gravity of the COVID-19 pandemic. Viable SARS-CoV-2 can be detected on surfaces after hours and not viable viral RNA after days according to the material and in laboratory conditions [5]. In addition, environmental interference, such as temperature, humidity, and heat makes its transmission ability by objects lower than expected in the public environment [7, 21]. Airborne transmission seems to be the dominant route of SARS-CoV-2 transmission [32]. New evidence suggests that smaller droplets present reduced airborne transmission because they carry fewer viruses and evaporate faster than large droplets, causing reduced virus viability in the environment [33].

Since environmental and saliva samples present lower viral loads than nasopharyngeal samples, up to 5 environments and saliva samples were pooled, while up to 10 nasopharyngeal samples were pooled. This technique reduced the cost of testing a large number of samples and efficiently detected positive samples, as described previously [16, 34, 35].

The saliva of all patients tested in the study was collected. The saliva can present viable virion isolation for SARS-CoV-2 [36] because salivary glands seem to be a reservoir of the virus [6]. Saliva is an easy and accessible sample source during dental care and its collection is less uncomfortable than collecting nasopharyngeal samples. Its PCR results present sensitivity (83.2%) and specificity (99.2%) that are very similar to nasopharyngeal samples (84.8% sensitivity and 98.9% specificity) [35]. This sampling technique allowed easy collection of samples from patients, including special care ones and children. In the present study, it was possible to detect an asymptomatic boy of 6-years-old, similar to the previous study that demonstrated a SARS-CoV-2 positive rate of 2.3% in pediatric dental patients,

with 50.9% of them being male at a mean age of 6 years and presenting no symptomatology for the disease, suggesting the practice of PCR testing in dental clinic as an adjuvant for screening questionaries [37].

Our study had a limitation in that not all patients visiting the clinics could be tested, and dental assistants were tested only when they were scheduled to be at the University. Most students and teachers were scheduled to be at the clinics every week and had <10% of missing data points. Thus, 76 participants (73.8%) were tested in all weeks of the study. Interestingly, our findings demonstrated that these individuals were not infected after receiving or delivering dental procedures.

Using viral genomics and phylogeny inferences, we showed that positive participants that became positives during the study were infected with different viruses more related to viral genomes from the city of Belo Horizonte than each other. To improve our analysis, we enriched our data set of references sequences with the zeta variant that was the most predominant in the area during the study. The genetic analysis reinforces the efficiency of PPE, constant testing, and environment clean-up to prevent virus spillover events in the dental clinic practice.

In conclusion, this study demonstrated that dental health care assistance possesses a low risk of cross-infection between the DHCPs and patients when biosafety and PPE protocols are adequately followed. Furthermore, our findings show that the infected people present in the clinic were contaminated when socializing with someone contaminated (family/friend) outside the clinic, reinforcing the need to instruct people about social distancing and the importance of using face masks to control the spread of the virus.

DATA AVAILABILITY STATEMENT

All data that underlie the findings reported on this study (participant's data, after de-identification, tables, figures, appendices, study protocol, cycling threshold results, and informed consent forms), will be available for 5 years, under request by contacting the corresponding authors to researchers or investigators with the sound proposal. Public genomes of LBI_279 and LBI_283 are available on the GISAID EpiCoV database (https://www.gisaid.org/) under the following codes EPI_ISL_1495039 and EPI_ISL_1495042, respectively. The proposal should be directed to the corresponding authors' e-mail.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Universidade Federal de Minas Gerais (Protocol CAAE n°31041720.3.0000.5149). All participants enrolled in this study were volunteers, and their samples and clinical data were collected only via signed consent forms. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

The project administration, resources, funding acquisition, and supervision were performed by RG,RPS, RA, and MA. Substantial contributions to the study conceptualization were performed by RG, RPS, RA, MA, CG, and RM-C. Data analysis and curation were executed by LM, SR, SS, and DM. The formal analysis was performed by LM, RPS, RA, and RG. Methodology was contributed by RG, RPS, RA, MA, AS, FJ, LS, TS, and LM. Software analysis was performed by FM and PF. Data validation was performed by FM, RPS, RA, and RG. Visualization was executed by LM, RPS, RM-C, VG, PF, and MS. Original draft and editing of writing were performed by LM, RM-C, CG, VG, RG, RPS, and RA. Data acquisition was contributed by LM, RM-C, VG, SR, SS, DM, RMS, DQ, HA, RF, AC, RM, LB, DA, AS, FJ, LS, TS, and RSG. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/froh.2022.871107/full#supplementary-material

Supplementary Figure 1 | Form applied before personal sampling collection. The form includes demographic information, medical history (including COVID-19 tests and results), signs, symptoms, travel behavior, and possible contact with SARS-CoV-2 positive person.

Supplementary Figure 2 | Workstation surfaces for the environmental testing in dental clinic. Figure shows dental chair area, and the samples site of collection. The black arrow shows a tube kept open during the whole procedure of environmental sampling. Red and yellow lines highlight the areas. The red arrow points to the internal part of the saliva ejector.

Supplementary Figure 3 | Purge area and sites collected. Red circles highlight areas where samples were collected.

Supplementary Figure 4 | Supporting area and sites collected. Red lines highlight areas where samples were collected. The blue circle shows the position of the tube kept open.

Supplementary Figure 5 | Dental care healthcare professionals' RT-PCR results for SARS-CoV-2, according to the presence in the clinic per week. **(A)** Dental students and work pair results. Three students (S#9, S#14, and S#51) had COVID-19 previously and returned to the dental school after this project started on the third and fifth week. All of them reported that they did not contact each other or with their work pair before the start of the study. They started to work at the clinic after negative RT-PCR results. The absence of S#22, and S#28 in the 9th week was because they concluded the undergraduation. **(B)** Teachers' results. L#10 were not present in the 1st week because had contact to a familiar positive to COVID-19. L#4, L#8, L#11, L#15 and L#28 were absent due to personal reasons not related to COVID-19 **(C)** Dental assistants' results. The presence of dental assistants was following company schedule. Both dental assistants positive for SARS-CoV-2 were present in the clinic after dental assistance, when no teachers or students were present. (†), zeta variant identified on samples with Ct<30 to N1 and N2 SARS-CoV-2 genes. (‡) S#55 is the unique student who worked without a partner.

Supplementary Figure 6 | IgG and IgM positive results in dental healthcare professionals during the nine weeks observed. **(A)** Shows IgM positive results. **(B)** Shows the number of IgG positive results. **(C)** Demonstrate the double IgM and IgG positive results. Black lines represent cumulative positive results.

Supplementary Figure 7 | Environmental results of samples collected from surfaces of each workstation (WS) collected in the eighth and ninth weeks. The figure illustrates different areas detected between the two weeks. The patient positive for COVID-19 was assisted in the eighth week at workstation#2 where indeterminate samples were on the sink bench, detergent dispenser, air sample, instrument table handle, and internal part of the saliva ejector were found (Ct = 35 ± 2 for N1 gene).

Supplementary Figure 8 | Phylogenetic tree of variants in Belo Horizonte City and the variants detected in dental healthcare professionals (highlighted in the purple circle). Sequenced samples resulted in a total of 183,560.5 reads with a genome span above 79.5% (mean: 89.6 ± 10.1%). The sequencing depth of the two samples were at least 740x (Mean 1226.0 ± 486).

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Complementarity of International Instruments in the Field of Biosecurity

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The COVID-19 pandemic has demonstrated the devastating impact of infectious disease outbreaks and the threat of emerging and re-emerging dangerous pathogens, independent of their origin. Natural, accidental, and deliberate disease outbreaks all need systems in place for an effective public health response. The best known international instrument in the field of public health is the WHO International Health Regulations (2005). Although the International Health Regulations are mainly focused on natural disease outbreaks, the actions to take to comply with them also contribute to biosecurity and non-proliferation. This paper examines in case of full implementation of the International Health Regulations, what other actions states should take to comply with international biosecurity instruments, including the Biological and Toxin Weapons Convention and United Nations Security Council Resolution 1540, to effectively prevent and defend against intentional biological threats. An overview of international instruments from different disciplines regarding biosecurity is presented. Furthermore, this paper clarifies the similarities between the international biosecurity instruments and addresses the additional requirements that instruments stipulate. From a detailed comparison between the instruments it can be concluded that, to adhere to all legally-binding international biosecurity instruments, specific non-proliferation and export control measures are necessary in addition to full implementation of the International Health Regulations. Additionally, an overview of non-legally binding instruments in the field of biosecurity is presented and practical implementation examples are highlighted. Compliance with legally binding instruments can be improved by precise guidance provided by non-legally binding instruments that are clear and attuned to the situation on the ground. To improve understanding of the existing international instruments, this paper aims to provide an overview of the international legal biosecurity framework to biosecurity experts, policymakers, civil servants, and practitioners. It offers possible practical applications for the politico-legal context and accommodates the enhancement of full employment of biosecurity resources for an improved multidisciplinary capacity to prevent, detect, and respond to infectious disease outbreaks.

Keywords: global health security, biosecurity, legal instruments, health policy, infectious disease, IHR, BTWC, UNSCR1540

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INTRODUCTION

The coronavirus SARS-CoV-2 causing the COVID-19 pandemic has stimulated global attention to the impacts of infectious disease and global health security threats. The virus emerged in Wuhan China in late 2019 presenting a local public health challenge (1), but quickly transformed into a global health emergency as the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern (PHEIC) (2), the highest level of alarm, in late January 2020 and a global pandemic in March of the same year (3). This rapid transition from a local outbreak to pandemic status raises questions about the systems in place to prevent and control infectious disease outbreaks. The COVID-19 pandemic is not the only PHEIC of this century. Since 2009, there have been five more PHEIC declarations: the 2009 H1N1 (swine flu) pandemic, the 2014 polio declaration, the 2014 outbreak of Ebola in Western Africa, the 2015–2016 Zika virus epidemic, and the 2018–2020 Kivu Ebola epidemic (4).

In October 2019, the Global Health Security Index analysis found no country to be fully prepared for epidemics or pandemics (5). The report states many countries do not show evidence of the health security capacities and capabilities that are needed to prevent, detect, and respond to significant infectious disease outbreaks. The COVID-19 pandemic demonstrated that the world collectively did not have sufficient capacity to prevent and control major infectious disease outbreaks (6). The SARS-CoV-2 outbreak causes serious reevaluations about the dangers of natural, accidental and deliberate disease outbreaks (7). The 2021 Global Health Security analysis shows all countries remain dangerously unprepared for future epidemic and pandemic threats, including threats potentially more devastating than COVID-19 (8). As with previous PHEICs, the COVID-19 pandemic again revealed that global collaboration and information sharing is critical, as infectious diseases do not stop at country borders (9). This emphasizes the necessity of global health diplomacy, which is at the intersection of public health and foreign affairs (10). A multidisciplinary and global approach is crucial to efficiently prevent and control pandemics. Sustained interaction between biosafety and biosecurity regimes strengthens the international systems for countering disease threats, regardless of their origins (11, 12). This underlines the need for improved implementation of cross-sectional international regulations and systems concerning global health security. Experts have warned for an urgent need to strengthen international arrangements intended to protect the world against chemical, biological, radiological, and nuclear threats (13).

The COVID-19 pandemic has increased attention toward the WHO's International Health Regulations 2005 (IHR) (14). One of the requirements of the IHR is for states to build effective disease surveillance capacities and to notify WHO immediately if an event is considered a public health crisis with the potential of international spread (14). The IHR focuses on infectious disease outbreaks with a natural origin and covers some aspects of accidental and deliberate releases. However, independent of the origin of a disease outbreak, an effective public health response is necessary to control it (15). Health surveillance (prevention of natural outbreaks), biosafety (prevention of accidental release), and biosecurity (prevention of misuse of biological agents and knowledge, with a focus on non-state actors) strive toward reducing public health risks and the means to reach this goal are largely similar. Obligations stemming from the IHR therefore also contribute to biosecurity and non-proliferation (preventing and controlling the spread of weapons of mass destruction, with a focus on state-actors) and, *vice versa*, measures from international non-proliferation instruments contribute to a reduced risk of natural outbreaks. The web of prevention for biosafety and biosecurity provides insight in this complementary relationship (11). The Biological and Toxin Weapons Convention (BTWC) and United Nations Security Council Resolution 1540 (UNSCR1540) are international legally binding non-proliferation instruments in place to reduce dangers of deliberate disease outbreaks in humans, animals, and plants (16). The BTWC also contributes to global disease surveillance as it requests international exchange of equipment, materials, and information to combat outbreaks of infectious diseases (17). UNSCR1540 emphasizes safe and secure handling, use, transport, and storage of pathogenic material, thereby contributing to biosafety and biosecurity (18). As the means to reduce the risk of natural, accidental, and deliberate disease outbreaks are similar, requirements stemming from the various international instruments show overlap. This paper focuses on the obligation stemming from IHR, BTWC, and UNSCR1540 regarding biosecurity. IHR is well-known by most countries and to date 174 of the 196 states parties (89%) submitted an annual IHR self-assessment report over 2020 (19). Therefore, this study examines what else should be in place to comply with international legally binding instruments in the field of biosecurity assuming a fully implemented IHR. Overlap in the requirements of IHR, BTWC, and UNSCR1540 with regard to biosafety and biosecurity has been previously described by Bakanidze et al. (16) and UPMC Center for Health Security published a synopsis of biological safety and security arrangements providing an overview of key international treaties, agreements, instruments, and guidelines (20). This paper builds on previously published work by providing a detailed and updated comparison of the specific requirements stated in each instrument. An up to date overview of legally binding and non-legally binding instruments in the field of biosecurity is given and overlap in the requirements of the legally binding instruments IHR, BTWC, and UNSCR1540 regarding biosecurity is discussed in detail. Requirements stemming from each of these instruments are compared on the level of exact wording of the convention, regulation or resolution in order to know more precisely what additional requirements BTWC and UNSCR1540 require regarding biosecurity when IHR is fully implemented. Furthermore, practical implementation examples are highlighted. This paper aims to facilitate identification of overlapping and complementary issues in international biosecurity instruments and improve understanding of policymakers, civil servants, biosecurity experts, and practitioners regarding these instruments. This accommodates the enhancement of full employment of national resources to comply with international requirements, ultimately

leading to an improved capacity to prevent, detect, and respond to infectious disease outbreaks, independent of their origin.

INTERNATIONAL LEGALLY BINDING INSTRUMENTS

IHR

The International Health Regulations represent "An agreed code of conduct adopted by the World Health Assembly in May 2005 to protect against the spread of serious risks to public health and, the unnecessary or excessive use of restrictions in traffic or trade" (21). These regulations are legally binding instruments for all WHO's Members, unless rejection or reservations are formally stated. The IHR aims to ensure a rapid gathering of information, a common understanding of what may constitute a public health emergency of international concern and the availability of international assistance to countries (14). A key element of the IHR is the requirement to notify the WHO if an event is considered to constitute a public health risk to other states through the international spread of disease and potentially require a coordinated international response. Furthermore, the IHR states WHO's responsibility to recommend measures for implementation for each specific emergency (22). The IHR also sets requirements for national core capacities, and member states are obliged to develop capacities to detect, assess, report, notify and respond promptly and effectively to public health events. The implementation of the IHR is a long-term process that calls for states to develop and strengthen specific national public health capacities, identify priority areas for action, develop national IHR implementation plans, and maintain these capacities and continue to build and strengthen as needed over time.

A Monitoring and Evaluation Framework was developed to provide states with a roadmap for assessing their current public health capacities, thus, enabling them to identify areas where improvement is needed, as well as adequate measures that are required for achieving a satisfactory level of capacities for the management of public health risks and emergencies. Although the framework is composed of four processes, the Joint External Evaluation (JEE) is the most apparent. The JEE is a voluntary and comprehensive process aimed at evaluating country's public health capacity across 19 technical areas in a collaborative effort between the country's own experts and the external evaluation team (23). The JEE creates a baseline assessment, enabling countries to have a greater understanding of their gaps and weaknesses in health security as well as to prioritize their efforts for closing those gaps. Although JEE has limitations in accuracy and consistency across the JEE process, JEE provides an informative, and practical assessment of IHR obligations.

BTWC

The Biological and Toxin Weapons Convention (formally known as the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction) was opened for signature on 10 April 1972 and entered into force 3 years later (17). The Convention prohibits to its contracting parties the development, production, stockpiling, or other ways of acquiring or retaining biological and toxin weapons or their means of delivery and requires that states prevent and prohibit the same activities within their territory, under their jurisdiction or anywhere else under their control. However, it does not prohibit peaceful microbiological activities, including the international exchange of microbial or other biological agents, or toxins and equipment for the processing, use or production of biological agents and toxins for prophylactic, protective, or other peaceful purposes.

The convention has been supplemented by the contracting parties through approval of a series of additional agreements and understandings at the Review Conferences. They either interpret, define or elaborate the meaning or scope of a provision of the Convention, or provide instructions, guidelines or recommendations on how a provision should be implemented. One of the interpretations and instructions these agreements have introduced in relation to Articles I–IV that require specific national "transposing" measures, are confidence building measures (CBM). At the Second Review Conference the states parties agreed to implement a number of CBMs in order to prevent or reduce the occurrence of ambiguities, doubts and suspicions, with the aim to improve international co-operation and transparency in the field of peaceful biological activities. Although these measures are not derived directly from the text of the Convention itself, participation in the CBMs is a requirement for all states parties to the Convention.

Another important additional agreement was the establishment of an Implementation Support Unit (ISU) with the mandate to assist the states parties in implementation of the Convention. The ISU provides administrative support and assistance, national implementation support and assistance, administers the database for assistance requests, and offers and facilitates associated exchanges of information. ISU also provides support and assistance for CBMs, and support and assistance for obtaining universality of the Convention. Furthermore, it supports states parties' efforts to implement the decisions and recommendations of the Review Conferences.

UNSCR1540

In 2004 the UN Security Council adopted under Chapter VII of the UN Charter Resolution 1540. By this resolution the UN Security Council obliged all states to refrain from providing any form of support to non-state actors that attempt to develop, acquire, manufacture, possess, transport, transfer or use nuclear, chemical or biological weapons and their means of delivery, and to adopt and enforce appropriate effective laws which prohibit any non-state actor to attempt, engage, participate, assist, or finance the foregoing activities. Under resolution 1540 countries should take and enforce effective measures to establish domestic controls to prevent the proliferation of nuclear, chemical, or biological weapons and their means of delivery. This includes establishing appropriate controls over related materials by means of (1) developing and maintaining appropriate effective measures to account for and secure such items in production, use, storage or transport; (2) developing and maintaining appropriate effective physical protection measures; (3) developing and maintaining appropriate effective border controls and law

enforcement efforts to detect, deter, prevent and combat, including through international cooperation when necessary, the illicit trafficking; (4) establishing, developing, reviewing and maintaining appropriate effective national export and trans-shipment controls over such items, including appropriate laws and regulations to control export, transit, trans-shipment and re-export and controls on providing funds and services.

Through resolution 1540, the UN Security Council called upon all states to present to the 1540 Committee a national report on steps they have taken or intend to take to implement this resolution. In the following years the Security Council adopted several new resolutions under Chapter VII whose aims were among others to restate the obligations stemming from Resolution 1540, urge its full implementation, call for further voluntary measures to be implemented (e.g., development of national action plans) and broaden the mandate of the 1540 Committee. These are Resolutions 1673 (2006), 1810 (2008), 1977 (2011), 2325 (2016), 2572 (2021), and 2622 (2022) (24–29).

REQUIREMENTS FOR COMPLIANCE WITH LEGALLY BINDING INTERNATIONAL INSTRUMENTS

In order to create insight in the actions to take to comply with the internationally-mandated requirements, the obligations stemming from IHR, represented by the JEE, UNSCR1540, and BTWC are compared in detail. In order to make a comparison, obligations stemming from the legally binding instruments were grouped, taking into account different methods.

A combination of the JEE's groups and similar tasks from the other two instruments were used to cluster the obligations into five fields of action: prevention; prohibition and penalties; detection; response; and international cooperation. The JEE's structure was selected as the basis for the comparison tables' (matrices) skeleton for several reasons. First of all, Resolution 1540 and BTWC are not divided in thematic sections. Therefore, one could either choose the only existing thematic division, or design a new one. Instead of inventing the wheel, we choose to use the JEE's structure which is at the same time the most natural grouping of measures for acting upon an emergency—one needs to prepare for it, to try to detect it and if it happens to respond to it. In addition to all this, it should be noted that the Joint External Evaluation Tool for IHR has the most extensive number of requirements (23) with detailed description of the ways and ranges within which these requirements may be implemented. This naturally makes it easier to "subsume" BTWC's and Resolution's requirements under its thematic groups or to align them with specific requirements from the JEE within one table. What was added to the JEE's structure as a direct consequence of the Resolution's and Convention's substance are the clusters on prohibitions and penalties, and on international cooperation; former containing exclusively requirements from the Resolution and Convention, while the latter has also some from the JEE which are originally within JEE's detection and response thematic groups. It was decided to position cluster on prohibitions and penalties immediately after prevention, as proscribing certain activities and setting appropriate civil and criminal penalties for them acts as a deterrent, i.e., can be considered as a preventive measure. Cluster international cooperation is the last one in the matrix as this is considered to be the "add on" to the national efforts. Hence, to compare the three legally binding instruments on these fields of action (clusters), a matrix was created for each field (**Supplementary Tables 1–5**). Each matrix is split into columns that include specific requirements stemming from UNSCR1540, BTWC and JEE. A short section of the matrices is displayed in **Figure 1**.

The matrices also include references to or extracts from non-legally binding international instruments, guidelines or best practices through which a specific requirement from the international legally binding instrument is being or can be implemented. These "implementation examples" include guidance documents and related projects for the implementation of Security Council resolution 1540 (2004) contained in the reports of 1540 Committee for 2008 and 2011 (30, 31), excerpts from the WHO Laboratory biosecurity guidance (32), and provisions of Regulation (EU) No 821/2021 regarding a community export regime of dual-use items (33). The matrices solely contain requirements regarding biosecurity and the wordings of the requirements were simplified. As safety and security aspects are often intertwined, selecting appropriate requirements from the JEE represented a special challenge. Requirements regarding JEE's technical areas zoonotic diseases and food safety were included, as surveillance and response systems for these areas have both safety and security roles.

A comparison of the three legally binding biosecurity instruments demonstrates both differences and similarities. Stemming from the Public Health domain, the International Health Regulations are more extensive than the UNSCR1540 and the BTWC. The IHR contains fields of action that are not represented in the UNSCR1540 and the BTWC. Fields of action that are exclusively stated by the IHR include emergency preparedness and response, risk communication, information sharing, trainings, coordination, communication and advocacy, zoonotic diseases, and food safety. In the fields of action that overlap between the three instruments, IHR is often more extensive than UNSCR1540 and the BTWC.

The differences between the instruments in the field of biosecurity were observed and assuming full implementation of IHR, indicating a maximum score of 5 in all JEE technical areas, it was assessed what else needs to be in place for a country to also comply to UNSCR1540 and BTWC. It can be concluded that in addition to full implementation of the IHR, a comprehensive export control system needs to be in place to also comply to UNSCR1540 and BTWC. Although, it should be noted that the JEE includes some references to export control systems. In JEE's Technical areas 1, 2 and 8 it is indicated in the footnotes that the term "relevant sectors" include, among others, "divisions/activities of other sectors which affect public health, such as ministries of agriculture (quarantine and movement control authority, import/export regulations, disease diagnosis and control financing, zoonosis, veterinary laboratory, etc.) ... trade and/or industry....foreign trade... treasury or finance (customs) …". (23). Additionally, JEE Technical Area

CLUSTER	SPECIFIC REQUIREMENTS			IMPLEMENTATION
	UNSC Res. 1540	BTWC	IHR (2005)	
ACCOUNT AND SECURE[18]	*Para 3, subpara (a) →* *Measures to establish domestic controls to prevent the proliferation of biological weapons and their means of delivery[19]; controls over related materials[20].*	*Article III → Not to transfer, or in any way assist, encourage or induce anyone else to acquire or retain biological weapons.* *Article IV → To take any national measures necessary to implement the provisions of the BTWC domestically*	*JEE Technical Area 6: (Biosafety and) Biosecurity → A whole-of-government multisectoral national (biosafety and) biosecurity system (for all sectors including human, animal and agriculture facilities) with dangerous pathogens[21] identified, held, secured and monitored in a minimal number of facilities according to best practices; biological risk management training and educational outreach conducted to promote a shared culture of responsibility[22], reduce dual-use risks, mitigate biological proliferation and deliberate use threats, and ensure safe transfer of biological agents; and country-specific (biosafety and) biosecurity legislation, laboratory licensing and pathogen control measures in place as appropriate.*	Tools facilitating implementation of this specific requirement stemming from Resolution 1540 mentioned in Annex XVII of the 1540 Committee's Report S/**2008**/493: - The Public health response to biological and chemical weapons: WHO guidance 2004 (especially Annex 5 Precautions against the sabotage of drinking-water, food, and other products); - WHO Laboratory Bio-safety Manual 2004 (includes guidance on laboratory biosecurity and regulations for the transport of infectious substances)[23]; - WHO Preparedness for the Deliberate Use of Biological Agents 2002. - WHO Guidelines for the Surveillance and Control of Anthrax in Humans and Animals, - WHO Guidelines on Tularaemia Tools facilitating implementation of this specific requirement stemming from Resolution 1540 mentioned in Annex XVII of the 1540 Committee's Report S/**2011**/579: - WHO Terrorist threats to food: guidance for establishing and strengthening prevention and response systems

FIGURE 1 | A short section of the matrices with obligations stemming from UNSCR1540, BTWC, and IHR and an implementation example.

6 does include a requirement for a mechanism for biosecurity oversight of dual-use research and responsible code of conduct for scientists. However, this requirement does not include an explicit "cross-border" element. An implementation example of comprehensive export control measures is the Regulation of the European Parliament and of the Council No 2021/821 "Setting up a Union regime for the control of exports, brokering, technical assistance, transit and transfer of dual-use items" (33).

Another difference observed in the comparison of IHR, BTWC, and UNSCR1540 is that, IHR and JEE do not deal with non-proliferation. Hence they do not require from countries to enact (criminal) legislation which prohibits and punishes persons or entities who engage in activities related to biological weapons, whereas BTWC and UNSCR1540 do have this requirement. Although IHR and JEE request timely and accurate disease reporting and information sharing, requirements related to cooperative action between states to prevent illicit trafficking in weapons, their means of delivery, and related materials is missing.

Another requirement not mentioned in IHR and JEE that is included in UNSCR1540 deals with participation in other related non-proliferation instruments and mechanisms. UNSCR1540 calls upon states to promote the universal adoption and full implementation of multilateral non-proliferation treaties (e.g., ratification/accession; participation at meetings; delivering of statements; submission of reports).

ADHERENCE TO AND EFFECTIVENESS OF INTERNATIONAL INSTRUMENTS

Although there are international instruments in place to prevent outbreaks, regardless of their origin, the COVID-19 pandemic has demonstrated that there is insufficient capacity to prevent and control such a major infectious disease outbreak. This raises questions if the IHR are perhaps deficient and could in fact constrain rather than facilitate rapid action (34). However, the Review Committee on the Functioning of the IHR (2005) during the COVID-19 Response found inadequate IHR implementation and adherence by WHO and its member states (35). States have largely failed to implement the required measures (36). The resulting lack of sufficient capacity to prevent and respond to COVID-19 was demonstrated by the 2021 Global Health Security Index report (8). The report found "Although many countries were able to quickly develop capacities to address COVID-19, all countries remain dangerously unprepared for meeting future epidemic and pandemic threats."

Global health security would benefit from increased adherence and effectiveness of international biosecurity instruments. Observing differences between legally binding and non-legally binding instruments, it can be assumed that the quality of being "legally binding" is not directly translatable in instrument's effectiveness. An analogy may be drawn to a study in the field of international climate regime that compared the effectiveness of legally vs. non-legally binding instruments. Although formulating an agreement in legally binding terms may

lead to stronger commitment, a legal character does not always translate to a higher effectiveness than non-legally binding instruments (37). Non-legally binding instruments can offer a flexible and efficient way to make informal arrangements (38). They may be formulated in a manner that is more technical and therefore "legible" for the experts in the field, opposed to the lofty and often general wordings of conventions and treaties.

Indeed, it is usually so, that non-legally binding instruments are quoted as source of "obligations" for the countries; as the effectiveness of an international instrument, measured by number of countries adhering to it, largely depends on its clarity, value it has for building national capacities and, of course, wide political neutrality. While resolutions, conventions and treaties (legally binding instruments), in their effort to set strategic and global goals, employ ambiguous language trying to encompass a variety of national systems, guidelines and similar tools that aim at building national capacities necessary to reach those strategic goals (non-legally binding instruments) are more precise and attune to the situation on the ground. The former ones are adopted in political forums, while latter are endorsed by expert bodies, which adds to their quality and usefulness. Very often, goal oriented technical discussions and their outcomes diffuse and reduce political frictions that exist on the margins of the central topic, allowing the adopted instruments to be adhered to by the widest audience possible. Therefore, clear non-legally binding instruments, such as national capacity building goals in the field of biosecurity and WHO's Laboratory biosecurity guidance (32), are key for adherence to the legally binding biosecurity instruments. Of course, this depiction is a generalization and does not apply to dichotomies of legally binding and non-legally binding instruments in all areas. In addition, international initiatives such as the Global Health Security Agenda (GHSA), Global Biosecurity Dialog (GBD), and Global Partnership Against the Spread of Weapons and Materials of Mass Destruction (GPWMD) play a major role in building biosecurity capacity and employing international legally binding biosecurity instruments (39).

INTERNATIONAL NON-LEGALLY BINDING INSTRUMENTS IN THE FIELD OF BIOSECURITY

Non-legally binding instruments are an important addition to legally binding instruments, as they provide practical tools that will help build national capacities. In addition to the legally binding instruments, IHR, BTWC, and UNSCR1540, there are several international non-legally binding instruments, such as guidelines and voluntary arrangements, in the field of biosecurity. Here the most relevant international non-legally binding instruments are highlighted, as these could support adherence and effectiveness of legally binding instruments. In addition, several guidance documents and assessment tools have been developed by national and international organizations, of which many of them have been collected in repositories freely available online (40–42).

In 2002, WHO member states have adopted resolution WHA55.16 on global public health response to natural occurrence, accidental release or deliberate use of biological and chemical agents or radio-nuclear material that affect health (43). This resolution was endorsed in response to the WHO Secretariat's Report on deliberate use of biological and chemical agents to cause harm (A55/20) (44). The resolution urges member states to ensure they have national disease-surveillance plans, to collaborate internationally, and provide mutual support. Furthermore, it encourages member states to treat any deliberate use of biological and chemical agents and radio-nuclear attack to cause harm also as a global public health threat.

The WHO Guidance document on the public health response to biological and chemical weapons was published in 2004 (45). The Guidance describes how biological and chemical agents may endanger public health as well as standard principles of risk management, which are used to outline the steps that member states may take to prepare themselves for the possibility that biological or chemical agents may be deliberately released with the aim of harming their population. It also considers how both national and international law can contribute to preparedness planning, including through established mechanisms for mobilizing international assistance.

The WHO Biorisk management Laboratory biosecurity guidance followed in 2006 (32). This guidance was developed with the aim to integrate the long-known biosafety practices, as described in the WHO Laboratory Biosafety Manual (46), and laboratory biosecurity concept into a comprehensive biorisk management approach. The basic proposition of the Guidance is that the systematic use of appropriate biosafety principles and practices also reduces the risks of valuable biological materials loss, theft or misuse. It provides practical guidance on implementing biosafety and biosecurity.

In 2007, a CEN Workshop adopted a Laboratory Biorisk Management Standard CWA 15793:2008 (47). The document specifies requirements for a biorisk management system that will enable an organization to develop and implement a biorisk policy, establish objectives and processes to achieve the policy commitments and improve its performance. It follows a risk based approach taking in legal requirements and current knowledge and is intended to apply to all types and sizes of organizations and to accommodate diverse geographical, cultural and social conditions. The document is performance oriented, i.e., it describes what needs to be achieved and it is up to the implementing organization to choose the methods and means. CWA 15793:2008 became the backbone of ISO 35001:2019 Biorisk management for laboratories and other related organizations (48). This ISO standard defines a process for identifying, assessing, controlling and monitoring the risks associated with high-risk biological materials.

In 1985, the Australia Group (AG) was established as a voluntary, export-control arrangement through which its participants coordinate their national export controls of chemicals and biological agents as well as related equipment, technologies, and knowledge (49). The Australia Group currently counts forty-three participating countries. The Group issues the Guidelines for Transfers of Sensitive Chemical or Biological Items as well as the Common Control Lists that serve for identification of items whose transfers require license. For the purpose of facilitating effective export controls on

TABLE 1 | Overview of international instruments in the field of biosecurity.

Instrument	Legal status	Domain	Scope
International Health Regulations	Legally binding	Public Health	To prevent, protect against, control, and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks and that avoid unnecessary interference with international traffic and trade (14)
United Nations Security Council Resolution 1540	Legally binding	Non-proliferation	All states shall refrain from providing any form of support to non-state actors that attempt to develop, acquire, manufacture, possess, transport, transfer or use nuclear, chemical or biological weapons and their means of delivery, in particular for terrorist purposes and shall enforce appropriate legal and regulatory measures against the proliferation of chemical, biological, radiological, and nuclear weapons and their means of delivery (18)
Biological Weapons Convention	Legally binding	Non-proliferation	Prohibits the development, production, acquisition, transfer, stockpiling and use of biological and toxin weapons (17)
World Health Assembly Resolution 55.16	Non-legally binding	Intersection of Public Health and biosecurity	Global public health response to natural occurrence, accidental release or deliberate use of BC agents or RN material (43)
WHO guidance: Public health response to biological and chemical weapons	Non-legally binding	Intersection of Public Health and biosecurity	Outline of steps that member states may take to prepare themselves for the possibility that biological or chemical agents may be deliberately released with the aim of harming their population (45)
WHO Biorisk management—Laboratory biosecurity guidance	Non-legally binding	Intersection of Public Health and biosecurity	Provides practical guidance on implementing biosafety and biosecurity and integrates the long-known biosafety practices and laboratory biosecurity concept into a comprehensive biorisk management approach (32)
ISO 35001:2019 Biorisk management for laboratories and other related organizations	Non-legally binding	Intersection of Public Health and biosecurity	This document defines a process to identify, assess, control, and monitor the risks associated with hazardous biological materials. This document is applicable to any laboratory or other organization that works with, stores, transports, and/or disposes of hazardous biological materials (48)
Australia group guidelines and lists	Non-legally binding	Non-proliferation	Voluntary, export-control arrangement through which its participants coordinate their national export controls of chemicals and biological agents as well as related equipment, technologies, and knowledge (49)
Wassenaar Arrangement	Non-legally binding	Non-proliferation	Voluntary export control for Conventional Arms and Dual-Use Goods and Technologies regime whose members exchange information on transfers of conventional weapons and dual-use goods and technologies, contributing to regional and international security and stability (51)

Australia Group listed items the United States Government produced the Australia Group Common Control List Handbook (50).

Where the Australia Group is focused on export controls of chemicals and biological agents, the Wassenaar Arrangement on Export Controls for Conventional Arms and Dual-Use Goods and Technologies, has a broader scope (51). The arrangement, formally established in 1996, is a voluntary export control regime whose members exchange information on transfers of conventional weapons and dual-use goods and technologies and currently counts 42 participating states. Among these states are 26 EU Member States, Argentina, Australia, RF, Mexico, South Africa, Turkey, Ukraine, UK, and US. It has been launched with the aim to contribute to regional and international security and stability, by promoting transparency and greater responsibility in transfers of controlled items, thus preventing destabilizing accumulations. Members apply export controls to all items set forth in the List of Dual-Use Goods and Technologies and the Munitions List (52), with the objective of preventing unauthorized transfers or re-transfers of those items.

An overview of all of the described international instruments in the field of biosecurity is presented in **Table 1**.

ACTIONABLE RECOMMENDATIONS

The first step for a country to reach a sustainable level of global health security and to adhere to international legally binding instruments in the field of biosecurity is full implementation of the IHR, as the IHR has the most extensive requirements, in sense of their number as well as scope. Both traits are especially pronounced when the requirements are considered in their "elaborated form" contained in the Joint External Evaluation tool. The implementation of the IHR can be greatly supported by non-legally binding instruments such as WHO Laboratory Biosafety Manual (46) and WHO Biorisk management Laboratory biosecurity guidance (32), providing clear and practical guidance, as well as several other non-legally binding instruments freely available in online repositories (40–42). An example of guidance documents proving to be beneficial to adherence to legally binding biosecurity instruments, is the guidance for stepwise implementation of a National Inventory of Dangerous Pathogens (53). Using this guidance, the government of Uganda successfully implemented a National Inventory of Dangerous Pathogens, which has been recognized by the WHO JEE as contributing to Uganda's developed capacities regarding biosafety and biosecurity (54).

In addition to full implementation of the IHR, countries should implement a comprehensive export control system in order to also comply with UNSCR1540 and BTWC. In this field, countries could make use of best practices from the European Union embodied in its Regulation of the European Parliament and of the Council No 2021/821 "Setting up a Union regime for the control of exports, brokering, technical assistance, transit and transfer of dual-use items" (33) or the World Customs Organization (WCO) Framework of Standards to Secure and Facilitate Global Trade (the WCO SAFE Framework of Standards) (55). States can also benefit from the voluntary, export-control arrangements such as Australia Group and Wassenaar Arrangement, as their tools include a detailed handbook and export control lists. It is recommended for countries to use these precise and hands-on tools to implement a comprehensive export control system and comply with international requirements. Apart from them, further implementation examples are provided in the **Supplementary Material**.

In addition to a comprehensive export control system, states should enact (criminal) legislation which prohibits and punishes persons or entities who engage in activities related to biological weapons. This legislation should include aspiration of cooperative action between states to prevent illicit trafficking in weapons, their means of delivery, and related materials. National implementation plans and national reports of other countries for UNSCR1540 and BTWC may provide guidance to other countries aiming to implement appropriate legislation.

Furthermore, states should promote the universal adoption and full implementation of multilateral non-proliferation treaties and so achieve their full compliance with international biosecurity legally binding instruments. This can be done by ratification or accession to the treaties, but also by participation in treaty meetings, delivering of statements and submission of country reports. Reports of the 1540 Committee contain shared experiences and related projects for the implementation of UNSCR1540, which cover also this area of implementation.

Lastly, the detailed comparison between the three legally binding international biosecurity instruments demonstrates that the obligations deriving from these instruments have a lot in common, despite the different scopes and domains of these instruments; preparedness and response to natural or accidental outbreaks of infectious diseases vs. a deliberate release with the intension to cause harm. Both domains contain stakeholders in the field of biosecurity, but the domains operate rather independently. As described by Evans et al. global health security could benefit from experimentation in biosecurity governance (56) and biosecurity governance should aim for more connection between the stakeholders concerned.

DISCUSSION AND CONCLUSION

As demonstrated by the COVID-19 pandemic, the spread of dangerous pathogens represents a serious global health security threat. International instruments from different disciplines address these health and security challenges, setting requirements for states to effectively prevent, detect, and respond to infectious disease outbreaks, either with deliberate or non-deliberate origin. From the detailed comparison between legally binding international biosecurity instruments, it can be concluded that in addition to full implementation of the International Health Regulations, specific export control and non-proliferation measures are necessary to comply with the obligations stemming from other legally-binding international biosecurity instruments. These other instruments also request participation in other related non-proliferation instruments and mechanisms. Adherence to and effectiveness of legally binding biosecurity instruments can be enhanced by clear non-legally binding instruments providing precise guidance and practical implementation examples. These insights highlight the increasing importance of global health diplomacy. Moreover, this paper could facilitate policymakers, civil servants, biosecurity experts, and practitioners to improve both national and international multidisciplinary capacity to protect and defend against biological threats, whether due to natural, accidental, or deliberate causes.

AUTHOR CONTRIBUTIONS

IV, MB, DB, and SR contributed to providing an overview and comparison of international biosecurity instruments and reviewed the document. IV wrote and revised the document. MB wrote the **Supplementary Material** and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.894389/full#supplementary-material

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Biosafety: From a traditional approach to an integrated approach

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Introduction

Organizational safety support covering all health and safety policies could provide antidotes to the physical and psychological problem experienced by employees (1). Biosafety is an important issue globally, as a line of defense that protects health personnel, the public and the environment from exposure to hazardous agents. Biosafety refers to the protection, control and accountability measures implemented to prevent the loss, theft, misuse, diversion or intentional release of biological agents, toxins and related resources as well as unauthorized access to, retention or transfer of such material (2). Most developing countries have weak health systems and consequently weak biosafety (3). Even today, there is great uncertainty among practitioners about the correct containment measures when using growth chambers for processed plants. Genetically modified microorganisms (GMMs) are used as vectors for sequences or entire genes, with the aim of silencing endogenous genes, or introducing genes modified to express proteins with characteristics designed by the researcher. Genetic engineering is used to produce vaccines, antibiotics, therapeutic antibodies, resistant or more productive plants or for the development of gene therapies, the treatment of neurological diseases or acquired genetic dysfunctions such as Alzheimer's disease, dystonia, diabetes, multiple sclerosis or arthritis (4–6). The extreme accessibility of GMMs and the latency period (sometimes years) with which some undesirable effects can emerge creates the uncertainty that their use occurs without a thorough awareness of the potential risks associated. In high-risk laboratories unsafe behavior among workers appears to be a critical factor in workplace accidents (7). Unsafe behavior can be motivated by internal and external factors, among which risk perception is a key internal one (8). Research has demonstrated the influence of risk perception on different kinds of safety behavior and involvement in safety management (9). Risk means "uncertainty about and severity of the consequences (or outcomes) of an activity with respect to something that humans value" (10). As risk perception is subjective and depends on a set of values, concerns, or knowledge (11), when workers perceive risk, they are likely to adopt different ways to judge risk. The rational risk perception meaning that workers tend to perceive risk through three rational risk formulations: the probability of risk occurrence, the severity of risk impact, and the

expected utility of risk (12). These perceptions or judgment serve as a basis for everyday decision making (13), and are also likely to influence decision making on safety behavior.

The perception of risk

The perception of risk is personal. In fact, people decide to face or avoid the risk situation in a subjective way (14). Each activity is based on the perception of risk and its more or less conscious evaluation. Moreover, the perceptual process of risk is strongly influenced and conditioned by the emotions generated when discovering and learning about a new danger and what possible harm it can bring. Contrary to what many believe, for humans, risk perception is scarcely dependent on rational factors, such as the use of probability and logic, but on the contrary, it is strongly determined by emotions (15). The personal perception of risk is influenced by habits and previous experience, is based on personal experience or that of others, varies in relation to the collective acceptability of risk which changes over time, places, work groups, cultures and with respect to personal and cultural values, age and gender. It is also influenced by knowledge of hazards, thus the feeling of immunity by those familiar with a given situation, the immediacy of harm, freedom in risk taking, the concentration of harm over time, the harmfulness of the hazards present and their frequency, personal exposure and subjective cost/benefit assessment (12).

Risk propensity increases if events are perceived to be controllable by the subject, so there is a perceived degree of modifiability in actions. Individual type variables such as attitudes toward safety and social type variables such as peer support can influence the likelihood of risk events occurring.

Risk is processed in the mind in two ways:

- Analytical: logical processing of information, based on theoretical knowledge.
- Experiential: automatic, made up of reactions due to the stimulus (through direct or indirect experience) and the emotion it arouses. Experience determines people's 'perception' of things and the beliefs they hold. These beliefs determine the way they act and the results they achieve.

Psychologists and Sociologists emphasize that risk perception can be irrational and influenced by diverse factors, such as characteristics of risk (16), personal variables (17, 18), as well as cultural and socioeconomic background (19, 20).

Risk assessment

A Traditional Approach to risk assessment (as shown in Table 1) considers exclusively technical and legislative knowledge to give a definition of risk for each workplace context (21–23). This approach is linked to reference theories to treat risk as a specific factor to be analyzed and managed alone (24) with the main objective to create standardized approaches and models for understanding, assessing, and communicating risk (25). This kind of risk management models and guidelines used exclusively self-report methodologies for analysis and do not take into account soft skills and transversal competences. Traditional risk management models, often are not strongly related with a high level of biosafety, because they do not take into account the organizational context and the decision-making processes of the employee.

An Integrated Approach (see Table 1) adds more factors of psychological interest to the traditional studies of risk assessment, which may contribute to correct some errors impacting on risk assessment in a biological laboratory (26). In fact, it takes into account: risk linked personality traits (27); emotional styles (28); empathy and team work capacity (29); cognitive errors and biases (30, 31); cognitive overload and monotonous routine (32); organizational risk communication (33); work-related stress (34); protective and preventive factors (35). They must necessarily be considered as a fundamental part of the risk assessment studies and not set aside as mere secondary variables of risk reference models. All these factors combine to create the need not only to enforce existing regulations and procedures, but also to create best practices to manage the new biosafety challenges in public research and hospitals.

TABLE 1 Traditional biosafety risk assessment and integrated biosafety risk assessment.

Approach	Methods	Main characteristics	Outcome of the approach
Traditional biosafety risk assessment	Technical and legislative information	Neglect worker and organizational factors	Product guidelines and reference models
Integrated biosafety risk assessment	Technical, legislative and organizational climate information	Add worker and organizational factors	Product guidelines, reference models, tangible best practices in safety climate and safety performance

To sum up looking at the table, it is possible see the added value that the Integrated Approach brings to the study of risk assessment. In fact, the Traditional Approach only considers technical and legislative knowledge in the field of biosafety, leaving out the organizational and psychological factors associated with the worker. On the other hand, the added value brought by the use of an Integrated Approach to risk assessment in achieving the outcome is to take into account aspects related to the work organization and the worker himself. Increase the level of safety climate and safety organizational culture could be effective in reducing incidents and improving safety performance indicators (36). The human and organizational factor is essential for the implementation of actions and policies based on the psychophysical wellbeing of the individual and thus on improving performance, organizational wellbeing and safe behavior (37, 38).

Discussion

The current laboratory safety guidelines published in "Biosafety in Microbiological and Biomedical Laboratories," 5th ed. (BMBL) (39) for effective biosafety management are derived from significant research has been conducted to understand the physical and psychosocial factors in the workplace that influence behavior, especially job roles, behavioral modeling and feedback, policy enforcement, availability and social support. Once again it is necessary to reiterate the importance of approaching the study of biosafety not only from the traditional - and fundamental - systematic and legislative approach, but it is also essential to investigate those predisposing and preventive factors linked to the cognitive and emotional aspect of workers and work organizations using an Integrated Approach.

Improvements come after significant research conducted to understand the physical and psychosocial factors in the workplace that influence the safe behavior. The effect of general organizational climate on safety performance was mediated by safety climate, while the effect of safety climate on safety performance was partially mediated by safety knowledge and motivation (38).

Risk assessment in biology is a process designed to estimate the risks to human health and the environment to prevent the release of biological agents and toxins. Biotechnology and Biosafety are a heavily discussed issues in almost every country, where opinions of the different parties vary considerably and sometimes are quite different. If you want your organization to change the paradigm of security analysis and prevention, you need to create new experiences and give them new meanings (40). You need to show new ways of working and use new models of thinking to help people develop new tools and keys to safety interpretation (41). To develop motivational and training paths that take into account the perceived risk in a biological laboratory with the aim of making users capable and motivated to manage risk.

Traditional risk assessments should be integrated with organizational and social considerations in order to design and implement risk management strategies able to prevent, reduce or eliminate such risk (42).

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A modified hand washing method for resource limited settings

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The Good Microbiological Practices & Procedures (GMPP) is the most significant risk control measure as per the fourth edition of the WHO laboratory biosafety manual. Among GMPP, one of the best practices is hand washing. WHO and other public health agencies have published several guidance documents on hand washing, that describe closing the tap using a disposable paper towel/tissue paper at the end of hand washing as one of the critical steps. In resource-limited settings, where disposable paper towels cannot be provided at all times, the staff is left with ambiguous instructions on how to close the tap. In this paper, a modified hand washing method is documented that doesn't necessitate the use of disposable paper towels. In this method, both hands and faucets remain in contact with soap for at least 40–60 s. The method was validated by the use of Glo Germ. A survey questionnaire was also designed and conducted for the lab staff ($n = 12$) of the two laboratories, where this method was implemented, to assess whether this hand washing method brought any improvement in their hand washing practices and implementation. All (100%) of the survey respondents reported that this method of hand washing is more applicable and implementable than the WHO-recommended hand washing technique. Eighty three percentage reported that this modified method of hand washing raised their hand washing compliance. The authors suggest that this hand washing method can be used in resource-limited laboratory settings as an effective GMPP to ensure infection control.

KEYWORDS

handwashing, laboratory, resource-limited settings, implementation, compliance

Introduction

Biosafety practices in laboratories are based on the principle of containing biological agents to reduce the risk of laboratory-acquired infections (LAIs) by preventing exposure of laboratory personnel and the outside environment (1). The fourth edition of the WHO laboratory biosafety manual prescribes core requirements that must be implemented in all laboratories regardless of the level of work that is being done in that lab. These core requirements can effectively control risks encountered in the majority of clinical and diagnostic laboratory activities (2). Activities that may pose a higher risk and cannot be mitigated by the core requirements, should be assessed using a risk assessment

framework. Once risk is assessed, relevant, and sustainable risk control measures that are commensurate with the risks should be implemented (2). The Good Microbiological Practices & Procedures (GMPP) is the most significant risk control measure to be incorporated into the core requirements. GMPP refers to a set of standard operating procedures and practices, often written in a code of practice, that applies to all forms of biological agent activity. Among GMPP, one of the best practices to be followed by all laboratory staff is hand hygiene (2). Hand hygiene is a simple and inexpensive practice to avoid LAIs. There is sufficient evidence to prove that hand hygiene alone, when properly implemented, can significantly decrease the risk of LAIs in laboratories (3). Public health agencies are, therefore, emphasizing the importance of improving hand hygiene keeping in view the increasing severity of infections, and the emergence of multi-drug resistant (MDR) pathogens (3). Handwashing is a cost-effective component of hand hygiene. A handwashing sink, which is an engineering control, is also one of the core requirements for a laboratory (2).

The World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention (US CDC), have produced several resources, including posters (4) and videos[1] that explain why, when, and how hands should be washed in a laboratory or hospital setting. These training materials break down the process of hand washing into 9 to 11 steps that can be completed with a hand/elbow-operated tap. In this method, closing the tap with a disposable paper towel/tissue paper at the end of handwashing is one of the critical steps. Hand washing sinks are either manual (hand/elbow-operated taps) or automated. Automated hand washing is an expensive option that is not feasible in most facilities because of its electricity requirements and sophisticated design. Manual hand washing is the only option left, which necessitates the use of tissue paper or paper towels, which adds to the cost of handwashing (5).

The majority of laboratories in resource-constrained countries like Pakistan have hand-operated taps. A few new laboratories are using elbow-operated taps, but closing elbow-operated taps while wearing street clothes or exposing bare elbow to the tap after removing PPE and before leaving the lab exposes street clothes/skin to contamination from the dirty faucet, which laboratory workers can bring home or outside the lab. Sinks with foot pedals are also not a viable option in all Pakistani laboratories because they are 10 times more expensive, take up more space in the lab, require specific design fits, and need changing and reinstalling water piping systems (6). The design is only suitable for new constructions and cannot be applied to existing systems without modifying the tap and/or the connections, which are frequently located inside the walls. Some designs necessitate altering the basin or its pillar (6). The majority of the labs, particularly those in the public sector, cannot afford to provide paper towels to their employees regularly. When paper towels aren't available, staff are left with ambiguous instructions on how to close the tap. This is a critical gap that we have addressed in Pakistan in two national antimicrobial resistance (AMR) reference laboratories. This paper aims to explain how this was addressed so that the global community can benefit from it.

The Fleming Fund is helping low- and middle-income countries in tackling AMR through its country grants (7). Health Security Partners (HSP) is part of a consortium that is supporting the Fleming Fund in Pakistan. As one of the project's first steps, two BSL-2 veterinary sector laboratories were identified as AMR reference laboratories. One of the objectives that the Fleming fund tried to accomplish in this grant was to develop and strengthen their biorisk management system using the new WHO risk assessment-based approach (2) following the biosafety program management monograph (8). In this monograph, step 3 in the biosafety program management cycle (8) is implementation through the development and communication of standard operating procedures for the safe work practices in these laboratories. Handwashing is the most critical and effective practice in biosafety and biosecurity. Therefore, to accommodate the unavailability of disposable paper towels, biosafety experts implemented a modified way of handwashing for the lab professionals working in these laboratories. We believe that this method can be employed in all research and diagnostic laboratories that deal with biological agents in a variety of fields.

Materials and methods

Due to the use of regular hand-operated taps and the unavailability of disposable paper towels in all sections of these laboratories, a modified method of handwashing was implemented by biosafety experts who were helping the two veterinary laboratories, designated as the AMR reference laboratories, in the implementation of a biosafety program. This experimental study only included the laboratory workers from the two veterinary sector AMR reference labs that implemented this modified handwashing method. In this method the following steps were initiated (Figure 1).

1. Open the tap
2. Wet hands with water
3. Apply enough soap on hand and rub hands palm to palm to make enough foam
4. Close the tap using the foamed hand evenly applying the foam all over the tap handle/faucet
5. Rub the area of the hand by placing right palm over left dorsum with interlaced fingers and vice versa
6. Rub hands palm to palm with fingers interlaced
7. Rub back of fingers with opposing palms with fingers interlocked

1 https://youtu.be/LWmok9avzr4

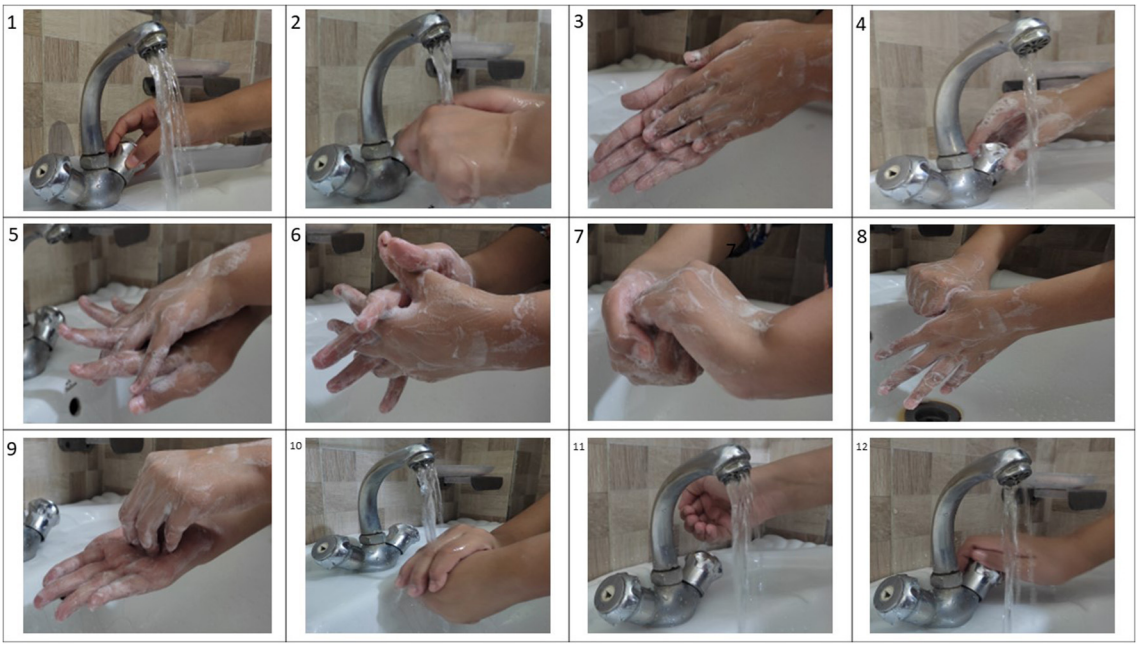

FIGURE 1
The steps for the modified hand washing method: 1. open tap, 2. wet hands with water, 3. apply enough soap on hand and rub hands palm to palm to make enough foam, 4. close the tap using the foamed hand evenly applying the foam all over the tap handle/faucet, 5. rub the area of the hand by placing right palm over left dorsum with interlaced fingers and vice versa, 6. rub hands palm to palm with fingers interlaced, 7. rub back of fingers with opposing palms with fingers interlocked, 8. perform rotational rubbing of left thumb clasped in right palm and vice versa, 9. perform rotational rubbing, backward and forward with clasped fingers of the right hand in left palm and vice versa, 10. open the tap and rinse hands with water, 11. rinse the faucet with enough water to remove any foam on the faucet, 12. now close the tap with clean hands.

8. Perform rotational rubbing of left thumb clasped in right palm and vice versa
9. Perform rotational rubbing, backward and forward with clasped fingers of the right hand in the left palm and vice versa
10. Open the tap and rinse hands with water
11. Rinse the faucet with enough water to remove any foam on the faucet
12. Now close the tap with clean hands

In this method, both hands and faucets should be in contact with soap for at least 40–60 s.

The method was validated by the use of Glo Germ (Glo Germ^{TM}, USA). Glo Germ is a visual tool for teaching proper handwashing and aseptic techniques. In this method, a nickel-sized amount of GloGerm gel was placed in the palm of one hand and applied to both hands completely especially under the nails, around the cuticles and between the fingers before starting the handwashing procedure. The hands were washed using the modified method mentioned above with plain soap and water for 40–60 s and the presence of Glo Germ was observed on the faucet and hands by placing hands under the UV light in a darkened room. A glow under the UV light was considered the presence of contamination.

A self-administered survey questionnaire consisting of one open and seven closed-ended questions (Supplementary Data File) was designed and conducted for the lab staff ($n = 12$) of these two laboratories to assess this handwashing method and determine whether it brought any improvement in their handwashing practices or implementation. The data were analyzed using SPSS v26 and frequencies and percentages were calculated for the survey responses.

Results

The modified method of handwashing enabled laboratory workers to wash hands with hand/elbow-operated taps without the use of disposable paper towels or tissue papers. With the use of Glo Germ on the hands and faucet, no glow was observed on the faucet or hands at the end of this hand washing method (Figure 2).

Six of the 12 laboratory staff members, surveyed from the two target laboratories, responded. The survey reported that 67% ($n = 4$) of the laboratory professionals working in these laboratories wash their hands 6–10 times daily. The remaining 33% ($n = 2$) wash their hands 1–5 times daily. All (100%)

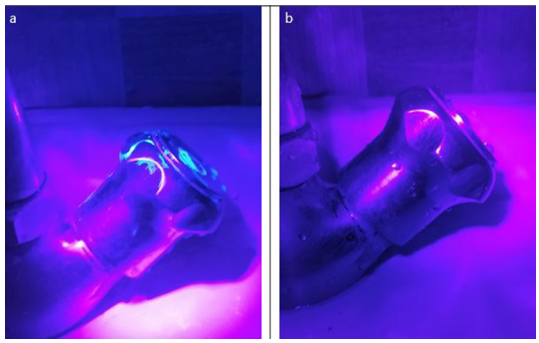

FIGURE 2
(a) Tap is contaminated during step one as visualized by Glo Germ; **(b)** Tap is clean (with no Glo Germ) at the end of the modified hand washing method.

of the survey respondents reported that this method of hand washing is more applicable and implementable in their setting than the WHO handwashing technique that required the use of disposable tissue papers/paper towels. This method enhanced handwashing compliance in their labs, according to 83% (n = 5) of laboratory workers. When asked how they used to wash their hands in case of the unavailability of paper towels or tissue papers before the adoption of this method, one person stated that they used to close the faucet with their hands after hand washing and then disinfect hands to remove any germs that remained. Other respondents provided ambiguous responses, stating that they preferred to use hand sanitizers and only washed their hands when required. Eighty three percentage reported that this modified method of handwashing raised handwashing compliance. Eighty three percentage of the lab professionals reported that in their opinion this method adequately disinfects the faucet and the hands of the lab workers.

Discussion

Laboratory-acquired infections can occur due to varying and suboptimal biosafety practices, and a lack of clear guidance and standard operating procedures (SOPs) (9). Direct contact through contaminated hands is an important mode of transmission of pathogens in laboratories and healthcare settings. Several studies have identified suboptimal hand hygiene as one of the several issues that might have facilitated the occurrence and spread of outbreaks in healthcare facilities (10, 11). Therefore, hand hygiene is considered one of the most significant risk control measures in biosafety. A lot of work has been done to promote hand hygiene across the globe but the global prevalence of washing hands with soap remains at 19%, and the African region's prevalence is even lower at 14% (12). Several studies in Asia including Pakistan reported a baseline hand hygiene compliance between 15 and 66% (13–17). Besides limited awareness of the importance of handwashing and a lack of a culture of biosafety, one important reason could be the lack of sufficient guidance to wash hands in resource-limited settings. No clear guidance is available from USCDC and WHO on how to wash hands when people don't have tissue papers or paper towels in resource-limited settings. A study conducted in Pakistan in 2012 (18) reported that a reusable cloth towel was being used for drying hands after hand washing in several public sector hospitals indicated the unavailability of disposable paper towels and raised questions about how these healthcare workers closed taps after rinsing hands with water to remove foam at the end of handwashing as proposed in the WHO handwashing method. 92.4% of the hospital staff reportedly used the same reusable cloth towel available in a relevant facility despite their dirty condition (86.5%). In this paper, we tried to cover this gap by documenting and implementing a modified handwashing method in which the use of paper towels and towels can be avoided to close the tap at the end of hand washing in two BSL-2 veterinary sector AMR reference laboratories. This doesn't only reduce the cost associated with handwashing but also reduces tissue paper usage making this method eco-friendly by reserving more trees (19). In this method, hands can be air-dried or wiped down with a clean reusable towel after hand washing. The results of this study showed promising outcomes. In this method, soap that is regularly used in laboratories is applied to the faucet for the same amount of time as it takes to wash hands. The use of soap and water for 40–60 min was reportedly enough to remove the majority of the germs that are handled in low-risk laboratories (20, 21). A liquid/solid soap contains chemical agents that have both hydrophilic and hydrophobic properties. One end of these molecules attaches to water while the other end attaches to dirt which is where the bacteria will be. The flow of water at the end of handwashing helps to remove germs from the skin (22) and the faucet. This handwashing method removed the need to apply sanitizer after washing hands, as practiced by some of the survey respondents, to remove any residual germs that can stick to hands by touching dirty faucets and the need for disposable paper towels that is not possible at all times in all resource-limited countries around the world. Hand sanitizers were preferred by the lab workers in these labs, although they are not a cost-effective alternative to hand washing. The preferred use of sanitizers not only reduced handwashing compliance but also increased the laboratory's fiscal burden. The high-risk laboratories may necessitate the use of disposable paper towels and antimicrobial soap as one of the enhanced requirements (23) after a thorough risk assessment in resource-limited settings. The authors believe that this new handwashing method may be in practice informally but has never been documented before. This paper attempted to formally document this method. However, more research is needed to confirm the effectiveness of this hand washing method by increasing

the sample size of the study participants and comparing different settings/labs.

Conclusions

The modified method of handwashing proposed in this paper can improve handwashing compliance in resource-limited settings, where disposable tissue papers are not available. This handwashing method should be validated for practice in resource-limited settings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical Review Committee, University of Haripur, Haripur, KP. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS: conceptualization, writing—original draft preparation, formal analysis, and project administration. JM: writing—review and editing and methodology. FS: investigation and writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.965853/full#supplementary-material

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Effectiveness of international virtual training on biorisk management in the context of COVID-19

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Introduction: The COVID-19 pandemic has resulted in enormous increases in laboratory activities to keep pace with diagnostic testing and research efforts. However, traditional training, technical assistance, and capacity-building approaches were disrupted by the travel and movement restrictions put in place to control the spread of the disease. To address the needs of laboratorians and managers to conduct laboratory activities safely and securely during the pandemic, a highly interactive virtual training (IVT) workshop on biorisk management during COVID-19 was conducted through active learning strategies that connected speakers with participants. The objective of the training was to increase the basic knowledge and standards of biosafety and biosecurity practices, risk assessment, and control measures with reference specifically to the context of the COVID-19 pandemic and apply a rigorous evaluation methodology to assess the effectiveness of the IVT. The training covered a broad range of topics and encompassed national to international guidelines.

Methods: Participants were selected through official channels at the national level, focusing on institutions within Pakistan. The sessions included lectures from international experts in biorisk management concepts, and incorporated poll questions as well as pre- and post-tests and feedback on the speakers' knowledge and presentation skills, to increase interactivity. The pre- and post-test comprised similar multiple-choice questions and provided to every participant to ascertain the impact of the training on awareness and knowledge of biorisk management topics and concepts, and results were compared using paired *t*-tests. For feedback on the speakers, participants were asked to submit their ratings measured on a five-point Likert scale. The reliability of the Likert scale was estimated using Cronbach's alpha. Analyses were performed using Microsoft Excel and SPSS version 23.

Results: In total, 52 individuals from different laboratories across Pakistan and Pakistani students from abroad (China) as well participated in at least one session of the IVT. The participants' pre- and post-test scores showed a significant increase in knowledge and awareness ($p < 0.001$). The obtained Cronbach's alpha score was >0.8, indicating high reliability of the generated feedback on the IVT approach and speakers.

Conclusion: The IVT on biosafety and biosecurity in the context of the COVID-19 pandemic proved beneficial for laboratory professionals and could be a useful model to continue in the future for raising awareness and knowledge.

KEYWORDS

biorisk management, International Virtual Training (IVT), COVID-19, GHSA, biosecurity

Introduction

Since ancient times, infectious disease has been a known threat to mankind. Due to the re-emergence of novel infectious diseases, countries all over the world have continued to investigate infectious diseases in laboratory settings. The safe running of biomedical laboratories has an impact on public safety and security in addition to the lives and health of the experimental team working in the facility (1, 2). To minimize risks and provide a safe work environment, biorisk assessment is a critical tool for the evaluation of infectious pathogens in the laboratory (3).

The Global Health Security Agenda (GHSA) is a collaboration between 100 countries including international organizations, and non-governmental bodies to achieve the goal of a future free of infectious disease-related global health risks (4). The pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS CoV-2) serves as a reminder of the importance of the threats and gaps to prevent, detect, and respond in time throughout the world (5). Despite significant regulations and stringent containment measures, countries continue to face health security threats posed by infectious diseases, whether unintentional, deliberate, or natural.

Biological materials are handled worldwide in laboratories for numerous genuine, justifiable, and legitimate purposes, where small and large volumes of live microorganisms are replicated, where cellular components are extracted, and many other manipulations were undertaken for purposes ranging from educational, scientific, medicinal, and health-related to mass commercial and/or industrial production. Among them, an unknown number of these biomedical facilities, large and small, work with dangerous pathogens or their products every day (6). However, despite advances in technology, the availability of more sophisticated instruments for laboratory use, and the availability of personal protective equipment, human error remains one of the most inherent factors at the origin of accidents (7). Inadvertent exposures to infectious agents in the laboratory, and associated laboratory-acquired infections, are more common in low and middle-income countries (8, 9). According to the WHO, dual-use research of concern (DURC) constitutes research that may be legitimately conducted for biomedical or other benefits, but which might also be misapplied to do harm. Recent studies have led to renewed attention to DURC, as well as a corresponding ongoing debate over the importance of Gain of Function (GoF) experiments (10). GoF experiments are those in which pathogens are manipulated in ways that result in an increase in the pathogen's transmissibility or pathogenicity, or ability to resist known countermeasures. Studies involving GoF may be scientifically useful, for example, to expand knowledge of pathogen evolution, and to assist in surveillance efforts for emerging diseases. However, it can also be catastrophic if the laboratories fail or if new knowledge is used to develop biological weapons (9).

During the COVID-19 epidemic in Pakistan, the healthcare system was overwhelmed. It was not easy to maintain and follow strict laboratory biosafety guidelines (10). It was very important to find ways to train laboratory workers without exposing them to the virus (11, 12). Laboratory biorisk assessment is the backbone of biorisk management according to the Laboratory biosafety manual, 4th edition, and is the basis for implementing effective mitigation strategies (13). During the pandemic, laboratory workers have encountered challenges, ambiguities, and, in some cases, controversies as they endeavored to enhance testing capabilities while maintaining the quality of laboratory operations (14, 15).

In early 2020, the COVID-19 pandemic resulted in restrictions on many types of in-person gatherings, including training. This led to a rapid rise in training courses and seminars that were instead delivered virtually, with the added benefit that these sessions could then be much more globally accessible (16, 17). The objective of the training was to help laboratory personnel including private and public laboratories in Pakistan to improve their skills in biorisk management in the context of the ongoing COVID-19 pandemic. A highly interactive virtual workshop on biorisk management was conducted through active learning strategies that connected speakers with participants. The impact of the training was thoroughly evaluated by developing poll questions, pre-/post assessments, and feedback surveys.

Materials and methods

An International Virtual Training on Biorisk Management (Biosafety & Biosecurity) for life sciences and healthcare laboratory professionals in the light of the COVID-19 pandemic

was developed. The virtual nature of the training took into account the restrictions related to in-person training and avoiding direct physical contact, while the content focused on the need for training in biorisk management in laboratories supporting SARS-CoV-2 diagnostics. This need was addressed by designing and developing a webinar series, which was conducted between 5 and 13 of April 2021. In total, there were seven sessions, every 3 h in duration. The program consisted of 16 speakers of international and national fame in Biorisk Management who delivered and contributed the same content on the following: (1) Introduction to National Biosafety and Biosecurity Policy - Classification of Biosafety Cabinets and Introduction to NS1/ANSI 49 Standards; (2) Advice on the use of masks in the context of COVID-19; (3) COVID-19 and Interim Biosafety Guidelines for Laboratory Workers; 4) Risk Assessment (gather information, evaluate the risks, and develop a risk mitigation strategy, control measures, and risk communication); (5) Diagnostic Testing for COVID- 19; (6) System Thinking Approaches (STA); (7) PPE Selection and Use including shipment and transportation of infectious agents in the epoch of COVID-19 according to CDC guidelines; (8) Occupational Health and Safety during pandemic and how to manage stress, and psychological effects of COVID-19 on lab staff; (9) Importance of Institutional oversight of research in the era of COVID-19; (10) Working in enhanced BSL-2 and BSL-3 with SARS-CoV-2; (11) Sanitation of facilities potentially contaminated with SARS-CoV-2; (12) Disinfection, Decontamination, Sterilization in the wake of COVID−19 for laboratory workers; (13) Surveillance, Reporting and referral of Specimens SARS-CoV-2; (14) Challenges of biosecurity and its importance in the recent pandemic; (15) Biological waste management in the context of COVID-19; (16) Biological waste management in the light of COVID-19; (17) Emergency preparedness in COVID−19. To evaluate laboratory biosafety and biosecurity knowledge in Pakistan the risk assessment was done, and topics were selected in the light of the current situation of the COVID-19 pandemic to prevent laboratory-acquired infections when incidents of COVID-19 were rising in Pakistan.

TABLE 1 Participants' sociodemographic information.

Variables	*n*	Percentage (%)
Gender		
Male	30	57.69%
Female	22	42.31%
Participants' Institute Jurisdiction		
From Balochistan	1	1.92%
From Baltistan	3	5.77%
From KPK	8	15.38%
From Punjab	13	25.00%
From Sindh	25	48.08%
From Overseas (China)	2	3.85%

The participants were selected through proper advertisement using social media platforms and organizational emails. Evaluation of the interactive virtual training (IVT) included the use of poll questions pre- and post-assessment tests before and after the training, consisting of multiple-choice questions administered to the participants, and feedback from the participants, measured using a Likert scale, regarding the speakers' knowledge and presentation skills as well as their impressions of the training overall. The comparison among different variables was analyzed through appropriate tables, graphs, and percentages. Pre- and post-test scores were compared

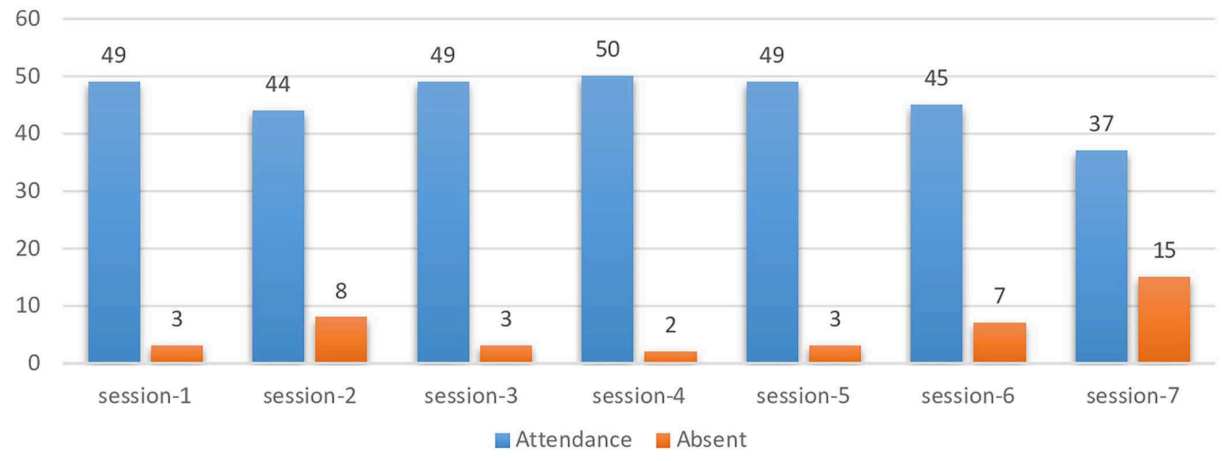

FIGURE 1
Participant's attendance in session.

TABLE 2 Pre-test and post-test score evaluation.

A

Paired samples statistics			
	Mean	***N***	**Std. deviation**
Pre_Test_Score	18.69	36	0.560
Post_Test_Score	24.00	36	0.676
Paired samples correlations			
	N	**Correlation**	**Sig.**
Pre_Test_Score & Post_Test_Score	36	0.710	0.000

B

Paired samples test							
	Paired differences					**t**	**df**	**Sig. (2-tailed)**
	Mean	**Std. deviation**	**Std. error Mean**	**95% confidence interval of the difference**				
				Lower	**Upper**			
Pre_Test_Score -Post_Test_Score	−5.306	2.896	0.483	−6.286	−4.326	−10.990	35	0.000

TABLE 3 Overall participant's feedback.

Item statistics						
Feedback questions	**Neutral**	**Agree**	**Strongly agree**	**Mean**	**Std. deviation**	**Cronbach's alpha if item deleted**
The training objectives were clear to me	1	9	29	4.72	0.510	0.866
I will be able to use what I learned in this virtual training	2	13	24	4.56	0.598	0.867
This training was a good way for me to learn about Bio risk management	1	10	28	4.69	0.521	0.866
The instructors were knowledgeable	2	15	22	4.51	0.601	0.864
The instructors were well prepared	0	8	31	4.79	0.409	0.872
The instructors were helpful and responsive to questions	1	5	33	4.82	0.451	0.877
The pace of this training was appropriate	2	15	22	4.51	0.601	0.864
This training lived up to my expectations	0	14	25	4.64	0.486	0.866
The training content was. [Relevant]	0	9	30	4.77	0.427	0.883
The training content was. [Easy to understand]	2	15	22	4.51	0.601	0.868
The training content was: (Comprehensive)	1	14	24	4.59	0.549	0.870

using paired *t*-tests at 95% CI. Reliability and consistency of feedback from the participants on the speakers and overall training were evaluated by using Cronbach's alpha. Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond) and SPSS version 23 (IBM, Armonk).

Results

The participants' sociodemographic information (Table 1) shows that a total of 52 participants enrolled to attend the webinars, out of which 30 (58%) were men and 22 (42%) were women.

TABLE 4 Cronbach's alpha reliability score on speakers' evaluation.

Reliability statistics	
Cronbach's alpha	***N* of speakers**
0.946	16

The weekly attendance of 52 participants is shown in Figure 1. While the exact numbers of attendance varied from week to week, overall, 37 participants attended all seven sessions, and the average attendance was 46 persons throughout the sessions.

Pre-test assessments at the beginning of the webinars and post-test assessments at the end of the webinars were conducted to ascertain the impact on participant awareness of the key topics. Only 36 (64%) participants out of 52 completed the pre- and post-assessments. As shown in Table 2A. The major difference in mean test scores of pre- and post-assessment results was observed to increase from 18.69 to 24 and their mean difference was −5.31. The correlation among pre- and post-tests scores was 0.71, showing that there was a moderate positive (uphill) linear relationship. The variation between both variables was around 50.41%.

The level of significance was determined using paired *t*-test with 95% CI that showed a highly significant *P*-value ($P < 0$) that is representing there is a significant difference between tested variables, i.e., pre-test score and post-test score (Table 2B).

To ensure the validity of the results and with the intention to improve the quality of the webinars in the future. The participants' responses/feedback regarding all the presented IVT webinars by different speakers are also evaluated and their ratings were measured on a five-point Likert scale (1-Strongly disagree, 2-Disagree, 3-Neutral, 4-Agree, and 5-Strongly agree) shown in Table 3. The reliability of the Likert scale was estimated using Cronbach's alpha, which showed all variables to have a maximum score >0.8 (0.946), indicating the high reliability of the generated feedback evaluation (Table 4).

Discussion

Biorisk management is a major problem that has been overlooked at various stages of graduate education, research training, and laboratory professional skill development in the context of Pakistan (18). In a past study, we highlighted the significance of biosafety and biosecurity protocols and policies (18). Thus, all laboratory professionals should have a basic knowledge of standard microbiological practices, risk assessment, and control measures (19).

Infections in laboratories not only threaten the health of laboratory workers, but they can also result in the unintentional release of organisms into the wider environment or community (19). A major gap has been seen in implementing biorisk management in laboratories due to a lack of awareness in Pakistan (20). These gaps can be addressed through educational initiatives on biosafety and biosecurity.

The online training program on "Biorisk Management in context of COVID-19" was very successful as confirmed by the increased average scores in the post-training evaluation and feedback survey questionnaire. This proves that virtual biosafety and biosecurity training program has significant importance in the recent pandemic and afterward. Participants shared their online training experience at the end of the webinar series and showed their interest in hybrid training programs including in-person to gain more hands-on training in the future.

This training course also identified several other challenges and gaps in developing and implementing resilient biosafety capacity-building programs. These challenges and gaps have been identified through discussion among participants. To ensure safe and secure conditions, laboratories must implement a comprehensive biorisk management system that fulfills the requirements of GHSA Action Package 3 (Biosafety and Biosecurity) and bioethical guidelines[1]. Recommendations were also received from participants in the feedback questionnaire.

In this workshop participants also discussed similarities and differences in the infrastructure and training associated with BSL-2 and BSL-3 laboratories. Participants also showed consensus that hands-on training, as well as didactic training, are essential for developing and implementing a researcher's competence to work in a high-containment facility.

Individuals who participated in the workshop also highlighted the training of laboratory professionals on risk assessment. These biosafety training programs should be flexible and adapted according to the target research facility, research area, and personnel working there as what may be appropriate to one context may not be suitable to another: one size does not fit all. In addition, effective awareness of biorisk management is still required, as well as resources and expertise for the successful implementation of biosafety and biosecurity at the national level. The biotechnology sector is continuously growing in Pakistan. Therefore, training on biorisk management should also be leveraged to sensitize the scientific community on dual-use research issues, which is a neglected area in Pakistan (21).

Conclusion

The recommendations that were received from participants during this IVT are important to properly fill the existing gaps in biosafety and biosecurity in Pakistan. Biosafety and biosecurity

1 https://www.cdc.gov/globalhealth/security/actionpackages/default.htm

training are of utmost significance in the current challenging situation of the COVID-19 pandemic. The findings of this project highlight the raising awareness of biorisk measures in public and private laboratories. Increasing knowledge on biorisk management can serve to reduce the risk of intentional or unintentional release of pathogens, thus improving the safety of laboratory workers, the community, and the environment. However, to continue with didactic training on risk assessment, it is observed that support from the public and private sectors at national and international levels will have an additional impact on the implementation of biorisk management.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Departmental Bioethics Committee, Bahawalpur Medical and Dental College, Bahawalpur, Pakistan. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SQ: conceptualization, methodology, writing, reviewing, and editing. FA: writing of the original draft, reviewing, and editing. SM: writing of the first draft conclusion. LM: statistical analysis and interpretation of the data. SQ, FA, and CS: critical review. SS: project administration, resources, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewers AA and SF declared a shared affiliation with the author SM to the handling editor at the time of review.

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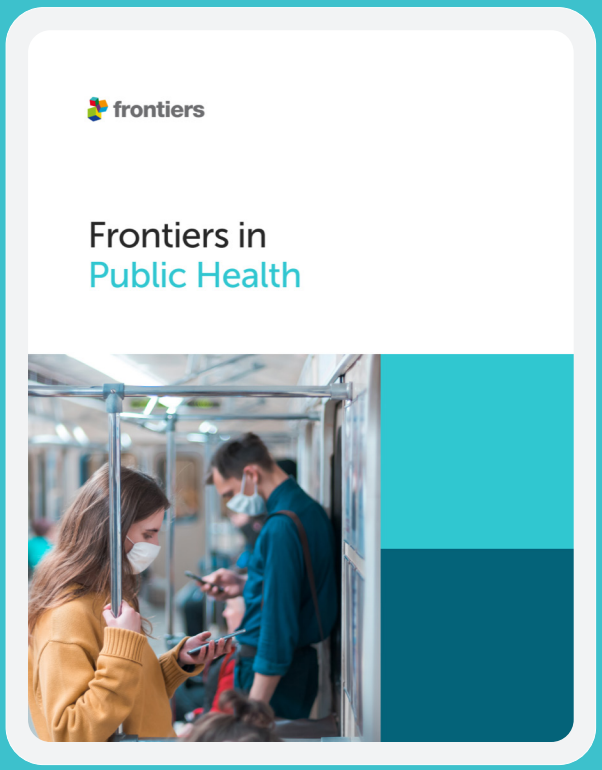

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