WHO Consultative Meeting on High/Maximum Containment (Biosafety Level 4) Laboratories Networking

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Meeting report

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Abbreviations

AAHL	Australian Animal Health Laboratory
ABSL-4	animal biosafety level 4
ACDP3	Advisory Committee on Dangerous Pathogens level 3
ASTM	American Society for Testing and Materials
BBSRC	Biotechnology and Biological Sciences Research Council (United Kingdom)
BSL4ZNET	Biosafety Level 4 Zoonotic Laboratory Network
BSL-4	biosecurity level 4
BSL-3Ag	biosafety level 3 agriculture
BMBL	*Biosafety in microbiological and biomedical laboratories*
Cat A	Category A (Infectious Substances)
CCHF	Crimean Congo haemorrhagic fever
CDC	Centers for Disease Control and Prevention (United States of America)
CEN	European Committee for Standardization
CEPRIS	Research Centre for Emerging Pathogens with High Infectious Risk (Côte d'Ivoire)
CICVyA	Centre for Research in Veterinary and Agronomic Sciences (Argentina)
China CDC	Chinese Center for Disease Control and Prevention
CLC	community liaison committee
CL4	containment level 4
CL4 Ag	Containment Level 4 Agriculture
CReSA	Centre de Recerca en Sanitat Animal (Spain)
CT	computed tomography
ELISAs	enzyme-linked immunosorbent assays
EMERGE	Efficient Response to Highly Dangerous and Emerging Pathogens at EU Level
ERINHA	European Research Infrastructure on Highly Pathogenic Agents
EU	European Union
HEPA filters	high-efficiency particulate air filters
HPAI	highly pathogenic avian influenza
HVAC	heating, ventilation and air conditioning
IEGBBR	International Experts Group of Biosafety and Biosecurity Regulators
INTA	National Institute of Agricultural Technology (Argentina)

IRF	Integrated Research Facility
ISO	International Organization for Standardization
KCDC	Korea Centers for Disease Control & Prevention (Republic of Korea)
MRI	magnetic resonance imaging
MTAs	material transfer agreements
NEIDL	National Emerging Infectious Diseases Laboratories (United States of America)
OIE	World Organization for Animal Health
PCR	polymerase chain reaction
PET	positron emission tomography
PIP	Framework Pandemic Influenza Preparedness Framework
PPE	personal protective equipment
PC4	Physical Containment Level 4
PHE	Public Health England
RG	Risk Group (1 through 4)
R&D	Blueprint Research and Development Blueprint (WHO)
SAPO4	Special Animal Pathogens Order level 4
SARS	severe acute respiratory syndrome
SOPs	standard operating procedures
SPECT	single photon emission computed tomography
SPF	specific pathogen free
URS	user requirement specification (document)
USAMRIID US	Army Medical Research Institute of Infectious Diseases
VHP	vaporized hydrogen peroxide
VIDRL	Victorian Infectious Diseases Reference Laboratory (Australia)

Executive summary

Bringing together experts from more than 20 countries and representing 53 institutions, WHO held the inaugural Consultative Meeting on High/Maximum Containment (Biosafety Level 4) Laboratories Networking in Lyon, France on 13–15 December 2017. The participants included facility operators, engineers, lead scientists and representatives of national regulatory authorities; they identified shared challenges, opportunities for collaboration and potential solutions to improve the design, maintenance, regulations and operations of maximum-containment laboratories (biosecurity level 4 – BSL-4).

The participants repeatedly emphasized the importance of BSL-4 laboratories in their ability to carry out highly specialized work during the Meeting. Public perception can significantly influence where and how these laboratories can operate, and concerns were expressed about how an incident in any BSL-4 laboratory would have direct implications for the reputation of the entire community. Key factors in dispelling misconceptions about and establishing public trust in this community included the promotion of scientific research, transparency, highlighting of biosafety achievements and strong community liaison committees.

A global shift from prescriptive to performance-based biosafety has occurred in recent years. To reflect these realities, the revised WHO *Laboratory biosafety manual Laboratory biosafety manual* will emphasize the use of practical measures to mitigate risks, including thorough risk assessments and evidence-based approaches to biosafety, rather than reliance on rigid classification systems. Much discussion focused on the consequences of this shift in approach, as many countries lacking formal regulatory requirements rely on the *Laboratory biosafety manual* as their sole guidance document.

Significant attention focused on best practices in the design of high-containment facilities. Selection of suit laboratories vs cabinet lines and planning for surge capacity through design flexibility must be considered at an early stage. Countries with limited resources have added restraints arising from the lack of well-trained biocontainment engineers, poor access to relevant engineering information and difficulty in reaching effective supplier networks. The participants, particularly those from lower-income countries, gave significant importance to the identification of mechanisms for the global dissemination of know-how and good practice relating to containment laboratory design. They received updates on high-containment laboratories that were planned, newly constructed or operational, which pushed discussions to develop a consensus on global standards or requirements for such facilities.

The need to share best practices in laboratory procedures and training programmes was a common theme of the Meeting. Many networks of high-containment laboratories presented their charters and activities to strengthen BSL-4 laboratories in their regions. This and other discussion mapped numerous opportunities for training at the local, regional and international levels, although many gaps remained to be addressed.

A final objective of the Meeting was to strengthen relations between regulators and operators, finding common solutions to enhance biosafety while furthering scientific progress. Through both separate breakout sessions and joint discussions, the two groups raised common concerns on issues related to laboratory safety and expressed a desire to address them together.

The participants identified several gaps for WHO to prioritize as part of its continued commitment to strengthening the global BSL-4 community. These included the coordination of networks of high-containment laboratories to avoid duplication of effort, the fostering of the development of a BSL-4 training curriculum, the dissemination of best practices and the sharing of materials. Most important was a need to establish benchmarks and official verification mechanisms for BSL-4 laboratories, to ensure that all such facilities operate to a global standard of biosafety and biosecurity, building trust within the scientific community and public alike.

Introduction

BSL-4 laboratories represent the highest level of biological containment, offering unparalleled protection for the user, sample and environment. At present, more than 50 maximum- and high-containment facilities around the globe handle some of the world's most hazardous pathogens to human and animal health for research and diagnostic purposes. BSL-4 laboratories are located in all WHO regions. While most are in North America or western Europe, a number have been built in Asia, and construction projects are underway in China, Japan and sub-Saharan Africa, raising questions related to sustainability in low-income countries. Irrespective of geography, all high-containment laboratories share numerous issues regarding training opportunities, maintenance and the building of confidence in the broader community. Many regional initiatives, but limited international efforts, have aimed to create a global forum to identify best practices, standards and opportunities for collaboration.

The WHO Consultative Meeting on High/Maximum Containment (Biosafety Level 4) Laboratories Networking aimed to further solutions to the challenges faced by all such laboratories. It had eight objectives:

1. to foster bilateral or multilateral collaboration of BSL-4 laboratories around the world, to work with WHO on the common mission of strengthening laboratories to maintain biosafety and biosecurity;
2. to discuss best practices employed at facilities and identify mechanisms for sharing and disseminating them to others;
3. to review challenges to consider in the development, expansion and maintenance of facilities and identify measures used to overcome them;
4. to strengthen relations between regulators and scientists relating to oversight and identify means to earn confidence from the global scientific community;
5. to address public perceptions of the risks associated with BSL-4 facilities and mitigate these concerns through outreach;
6. to explore the possibility of forming an international review mechanism to provide international recognition of new BSL-4 facilities through on site observation and guidance;
7. to facilitate material transfer to/between laboratories that have demonstrated competence; and
8. to update the global audience on planned and newly developed BSL-4 facilities and discuss the support required to ensure their success and safe operation.

Annexes 1–3 to this report give the agenda of the Meeting, list BSL-4 laboratories worldwide and list the Meeting's participants, respectively.

Welcoming remarks by Dr Guenael Rodier, Dr Florence Fuchs and Dr Sebastien Cognat (WHO headquarters) emphasized the importance of BSL-4 capacity in the context of the WHO Health Emergencies Programme, where they played a central role in diagnostics and countermeasure development against the world's most dangerous biological agents. This networking meeting aimed to build a community of practice and encourage participants to take active roles in future world health emergencies. Most important, it provided a venue for the BSL-4 community to express its expectations of WHO in maintaining and strengthening joint activities to enhance biosafety and biosecurity at the global level.

Global BSL-4 laboratories – unprecedented opportunities and unique challenges

In the keynote address, Dr Jim LeDuc (University of Texas Medical Branch, United States of America) highlighted the specialized role played by BSL-4 laboratories in the advancement of science and the battle against high-consequence pathogens, as well as the particular challenges encountered in the planning, operation and upkeep of these facilities. BSL-4 laboratories provide an environment where diagnostics, research, and assessment of novel diagnostic tests and therapeutics can be carried out on the actual target agents of disease, rather than surrogates. They allow for characterization of newly emerging pathogens and provide appropriate biocontainment levels for particular types of gain-of-function research. As the field of synthetic biology moves forward, high-containment facilities may be required to accommodate resulting new agents.

With all of their potential, maximum-containment facilities come with many associated challenges, including extraordinary running costs. A 2017 report from the Science and Technology Policy Institute revealed average annual operating costs of US$ 8–13 million in the four BSL-4 laboratories in the United States of America that were surveyed. Operations and maintenance, required for constant upkeep and rapid response to breakdowns, account for the greatest proportion of laboratory spending. Security, utilities, staff training, animal care and use, pathogen inactivation and waste stream management all have high associated costs for BSL-4 laboratories. In addition to these costs, the repair of highly specialized instruments and equipment located inside the BSL-4 space has an extra layer of complication: service contracts are often not honoured when equipment is housed in maximum-containment zones, leaving laboratory staff with additional training costs for inhouse maintenance.

Managing public perception through strong and positive community relationships is crucial for laboratory success. So-called not-in-my-backyard movements can have devastating consequences for a facility's capacity to carry out important work. Laboratories working with both Risk Group 4 (RG4) pathogens and live animals have extra responsibilities to dispel myths to community members and animal rights activists. A strong community liaison committee (CLC) – with membership from community leaders in the business, religion and education sectors – is the best means of achieving all of this. As CLC members learn about activities at the laboratory, they become important advocates and educate the public through formal and informal interactions. For example, the Galveston laboratory of the University of Texas Medical Branch has taken a proactive approach to CLC engagement, informing the members of any incident prior to announcements from the press.

Additional challenges faced by BSL-4 laboratories include complying with numerous national regulations (sometimes from more than one governing agency), ensuring secure yet convenient access to and storage of pathogens, developing robust training programmes for both research and engineering/maintenance staff, and devising detailed plans for safety and accident response through close collaboration between laboratory administrators and occupational health partners.

BSL-4 facilities should be promoted as a source of pride; they are unique resources to many organizations and countries, and provide global benefits through safe and secure cutting-edge responses to high-consequence pathogens. The BSL-4 community as a whole must work to enhance its public image, publicize its excellent track record for safety and security, and realize that any newsworthy incident in any facility, positive or negative, will have direct influence on all facilities in the global BSL-4 enterprise.

Update on the revision of WHO´s *Laboratory biosafety manual*

Dr Kazunobu Kojima (WHO headquarters), focal point for biosafety and laboratory biosecurity, described the progress made in revising the 2004 edition of the WHO *Laboratory biosafety manual*.[1] The new edition will feature a significant change from a prescriptive to an evidence- and risk-based approach. The manual will also have a new format: a concise central core accompanied by annexes published as monographs on specific topics.

The WHO biosafety audience varies. While many scientists and biosafety practitioners come from highly specialized facilities, others come from very different realities. For some, even in national infectious disease hospitals, access to personal protective equipment (PPE) and regular certification and maintenance of critical equipment are luxuries with limited availability. The concept of a BSL also varies greatly by location and even within countries. Some BSL-3 laboratories, for example, are very similar to BSL-4 laboratories, while others resemble BSL-2 or are modular BSL-3 with varying designs. For maximum-containment facilities, average annual operational costs upwards of 10% of total construction costs demonstrate challenges in sustainability for many who consult the *Laboratory biosafety manual* for guidance. During outbreaks, even Ebola virus has been safely manipulated in a makeshift glove box in a field laboratory setting, without a positive pressure suit.

Rather than equating RGs with BSLs, both the pathogens (hazards) and associated processes (likelihood) should dictate appropriate containment measures. Risk does not arise from the pathogen alone, but results from the process, each having its own likelihood of generating harm with varying degrees of severity. Procedures involving animal inoculations and aerosol generation come with higher inherent risks than running enzyme-linked immunosorbent assays (ELISAs) and preparing serial dilutions.

The new edition of the *Laboratory biosafety manual* would therefore focus on practicality, taking a more evidence- and risk-based approach to biosafety to enhance flexibility. The new manual's three key elements would be: a renewed focus on good microbiological practices, emphasis on staff competence and training, and highlighting of the importance of proper risk assessments. Specifically, the manual intended to remove the focus on risk groups and BSL at the global level to allow for appropriate and practical measures to mitigate risks. Instead, risk assessments must determine core requirements, referring to a combination of elements to implement as minimum requirements for working with any given pathogen.

[1] Laboratory biosafety manual, third edition. Geneva: World Health Organization; 2004 (http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en, accessed 14 November 2018).

As assessed risk increases owing to processes, additional safety measures must be in place. Maximum containment might be required with eradicated diseases such as smallpox, known agents of high consequence or unknown agents and procedures with a high likelihood of exposure and impact on the environment if released.

Ultimately, the *Laboratory biosafety manual* was not intended to replace or compete with national regulatory frameworks, which would dictate how to deal with benign versus high-consequence agents. Instead, the preference was to be risk/performance based and for ultimate decisions to come from each government. Countries such as the United States, which relied on *Biosafety in microbiological and biomedical laboratories* (BMBL)[2] for biosafety guidance, were not expected to abandon their national regulations. Instead, the *Laboratory biosafety manual* would be important for the resource-limited audience.

Varying approaches to high-containment facilities

Dr Kathrin Summermatter (Institute of Virology and Immunology, Switzerland) described varying approaches to high-containment facilities, highlighting the absence of a one-size-fits-all solution. The Institute of Virology and Immunology decided to upgrade an existing facility, rather than undertake a new construction project. Project planning discussions with architects raised many questions that are common to the global BSL-4 community and warrant discussion for shaping future facilities.

Containment laboratory terminology is not universal, with interchangeable terms used by different countries, regions and international organizations. These include containment level 4 (used in the European Union (EU) and Canada), BSL-4 and animal biosafety level 4 (ABSL-4) (United States, WHO), and Physical Containment Level 4 (PC4) (Australia). Practices within different maximum-containment facilities also vary, with human pathogen BSL-4 laboratories consisting of suit laboratories or glove boxes while Containment Level 4 Agriculture (CL4 Ag) (BSL 3 agriculture – BSL3Ag) lack such special protection for workers. Beyond the facility level, classification schemes for biological material also vary by region, field (human versus veterinary) and endemicity. In dealing with globally eradicated agents, specific regulatory control and higher containment levels may be required out of fear of reintroduction, as with rinderpest and smallpox. While classification schemes may be useful at the national level, they may therefore not be applicable internationally.

Moving from this traditional approach, the selection of appropriate containment levels and controls should focus on risk-based approaches, taking account of the activities and procedures to be carried out. According to BMBL, hantavirus, for example, can be safely handled in BSL-2 facilities with BSL-3 practices for diagnostic purposes. If the same agent will be used for chronic infection studies in rodents, however, then ABSL-4 is required. Giving careful consideration to realistic needs is especially important, given the high associated costs and issues of sustainability with high-containment facilities. This becomes even more critical with the tendency to gravitate towards new to market containment technologies whose added benefits are yet to be proved.

[2] Biosafety in microbiological and biomedical laboratories (BMBL), 5th edition. Atlanta: US Department of Health and Human Services; 2009 (https://www.cdc.gov/biosafety/publications/bmbl5/index.htm, accessed 18 November 2018).

On a simplified level, all forms of maximum-containment laboratories have many commonalities. Design features include air handling units, breathing air systems for suit laboratories, supply and exhaust high-efficiency particulate air (HEPA) filters, material transport docks (dunk tanks, pass-through chamber, autoclaves), shower barriers, effluent treatment systems and built-in redundancy for critical systems. Areas of debate include the precise placement of HEPA filters, the specific type to use and the installation of fixtures entirely within or outside the containment zone.
In large-animal facilities, the room itself becomes the primary containment barrier, putting greater requirements on the whole building. Building flexibility into the facility is highly desirable to enable unexpected needs during outbreaks of emerging and re-emerging infectious disease to be met.

While establishing a standard definition for BSL-4 laboratories may be difficult, exchanging information on how best to integrate safe systems will assist the building of new facilities that are sustainable and allow the scientific programme to continue. Whether new technologies and engineering requirements are beneficial or burdens to laboratory operations and sustainability, and how best to integrate experiences and lessons learned into new projects were additional areas to address.

Update on BSL-4 facilities

Planned high-containment laboratories

Nagasaki University, Japan

In 2010, the President of Nagasaki University publicly announced that the possibility of BSL-4 construction was being explored. Since 2011, the University had actively engaged with community members to educate the public and establish trust prior to the start of construction. These activities included over 50 briefing sessions for neighbourhood residents, 12 community meetings since 2016 and 38 science seminars open to the public. By 2016, the Government had provided official support and set aside money in the 2017 national budget.

The planned facility would be five storeys high, with 1000 m_2 divided between two independently operated BSL-4 units, each with a laboratory and animal room. While Nagasaki does not sit on active earthquake fault lines, seismic isolation layers for building construction on a vertical isolation device were being planned as an extra precaution. The proposed timeline consisted of construction in 2018–2019, commissioning in 2020 and commencement of operations by 2021.

Chinese Center for Disease Control and Prevention BSL-4 Laboratory, China

The Chinese Center for Disease Control and Prevention (China CDC) was established in Beijing in 2002, housed numerous WHO reference laboratories and collaborating centres on viral and vector-borne diseases, and had the largest BSL-3 facility in China, yet lacked a maximum-containment facility. Given China's enormous population and increasing pressure from infectious diseases as the economy shifted, China CDC recognized the need for and obtained government funding to construct a BSL-4 facility.

The China CDC BSL-4 would be a suit laboratory, designed in accordance with Chinese and international standards (including the WHO *Laboratory biosafety manual*), with activities including diagnostics, the evaluation of new kits and vaccines, and research into

pathogenicity and animal models. Thus, the facility would include both a laboratory and an animal suite capable of housing nonhuman primates, pigs, rabbits and rodents. The project was at the very beginning of planning and a suitable construction site had yet to be determined.

Public Health England, United Kingdom

Public Health England planned a world-class, £400-million new construction project, relocating staff and facilities from Porton Down and London. In 2017, it purchased a vacant site in Harlow, and the Harlow district council approved construction plans in December.

The new facility at Harlow would house a number of laboratories, particularly the first BSL-4 suit laboratory in the United Kingdom, which had previously permitted only cabinet lines for work with RG4 pathogens. To obtain approval, a tripartite working group was established to address multiple regulatory issues surrounding a suit laboratory. A great deal of work remained in the planning stages, from addressing issues relating to the chemical shower, selection of disinfectants and technologies for room decontamination, communications and ergonomics, ways to continue business as usual in this transition phase, handling of health surveillance questions, mock-ups for training and external suit training opportunities for staff.

The Harlow facility was hoped to be operational by 2024, with construction work beginning in 2019 and retrofitting of an existing building for BSL-3 starting in 2021.

High-containment laboratories under construction

Research Centre for Emerging Pathogens with High Infectious Risk, Pasteur Institute Côte d'Ivoire

The Pasteur Institute currently operated two facilities in Abidjan, Côte d'Ivoire, housing recently constructed BSL-2 laboratory space for virology work, the biobank and the molecular biology unit. The need for a BSL-4 facility in the region was identified following recent outbreaks of dengue fever in Côte d'Ivoire and Ebola virus disease in neighbouring countries. A call for funding was made in 2015 to construct a new laboratory, the Research Centre for Emerging Pathogens with High Infectious Risk (CEPRIS), to include a BSL-4 suit laboratory and a BSL-3 laboratory, plus an animal suite and insectarium at BSL-3. Built-in flexibility would come from the ability to convert the BSL-4 facility to BSL-3 as required by the work volume. The scientific programme of CEPRIS would take a One Health approach, focusing on pathogens of human, animal and environmental origin. Planned activities included surveillance and diagnosis, research and characterization of pathogens; biobanking; and hosting and training of local and international teams.

Côte d'Ivoire's national budget provided about 90% of the funding required, and the remaining 10% came from international organizations such as WHO; the Centers for Disease Control and Prevention (CDC), United States of America; and the Pasteur Institute, Paris, France. Construction began in 2016, after consultation and planning with architects and industrial partners, and establishing compliance with national and international laws and conventions on such issues as ethics, biosecurity and privacy. Many partners at the national level (the ministries of health and defence) and the international level (CDC, WHO and the Jean Mérieux BSL-4 laboratory, in Lyon, France) also played significant roles in project planning and implementation. The project was predicted to be completed in 2019.

National Bio and Agro-Defense Facility, United States of America

The National Bio and Agro-Defense Facility,a state-of-the-art BSL-3 and -4 facility, was being constructed in Manhattan, Kansas, following a presidential directive in 2003 to replace the Plum Island laboratory. The facility was a joint project of the US Department of Homeland Security, the US Department of Agriculture and the Agricultural Research Service and Foreign Animal Disease Research and Diagnostic programmes, and would thus offer a One Health approach to detect, diagnose and develop countermeasures against high-priority foreign animal disease.
The phase of facility design ran from 2007 to 2012. Site preparation started in 2010 and was completed in August 2012, and construction began in 2015. About 45% of the budget of US$ 1.25 billion had been spent. The main laboratory building would offer 174 955 m^2 of laboratory space, largely occupied by a BSL-3 laboratory and large-animal areas, as well as BSL-2 and biologicals development module for in-house vaccine manufacturing. The BSL-4 suite would cover about 4 084 m^2, and be the first BSL-4 facility in the United States to accommodate large animals. The building design would also allow for flexibility, where the large-animal BSL-4 suite can be operated at BSL-3Ag. If progress continued on schedule, NBAF would be commissioned by May 2021.

Facilities at the Pirbright Institute, United Kingdom

The Pirbright Institute is an international centre of excellence for livestock pathogens of economic significance, as well as exotic zoonotic agents. For nearly nine years the United Kingdom Government and the Biotechnology and Biological Sciences Research Council (BBSRC) had made major investments to replace aging facilities, some being up to 100 years old. The BBSRC National Centre for Virology was constructed entirely to BSL-4 standards to allow for diagnostic activity and in vitro research with RG3 and 4 animal pathogens (Specified Animal Pathogens Order level 4 – SAPO4) and Advisory Committee on Dangerous Pathogens level 3 (ACDP3) according to the United Kingdom's human and animal health classification scheme), as well as zoonotic agents (ACDP4). The Plowright Building cost £135 million, had been occupied since 2015 and employed entirely cabinet lines for work with ACDP4 pathogens. An additional facility, the BBSRC National Centre for Vaccinology (the Jenner Building) had been operational for about a year.

Several additional construction projects were planned or underway at Pirbright. A new hatching facility for specific pathogen free (SPF) poultry had been designed and was expected to be operational by 2019. Updates to current animal facilities would create a poultry experimental facility, with open pens capable of ACDP3 animal work with isolators, that was expected to be operational by 2019. Finally, a new SAPO4/ACDP3 (BSL-3Ag+) large-animal facility had been designed and the contractor selected, and operations were set to begin by February 2021. This high-containment facility would be built to BSL-4 standards, with the potential to add air lines for a future suit laboratory.

National High Containment Facilities for Animal Diseases Control and Prevention, Harbin, China

The Harbin Veterinary Research Institute houses numerous facilities for research and diagnostics of animal diseases. The campus includes a veterinary school, veterinary biotechnology development company, a BSL-1/2 facility with 8000 m^2 of laboratory space, a BSL2/3Ag facility of 17 000 m^2, and a facility with capabilities for housing small animals in isolators and large animals in modular open pens. There are also facilities for breeding SPF pigs, ducks and chickens.

China has the largest population in the world, hosts hundreds of millions of tourists each year and has become the largest and fastest-growing import market. It is also home to over 20% of the world's poultry and 50% of the world's pigs, and has a fast-growing cattle industry. These facts, combined with China's limited natural resources, created major biosecurity concerns about the accelerated replication, mutation and transmission of infectious pathogens. As a result of the 2003 outbreak of severe acute respiratory syndrome (SARS), the Chinese Government planned to build three BSL-4 facilities to address these issues.

The National High Containment Facilities for Animal Diseases Control and Prevention, constructed at the Harbin Veterinary Research Institute, would be China's only facility capable of large-animal BSL-4 studies. Nearly 4500 m^2 were dedicated to high-containment laboratories, including four BSL-3 spaces, four ABSL-3 rooms, one necropsy room, four BSL-4 laboratories and four ABSL-4 suites. Construction was completed in December 2016 and the facility obtained accreditation for work with pathogens in RG3 from the China National Accreditation Service for Conformity Assessment. By the end of 2017, the facility was hoped to have accreditation for RG4 pathogens, and work on these was hoped to start in 2018.

Recently constructed BSL-4 laboratories that are operational

National High-level Biosafety Laboratory, China

The National High-level Biosafety Laboratory, in Wuhan, represents one of China's major investments in strengthening the public health system and biosafety management following the SARS outbreak. The building features 3000 m_2 of BSL-4 space, including four independent laboratories areas and two animal suites, in addition to 20 BSL-2 and two BSL-3 laboratories. The Laboratory's main objective is to work for the prevention and control of emerging infectious diseases through diagnostic activities, as well as research and development in the areas of pathogenesis studies and antiviral drugs/vaccines.

The Laboratory is the result of a 2004 memorandum of understanding between China and France, which collaboratively engaged in the design and commissioning of the project. Both French and Chinese companies validated the Laboratory, which was fully accredited by both countries as of December 2016 and certified to International Organization for Standardization (ISO) standards.

During the commissioning process, much investment was made in staff training. Researchers were trained in Australia, Canada, France and the United States of America and then in house before the Laboratory became operational. A validation system for training was then established to demonstrate staff competency for work or maintenance in the BSL-4 laboratory, establishing management systems and drafting of guidelines and standard operating procedures (SOPs). The BSL-4 laboratory could carry out projects on many diseases, would work as a national centre for research and development and aimed to become a WHO reference laboratory or collaborating centre.

The BSL-4 laboratory was not currently operating at full capacity, as animal experimentation would commence only after significant hands-on experience with in vitro work, owing to increased risk. The Laboratory was intended to be a transparent public platform for China.

Korea Centers for Disease Control and Prevention BSL-4 Laboratory, Republic of Korea

The Korea Centers for Disease Control and Prevention (KCDC) BSL-4 laboratory, located in Cheongju, was established to respond rapidly to public health emergencies through the diagnosis of high-risk pathogens and development of vaccines and drugs against emerging infectious diseases.

The construction project for the Laboratory was launched in 2009, with design completed in 2012 and construction in 2014. Biosecurity was a major consideration in all stages of the project, from the geographic location selected to facility access. By June 2016, the Laboratory had been accredited and begun operation. The facility housed BSL-2 and -3 laboratories, as well as 300 m^2 of BSL-4 laboratory space.

The Division of Bioterrorism Preparedness and Response operated the BSL-4 laboratory, which had undertaken immense work in the area of biological risk management, the development and continuous revision of SOPs and the establishment of emergency response drills to ensure safe operation of the facility. Facility staff attended international training courses in collaboration with the Public Health Agency of Sweden, the University of Texas Medical Branch and CDC. A rigorous internal programme was established that provided BSL-4 training to researchers, operations staff and maintenance personnel; this included task-specific theoretical, practical and mentoring components prior to certification.

Victorian Infectious Diseases Reference Laboratory, Australia

The Victorian Infectious Diseases Reference Laboratory (VIDRL) is part of the Royal Melbourne Hospital and housed at the Doherty Institute. It is a national public health laboratory with diagnostic functions, performing about 300 000 serological, molecular and microbiological tests per year. VIDRL houses many national reference laboratories and WHO collaborating centres and is home to over 700 scientists, educators, clinicians and students.

In 2014, the National High Security Quarantine Laboratory at VIRDL was commissioned as a high-containment diagnostic laboratory to detect imported viral haemorrhagic fevers, as well as diagnose smallpox and other high-threat pox viruses.

The BSL-4 laboratory at VIRDL is a single suite of about 90 m^3 located in a high-containment facility with seven BSL-3 laboratories. Particular design features include an off-the-shelf chemical shower, built-in vaporized hydrogen peroxide (VHP)/gas decontamination pipework, a pass-in chamber and a dunk tank. Ultimately a decision was made to switch from VHP to the more gas-like ionized hydrogen peroxide, so the laboratory uses a stand-alone unit for decontamination and the VHP piping remains unused. In addition, the laboratory was designed with an adjacent control room with a large window. This room is constantly staffed whenever BSL-4 laboratory work is carried out, with the controller acting as a biosafety practitioner, as well as record keeper and note taker for the laboratorian. During the Ebola virus crisis of 2014–2016, the laboratory was activated 33 times for diagnostics on suspect cases. In the absence of diagnostic work, the laboratory is involved in assay development, testing, antiviral drug screening; it is open to future collaboration.

BSL-4 laboratory at the Robert Koch Institute, Germany

The Robert Koch Institute, in Berlin, is a federal institute under the Federal Ministry of Health, working to safeguard public health in Germany. The final designs for its BSL-4 laboratory were approved in 2006, with construction taking place in 2010–2015. German legislation requires all authorizations and permissions to come from state or federal regulators. This resulted in the laboratory approaching multiple authorities for permissions in accordance with the Genetic Engineering Act, Biological Agents Ordinance, Animal Welfare Act and Protection against Infection Act. As of July 2017, the laboratory satisfied all external review committees and authorities for compliance with nearly 140 regulations, and obtained licences to work with mice, guinea pigs and hamsters.

The 330-m² BSL-4 facility is subdivided into two suites that can operate independently, each with a laboratory space, animal room and necropsy room. In total, the laboratory contains eight Class II biosafety cabinets and can accommodate up to 10 operators at a time. All processes were validated, including the chemical shower via use of fluorescent material to show coverage of entire suite, and the necropsy room autoclave by embedding spores in carcases prior to runs. The BSL-4 laboratory was running in a mock phase, using BSL-2 agents, and expected to begin work with RG4 pathogens in March 2018.

Established high-containment laboratories - moving to the future

Australian Animal Health Laboratory, Australia

The Australian Animal Health Laboratory (AAHL), operated in Geelong under the Commonwealth Scientific and Industrial Research Organisation, had been operational since 1985 and played a vital part in the Australian biosecurity infrastructure. It was designed to carry out research and diagnostic activities to protect Australia's livestock and general public from emergency and zoonotic disease threats, with approximately 400 m^2 of BSL-4 laboratory space plus 127 m^2 of BSL-4 animal suites. AAHL's uniqueness lies in its ability to conduct high-containment research at all levels, from in vitro through insects to large animals. While the building was designed for a 100-year lifespan, changing research demands and technologies made this goal unrealistic. The cost of construction was approximately A$ 185 million in 1985, whereas the current cost to rebuild would be over A$1 billion. As the annual budget was A$ 63 million, a new construction project was unlikely.

AAHL was designed with a modular concept, and contained numerous suites. It also contained a large training laboratory that provided critical training for staff involved with large-animal work, providing technical training while suited prior to working with RG4 agents. Major refurbishing projects in recent years had greatly added to AAHL's capacity for BSL-4 research: BSL-3 spaces were upgraded to BSL-4. A 350-m^2 BSL-4 zoonosis suite had recently been added that contained laboratory space and insectary, two small-animal rooms, and a bioimaging facility. A BSL-3 insectary had also been built, with space for rearing and feeding insects, as well as animal accommodation for transmission studies. A new, extensive expansion project being planned and funding negotiations were underway.

US Army Medical Research Institute of Infectious Diseases, United States of America

The US Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, in Frederick, Maryland, is arguably the oldest high-containment facility. Its mission is to provide leading-edge medical capabilities to deter and defend against biothreats, and its vision is to be a leader in advancing medical biodefence to protect US military forces and the nation. Its core competencies are to prepare for uncertainty and emerging infectious diseases, achieved through:

1. developing, testing and evaluating medical countermeasures;
2. providing world-class expertise in medical biological defence;
3. rapidly identifying biological agents;
4. training and educating the force;
5. maintaining biosafety, biosecurity and biosecurity standards; and
6. preparing for technological uncertainty.

Through these competencies and with the efforts of subject matter experts from a variety of fields, USAMRIID fulfils its vision. Using appropriately developed animal models, it generates data on medical countermeasures of such quality that they can go directly to the US Food and Drug Administration for licencing when human clinical trials are not possible. Vaccines and countermeasures had been developed at USAMRIID targeting a range of biological threats, including anthrax, plague, hanta- and filoviruses, ricin toxin and Staphylococcal enterotoxin B.

USAMRIID planned to move from its current facility to a newly constructed site in the coming years. The new building would be the largest, most complex biocontainment facility ever designed, nearing 304 800 m^2. Scientific capacity was expected to be 4–5 times as large, and new capabilities for BSL-4 studies would include positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI) and structural biology.

New laboratories and public opinion: earning public trust and support

The many challenges and lessons learned in earning public support, and the link between public perception and concerns and mistrust were discussed, using the examples of laboratories in the United States and Japan.

National Emerging Infectious Diseases Laboratories, United States of America

The mission of the National Emerging Infectious Diseases Laboratories (NEIDL), in Boston, is to conduct research on infectious disease for the local, national and global good. Messaging around this and other national biocontainment laboratories included a mission to develop countermeasures against bioterrorism agents, which often overshadowed the real public health concerns surrounding emerging and re-emerging infectious diseases. While initial local press releases seemed quite favourable, messaging on NEIDL gradually became more negative, and the use of terms such as bioterror lab and bioweapons lab increased public mistrust.

NEIDL is in a populated area, near Boston University Medical Campus and many residences, ranging from low-income public housing to multimillion-dollar condominiums. Despite the diverse income levels, the public's underlying assumption was that NEIDL's site had been selected because many poor people lived in that area. Specific concerns raised in Boston were that BSL-4 laboratories pose unacceptable public risk, that secret work on bioweapons would be done and that there were more than enough other BSL-4 laboratories to handle the existing scientific problems. Movies, books and even news releases gave sensational accounts of the public's exposure to high-consequence pathogens, and there was a misperception that any breach in containment would result in a major pathogen release. Incidents in any high-containment laboratory further add to public unease about any nearby facilities.

The city of Boston had a long history of community activism by neighbourhoods and of questioning government and other authorities. Federal and state lawsuits filed against the National Institutes of Health and the State of Massachusetts in 2005 and 2006 stated that risk assessments for NEIDL had failed to address worst-case scenarios. A supplemental risk assessment was requested and undertaken shortly afterwards. It required nearly four years to complete, considered 13 pathogens and 300 failure scenarios, and addressed environmental justice issues. Once the lawsuits were favourably resolved in 2014, NEIDL began actively inviting members of the public for tours and conversation inside the facility. These events allow personnel to provide information addressing their specific concerns. As a result, almost 3000 people had visited NEIDL; in addition, scientific staff regularly attended public meetings and participated in other outreach activities, and the community liaison committee was active.

Many lessons were learned on the path to gaining acceptance for NEIDL in Boston. In particular, the personnel were not fully prepared to communicate effectively with the public about either science or risk. As misperceptions are difficult to predict, they must be drawn out of people in order to be addressed. People's beliefs and individual histories influence how well they listen and what they truly hear.

No laboratory can promise that no incident will ever occur. If/When one does happen, however, communicating about it and using the opportunity to teach the public about redundancies and maintaining safety are critical. Scientists and safety professionals need to engage more actively in communicating why their work is important and how safe and secure science is carried out, and helping to distinguish minor from serious incidents.

National Institute of Infectious Diseases Laboratory, Japan

The National Institute of Infectious Diseases Laboratory, in Tokyo, constructed a laboratory was in 1981 with a cabinet line for BSL-4 capabilities. It had been used only as a BSL-3 laboratory since that time, however, owing to the lack of approval from the Ministry of Health, Labour and Welfare, compounded by lack of mutual understanding between the Laboratory and the local government.

The Laboratory's responsibilities included preparing against viral haemorrhagic fevers and the threat of bioterrorism associated with these fevers and smallpox, preparing for emerging virus infections such as SARS and Middle East respiratory syndrome-related coronavirus, and training scientists to develop surge capacity to work with diagnostic specimens containing highly pathogenic agents in the event of an outbreak. The Laboratory was also involved in many research projects, including the development of diagnostic systems and

vaccines for viral haemorrhagic fevers and other emerging viruses, studies on virus therapies for monkeypox and severe fever with thrombocytopenia syndrome, and studies of the efficacy of a highly attenuated smallpox vaccine in a nonhuman primate model.

In 2015, the National Institute of Infectious Diseases Laboratory finally received approval to use the gloveboxes for work with RG4 agents. It pursued a long process to promote mutual understanding with local communities and understanding of BSL-4 work. Activities to engage the public included open houses, inviting local community members to tour the BSL-4 laboratory, and regular meetings of the communication committee with local residents, local municipal government, the Ministry of Health, Labour and Welfare and medical experts. Transparency was essential in obtaining support and trust from the public, and the National Institute of Infectious Diseases Laboratory was committed to playing a role in controlling, combating and managing infections associated with highly pathogenic agents in Japan and abroad.

Activities of other organizations and high-containment laboratory networks

World Organisation for Animal Health

The World Organisation for Animal Health (OIE), located in Paris, France, is an intergovernmental organization aiming to deliver timely, high-quality information and services to allow the management of risks to the health and welfare of terrestrial and aquatic animals, minimize associated dangers to human health and economy, and protect the environment and biodiversity, using a One Health approach. Founded in 1924 in response to rinderpest, OIE currently had 181 Members (countries), 12 regional and subregional representatives, 73 partner organizations, 267 reference laboratories with expertise on designated pathogens or diseases, and 55 collaborating centres with expertise on specialty knowledge areas, such as biosafety.

OIE's major responsibility is to ensure transparency of the global situation of animal disease through gathering and sharing information. When Members notify OIE of important disease events, it makes official reports and disseminates them to national delegates and the public via the World Animal Health Information Database. Members have an obligation to report on over 100 OIE-listed diseases, as well as emerging diseases and significant epidemiological events.

In addition, OIE aims to improve veterinary services by preventing and controlling the spread of important animal diseases, setting international standards, and sharing data and core competencies. OIE's science-based standards, including the terrestrial animal health code[3] and the manual of diagnostic tests and vaccines for terrestrial animals,[4] include specific sections related to biosafety. As outlined in Chapter 1.1.4 of the manual, "individual biosafety and laboratory biosecurity measure or composite measures, rather than a designated biosafety level … guides a laboratory in the safe and secure handling of any individual

[3] Terrestrial animal health code 2018. Paris: World Organization for Animal Health; 2018.

[4] Manual of diagnostic tests and vaccines for terrestrial animals 2018, Vol. I and II, eighth edition. Paris: World Organization for Animal Health; 2018.

biological agent or toxin". While OIE does not have a particular BSL-4 focus group, it is a standard-setting organization, an information hub and a very valuable network with reference centres in 38 countries.

International Experts Group of Biosafety and Biosecurity Regulators

The International Experts Group of Biosafety and Biosecurity Regulators (IEGBBR) is an informal group of biosafety and biosecurity regulators from 11 different countries, as well as observers from WHO and OIE. Its mission is:

1. to provide a forum for the sharing of knowledge and experience with issues related to the oversight of human and animal pathogen biosafety and biosecurity;
2. to promote international cooperation among competent regulatory authorities to strengthen and advance global regulatory mechanisms for the oversight of biosafety and biosecurity; and
3. to support more global or mutually complementary responses to emerging issues and threats posed by human and animal pathogens.

All members have oversight functions in their countries on biosafety biosecurity or both. New memberships are discussed with a steering committee (comprising a chair, co-chair and member) and there are no restrictions on the geographical location of members.

IEGBBR meets on a biannual basis, with its first meeting in Canada in 2007. Topics discussed include updates in member countries on issues such as regulatory revisions, dual use, and the regulation of technologies (clustered regularly interspaced short palindromic repeats (CRISPR), synthetic biogy), incidents and inspection regimes . Current activities included constructing a website, preparing a compendium of regulation and oversight of biosafety and biosecurity in different countries, sharing information on the oversight of dual-use research and outreach to the European Commission on the revision of directives and to WHO on poliovirus containment.

In addition, IEGBBR is willing to provide expertise to international groups and organizations – from the International Genetically Engineered Machine Competition Foundation to ISO and the Global Partnership against the Spread of Weapons and Materials of Mass Destruction – to promote the building of capacity for global biosafety and biosecurity.

Biosafety Level 4 Zoonotic Laboratory Network

The Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNET) was established in March 2016 to strengthen international coordination, improve knowledge sharing and leverage partnering capacity to respond to current and emerging high-consequence zoonotic biothreats through partnerships between animal health and public health laboratories. It emphasizes the word zoonotic, as the initiative stemmed from the Canadian Food Inspection Agency, national regulators of food safety and animal health.

BSL4ZNET consists of 12 member organizations from five countries: Australia, Germany, Canada, the United States and the United Kingdom. Activities centred on four main strategic focus areas, each with its own working group: knowledge sharing and institutional cooperation, international response and surge capacity, scientific excellence and training.

After its inception, BSL4ZNET established direct and efficient communication lines between BSL-4 professionals in 60 active members, with over 100 documents shared and hundreds of participant hours invested in working groups' teleconferences. Key outcomes achieved through BSL4ZNET included creating partnerships and sharing best practices between international animal and public health laboratories, facilitating international staff exchanges and a process map for material transfer and exchange between network partners, addressing critical gaps in research knowledge via the DISCONTOOLS database and building capacity for BSL-4 laboratories through a systematic evaluation of positive pressure suits.

BSL4ZNET planned to continue building capacity through a workshop on high-containment necropsy, develop broader partnerships to address critical research gaps and develop effective countermeasures, and transfer knowledge and technology globally to areas of particular need.

Group of High Containment Laboratories Directors

The Group of High Containment Laboratories Directors (GOHLD) provides an informal trusted environment in which laboratory directors can meet and openly discuss operational and management issues in their high-containment laboratories working with animal pathogens and/or high-threat zoonotic agents. The Group's members provide mutual support, facilitate the sharing of best practices for biological risk management and have the opportunity to harmonize top-level procedures. Further, the Group enables facility directors from around the globe to provide a united response on issues related to high-containment laboratories to, for example, WHO and OIE. In 2016, the Group published Guidelines for Livestock Biosafety Manual Development, which covered topics ranging from general directives on biological safety to special safety arrangements, stretching from PPE to risk management and laboratory inspections. Further direct benefits included collaboration between members during laboratory commissioning, decommissioning and demolition projects with the Pirbright Institute, United Kingdom and the US Department of Agriculture.

In addition to its role as forum for directors, the Group promotes cooperation in the area of applied research on laboratory biosafety and biosecurity and facilitates national and international training in biocontainment, biological risk management, biosafety and laboratory biosecurity. It also cooperates with external groups in facilitating access to BSL-3 animal facilities across Europe, should an outbreak of animal or zoonotic disease occur.

Efficient response to highly dangerous and emerging pathogens at EU level

Efficient response to highly dangerous and emerging pathogens at EU level (EMERGE) is an EU-funded joint action with 38 partner institutes from 25 countries, created to address the need for an efficient, rapid and coordinated response to high-threat pathogens causing serious cross-border outbreaks. Coordinated by the Robert Koch Institute and with funding for 2015–2018, EMERGE contains seven work packages and stems from previous joint actions that linked existing EU-funded networks on highly infectious bacteria and viruses with a European BSL-4 network.

EMERGE has three main objectives: to ensure efficient responses to emerging and re-emerging cross-border events, to ensure coordinated and effective responses to such outbreaks by linking up laboratory networks and institutions, and to perform external quality assurance exercises and provide appropriate training that ensure laboratory preparedness to perform diagnostics and manage biological risks in case of an outbreak. Annual assessments

are carried out to determine the priority agents, viruses and bacteria in RG3 and RG4 that have the greatest cross-border potential. If gaps in diagnostic capabilities are not addressed and no other networks are engaged in such activities, the agent is prioritized under the joint action.

In line with its objectives, EMERGE has two operational modes. For the interepidemic mode, priorities include the development of protocols and guidelines, and the assessment and enhancement of laboratory performance. For the outbreak response mode, dedicated funding is released to support network interoperability, the development of recommendations for diagnostic approaches, quality assurance for diagnostics, the provision of ad hoc training, and the validation and improvement of biological risk management. The switch from one mode to the other follows initial input from international organizations such as OIE and WHO, followed by evaluation by the EMERGE steering committee.

European Research Infrastructure on Highly Pathogenic Agents

The European Research Infrastructure on Highly Pathogenic Agents (ERINHA) is an EU research infrastructure dedicated to RG4 pathogens and the study of emerging highly infectious microorganisms. It is a distributed research infrastructure that links members and external users, including scientists from academe and industry, with European BSL-4 laboratories and complementary facilities, to allow for high-calibre research and development projects and services that could not be provided by a single national infrastructure or BSL-4 network. ERINHA was initiated before 2008 and entered its formal preparatory phase in 2010. As of July 2017, it was recognized as an international non-profit-making association under Belgian law and had a central administrative hub in Paris. It was planned to become operational in 2018. ERINHA would have a general assembly (decision-making body), executive board (executive body and source of proposals) and a director-general.

ERINHA's research portfolio particularly prioritized RG4 pathogens based on the WHO Research and Development (R&D) Blueprint. Its internal research agenda focused on increasing its capabilities, expertise and competitiveness, while its external research agenda addressed external collaboration, project hosting and research contracts.

The central coordination unit would be the access point for any requests to use ERINHA. It would perform scientific management, and provide access to services, advice and project coordination.

Current ERINHA activities included finalizing operational frameworks and recruiting the central coordination unit. Proposals for new scientific programmes (internal and external) were being developed; new European members countries were being recruited and international collaboration was being established. In addition, ERINHA advocated on the EU and international levels to keep research on highly infectious diseases a high priority on funding agendas.

Unique opportunities to advance global health enabled by high-containment facilities

Next the participants discussed the unique opportunities offered by BSL-4 facilities to advance health, using the examples of facilities in the United States, India and Spain. BSL-4

laboratories are expensive to run and difficult to construct and bring online, and require tremendous investment for maintenance, but the need for such facilities cannot be understated. While some studies can be performed in the field, others really require a BSL-4 facility. Similarly, studies utilizing surrogates do not necessarily provide data that are fully applicable for the agent in question. BSL-4 laboratories provide added benefits at a global level, where the highly trained biocontainment workforce can be deployed in emergency outbreaks and provide expertise based on experience with diagnostics, packaging of samples for shipping, and correct PPE usage for people at risk. Further, deployments may evolve into partnering opportunities, in which where laboratorians and clinicians from areas receiving outside assistance obtain training in biocontainment not only during outbreaks but also in-house at host high-containment facilities.

BSL-4 laboratories offer additional benefits, including the isolation and characterization of unknowns, testing of novel inactivation products and procedures, and modifications of assay parameters as new discoveries are made. For example, the Ebola-virus-specific ELISA was originally developed for use with whole blood and later modified for testing of semen samples. In addition, animal models are being developed to mimic the persistent infections observed in the most recent Ebola virus outbreak.

Integrated Research Facility, National Institute for Allergy and Infectious Diseases, United States of America

Construction of the Integrated Research Facility (IRF) of the National Institute for Allergy and Infectious Diseases, which is located at Fort Detrick and houses two BSL-4 laboratories, began in 2005; it began operations in 2012 and obtained CDC select agent approval in 2014.

IRF's mission is to manage, coordinate and facilitate research on emerging infectious diseases, to develop medical countermeasures that directly benefit patient management. IRF projects vary widely in scope, including the discovery of candidate countermeasures, in vitro and in vivo drug screens, the identification of candidate immune-therapeutics, the development of candidate vaccines and clinical care paradigms, and the identification of host-directed therapeutics. IRF undertakes research in a way that ensures that all aspects of any given model, from in-vitro and in-vivo models to the assays selected to analyse results, are developed to most accurately reflect human disease. Results should always be translational, with real meaning at the bedside. Critically questioning every project as to whether the research questions are valid and results generated will be truly useful, is paramount.

In addition to its variety of study areas and subject matter experts, IRF was unique in the BSL-4 community for its imaging suite, designed with animal loading zones in BSL-4 and manning stations in the adjacent clean area. Medical imaging capabilities include PET/CT, single photon emission computed tomography (SPECT)/CT, X-ray fluoroscopy and MRI. Through these technologies, disease progression and response to therapeutics in animal models can be followed and quantified in real time without reliance on animal sacrifice and pathology reports. Medical imaging has been used with animal infections with the Nipah, Hendra, Marburg and Ebola viruses, and numerous animal models are well developed for each pathogen under study. Likewise, IRF also has vast in vitro drug screening capabilities through the use of fluorescently labelled viruses.

Microbial Containment Complex, National Institute of Virology, India

The Microbial Containment Complex of the National Institute of Virology, located in Pune, India, conducts research on pathogens of high consequence, which provides an opportunity for supporting public health programmes.

The BSL-4 facility in India was built with a mandate to handle clinical samples from outbreaks caused by highly pathogenic RG4 agents. It detects, identifies, propagates and manipulates these viruses in the laboratory to develop diagnostics, therapeutics and vaccines. The 848-m^2 BSL-4 facility was accredited in 2012, one year after the first cases of Crimean Congo haemorrhagic fever (CCHF) were found in India. Owing to the unprecedented nature of the outbreak, molecular evolution studies were undertaken to investigate whether cases resulted from a bioterrorist attack. The BSL-4 laboratory developed ELISA kits and performed serosurveillance of livestock in different districts; it noted seropositivity over the country, especially in sheep and goats. Results indicated that the CCHF virus had probably circulated for many years, but perhaps was masked by some other disease and not properly detected. As differential diagnosis is a problem with this virus, due to the short incubation period combined with similar clinical signs to dengue, the National Institute of Virology developed an algorithm for segregating suspected CCHF patients based on retrospective clinical and biomedical data. The laboratory provides continuous CCHF diagnostic support to the state of Gujarat.

In addition to CCHF, the Institute has done extensive work with Kyanasur Forest disease, which causes significant human disease and mortality. It developed multiple disease-specific assays, including polymerase-chain-reaction(PCR)-based and serological (IgG and IgM ELISA) tests. Through extensive epidemiological studies in wildlife, humans and ticks, the Institute also provided critical information on seasonality of the virus in different tick species and risky behaviour that increases the likelihood of infection.

The Institute's BSL-4 laboratory provided multiple unforeseen benefits to the country after its commissioning, working on outbreak investigations, testing referred clinical samples and responding to public health emergencies, including those caused by Zika, Ebola and yellow fever viruses. It became a poliovirus repository, including laboratory confirmation of the first identified human cases of several viruses in India, provided the first report of H5N8 avian influenza virus in India and characterized two novel virus species. In addition, it provides technical support to medical colleges in improving laboratory infrastructure and diagnosis and developed protocols for maintaining biosafety measures for performing tests in the colleges.

Centre de Recerca en Sanitat Animal, Institut de Recerca i tecnologia Agrolimentàries, Spain

Centre de Recerca en Sanitat Animal (CReSA), located in the Bellaterra quarter of Barcelona, was created in 1999, with a biocontainment unit commissioned in 2005. The facility was constructed as an animal BSL-3/4 facility but works with RG3 pathogens, inspired by the Institute of Virology and Immunology Mittelhäusern design. The box-in-a-box design strictly differentiates BSL-3 and -2 spaces. CReSA gave top priority to quality assurance from the beginning, and received Good Laboratory Practice certification since 2009 in viral safety, immunogenicity, administration of test products and obtaining of samples, and immunological drug safety. CReSA was have ISO 17025 accredited in2009 in molecular and immunological diagnosis of numerous viral diseases and prions, and earned ISO9001 certification in 2015.

The CReSA biocontainment facility was designed with flexibility and redundancy. Rather than being built to house a specific pathogen or animal model, it is able to take up a broad range of studies to accommodate requests from government and or researchers. Animal suites can be modified if necessary to add equipment for work with vector-borne diseases. This flexibility allowed CReSA to take up unforeseen opportunities; for example, although the initial plans did not include work with vectors, requests arrived for this type of work and now the laboratory has breeding facilities for *Aedes aegypti* and *Anopheles stephensi* for dengue fever, yellow fever and malaria studies. In addition, it has conducted vector studies with chikungunya fever, West Nile fever and Rift Valley fever viruses.

The biocontainment unit has designated management staff, comprising six animal care workers and one technical coordinator. Four technical staff and a coordinator operate the BSL-2/ 3 laboratory, and a subcontracted company provided engineering service.

The CReSA biocontainment facility serves over 70 internal users, participates in multiple national and EU-funded projects, and provides services through private contracts. Looking to the future, CReSA hopes to increase the participation of the BSL-3 unit in EU projects by offering the space and expertise of the facility and to enhance relationships with private industry for research and development work, particularly in testing vaccines and prophylactics. Finally, the laboratory aims to be enrolled in initiatives on biocontainment, biosafety and international biological risk management (including life-long education).

Issues in biosafety and biosecurity in high-containment laboratories

Establishing and maintaining biosafety and biosecurity: the National Bio and Agro-Defense Facility, United States of America

The National Bio and Agro-Defense Facility, in Manhattan, Kansas, carried out significant amounts of evidence-based facility engineering through the use of mock-up laboratories. This ensured the long-term functionality of the laboratory by providing an opportunity to correct any details with lower quality levels than expected.

As the Facility is located in a geographical area nicknamed Tornado Alley, significant structural integrity testing was performed to evaluate the building's ability to withstand high wind speeds and possible projectiles without compromising negative pressure. A mock-up laboratory space was built within a stainless-steel-and-concrete frame, containing ductwork, electrical lines and plumbing. Pressure decay testing compared different types of concrete with varying cure times (90 versus 180 days) and assessed varied embed types and sizes and amounts of water stop material for their ability to maintain negative pressure.

Fibre-optic-cable installations and trench-drain options were also evaluated. Multiple readers were utilized for the analysis, including a differential pressure manometer, temperature thermocouple and particle counters. Overall the percentage of volume lost or gained per hour for embeds was similar to that of a Class III Biosafety Cabinet, although atmospheric temperature affected the phenomenon.

In addition to structural resistance against wind and projectiles, engineers at the Facility

constructed mock-ups of large-animal holding facilities to test numerous other factors, including load testing and finishings on penning and gating materials. Further, they performed multiple studies using tribology and tribometry to determine the best flooring for large-animal cubicles using the American Society for Testing and Materials (ASTM) F2913–11 testing method. Analyses were carried out with both the animals and workers caring for them in mind, and resulted in precise formulas for the needs of different species of animals.

All the analyses carried out were compiled in a document to assist select agent regulators during the eventual accreditation phases. Finally, the Facility's engineering team made a traceability matrix as a tool for regulators to disseminate best design practices.

Cooperation between scientists and engineers on laboratory design: National Biosafety Laboratory, Hungary

The National Biosafety Laboratory, in Budapest, experienced challenges during construction of its maximum-containment facility that pointed to ways forward. The lack of highly specialized biocontainment engineers, combined with limited published information on the best engineering practices and difficulty in accessing supplier networks, creates great difficulties when constructing maximum-containment facilities in many regions of the world. Close cooperation between scientists, engineers and designers/architects is required throughout all stages of laboratory creation to ensure that the construction project takes account of users' needs.

During initial planning stages, the creation of a user requirement specification (URS) document can greatly facilitate understanding between scientists and engineers. The URS reflects the primary needs of the users, taking input from management, scientists, engineers and safety staff, and lists all features, components, process flows, and operating parameters needed. When shared with the design team, the URS will translate to a feasible, sustainable, safe and functional facility able to carry out its objective. As such, the scope of the facility must be set out prior to construction, as laboratories intended for diagnostic work without culture, and in vitro and/or in vivo research will have significantly different footprints.

Even with a well-defined URS, engineers face many challenges with high-containment facilities. Reliance on engineering aspects (such as heating, ventilation and air conditioning (HVAC) systems and biosafety cabinets) with increasing degrees of complexity is rising, although little evidence is available to quantify the additional safety benefits of these layers for staff and the environment in comparison to good microbiological practices. In addition, while national and international guidelines on facility design may exist, they often disagree. Energy consumption must be carefully considered for its environmental implications, as well as operational costs. Cost-reduction strategies can include reducing the number of air changes during off hours, use of renewable energy and power saving options, and flexibility with HVAC, so that conditioned air is slightly warmer in the summer and cooler in the winter. The availability of evidence-based information detailing the best methods to test the effects of such energy-saving mechanisms on containment integrity will be critical for future construction projects, especially in lower-resource settings.

Many challenges in the realm of maximum-containment engineering must be addressed. The theoretical, practical and biosecurity training of engineers, upgrades of relevant international guidelines, dissemination of evidence-based practices and increased access to supplier networks would all facilitate the construction process. Combined with cooperation between scientific and engineering teams, these would ensure that facilities are designed with the primary needs of users in mind, to successfully carry out their intended mission.

Cabinet line systems: Public Health England, United Kingdom

The example of the High Containment Microbiology Department at Public Health England, in Salisbury, provided an overview of the biosafety measures offered by the cabinet lines and the changes required in switching to positive-pressure suits. There were currently no active suit laboratories in the United Kingdom. The guidance of the country's Health and Safety Executive on the principles, design and operation of CL4 laboratories had greatly influenced high-containment environments. While not necessarily legally binding, the guidance covered many aspects of the requirements for BSL-4 laboratories and animal cubicles, as well as the expectations of health and safety management.

BSL-4 cabinet lines were the current design standard for maximum-containment facilities in the United Kingdom. Legislation required that these laboratories undergo servicing every six months, at which time all systems were tested to EU or Public Health England standards. At that time, everything in the laboratory was checked and certified: including BSL-4 suite supply and exhaust HEPA filters, pressure decay, effluent systems and autoclaves. Cabinet lines underwent thorough testing as well, from thermal mapping of motors, testing uninterrupted power supply, and checking seals, pressure decay, electrical and air change rates. Worker competency was also assessed during these periods.

Frequently performing such rigorous testing basis provides many benefits. It ensures reliability and continued operation of a laboratory; ensures protection of staff, the general public and the environment; and provides an opportunity to trend data over time to predict the lifetime of any given component of the laboratory. In addition, the comprehensive service reports generated as a result provide evidence for review during regulatory audits and demonstrate compliance with the law. The High Containment Microbiology Department's planned switch to a suit laboratory in its newly planned facility would require extensive servicing and testing regimes and in-depth training of engineers to allow for maintenance and servicing during operations.

Evidence-based biosafety: BSL-4 OIE laboratory at the Institute of Virology, Centre for Research in Veterinary and Agronomic Sciences, National Institute of Agricultural Technology, Argentina

The BSL-4 OIE laboratory at the Institute of Virology, Centre for Research in Veterinary and Agronomic Sciences (CICVyA), National Institute of Agricultural Technology (INTA), in Buenos Aires, followed evidence-based biosafety and engineering provisions at INTA. Numerous regulatory authorities oversaw the Institute, including an Argentinian regulatory authority that reports to OIE, and many design features and procedures were set to BMBL and *Laboratory biosafety manual* standards.

The BSL-4 OIE laboratory contained two high-containment spaces, including a laboratory and large-animal vivarium. This facility was constructed for work with many high-consequence agricultural pathogens, although work with RG4 pathogens was not permitted.

All aspects of the laboratory were subject to a high degree of control through a building automation system that constantly monitored and reported on critical systems, such as airlocks, pass-throughs, security access, autoclaves and effluent treatment tanks. Redundancy was a key theme to many of these systems, involving duplication of not only pieces of equipment (for example, two effluent decontamination tanks) but also their key components, such as pumps and crushers.

The BSL-4 laboratories in Argentina invested significant efforts in developing their design and operating standards. Using OIE recommendations as a baseline, pressure differentials, HEPA filters and other biosafety measures were selected after significant in-house testing to ensure no loss of containment or mixing of air between rooms. For example, an air pressure differential of –50 Pa was selected for the laboratory, even though standards require only –35 Pa. Higher air differentials were similarly selected for centrifuge rooms, viral seeding rooms and animal suites. All air pressures were registered every two seconds, with alarms alerting to variations of ± 10 Pa from set points. Based on its experience, INTA specifically recommended the use of two different pressure references in the physical space of interest, as opposed to ducts, relative to the outside. In addition, testing revealed that Class II A Biosafety Cabinets were preferable to those in Class II B to avoid fluctuations in laminar flow resulting from fluctuations in room pressure.

Detailed protocols and rationale for the transport of samples from animal cubicles to the laboratory, selection of decontamination methods for solid effluent and large-animal waste, disinfection of containment suites and establishment of quarantine times for vivarium staff were also developed and described in detail. Most important was the sharing of such in-house data with the authorities, to provide regulators with access to them.

Surge capacity: Animal and Plant Health Agency, United Kingdom

The Animal and Plant Health Agency took various engineering and procedural steps in ramping up from a CL2 to an SAPO4 facility in the event of an outbreak.

The Agency focused on livestock production sectors, including diagnostic work, United Kingdom surveillance, regional laboratory network, training and response to outbreak emergencies. The facility in Weybridge, Surrey contained two high-containment laboratory

facilities operating at SAPO4/ACDP3 levels, as well as a large-animal high-containment facility. In addition to these spaces, the building was designed with an outbreak contingency plan in mind, where facilities normally operating at CL2 could ramp up to SAPO4 during outbreaks of, for example, foot-and-mouth disease, classical and African swine fever, African horse sickness virus and bluetongue virus. This was accomplished by a specially designed CL2 facility, which operated under negative pressure at all times and contained HEPA filters fitted to the air supply. Sealability was tested every six months to ensure that the facility could be fumigated if needed, and effluent treatment plants, autoclaves and the incinerator were regularly tested. The facility had not been activated to CL4 in 10 years, so training to maintain staff competency was important. Regular, semiannual training was given for two-week periods in mock-hot situations.

Using a two-phase activation process, the Agency could accommodate the testing of tens of thousands of SAPO4 required-suspected samples. The first phase involved the activation of a smaller, core suite, in which nonessential materials were removed, appropriate signage was affixed, biosecurity was enhanced through restricted access and showers were activated, and an effluent treatment plant switched to CL4 mode. This process required about four working days to complete, and processing capacity could reach 40 000–60 000 samples per week. Procedural changes accompanied the facility changes, including completely changing all clothing, showering out, utilizing a lunchroom inside for breaks, and using pass-through boxes and disinfectants. Sample receiving rooms and robot rooms for automated sample processing were also utilized. When sample numbers were too high, a second extended CL4 laboratory space was added. This process required about two weeks and led to processing scales of up to 120 000 samples per week. The Government would eventually make the decision for the Agency to downscale and come out of outbreak mode.

Training for high-containment laboratories: networks, requirements and opportunities

BSL4ZNET

The training work group within BSL4ZNET had regular teleconferences with invited guest speakers, covering topics from training and onboarding procedures, certifications and annual refreshers, to comparisons of train-tracking software, training needs and available opportunities. It supported laboratory exchanges between partner institutes, enhancing personnel competency levels and promoting collaboration and capacity building between partners. By mapping training needs and current opportunities, it identified specific gaps. In particular, needs were identified for training in best practices in handling sharps and conducting large-animal necropsy in BSL-4. As a result, a necropsy workshop with an experienced pathologist was planned for February 2018 to provide hands-on training and establish guidelines and a community of practice. Additional capacity-building projects were planned through twinning NBAF with the National Centre for Foreign Animal Disease laboratory in Winnipeg, Canada, where future NBAF research staff would gain practical experience in the BSL-4 laboratory and animal cubicle through supported long-term stays.

Public Health Agency of Sweden

The Public Health Agency of Sweden, in Stockholm, developed a comprehensive BSL-4 training programme. The Swedish BSL-4 laboratory, operational since 2001, designated training as one of its core capacities under biological risk management. The training programme covered all appropriate laboratory personnel, including researchers, engineers and maintenance staff, as well as biosafety professionals and laboratory managers. The Agency organized training courses and awareness-raising campaigns for both local and international partners, assisted the development of training tools and provided advice on aspects of biothreats and preparedness.

Before the BSL-4 training programme was established, Agency staff visited several sites in Europe and North America. All the trainers had experience in BSL-3 but not BSL-4; nevertheless, many had previous scuba experience that was utilized for developing suit training.

Several general factors should be considered in developing BSL-4 training programmes. First, training should be integrated with specific personnel tasks, be based on scenarios, build capacity and utilize a know–feel–do approach. In addition, it should contain both biosafety and biosecurity components. Consideration must also be given to timing, perhaps treating training as a continuous learning process, rather than a requirement for access. Finally, checklists should be used to ensure that learning objectives are covered and measurable outcomes are reached, such as enhanced individual capacity, improved teamwork and/or greater compliance with regulations. Laboratories intending to launch external in-house training programmes for international visitors should be aware of potential financial, legal and security challenges.

Further to the continuing capacity-building activities for biosafety and biosecurity, the Public Health Agency of Sweden prioritized the development of a training curriculum for BSL-4 laboratories and the recognition of best practices. This could include a BSL-4 training handbook, sharing of training tools and tutorials.

IEGBBR member countries

An overview of regulatory requirements related to training in IEGBBR member countries showed that, in Asia-Pacific countries, both Australia and Singapore required training and competency assessments for any person with access to security-sensitive biological agents, and the regulations of both countries described the scope of training. In Japan, personnel handling pathogens and toxins must have relevant knowledge and skills, although the specific scope of training was not laid out.

In the Americas, Canadian regulations similarly specified the training areas required for anyone with access to select agents and toxins, while regulations in the United States require that any individuals approved through security risk assessment received relevant training, though its scope was not strictly defined.

Of the European IEGGBR member countries, France had a ministerial order on training, and Denmark required training as a licensing condition. The Netherlands Biosecurity Office provided training workshops and electronic learning toolkits for stakeholders, and Switzerland offered a biosafety curriculum for biosafety officers and subject-specific curricula for various topics. Finally, the United Kingdom required safety training under the Health and Safety Executive, though this was not specific to biosafety and biosecurity.

All IEGBBR member countries offered multiple, varied approaches to training in biosafety and biosecurity, including formal courses, public resource documents and in-house, institutional-level courses. National biosafety associations, the International Federation of Biosafety Associations and EU centres of excellence offered additional training opportunities and efforts to enhance competency in biosafety and biosecurity.

High-containment laboratories in Novosibirsk, Russian Federation

The Russian regulatory framework for high-containment facilities required national- and institutional-level inspections of all facilities. As these facilities contained one of the two WHO-designated smallpox reference laboratories, they were subject to annual WHO expert review of biosafety and biosecurity. As a national mandate, all people working with highly pathogenic organisms must go through training at least once every five years. The biosafety department at the Russian State Research Centre for Virology and Biotechnology carried out training of Centre personnel and researchers from other Russian federal institutes. It delivered both site- and agent-specific training and conducted training assessments and monitoring of personnel awareness through annual examinations. In the Russian Federation, only people who passed these examinations were permitted to work with highly pathogenic organisms.

BSL-4 laboratory oversight

Introduction

Speakers with diverse roles and geographical locations extensively covered the role of competent regulatory bodies in oversight and enhancement of biosafety and biosecurity in BSL-4 laboratories. Regulatory authorities have many public health responsibilities and accountabilities as government or multinational agencies. Their mandates include protecting public health, ensuring the availability and delivery of timely diagnosis and treatment, and promoting the advancement of science and research. Their policies should advance public health by helping to speed innovations that make diagnostics, drugs and vaccines more effective, safe and affordable. Finally, they assist in the diffusion of accurate, science-based information to the general public.

Federal Select Agent Program, United States of America

The Federal Select Agent Program had an important role in the regulation and oversight of high-containment laboratories. It was a list-based regulatory programme that oversaw the possession, use and transfer of select biological agents and toxins considered to pose severe threats to human, animal or plant health. The list of select agents covered 66 pathogens and toxins, with Tier-1-classified agents presenting the greatest risks of deliberate misuse with the most significant potential consequences for public health or the economy. Any agency wishing to work with a listed agent or toxin must be officially registered and certified.

The Division of Select Agents and Toxins of CDC was involved in the oversight of BSL-4 laboratories on numerous levels, splitting attention evenly between issues of biosafety and biosecurity. It carried out facility inspections prior to issuing certificates of registration, upon recommissioning of a facility, during annual inspections and following incidents or mitigation of major containment issues. Through these inspections the Division ensured that registered entities had appropriate measures in place to protect staff, the public and the environment. Accordingly, it also took appropriate actions on regulatory violations, to address identified risks and increase future compliance with the regulations of the Federal Select Agent Program.

The inspection process reviewed several areas, including records and checks of HVAC systems, effluent decontamination systems, building automation systems, security systems reviews and inventory access records. Inspections were carried out to BMBL standards to ensure that appropriate biosafety measures were in place, emphasizing proof of agent-specific training, the use and availability of appropriate PPE, equipment certification records (including primary containment, equipment with potential for aerosols generation and decontamination technologies) and all specialized support systems for BSL-4 suit laboratories and ABSL-4 facilities.

From a biosecurity perspective, the Division of Select Agents and Toxins:

- carried out security risk assessments in conjunction with the Federal Bureau of Investigation prior to granting individual access to select agents and toxins;
- supported continuous monitoring and self- and peer reporting;
- had guidelines for physical laboratory security;
- oversaw agent inventory and accountability; and
- handled reports of theft, loss or release of select agents or toxins.

Since 2003, there had been no reported thefts of a select agent or toxin from a registered entity, no deaths among laboratory workers and no reported cases of illness or death in the general public due to work with these agents in regulated laboratories. The Federal Select Agent Program provided guidance, training and outreach to help entities meet the requirements of the regulations, and collaborated nationally and internationally on the development of biosafety and biosecurity oversight programmes.

Regulators and institutional review committees in the promotion of responsible science,

Switzerland

Swiss legislation did not require an institutional biosafety committee, but every institution must have at least one biosafety officer who liaised between national regulators, principal investigators and laboratory personnel. A national biosafety committee of 15 experts advised the competent regulatory agency and issued recommendations in all biosafety-related areas, from required training to major decisions on new facility construction projects.

National regulators were well aware of what went on in which institution, but did not influence the type of research carried out. Through their oversight roles, they aimed to harmonize practices between laboratories through strong communication with the biosafety officers and evaluation of institutional risk assessment and mitigation measures. Regulators in Switzerland handled numerous authorization requests from laboratories that informed them of the particular organisms utilized, the volumes used, genetic modifications and the publication of scientific papers. They were also involved in making major decisions on national biosafety

issues. Examples included requirements for any future gain-of-function research with highly pathogenic avian influenza (HPAI) to be conducted in BSL-4 facilities, despite other countries allowing such work under enhanced BSL-3 conditions, and the designation of Spiez as the new site for a BSL-4 facility with human pathogen capacity and of a national high-containment laboratory network that included Spiez and the Mittelhäusern site of the Institute of Virology and Immunology.

Regulators' perspective

A break-out session held exclusively for regulators enabled them to discuss common challenges and concerns in BSL-4 laboratory oversight. The discussions touched on numerous topics, such as national standards, prescriptive versus performance-based biosafety, training requirements, inspections, inventory control and reporting of laboratory incidents. As legal systems and national laws and bureaucratic processes varied greatly around the world, so did the regulatory regimes governing high-containment facilities. The regulators pointed to numerous differences in the guidelines that shaped laboratory design and operations, the frequency with which conformity to such regulations was officially inspected and the nature and depth of such inspections.

The inspection process could comprise internal audits, federal- or state-level inspections or a combination of both. In some cases, national frameworks granted laboratories flexibility regarding internal audits, granting each institution the right to determine the frequency at which they occurred. In other cases, the requirement was altogether absent. The frequency of national BSL-4 inspections was also highly variable, ranging from twice per year to annually to every three years.

The availability of national standards or guidelines varied greatly in different regions of the world. Some countries, such as Canada, had established extensive legally binding standards covering biosafety at the user, institutional and even engineering levels. Others had less detailed national guidelines, which may or may not include requirements for facility construction, and yet others had no specific national requirements. In many of these instances, the WHO *Laboratory biosafety manual* served as an important guidance document. The countries that had national standards varied widely in the intervals at which these were revised.

The shift from prescriptive to performance-based regulatory approaches to biosafety was a challenge for many regulatory bodies. Inspecting laboratories through a performance-based approach was much more difficult for the regulator. Adding more flexibility gave more room for interpretation; this could often lead to confusion for management and operators, which in turn resulted in some facilities taking a more stringent approach than necessary out of fear of possible noncompliance.

Approaches to training oversight also varied. These ranged from a requirement for agent-specific training in some countries to a general, nonprescriptive requirement for training in others. For countries without specific requirements, national systems allowed for institutions to interpret international guidelines relating to the training of personnel, but each institution was responsible for organizing training sessions and decided on content on the basis of its own priorities. Thus, the review of documentation to ensure that training had taken place was not a set part of all national inspection processes.

Regulations around laboratory inventory control were widely discussed. Many national systems had diverse regulatory bodies for work with human and animal pathogens, while zoonotic agents were often regulated on both sides. In certain countries with BSL-4-trained inspectors, the inspection process included physical inventory checks. Depending on the country and agency in question, there might be requirements for precise titres and volumes of all RG4 agents, the specific number and physical locations of receptacles, passage history and user access records. In general, even if the regulatory agency did not hold specific details of an institute's inventory, a designated officer within the entity was expected to have the information accessible.

Most countries represented at the breakout session required notification of laboratory incidents and exposures to regulating bodies, with distinctions often made between incidents and LAIs. The timeframe within which notifications were required ranged from immediate (made by telephone) to within two days or longer. In other cases, written records of incidents were sufficient and provided to regulatory bodies during the auditing process, although national records were not kept. As a result of these discussions, the regulators noted an opportunity for WHO to collate global information on LAIs as a contribution to evidence-based approaches to biosafety. Further, owing to differences in methods and attempts to carry out root-cause analyses, WHO could further play a role in the sharing of best practices.

Operators' perspective

In another breakout session, laboratory operators and leaders discussed aspects of the oversight of laboratory personnel and operations, in order to compare and contrast institutes' diverse approaches and identify best practices and common concerns to share with their regulatory counterparts.

With the shift towards performance-based biosafety allowing laboratories more freedom, laboratory operators had a common desire for increased interaction and discussion with regulators, to help shape policies satisfactory to both. Operators noted that both top-down and bottom-up approaches were employed to ensure adherence to regulations and safe laboratory operations: some regulations came from within while others came from above.

The group considered a combination of self-auditing for continued improvement (including yearly SOP evaluations, consultations with biosafety officers and review of laboratory procedures to take corrective action), internal institutional reviews and external audits to be beneficial in proactively tackling operational issues.

Inventory management systems varied greatly among BSL-4 laboratories, with each using diverse systems with varying degrees of complication for tracking pathogen stocks. The participants overall felt satisfied with the systems they had in place, although most felt there was room for improvement. In addition, while no specific requirements were laid out as to types of acceptable systems for inventory management, operators recognized the importance of using a system that could easily be audited and said they would appreciate input on preferences from their regulatory partners.

Operators and regulators showed a major difference when pathogen-specific training was discussed. For the operator, working safely in the environment was more important than focusing on a specific pathogen. Some institutes had scientists working with only one pathogen and others had groups that worked with many different agents. Thus, specific

training on the processes being carried out should have the greatest importance. The participants in the operators' session suggested a role for WHO in identifying potential partners to facilitate training or establish a training network for BSL-4 facilities across the globe, in order to harmonize best practices.

The laboratory operators were interested in the establishment of best practices for incident response, as they were concerned about how a major incident in any BSL-4 facility could negatively affect the entire high-containment laboratory community. They agreed that the development of standardized plans to respond to emergencies must involve input from the institutional biosafety committee, occupational safety and health, the CLC and local first responders. In addition, the establishment of mechanisms and checks to ensure that laboratory personnel were fit to work as key to incident prevention. The operators noted a large range of approaches to making such decisions, with personality, performance and overall health as influencing factors. For those granted access to BSL-4, a high level of trust between supervisors and personnel, combined with nonpunitive reporting systems, were shared ideals to encourage communication and ensure that laboratory personnel avoided work in containment if they felt unwell for any reason.

Pressing issues in sharing pathogens

Nagoya Protocol

From WHO's perspective, the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization,[5] a supplementary agreement to the Convention on Biological Diversity, has the objective of ensuring fair and equitable sharing of the benefits that arise from use of genetic resources, including access to them. This formal agreement creates a global framework in which Member States commit themselves to fulfilling two basic requirements:

1. prior informed consent: entities wishing to access genetic resources first obtain permission from their country of origin; and
2. mutually agreed terms: bilateral agreement between provider and recipient on how benefits arising from use of this material are shared with the country of origin.

At present, 101 governments had officially signed on to the Nagoya Protocol. WHO is not a Party, but an observer of intragovernmental meetings, and provides expert scientific advice on issues surrounding the Protocol. In response to concerns about the implications of this agreement, WHO worked to identify areas where the Nagoya Protocol may affect public health programmes that require access to pathogens. Study questions specifically examined the Protocol's implications for access to: influenza virus with pandemic potential, seasonal influenza viruses and other pathogens that affect human health. In addition, WHO examined the functionality of a bilateral approach versus a multilateral approach in terms of potential bureaucratic delays that could affect response times to health emergencies.

[5] The Nagoya Protocol on Access and Benefit-sharing. In: Convention on Biological Diversity [website]. Montreal, Secretariat of the Convention on Biological Diversity; 2018 (https://www.cbd.int/abs/, accessed 10 December 2018).

WHO received about 30 responses from Member States, nongovernmental organizations and vaccine companies. The results showed that the Nagoya Protocol had implications for public health responses to infectious diseases: some positive and others causing concern. Particular issues surrounded legal uncertainty resulting from the implementation of the Protocol, where bilateral agreements between countries with highly diverse laws could prove highly complex and the increased costs associated with this legal uncertainty could result in delayed development of health countermeasures. In addition, the broad principles set out by the Nagoya Protocol allow individual Member States to dictate how implementing legislation will address pathogens and how to implement health emergency measures.

As article 4.4 of the Protocol specifies that, where specialized international access and benefit-sharing frameworks exist for any particular genetic resource and are consistent with the objectives of the Protocol, such a framework would supersede the Nagoya Protocol for that particular genetic resource. The Pandemic Influenza Preparedness (PIP) Framework, for example, recognized by the EU as a specific framework for the transfer of pandemic influenza virus strains, would allow EU countries to bypass the legal aspects of the Nagoya Protocol for sharing of influenza viruses. Aside from the PIP Framework and the WHO advisory committee presiding over all live-variola-related decisions, however, no other pathogen-specific oversight groups existed.

The WHO report set out a number of specific actions to implement the Nagoya Protocol in harmony with public health programmes requiring access to pathogens. These included the promotion of dialogue, consultation, international cooperation and public awareness around the Protocol. Articles 19 and 20 of the Protocol require each signing country to develop guidelines, standard templates, common sets of principles and codes of conduct to clarify rules for access to pathogen samples, and others to accelerate the sharing process.

Member States showed considerable interest in the results of the WHO study, which also provoked further questions. These included the implications of the PIP Framework for non-EU countries and implications for establishing sharing practices for non-influenza pathogens and genetic data. To answer these questions, WHO worked closely with the Secretariat of the Convention on Biological Diversity and focused particularly on genetic data. WHO also convened consultations on the PIP Framework, had the R&D Blueprint and was developing a tool for material transfer agreements (MTAs) that would help countries protect their interests when bilateral agreements are made.

WHO strongly encouraged stakeholders to better understand the Protocol, as it might have great implications for public health. The global issue of the Nagoya Protocol relating to pathogen sharing was still at a preparatory phase, providing an opportunity to shape policy decisions surrounding its implementation. The decisions in the future meeting relating to pathogen sharing could have unintended consequences for public health and how laboratories can share pathogens and/or their sequence data. The scientific community needed to share its questions and concerns with government ministries and agencies involved in decision-making.

The participants discussed their concerns about the consequences of the Nagoya Protocol. For example, it might require the revision of existing arrangements between academic or research laboratories, including memorandums of understanding and MTAs, though this would depend on the laws of the countries concerned. Even contracts made prior to 2014 might require examination to ensure their terms were compliant with the Protocol. The

ability to access and share reference collections, critical to laboratory work around the world, was another serious concern. While the Protocol was unlikely to affect strains pre-2014, this would depend on regulations set out by each member country; added complications would arise when a third country requested a genetic resource from a recipient country, rather than the original supplier/donor country. Other potential issues arising from metagenomics analyses and unexpected results from diagnostic samples must also be addressed.

As the number of countries that were Parties to the Nagoya Protocol continued to increase, others would likely be constrained to join, although some developing nations might be unable to do so, owing to the lack of government infrastructure. Mechanisms to assist pathogen sharing between Parties and other countries must therefore be devised.

Shipping of Category A Infectious Substances

A review of issues surrounding the shipment of Category A (Cat A) Infectious Substances fostered discussion on possible solutions to its overregulation. The recommendations of the United Nations Committee of Experts on the Transport of Dangerous Goods established tightly regulated guidelines for shipping hazardous agents and materials, with varying requirements depending on the particular agent and sample matrix.

The most stringent regulations applied to Cat A agents, which were defined as infectious substances transported in a form capable of causing permanent disability or life-threatening or fatal disease in otherwise healthy human beings or animals upon exposure. Within this category, pathogens classified as United Nations 2814 (affecting humans) and United Nations 2900 (affecting animals only) were subject to the strictest requirements, regardless of their form, including cultures, clinical specimens, and even suspected clinical specimens, depending on the pathogen. Category B (United Nations 3373) material, on the other hand, refers to biological substances, including patient specimens from HPAI infections or anthrax.

Combining the Committee of Experts' specifications with the diverse shipping regulations of each mode of transportation (air versus sea or land) made the transport of Cat A agents highly complex. Very few couriers were licenced to handle these packages and enormous paperwork and financial requirements often resulted in shipment delays. In addition, even licenced couriers might decline to transport specific Cat A substances, which had occurred with packages containing Ebola virus samples. On the other hand, shipping Cat B agents did not require licenced carriers, was timely and less costly, and could be done even through postal services. Further, aside from a difference in drop-test resistance, the packaging requirements for Cat A and Cat B agents were essentially identical, suggesting that the same level of risk protection was achieved in either scenario.

No documented cases had ever been recorded of accidents involving shipped infectious substances resulting in infection of personnel. Combined with the abovementioned facts, this raised the question as to whether the regulations surrounding Cat A shipments were truly essential and helpful for protecting public health. If the Cat A classification were re-examined, and agents could be shipped with the same degree of safety as Cat B agents, the greater number of capable shippers, combined with the decreased cost, might have significant public health benefits. As far as clinical specimens are concerned, Cat B practices should perhaps be seriously considered for the shipping of Cat A agents. WHO hoped to organize a stakeholder meeting on the shipment of infectious substances in the near future to address these issues.

MTAs

MTAs needed to be well constructed, and the strategy adopted by the Institute of Novel and Emerging Infectious Diseases at the Friedrich Loeffler Institute, in Germany, exemplified its commitment to public sharing. MTAs between high-containment laboratories serve many important purposes, from virus discovery, to the development and validation of assays, to animal studies. They should be designed for two different scenarios – normal business and emergency situations – as stated in the Nagoya Protocol. Material to be shared includes samples, pathogens, antibodies and genetic constructs. Ultimately, the capability for material exchange and transfer is a key performance indicator of international research agencies; those incapable of it are probably not fit to play a great role in international interventions.

In the past, collaboration had often been collegial; materials were transferred based on mutual trust, scientific interest and ethical values. This sort of collaboration was more difficult at present, as institutions usually had formal systems, profit interests and reputations to uphold. Governance issues could also complicate material transfers, as the ultimate signing authority was not always clear and responsibilities towards third parties might come into play. In addition, issues surrounding the place of jurisdiction, claims for damages and guarantees of material fitness might have legal implications. Further, approaches to dealing with legal issues varied between continents.

The Friedrich Loeffler Institute was a recently constructed facility for research and diagnosis of high-risk animal pathogens. In addition to significant BSL-3 and BSL-3+ large-animal cubicle spaces, the Institute was the only maximum-containment facility in Europe with capacity for large-animal BSL-4 work. In addition to work in Europe, the Institute participated in several international collaborations and had received a total of 25 000 mammalian samples from African partner countries between 2013 and 2017. This was largely achieved through the Institute's simplified approach to MTAs, which had removed any clauses related to profit orientation and government issues. An MTA contained 10 simple clauses pertaining to ownership of original material, use for noncommercial purposes, liability for fitness of the material, confidentiality and proprietary aspects of the results obtained. In its MTA, the Institute granted the beneficiary ownership of all research results, sought no royalties, permitted publications with written approval and stated that material should be destroyed at the study's conclusion, although no time stipulations were attached.

The use of simplified MTAs with plain language that regulate only truly relevant issues can greatly facilitate collaboration. Having a streamlined internal MTA process with downgraded authorization procedures can shorten timelines, simplify negotiations and increase the likelihood of successful collaboration.

Building confidence between high-containment laboratories and the global community: cultivating a safety-oriented culture

Public Health Agency of Sweden

Intensive risk communication by the Public Health Agency of Sweden changed the community's perception of its BSL-4 laboratory from a high-risk to a high-security facility, seen as a resource rather than a threat. Since opening the laboratory 2001, the Agency had invested heavily in promoting biosafety and training through many activities, including the

establishment of a Nordic biosafety network, development and delivery of the first postgraduate biosafety course in Sweden, capacity-building projects and involvement in workshops of the European Committee for Standardization (CEN).

The BSL-4 laboratory had been fully operational for 16 years, contained two fully functional BSL-4 units and had hosted eight onsite training courses for international participants. During this period, it had had zero shutdowns, zero biosecurity breaches and zero major staff incidents. There was a nearly 100% (assumed) reporting of deviations in the BSL-4 laboratory, a much higher rate than in lower-containment areas. Having the right people in all areas of laboratory operations and ensuring their willingness to interact were key to success. Other critical factors included a solid research, diagnostics and biosafety infrastructure; permanent financial support through government funding; long-term strategies for national preparedness; and international collaboration.

BSL-4 laboratories should prioritize particular areas to increase confidence with the global community. The first was performance-based validation of risk management. Having validation mechanisms in place increased the implementation of a safety-oriented culture and the likelihood of collaboration with other laboratories. Sharing of best practices, from biosafety measures to inactivation procedures and training resources to facility operations, was another key means for BSL-4 laboratories to build trust. Participating in formal laboratory networks and establishing bilateral memoranda of understanding were excellent means to this end.

Finally, as described by CEN workshop agreement 15793 on laboratory biorisk management provisions, BSL-4 laboratories must make personnel reliability assessments to ensure that staff are fit for the job and would promote the Agency. The Agency employed a thorough screening process, generating an overall candidate profile based on health checks and medical examinations, background checks and behaviour-based screening. Psychological assessments were included to assess emotional stability, capacity for communication and cooperation, judgment, integrity and capacity to resist external pressure, acceptance of and capacity to follow instructions, and an active approach to safety and security management.

KCDC, Republic of Korea

National and institutional systems fostered a culture of biosafety in the Republic of Korea. Biosafety and biosecurity were part of the national budget and were governed by numerous regulatory acts. All laboratories in the country must be registered with the appropriate ministries governing the use of pathogens with which they worked.

Laboratories required ministerial approval before starting work with RG3 and RG4 pathogens, and must apply for reauthorization every three years. Those dealing with high-consequence pathogens were subject to regular inspections of facilities, operations and biosafety and biosecurity management.

The county made significant investments in enhancing biosafety and biosecurity. Numerous published national guidelines specified containment levels, standards for animal facilities and biosafety and security in general, and even the verification processes for high-containment facilities. Annual education and training were required for all research and laboratory staff, and biosafety training workshops and conferences were regularly held for research personnel. Targeted efforts to enhance institutional biosafety committees included professional training and national workshops for their members, and the development and distribution of guidelines for the committees.

At KCDC, biosafety systems were governed at the national (BSL-4 certification, revalidation, inspection, biosafety education) and institutional levels (SOP development, education, training, and emergency-response drills). The BSL-4 training process was highly structured, with general theoretical training provided to all new staff, followed by practical training in a mock laboratory and significant onsite training by experienced supervisors. Overall, scientific staff participated in over 80 hours of training prior to testing and task-specific certification. Regular incident-response training and emergency drills familiarized workers with emergency procedures and evacuation routes, and periodic reassessment and retraining of existing staff ensured that knowledge and skills remained up to date. Within the institution, management and biosafety officials ensured attention to biosafety during the development of SOPs, by holding periodic meetings for dialogue between stakeholders, and continuing to improve the expertise of the institutional biosafety committee.

Through a combination of national, institutional and internal regulations, the KCDC BSL-4 laboratory was committed to a culture of biosafety, leading to safer science and building confidence and trust in the global high-containment community.

CDC, United States of America

The BSL-4 research groups at CDC took a particular approach to achieving a safety-focused culture. Many research groups studying diverse pathogens occupied CDC's high-containment facility. To improve coordination between the many stakeholders, CDC established a high-containment laboratory operations group as a forum to discuss scheduling requirements, set standards for routine training, guide protocol and manual development, and ensure safe working practices. Members included representatives of research staff, the sections dealing with animal care, engineering and security, the internal select agent programme and linked parties. CDC linked the high-containment operators with upper management by creating a high-containment laboratory governance council with representatives of CDC management, biosafety and security, and the high-containment laboratory operations group. This council approved policies, set priorities for the high-containment laboratory and resolved issues on which the operations group could not reach consensus.

CDC applied a standard training regimen for the BSL-4 laboratory. All staff received initial training on general entry/exit and emergency procedures from the office of laboratory safety, and annual refresher training thereafter. Each research programme then offered pathogen-specific training, beginning with practical training in BSL-2 and followed by closely monitored, mentor-based training in BSL-3 and -4. CDC stipulated a minimum number of required hours or training sessions prior to granting individual access, although mentors might require additional entries before deeming a person competent to work alone.

CDC enforced a regular standard review procedure for many critical procedures. A laboratory safety review board examined all SOPs on an annual basis, conducted quarterly reviews on records of material inactivation and removal from BSL-4, assessed validation data for inactivation protocols and approved inactivation SOPs. Drills on emergency procedures were reviewed annually, and staff competency was regularly assessed; other BSL-4 research groups peer reviewed the study plans of BSL-4 research programmes.

Biosafety controls for newly emerging pathogens in a limited-resources setting

The final speaker challenged the participants to resolve a scenario-based dilemma: the selection of biosafety controls and laboratory handling procedures for the diagnosis of an unknown pathogen in a limited-resource setting.

The selection of biosafety and containment measures is usually based on an understood or assumed level of risk associated with the material, and greatly influenced by a number of factors, such as the location of testing (in the field versus on site), availability of resources and information to work with, cost considerations, time pressures to provide results, political and community consent, and legislative requirements. When the agent is unknown, the determination of risk is often based on extrapolation from what is known of similar pathogens. In other cases, even this may not be possible. Well-equipped BSL-4 laboratories allow for a broader range of manipulations than work in the field, where limited risk mitigation measures accommodate only methodologies that do not require pathogen propagation.

In countries such as New Zealand, which had no RG4 endemic organisms, laboratorians neither expected nor were accustomed to handling materials containing such organisms. Nevertheless, increasing border pressure due to international travel (where ill visitors or returning travellers may present with symptoms questionable for high-consequence pathogens) presented a need for RG4 diagnostic capabilities in nonendemic countries. In response to this pressure, New Zealand was building a high-containment enhanced CL3+ facility, to contain a separate high-biosafety laboratory suite with BSL-4 design features, where initial diagnostic screening using inactivation methods could be performed. In anticipation of future activities, the participants were asked to describe appropriate biosafety controls and guidance to laboratorians dealing with suspected diagnostic samples of potentially uncharacterized RG4 agents.

The participants strongly recommended that a rigorous training programme, including risk assessment training and biosafety cabinet training, be required. Building on this, pairing staff inexperienced in high-containment work with experienced mentors would build the former's confidence in using enhanced PPE and other procedures specific to high containment.
The majority of participants strongly encouraged the use of inactivating agents, with suggestions including immediate inactivation at the field collection site or the use of partial inactivation methods, such as Triton X-100 in the case of Ebola virus, which greatly reduce virus titre and infectivity without interfering with biochemical tests. Other options include the addition of inactivating buffers directly to vacutainer tubes, and a method developed by the National Centre for Virology in India: a one-minute inactivation method that does not interfere with downstream nucleic acid or serological testing. Alternatively, and perhaps ideally, initial samples from an unknown suspected outbreak situation should be immediately aliquoted with a portion inactivated and sent for next-generation sequencing characterization, while the remainder is stored safely in its nascent form until further information is acquired.

While some participants felt that attempts to propagate unknown samples could be considered when associated case fatality rates are not unusually high, others called for caution in testing samples for known/expected agents, rather than the unknown. For example, at the US Department of Agriculture attempts to propagate suspected porcine reproductive and respiratory syndrome virus samples in cell culture revealed co-infection with Reston ebolavirus, an agent with no prior history of swine or other livestock infection. Ultimately, having well established SOPs in place that account for process-associated risks in different scenarios is key to guiding staff in their initial decision-making. Beyond the facility level, having well established relationships between laboratories would provide remarkable strength to collaborative international responses to outbreaks.

Collaboration between high-containment facilities and WHO: moving forward

The coming together of participants from over 50 countries for the WHO Consultative Meeting on High/Maximum Containment (Biosafety Level 4) Laboratories Networking resulted in intense discussions from operators' and regulators' perspectives. All participants showed keen interest in collaborative opportunities in areas ranging from scientific research and training to recruitment strategies, operations and facility design. Discussions highlighted several critical points where commitment from networking partners and WHO is required to strengthen the global BSL-4 community in moving forward.

Creation of a community of practice

With the unprecedented expansion of BSL-4 laboratories worldwide, opportunities and mechanisms to promote the sharing of best practices would lead to enhanced biosafety and biosecurity as early as the planning stages. Many critical areas were noted, including:

- the efficacy of inactivation methods, with a focus on effects on infectious dose;
- the environmental impact of chemically inactivated waste;
- the validation of chemical showers;
- waste disposal plans for emergency situations, such as excessive waste from Ebola patients;

- information on facility engineering, operations and maintenance for new projects in the design stage;
- facility decommissioning;
- strategies for community engagement and messaging on working together for responsible science;
- the availability of countermeasures or postexposure protocols for LAIs;
- recruitment strategies for new laboratories;
- inventory management systems;
- incident response plans;
- auditing and regulations; and
- tools and metrics for risk assessment.

Facility sharing

Collaborative facility sharing for operator cross-training would increase capacity and confidence building in the BSL-4 community. It would be especially important when new laboratories were constructed, so that new recruits could gain real experience prior to working in their own facilities. Participants suggested twinning through bilateral agreements as the best approach. Further, a commitment from BSL-4 laboratories to provide surge capacity for other countries was warranted in anticipation of future emergencies.

Mapping of training opportunities

The importance of training for laboratory operators and facility staff was among the most discussed topics at the Meeting. The participants identified numerous gaps in BSL-4 training, from the identification of best training practices and maps of training opportunities and rosters of expert trainers to institutional assessment mechanisms to demonstrate comprehensive and effective training programmes. They repeatedly stressed the value of creating a platform to map training opportunities and share best practices.

Sample sharing

With complications likely to arise from the ratification of the Nagoya Protocol, there was a need to establish sample sharing frameworks that include legal conditions. Suggestions included placing certain pathogens in the public domain, and establishing a set of laboratory strains without consensus on ownership that could be shared without any conditions.

International recognition of BSL-4 laboratories

Differences in national regulatory systems and guidelines led to varied interpretations of requirements for BSL-4 facilities and programming between countries using the WHO *Laboratory biosafety manual* as a guidance document and those employing particular national frameworks. The rapid expansion of BSL-4 laboratories, combined with a lack of internationally designated inspection teams, had resulted in a certain level of mistrust between well established and newly operational facilities. New facilities in countries without strong international research networks met hesitation from international partners about admission to cooperative and collaborative agreements, particularly on material sharing, even when significant investments in biological risk management had been made. As a result, there was a clear need to establish baseline standards for an acceptable BSL-4 facility. The participants encouraged WHO to take part in designating a formal group of international experts to perform site visits and officially vouch for facilities and their operations.

Suggested future roles and responsibilities for WHO

The participants suggested that WHO take on or continue several initiatives to support the global BSL-4 community of practice. These included:

- facilitating collaboration between high-containment laboratories;
- identifying competent partners to provide global biosafety training ;
- mapping and coordinating existing networks;
- continuing messaging on the revised *Laboratory biosafety manual*;
- gathering data on LAIs and incidents on a global scale; and
- designating and deploying experts for validation of and expertise sharing with new BSL-4 laboratories.

The participants expressed an overwhelming interest in a WHO-coordinated, designated web space to serve as an information hub for BSL-4 laboratories, which would facilitate the dissemination of data and access to network partners to all members of the BSL-4 community.

Annex 1. Agenda

Day 1: Wednesday, 13 December

Topics	Speakers
Registration of participants	
Opening remarks • Meeting objectives and expected outcomes • Introduction of chairperson for the day and rapporteur • Housekeeping announcement	Guenael Rodier Florence Fuchs Sébastien Cognat Kazunobu Kojima
Keynote talk	Jim LeDuc
WHO *Laboratory Biosafety Manual* revision and high-containment approaches • Revision principles, concepts, and updates • Biosecurity level 4 (BSL-4)/high containment/varying approaches • Open discussion	 Kazunobu Kojima Kathrin Summermatter
Activities of other organizations, networks and their role regarding high containment work • World Organisation for Animal Health • International Expert Group on Biosafety and Biosecurity Regulation • Biosafety Level 4 Zoonotic Laboratory Network • Group of High-Containment Laboratory Directors • Quality Assurance Excercises and Networking on the Detection of Highly Infectious Pathogens • European Research Infrastructure on Highly Pathogenic Agents	 Christine Uhlenhaut Thomas Binz Primal Silva Christine Bruce Antonino Di Caro Hervé Raoul

Activity update: planned, under construction, newly constructed and established high-containment laboratories
 	
• *High-containment laboratories planned*
  ○ Nagasaki University, National Research Centre for the Control and Prevention of Infectious Diseases BSL-4, Japan
  ○ Chinese Center for Disease Control and Prevention, China
  ○ Centre for Emergency Preparedness and Response, Public Health England, United Kingdom
• *High-containment laboratories under construction*
  ○ Institute Pasteur de Côte d'Ivoire, Ministry of Higher Education and Scientific Research, Côte d'Ivoire
  ○ National Bio and Agro –Defense Facility, Department of Homeland Security, United States of America
  ○ High Containment Large Animal Facility, Pirbright Institute, United Kingdom
• *Newly constructed high-containment laboratories*
  ○ Chinese National High Containment Facilities for Animal Diseases Control and Prevention, Harbin Veterinary Research Institute, China
  ○ National Biosafety Laboratory, Wuhan Institute of Virology, Chinese Academy of Sciences, China
	
	Jiro Yasuda
	
	Zhao Chihong
	
	Allen Roberts
	
	Mireille Dosso
	
	Eugene Cole
	
	Michael Johnson
	
	Zhigao Bu

○ Osong BSL-4 Laboratory, Korea Centers for Disease Control & Prevention, Republic of Korea	Yuan Zhiming Min Woo Park
○ Victorian Infectious Diseases Reference Laboratory, Australia ○ Centre for Biological Threats and Special Pathogens, Robert Koch Institute, Germany • *Established high-containment laboratories moving into the future* ○ Commonweath Scientific and Industrial Research Organization, Australia ○ US Army Medical Research Institute of Infectious Diseases, United States of America	Julian Druce Andreas Kurth James Watson Sina Bavari
New laboratories and public opinion: earning support and trust of the public • Allocation of funds for construction and operation • Addressing diverse opinions of citizens • Communication with community • Maintaining support through showing a safety record to the public and good laboratory practice	Ronald B. Corley Masayuki Saijo
Unique opportunities enabled by high-containment facilities to advance global health • Research on pathogens of high consequence • Capacity to develop and test novel therapeutics • Ability to address recently identified global health threats • Opportunities to safely conduct high risk research	Lisa Hensley D.T. Mourya F. Xavier Abad Morejón de Girón

Day 2: Thursday, 14 December

Topics	Speakers
Recap of Day 1 **Appointment of chairperson**	Day 1 chairperson (Bryan Charleston) Kazunobu Kojima
Overview of the Nagoya Protocol and how it relates to high-containment laboratories **Shipment of Category A infectious substances** • Associated challenges • Perceived benefits and enhancements to safety • Value in expanding or limiting the scope of the programme	Jakob Quirin Kazunobu Kojima
Establishing and maintaining biosafety and biosecurity in high-containment laboratories: engineering • Evidence-based facility engineering • Adaptability to meet changing scientific needs • Dissemination of best laboratory design practices	Eugene Cole Zoltan Kis

Selection of biosafety measures approved, validated and implemented at high-containment laboratories • Heating, ventilation and air conditioning (HVAC) system and air pressure cascade • Positive pressure suit system • Cabinet line system • Chemical shower system • Access controls implemented to maintain security • Discussion on best containment practices for vivariums	Samuel Edwin Allen Roberts Juan Manuel Schammas

Shared challenges and opportunities for strengthening high-containment laboratories
 	
• *Surge capacities*
  o Readiness strategies for sample influx
  o Streamlined processing of samples
  o Lines of communication for laboratory coordination
• *Roles of regulators and institutional review committees in the promotion of responsible science*
  o Improved communication among stakeholders
  o Value of diligence by an institutional review committee
  o Mitigated risks in favor of scientific benefits
	Steve Lever
	
	Wendy Shell
	
	Thomas Binz
	
	Giuseppe Ippolito

Laboratory oversight and biosafety enhancement: the regulator´s perspective (meeting room 1)
 	
• *Laboratory oversight: compliance monitoring and verification*
  o Intercountry comparison of standards for effective and achievable engineering controls
  o Oversight of laboratory training programmes
  o Inventory management systems for dangerous pathogens
  o Inspections
• *Laboratory incident and exposure response*
  o Identification of best practices for incident reporting
  o Identification of best practices for exposure reporting
  o Corrective actions to address the root cause
  o Encouraging reporting while discouraging non-reporting
 	
Laboratory oversight and biosafety enhancement: the operator's perspective (meeting room 2)
• *Oversight of laboratory personnel*
  o Adherence to regulations and safe laboratory operation
  o Inventory management policies that reflect regulations
  o Mentored pathogen specific training
• *Plan do check act of laboratory operations*
  o Identification of best practices for incident response
  o Establishment of trust between the supervisor and laboratory personnel
  o Reviews of laboratory procedures to correct deficiencies
  o Self-/internal auditing mechanism to ensure continual improvement
	Session chair:
	Mary Louise Graham
	
	Session chair:
	Bradley Pickering

Laboratory oversight and biosafety enhancement plenary session	Breakout session chairpersons

Establishing and maintaining biosafety and biosecurity in high-containment laboratories
• **Training**
  ○ Identification of best training practices
  ○ Institutional assessment mechanisms to improve training
  ○ International network of training: mapping of training opportunities and roster of trainers
  ○ Evidence demonstrating establishment of comprehensive and effective training programmes in a laboratory
  ○ Regulatory requirements in different countries
	Primal Silva
	Sergei N. Shchelkunov
	Åsa Szekely Björndal
	
	Su Yun Se Thoe

Confidence building between high-containment laboratories and global community
• *Framing the recognition of laboratories with demonstrated proficiency in biosafety and biosecurity*
  ○ Metric utilized to assess safe laboratory operation
  ○ Assessment of laboratory personnel training
  ○ Framework for recognition of laboratories
• *Cultivating a safety oriented culture in high containment laboratories*
  ○ Guidance establishing laboratory review committees and biosafety offices
  ○ Approach to support laboratories
• *Material transfer between high containment laboratories*
  ○ Procedures to facilitate the development of research programmes in the growing high containment community
	Åsa Szekely Björndal
	
	Haesun Yun
	
	Victoria Olson
	
	Martin Groschup

Day 3: Friday, 15 December

Topics	Speakers
Recap of Day 2 **Appointment of chairperson**	Day 2 chairperson (Stephan Gunther) Kazunobu Kojima
Biosafety controls for newly emerging pathogens • Consensus on initial biosafety controls employed • An optimized approach to handling clinical samples and conducting research in varying settings	Joseph O'Keefe Amadou Alpha Sall
Collaboration between high-containment facilities and WHO: open discussions for identifying mechanisms that promote: • increased access through collaborative facility sharing • sharing of best biosafety and biosecurity practices • mapping of training opportunities • global consensus outlining biosafety and biosecurity • identification of WHO´s role in facilitating collaboration between high-containment laboratories	Day 3 chairperson (Mary Louise Graham)
Summary, recommendations and plan of action • Summary	Mary Louise Graham

• Discussion • Conclusions and recommendations • Future plan of action	
Adjournment	

Annex 2. Summary of biosecurity level 4 (BSL-4) laboratories in the planning or operational phases as of December 2017, based on available information

Institute/Organization	Country	BSL	Operational status	Laboratory type	Human or animal	WHO region
Institute of Virology, National Institute of Agricultural Technology (INTA)	Argentina	3+	Operational	–	Animal	Americas
National Food Safety and Quality Service (SENASA)	Argentina	3+	Operational	–	Animal	Americas
Australian Animal Health Laboratory, Commonwealth Scientific and Industrial Research Organization (CSIRO)	Australia	4 (ABSL4)	Operational	Suit	Animal	Western Pacific
Emerging Infectious Diseases and Biohazard Response Unit (EIBRU), Westmead Hospital	Australia	4	Operational	Suit	Human	Western Pacific
Victorian Infectious Diseases Reference Laboratory (VIDRL), Peter Doherty Institute for Infection and Immunity	Australia	4	Newly constructed	Suit	Human	Western Pacific
Pan American Foot-and-Mouth Disease Center (PANAFTOSA)	Brazil	3+	Operational	–	Animal	Americas
National Centre for Foreign Animal Disease, Canadian Food Inspection Agency	Canada	4	Operational	Suit	Human	Americas
National Microbiology Laboratory (NML), Public Health Agency of Canada	Canada	4 (ABSL4)	Operational	Suit	Human	Americas
Chinese Center for Disease Control and Prevention, Beijing China BSL-4	China	4	Planned	Suit	Human	Western Pacific
Chinese National High Containment Facilities for Animal Diseases Control and Prevention, Harbin Veterinary Research Institute	China	4 (ABSL4 and BSL4)	Newly constructed	Suit	Animal	Western Pacific
Wuhan Institute of Virology, Chinese Academy of Sciences	China	4	Newly constructed	Suit	Human	Western Pacific
Institut Pasteur de Côte d'Ivoire, Ministry of Higher Education and Scientific Research	Côte d'Ivoire	4	Under Construction	Suit	Human	Africa

Institute/Organization	Country	BSL	Operational status	Laboratory type	Human or animal	WHO region
Department for Biological Defence, Military Institute of Health	Czech Republic	4	Operational	Suit	Human	Europe
Laboratory for Biological Monitoring and Protection, National Institute for Nuclear, Chemical, and Biological Protection	Czech Republic	4	Operational	Suit	Human	Europe
National Veterinary Institute, Technical University of Denmark	Denmark	3+	Operational	–	Animal	Europe
Jean Mérieux Laboratory P4, National Institute of Health and Medical Research of France (INSERM)	France	4	Operational	Suit	Human	Europe
Bernhard Nocht Institute for Tropical Medicine	Germany	4	Operational	Suit	Human	Europe
Friedrich Loeffler Institute (FLI), Federal Research Institute for Animal Health	Germany	4	Operational	Suit	Human	Europe
Institute for Virology, Philipps University of Marburg	Germany	4	Operational	Suit	Human	Europe
Robert Koch Institute	Germany	4	Newly constructed	Suit	Human	Europe
National Biosafety Laboratory (OKI), National Public Health Institute (former National Center for Epidemiology)	Hungary	4	Operational	Suit	Human	Europe
High Security Animal Disease Laboratory, National Institute of High Security Animal Diseases (NIHSAD)	India	3+	Operational	–	Animal	South-East Asia
Microbial Containment Complex (MCC), National Institute of Virology	India	4	Operational	Suit	Human	South-East Asia
Lazzaro Spallanzani National Institute for Infectious Diseases	Italy	4	Operational	Suit	Human	Europe
L. Sacco University Hospital, University of Milan	Italy	4	Operational	Suit	Human	Europe
Nagasaki University BSL-4, Nagasaki University	Japan	4	Planned	Suit	Human	Western Pacific
National Institute of Infectious Diseases (NIID)	Japan	4	Operational	Cabinet line	Human	Western Pacific
Wageningen Bioveterinary Research (WBVR)	Netherlands	3+	Operational	–	Animal	Europe
National Biocontainment Laboratory, Ministry for Primary Industries	New Zealand	3+	Operational	–	Animal	Western Pacific

Institute/Organization	Country	BSL	Operational status	Laboratory type	Human or animal	WHO region
Osong BSL-4 Laboratory, Korea Centers for Disease Control and Prevention (KCDC)	Republic of Korea	4	Newly constructed	Suit	Human	Western Pacific
Federal Budgetary Research Institution – State Research Centre of Virology and Biotechnology VECTOR, Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor)	Russian Federation	4	Operational	Suit	Human	Europe
National Health Laboratory, Saudi Ministry of Health	Saudi Arabia	4	Planned	Suit	Human	Eastern Mediterranean
Special Pathogens Unit, National Institute for Communicable Diseases (NICD) in South Africa	South Africa	4	Operational	Suit	Human	Africa
Centre for Research into Animal Health (CReSA), Autonomous University of Barcelona (UAB) and the Institute of Agri-food Research and Technology (IRTA)	Spain	3+	Operational	–	Animal	Europe
Unit of Highly Pathogenic Microorganisms, Department of Preparedness, Swedish Institute for Communicable Disease Control	Sweden	4	Operational	Suit	Human	Europe
Institute of Medical Virology, University of Zurich	Switzerland	4	Operational	Suit	Human	Europe
Institute of Virology and Immunology (IVI), Federal Department of Home Affairs	Switzerland	3+	Operational	–	Animal	Europe
Laboratory of Virology, Geneva University Hospitals	Switzerland	4	Operational	Suit	Human	Europe
Animal and Plant Health Agency (APHA), Department for Environment, Food, and Rural Affairs (DEFRA)	United Kingdom	4	Operational	Suit	Human	Europe
Centre for Emergency Preparedness and Response, Public Health England (PHE)	United Kingdom	4	Operational	Cabinet line	Human	Europe
Defence Science and Technology Laboratory (DSTL), Ministry of Defence	United Kingdom	4	Operational	Suit	Human	Europe
High Containment Large Animal Facility (HCLAF), Pirbright Institute	United Kingdom	4	Under Construction	Suit	Human	Europe

Institute/Organization	Country	BSL	Operational status	Laboratory type	Human or animal	WHO region
National Institute for Biological Standards and Control (NIBSC), Department of Health	United Kingdom	4	Operational	Suit	Human	Europe
Foreign Animal Disease Diagnostic Laboratory (FADDL), Plum Island	United States of America	3+	Operational	–	Animal	Americas
Galveston National Laboratory, University of Texas Medical Branch	United States of America	4 (BSL4 and ABSL4)	Operational	Suit	Human	Americas
Integrated Research Facility at Fort Detrick, National Institute of Allergy and Infectious Diseases (NIAID)	United States of America	4	Operational	Suit	Human	Americas
National Bio and Agri-Defense Facility (NBAF), US Department of Homeland Security	United States of America	4 (ABSL4)	Under Construction	Suit Laboratory	Animal	Americas
National Biodefense Analysis and Countermeasures Center (NBACC)	United States of America	4	Operational	Suit	Human	Americas
National Emerging Infectious Disease Laboratories (NEIDL), Boston University	United States of America	4	Newly constructed	Suit	Human	Americas
Plum Island Animal Disease Center, US Department of Homeland Security	United States of America	3+	Operational		Animal	Americas
Rocky Mountain Lab (RML), National Institute of Allergy and Infectious Diseases (NIAID)	United States of America	4	Operational	Suit	Human	Americas
Special Pathogens Branch, Centers for Disease Control and Prevention	United States of America	4	Operational	Suit	Human	Americas
Texas Biomedical Research Institute	United States of America	4	Operational	Suit	Human	Americas
US Army Medical Research Institute of Infectious Diseases (USAMRIID), US Department of Defense	United States of America	4	Operational	Suit	Human	Americas
Viral Immunology Center, Georgia State University	United States of America	4	Operational	Cabinet line	Human	Americas

Annex 3. Participants[6]

Argentina

Mr Ezequiel Matias Roqueiro, Biosafety Officer, National Food Safety and Quality Service (SENASA), Buenos Aires

Mr Juan Manuel Schammas, Biosafety Responsible Official, Institute of Virology, National Institute of Agricultural Technology (INTA), Buenos Aires

Australia

Dr Julian Druce, Head of Virus Identification Laboratory, Victorian Infectious Diseases Reference Laboratory (VIDRL), Peter Doherty Institute for Infection and Immunity, Melbourne

Dr Vitali Sintchenko, Director, Centre for Infectious Diseases and Microbiology – Public Health, University of Sydney, Westmead

Dr James Watson, Veterinary Investigation Leader, Australian Animal Health Laboratory, Commonwealth Scientific and Industrial Research Organization (CSIRO), Geelong

Brazil

Dr Ottorino Cosivi, Director, Pan American Foot-and-Mouth Disease Center (PANAFTOSA), Rio de Janeiro*

Canada

Dr Bradley Pickering, Lead Scientist BSL-4 Program, National Centre for Foreign Animal Disease, Canadian Food Inspection Agency, Winnipeg

Dr David Safronetz, Chief of Special Pathogens, National Microbiology Laboratory (NML),

[6] Participants listed with an asterisk were invited but unable to attend.

Public Health Agency of Canada, Winnipeg

Dr Primal Silva, Chief Science Operating Officer, Science Branch, Canadian Food Inspection Agency, Ottawa and Biosafety Level 4 Zoonotic Laboratory Network (BSL-4ZNET)

China

Professor Zhigao Bu, Director-General, Harbin Veterinary Research Institute, Chinese Academy of Agricultural Sciences

Dr Jinxiong Liu, Associate Professor, Harbin Veterinary Research Institute, Chinese Academy of Agricultural Sciences

Dr Zhiming Yuan, Director, National Biosafety Laboratory, Wuhan Institute of Virology, Chinese Academy of Sciences

Dr Chihong Zhao, Director, Office of Laboratory Management, Chinese Center for Disease Control and Prevention, Beijing

Côte d'Ivoire

Professor Dr Mireille Dosso, Director, Institute Pasteur Côte d'Ivoire, Abidjan

Czech Republic

Dr Michal Kroca, Director, Department for Biological Defence, Military Institute of Health, Techonin

Dr Michal Dřevínek, Laboratory for Biological Monitoring and Protection, National Institute for Nuclear, Chemical and Biological Protection, Milin

Denmark

Dr Kirsten Tjørnehøj, Senior Advisor Biosafety, National Veterinary Institute, Technical University of Denmark, Lindholm

France

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Professor Maria Rita Gismondo, Chief of Clinical Microbiology, Virology and Bioemergency, L. Sacco University Hospital, Milan

Dr Giuseppe Ippolito, Scientific Director, National Institute for Infectious Diseases Lazzaro Spallanzani, Rome

Japan

Professor Daisuke Hayasaka, Associate Professor, National Research Center for the Control and Prevention of Infectious Diseases (CCPID), Nagasaki University

Dr Masayuki Saijo, Director, Department of Virology, National Institute of Infectious Diseases (NIID), Tokyo

Professor Jiro Yasuda, Director, BSL-4 Facility Project Office, CCPID, Nagasaki University

Netherlands

Mr Douwe Kuperus, Biosafety Officer, Wageningen Bioveterinary Research

New Zealand

Dr Joseph O'Keefe, Director, National Biocontainment Laboratory Project, Wallaceville

Republic of Korea

Mr Min Woo Park, Staff Scientist, Division of Bioterrorism Preparedness and Response, Korea Centers for Disease Control and Prevention (KCDC)

Dr Haesun Yun, Scientist, Division of Biosafety Evaluation and Control, KCDC, Korea National Institute of Health

Russian Federation

Professor Sergei N. Shchelkunov, Head, Department of Genome Studies and Development of DNA Diagnostics of Poxviruses, Federal Budgetary Research Institution – State Research Centre of Virology and Biotechnology VECTOR, Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor), Koltsovo

Saudi Arabia

Dr Waleed Saleh Alsalem, Chief Executive Officer, National Health Laboratory, Ministry of Health, Riyadh*

Senegal

Dr Amadou Alpha Sall, Institut Pasteur in Dakar (WHO Collaborating Centre for Reference and Research of Arboviruses and Viral Haemorrhagic Fever Viruses)

South Africa

Professor Janusz T. Paweska, Head, Centre for Emerging Zoonotic and Parasitic Diseases, National Institute for Communicable Diseases (NICD), Sandringham-Johannesburg*

Spain

Dr F. Xavier Abad Morejón de Girón, Head, Biocontainment Unit, Centre for Research into Animal Health, Institute of Agri-food Research and Technology, Barcelona

Sweden

Dr Åsa Szekely Björndal, Officer/Senior Expert Advisor, Institutional Biosafety, Public Health Agency of Sweden (PHAS), Stockholm

Dr Åsa Rosenquist, Head, Unit for Diagnostic Preparedness of Notifiable and High Consequence Pathogens, PHAS, Stockholm

Switzerland

Dr Pascal Cherpillod, Biosafety Officer, Laboratory of Virology, Geneva University Hospitals

Dr Michael Huber, Institute of Medical Virology, University of Zurich

Dr Kathrin Summermatter, Head Biosafety and Deputy Director, Institute of Virology and Immunology (IVI), Federal Department of Home Affairs, Mittelhäusern

United Kingdom

Dr Christine Bruce, Head of Operational Delivery, National Infection Service, Public Health England (PHE), Salisbury

Dr Bryan Charleston, Director, National Institute of Bioscience, Pirbright Institute

Dr Michael Johnson, Director of Capability, National Institute of Bioscience, Pirbright Institute

Dr Steve Lever, Principal Scientist, Defence Science and Technology Laboratory (DSTL) Porton Down, Salisbury

Dr Allen Roberts, Director, High Containment Microbiology Department, PHE, Salisbury

Dr Wendy Shell, Bio Risk Manager, Safety, Health and Well-being (SHaW), Animal and Plant Health Agency (APHA), Addlestone

Dr Matthew Smith, SAPO4 Facility Manager/Head of Pandemic Flu Are, National Institute for Biological Standards and Control (NIBSC), Potters Bar

United States of America

Dr Sina Bavari, Chief Scientific Officer/Scientific Director, US Army Medical Research

Institute of Infectious Diseases (USAMRIID), Frederick

Mr L. Eugene Cole II, Program Technical Director, Program Executive Office, National Bio and Agri-Defense Facility (NBAF), Science and Technology Directorate, US Department of Homeland Security, New York

Dr Ronald B. Corley, Director, National Emerging Infectious Disease Laboratories (NEIDL), Boston University

Dr Robert Davey, Director ABSL4, Department of Virology and Immunology, Texas Biomedical Research Institute, San Antonio

Dr J. Patrick Fitch, Director, National Biodefense Analysis and Countermeasures Center (NBACC), Fort Detrick

Dr Elaine Haddock, Senior Research Assistant, Rocky Mountain Laboratories (RML), National Institute of Allergy and Infectious Diseases (NIAID), Hamilton

Dr Lisa Hensley, Associate Director for Science, Integrated Research Facility, NIAID, Fort Detrick

Dr Julia Hilliard, Director, Viral Immunology Center, Georgia State University, Atlanta

Dr James LeDuc, Director, Galveston National Laboratory, University of Texas Medical Branch

Dr Charles Lewis, Foreign Animal Disease Diagnostic Laboratory (FADDL), United States Department of Agriculture, Plum Island

Dr Victoria A. Olson, Chief, Poxvirus and Rabies Branch, National Center for Emerging and Zoonotic Infectious Diseases, Division of High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention (CDC), Atlanta

Other organizations

International Expert Group on Biosafety and Biosecurity Regulation (IEGBBR)

Dr Thomas Binz, Head, Section Biological Safety and Human Genetics, Federal Office of Public Health, Federal Department of Home Affairs, Liebefeld, Switzerland

Dr Samuel S. Edwin, Director, Office of Public Health Preparedness and Response, Division of Select Agents and Toxins, CDC, Atlanta, United States of America

Dr Tatsuhiro Isogai, Director, Infectious Diseases Information Surveillance Office, Tuberculosis and Infectious Disease Control Division, Health Service Bureau, Ministry of Health, Labour and Welfare, Tokyo, Japan

Ms Relus Kek, Public Health Group Biosafety Branch, Ministry of Health, Singapore
Dr Gary Lum, Principal Medical Adviser, Office of Health Protection, Department of Health, Canberra, Australia

Dr Yann Meslier, Inspector, Inspection Division, French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France*

Dr Keith Stephenson, Intervention Programme Manager, Microbiology and Biotechnology Unit, Health and Safety Executive, Leeds, United Kingdom

Dr Su Yun Se Thoe, Deputy Director, Public Health Group Biosafety Branch, Ministry of Health, Singapore

World Organization for Animal Health (OIE)

Dr Christine Uhlenhaut, Coordinator, Scientific Committee, Paris, France

WHO Collaborating Centre for biosafety and biosecurity

Ms Mary Louise Graham, Director, Centre for Biosecurity, Office of Biosafety and Biocontainment Operations, Public Health Agency of Canada, Ottawa, Canada

Rapporteur

Dr Samantha Kasloff, Postdoctoral Fellow, National Centre for Foreign Animal Disease, Canadian Food Inspection Agency, Winnipeg, Canada

World Health Organization

Headquarters

Dr Guy Boivin

Dr Sebastien Cognat

Dr Pierre Formenty*

Dr Florence Fuchs

Dr Matthew Huante

* * unable to attend

Dr Kazunobu Kojima

Ms Dhamari Naidoo*

Mr Jakob Quirin

Dr Guenael Rodier, Director, Country Health Emergency Preparedness and IHR

Regional Office for Europe

Dr Joanna Zwetyenga, Division of Communicable Diseases and Health Security