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The Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNet): Report of a workshop on live animal handling

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Abstract

The Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNet) was established in 2016, to provide a means of communication and support for the global high-containment laboratory community. Its working groups focus on international response, institutional cooperation and knowledge sharing, scientific excellence and training. In the latter role, BSL4ZNet sponsored its first international workshop in February 2018, held at the USDA National Centers for Animal Health, Ames, Iowa, USA, focused on necropsy procedures in high-containment laboratories. A second workshop, in November 2018, was held at the National Microbiology Laboratories (CFIA/PHAC) in Winnipeg, Canada, and focused on decontamination. A third workshop, held at the Australian Animal Health Laboratory in Geelong, Australia, in February 2019, was devoted to handling methods and ethical concerns for live animals in high-containment laboratories. The third workshop brought together 12 laboratorians from seven partner organizations in Australia, Canada, Germany, the United Kingdom and the United States. It included both discussion-based and hands-on training sessions on animal welfare, animal models, site-specific infrastructure

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constraints, health monitoring and humane endpoints, sampling procedures, and carcass disposal. This report summarizes the inception, development, and structure of the BSL4ZNet, and highlights the aims and results of the Geelong workshop.

1. Introduction

The Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNet) was established in 2016, as a network of government mandated organizations with national level responsibility for protecting animal and human health by working together to enhance knowledge, competency and capacity to meet current and future high-containment needs (Cemma et al., 2017; Pickering, 2018). One of the major strategic focus areas of the network is strengthening laboratory personnel training, which thus far has been accomplished through several training workshops. The first in this series of international training workshops hosted by BSL4ZNet, was held February 20–22, 2018, at the United States Department of Agriculture (USDA) National Centers for Animal Health in Ames, IA, USA. It focused on animal studies, with an emphasis on necropsies performed in high-containment. A second training workshop, held at the National Microbiology Laboratories (CFIA/PHAC), Winnipeg, Canada, November 6–7, 2018, concentrated on the topic of decontamination. The third training workshop was held at the Australian Animal Health Laboratory in Geelong, Australia, February 11–15, 2019, focused on considerations for handling live animals in high-containment laboratories. This report begins by describing the history, aims, structure, and achievements to date of the BSL4ZNet. It then summarizes discussions and information presented at the third international BSL4ZNet training workshop.

2. Origin and development of the BSL4ZNet

High-containment BSL-4 laboratories are unique facilities that make up a small percentage of laboratories worldwide. Although few in number, these laboratories perform high-impact studies on the world’s most deadly pathogens for which readily available vaccines or therapeutics are limited or lacking. Many of these laboratories are reference centers, providing scientific advice in addition to diagnostic support and tools to countries throughout the world. Reference laboratories exist as centers of excellence to support human and animal health.

BSL-4 laboratory studies often focus on emerging and re-emerging zoonotic diseases that cross from animals to humans, potentially resulting in public health crises. These zoonotic agents may cause significant morbidity and mortality or may be silent in their animal host. Predicting the influx of new disease threats and establishing where and when they will occur is extremely difficult. Therefore, a One Health initiative is the best and most effective way to combat emerging diseases. This need is what led to the realization of a network joining both the public and animal health high-containment laboratories together into one working community.

Conducting research in high-containment laboratories requires many considerations, including specialized facilities and equipment, enhanced biosafety practices, and highly trained personnel. To help address these and other unique considerations, a network of

collaborators is beneficial for identifying best practices for working in biosafety level 4 (BSL-4) laboratories. The BSL4ZNet was envisioned as a network to provide support to the high-containment laboratory community, establish open lines of communication, and identify and address gaps across government agencies.

In 2016, the Canadian Food Inspection Agency (CFIA) hosted an inaugural meeting by bringing together representatives from various animal and public health government agencies to address the rising challenges and risks posed by zoonotic pathogens and the potential to move forward collectively to establish a functioning network. The meeting engaged international partners and stakeholders with the aim to support and establish BSL4ZNet. The workshop developed the strategic direction to coordinate the framework and identify areas of collaboration. The meeting established a network of BSL-4 laboratories charged with establishing avenues to share information, knowledge, materials, and expertise to push forward a concerted effort against future threats.

Following this meeting, a number of hurdles impeded the establishment of the network, the largest of which was securing funding for the BSL4ZNet. To address this, a proposal was generated and submitted to the Canadian Safety and Security Program (CSSP), a federally-funded program through the Canadian Defense Research and Development Canada's Centre for Security Science (DRDC CSS). The DRDC works both domestically and internationally to increase capabilities to better respond to potential threats. The CFIA applied for a funding opportunity and was successful in its bid, ultimately being awarded a two-year grant to establish the network and ascertain its impact across the global community. Following the awarding of funding, the Network secretariat was formed at the CFIA headquarters and a steering committee was established to identify working groups and chairs to lead each. Since this initial support from the DRDC, BSL4ZNet has received additional funding to remain in operation and expand with additional agency involvement to further strengthen the network.

3. Network structure and governance

In March 2016, the BSL4ZNet was officially established. At the time, the network comprised 60 participants representing 12 partner organizations. Over three years, the Network has grown to ~90 participants, including laboratorians, veterinarians, researchers, facility management, biosafety, and regulatory personnel, representing 15 partner organizations (Table 1). Upon initiation of the BSL4ZNet, partner organizations defined 4 key areas to be most beneficial to the network, and created 4 active working groups (WG) to address specific gaps in these areas and to meet existing and emerging high-containment laboratory needs. These WG are: (1) International Response, (2) Institutional Cooperation and Knowledge Sharing, (3) Scientific Excellence, and (4) Training (Fig. 1). The International Response WG promotes laboratory preparedness and response by developing strategies that enhance institutional vigilance to respond to existing and emerging biothreats. The Scientific Excellence WG promotes collaboration and learning within the network through virtual research symposia and identification of target BSL-4 pathogen research gaps. The Knowledge Sharing and Institutional Cooperation WG promotes exchange of biosafety practices and procedures for the management and operation of BSL-4 laboratories by conducting surveys and maintaining a repository of guidelines and protocols. Finally, the

Training WG promotes exchange of best practices among BSL4ZNet partner organizations through workshops and laboratory personnel exchanges.

Each WG is led by 2–3 co-chairs who are responsible for developing strategic direction for the group, planning meetings, identifying and engaging guest speakers and experts, and representing the network within their respective organizations. BSL4ZNet WGs are governed by a steering committee that meets on a quarterly basis and consists of BSL4ZNet co-chairs, working group co-chairs, and key partner institutions' decision/policy makers, who provide strategic direction and delegate tasks to achieve overall network goals. Finally, the day-to-day activities of BSL4ZNet are coordinated by a Network Secretariat, currently from the CFIA.

BSL4ZNet uses an online document sharing platform developed by the Public Health Agency of Canada (PHAC) called Canadian Network for Public Health Intelligence (CNPHI). To date, more than 200 documents and resources have been shared among partners on CNPHI, and the Network has hosted over 100 working group, subgroup and steering committee meetings, as well as various online seminars. In addition, funding has been provided by the BSL4ZNet to support laboratorians and research projects that aid in fulfilling network objectives (Kroeker et al., 2018).

4. Training

There are many challenges to performing research in a high-containment laboratory setting, including the need for a highly-trained workforce, flexible operational methods, and specialty regulatory compliance (Michelotti et al., 2018). The Training WG seeks to strengthen BSL-4 laboratory personnel skills and capacity by identifying and developing workshops that provide opportunities for exchange of information and best practices in BSL-4 laboratories. Training opportunities are identified through regular WG meetings, during which BSL4ZNet partner organization members share information on their specific institutional practices, identify gaps, and prioritize topics or techniques that would be of value to network agencies. BSL4ZNet's Training WG has successfully developed and completed three training workshops, each hosted by one of the partner institutions. Two of the workshops were initiated to foster open discussion, provide training and promote knowledge transfer between partner organizations working specifically with small and large animals in high-containment settings; the third was organized to discuss approaches to decontamination.

The first in this series was the Animal Necropsy Workshop, hosted at the National Centers for Animal Health (USDA), Ames, Iowa, USA, in February 2018. The workshop brought together 13 participants from seven BSL4ZNet partner agencies (PHAC, CFIA, Centers for Disease Control and Prevention [CDC], USDA, Public Health England [PHE], Animal and Plant Health Agency [APHA], and Commonwealth Scientific and Industrial Research Organisation [CSIRO]) representing four countries (Canada, USA, UK, and Australia). This workshop was developed to address training gaps that exist in post-mortem sampling and necropsy of small and large animals inside high-containment laboratories. Through a series of hands on demonstrations and presentations, participants were able to share best practices

in animal pathology, sample management, sharps handling and risk assessment. The workshop was effective in not only building a network of high-containment animal health scientists, but also provided the opportunity for this group to become familiar with challenges that exist in different facilities when planning and executing experiments involving animals of different sizes. The regulatory and biosafety hurdles are different in each facility (e.g. distinct requirements to include non-infected controls in experimental setups) and to overcome such barriers participants can draw on experiences and insights gained from participating at an international workshop.

The second workshop was a Decontamination Workshop, hosted by the National Microbiology Laboratory in Winnipeg, Canada, in November 2018. This workshop was held at the Canadian Science Centre for Human and Animal Health, a facility that collocates CFIA and PHAC laboratories. The objectives of the workshop were to share and exchange information, best practices and experiences, and discuss and demonstrate new technologies in decontamination. Seventeen representatives, including biosafety scientists, decontamination personnel and facility engineers, from 8 BSL4ZNet partner organizations (USDA-APHIS, CDC, DHS, APHA, FLI, CSIRO-AAHL, PHAC and CFIA) representing five countries were in attendance. Through a number of presentations and hands-on demonstrations, attendees exchanged decontamination best practices for both BSL-3 and BSL-4 laboratories from each participating organization. Topics discussed included decontamination of surface, waste and equipment, annual preventative maintenance strategies, biological indicators, and evaluation and validation methods. Representatives from each facility shared their institutional decontamination methods for HEPA housing, PALL filters (plumbing air vents and autoclave chambers), animal rooms and other high-containment lab spaces. These methods included vaporized hydrogen peroxide, formaldehyde fumigation, VIRKON, chlorine dioxide and dry fog technology. Decontamination using formaldehyde has been an effective method for most institutions as it is known to penetrate any organic matter potentially missed by other disinfectants. However, due to its potential carcinogenic effects and limited availability on the market, particularly in Europe, participants explored other methods and new technologies available.

The third workshop was conceptualized by the establishment of a Community of Practice (CoP) of animal handlers with BSL-4 experience following the first animal focused workshop. The CoP identified new gaps in training, forming the basis for the Live Animal Handling Workshop, hosted by Australian Animal Health Laboratories, CSIRO, Geelong, Australia, in February 2019. The remainder of this report focuses on the Live Animal Handling Workshop.

5. The Live Animal Handling Workshop

The Live Animal Handling Workshop was hosted by the Australian Animal Health Laboratories (CSIRO-AAHL), in Geelong, Australia, in February 2019. All training was conducted with uninfected animals and approved by the CSIRO-AAHL Animal Ethical Committee (AEC1929) prior to the workshop. In attendance were 12 high-containment laboratorians, 1–2 from each of seven agencies (PHAC, CFIA, CDC, USDA, APHA, Friedrich-Loeffler-Institut [FLI], and CSIRO) representing 5 countries (Canada, USA, UK,

Germany, and Australia) (Fig. 2). The 5-day workshop incorporated table-top discussions, guest presentations, and hands-on laboratory sessions to address a variety of topics, including: animal welfare, animal models, health monitoring and humane endpoints, handling and sampling techniques for use with alert or sedated animals, animal transportation and carcass disposal, and BSL-4 suits. Additional sessions allowed open discussions of topics like site-specific regulatory and infrastructure considerations. For the hands-on portion of the workshop, one small animal species (ferrets) and one large animal species (pigs) were selected based on input from partner agencies. In addition, preceding the workshop, a two-day introductory session was offered to participants interested in more extensive familiarization with the positive pressure suits used at CSIRO-AAHL. The following sections provide a summary of the topics discussed and the techniques performed at the workshop.

5.1. Animal welfare

Animal welfare concerns are a critical component of all studies involving animals. A variety of accreditation and regulatory authorities are present across participating agencies and countries to ensure that work with animals is performed to the highest standards. Charles Lewis (USDA-APHIS) led the discussion on animal welfare. U.S. regulations and regulatory agencies were presented as a platform to initiate conversation identifying parallels and divergence across partner organizations. Participants discussed acclimatization periods, housing (caging, gating, flooring, enrichment, light-dark cycles, etc.), use of analgesia, legislation requirements of each country, and approval from institutional care and use committees or the equivalent. The use of control animals was also discussed with a focus on maintaining the scientific rigor of the study while minimizing the number of animals used. Challenges for incorporating control animals in large animal studies, which may be restricted by space limitations, were discussed. For example, in large animal studies, obtaining all samples from an animal just prior to the infection period could supply control tissues in studies that would require co-housing of uninfected and infected controls in the same suites. This is opposed to small animal studies, which allow individually ventilated cage (IVC) systems and support co-housing of uninfected and infected controls in the same suites without concern for cross-contamination of experimental groups.

5.2. Animal models

A variety of small and large animal species are used in BSL-4 laboratories. Anne Belkema-Buschmann (FLI) and Jessica Spengler (CDC) presented an overview of animal models currently used in BSL-4 laboratories. Cattle, horses, pigs, sheep, bats, guinea pigs, hamsters and mice were discussed. General considerations for each species, as well as BSL-4 pathogen-associated use of specific animal models, were presented. General considerations included behavior, handling, and housing. In addition, clinical signs and disease progression in a subset of disease models for BSL-4 pathogens, including a mouse model of Ebola virus disease, a hamster model of Nipah virus disease, and a mouse model of Crimean-Congo hemorrhagic fever, were presented in detail.

5.3. Health monitoring, clinical scoring, and humane endpoints

Jessica Spengler and Stephen Welch (CDC) moderated discussions on health monitoring, clinical scoring, and humane endpoints, with a focus on permanent identification approaches, clinical observations, clinical endpoints, and euthanasia techniques. Identification options for small animals that were discussed included ear notching, ear tagging, shaving patterns in animals' coats, tail marking or tattoos, and micro-chip transponder technology. Presented identification options for large animals included tattoos, ear tagging, marker spray paint, and micro-chipping. Data from naïve Strain 13 guinea pigs comparing transponder readings to rectal temperatures were presented; in general, the transponder temperature readings were higher than values obtained by rectal probes. Interestingly, this discrepancy was more apparent at lower temperatures; at higher temperatures the increases observed in transponder readings were minimal or values were found to be equivalent to those obtained by rectal probe. Clinical observations of small animals were described, including to the use of biosafety cabinets and/or downdraft tables for handling animals. Examples of clinical scoring systems and humane endpoint determination were discussed. Overall, these systems were very agent- and species-specific. Examples from both CDC (mice, guinea pigs) and PHAC (ferrets) were shown to illustrate how clinical scoring can be used in practice and to note the inherent subjectivity in the scoring process. Suggestions were made to increase objective criteria and design scoring templates to reduce potential person-to-person variability, and advantages to consistency in clinical scoring across institutions were highlighted. Euthanasia guidelines and procedures were discussed, considering both euthanasia and verification of euthanasia (e.g., by physical means when a primary chemical approach to euthanasia has been used). Finally, data were presented to support consideration of clinical stages of disease, in addition to time post infection, when analyzing data.

5.4. Handling and sampling techniques: ferrets

Safe handling of animals at BSL-4 is a significant consideration. Handling and sampling approaches are often modified from those used in lower containment-level labs. Kevin Tierney (PHAC) provided background information on ferret behavior and handling. Exhibiting the current approaches to ferret movement, handling, and sampling used at the National Microbiology Laboratory (Winnipeg, MB, Canada) as a model, Kevin moderated an interagency discussion highlighting similarities and differences in approaches. These discussions provided a didactic introduction to the subsequent hands-on sessions. Over the course of the workshop, 3 hands-on sessions with live ferrets were held in a decontaminated BSL-4 suite. Participants practiced handling, sedating, physically examining (e.g., determining weight and body temperature), and sampling (cranial vena cava blood samples and nasal washes), and then performed these techniques while wearing a BSL-4 suit. Significant discussion followed on approaches to sedation, which included sedation prior to handling/removal from caging (using a squeeze gate/injectable approach) and inhalation isoflurane anesthesia after removing the animal from caging while wearing protective gloves. At the completion of the final hands-on training session, participants performed terminal sampling techniques (intracardiac blood collection), humane euthanasia, and post-mortem sample collection and necropsies.

5.5. Handling and sampling techniques: pigs

A limited number of laboratories work with large animals in BSL-4. Large laboratory animals pose unique logistical and safety challenges, especially in high-containment settings. Brad Pickering and Cory Nakamura (CFIA) presented techniques currently in use for handling and sampling swine at the CFIA National Centre for Foreign Animal Diseases (Winnipeg, MB). For example, the presenters found that dry nasal swabs produced better data than swabs first placed in media, with the caveat that dry swabs must be used carefully to prevent damage to the mucosa. A variety of large animal handling approaches were presented, allowing the participants to discuss the variables to consider with each approach. In addition to the tabletop session, 3 large animal handling sessions were provided. The first session was performed without BSL-4 personal protective equipment to allow ease of communication and familiarization with the large animal cubicle. Both the CFIA and CSIRO-AAHL techniques were demonstrated and discussed during and after each hands-on session. Accordingly, alternative sedation was shown, including injectable and inhaled agents, with the benefits and drawbacks of each discussed. Demonstrations of sampling techniques included: blood collection (cranial vena cava), and oral, nasal, and rectal swab collection. Two additional mock “hot” sessions were provided, enabling participants to experience performing these techniques while working in a BSL-4 suit. The last handling session provided the opportunity to review handling sharps during post-mortem sampling while under mock BSL-4 conditions. Significantly, pitfalls and alternative approaches were discussed following each session to highlight the importance of spatial awareness with reduced visibility, additional protective gloves, and working in pairs with large animals.

5.6. Animal movement, tracking, and carcass disposal

Timm Konold (APHA) moderated discussions on animal transportation, tracking, and carcass disposal. Approaches to animal movement and tracking were highly variable based on facility design and both agency and governmental regulatory requirements. Participants from large animal facilities noted advantages and disadvantages of gating design and strategies for working with the respective systems. Transport of animals into the BSL-4 was also discussed. More options were available for small animal species, as they are often shipped in sealed filtered cages and placed directly into containment. Movement of large animal species into BSL-4 involves entry through a series of interlock doors from a clean corridor to hot suites, followed by decontamination of the transport corridor. Participants discussed how transport to disposal highly depended on where the animal was euthanized in proximity to the disposal facilities. In some countries, the animal cannot be euthanized in the same room with other live animals, or euthanasia must occur out of sight of the live animals. Other discussions included maximum allowances of, for example, weight for autoclaving and differences in general autoclave procedures amongst participant agencies.

5.7. Guest seminars

Two guest lectures were presented remotely to participants over the course of the workshop. The first, by Jonathan Arzt (USDA-ARS), described studies comparing intranasopharyngeal (INP) and intraoropharyngeal (IOP) inoculation in pigs. Route of inoculation can directly affect clinical signs, disease progression, and outcome in experimental infection studies

(Pacheco et al., 2016; Stenfeldt et al., 2014). Significant progress has been made in approaches to virus inoculation that more faithfully recapitulates natural infection for several animal diseases, including foot-and-mouth disease virus (Stenfeldt et al., 2014), African swine fever virus (Howey et al., 2013), and vesicular stomatitis virus (Velazquez-Salinas et al., 2018). This work indicated that the IOP route was more effective with low virus doses than INP, and simulated a more natural infection with foot and mouth disease virus. IOP is performed by laying sedated pigs on their backs; inoculum is instilled directly on the tonsil of the soft palate after which the pig is kept still for one minute. Alternatively, the INP method requires the use of a catheter, the length of which is measured externally as the distance from the tip of nose to the medial canthus of the eye, to reach the appropriate level of the nasopharynx through the nares.

The second guest lecture, by Samantha Kasloff (PHAC), summarized studies comparing comfort, ease of use, and performance of 9 different positive pressure BSL-4 suit designs (Kasloff et al., 2018). Suits were assessed for: (1) durability when exposed to disinfecting solutions; (2) user preference, including factors like visibility, weight, ease of movement, and ease of connecting and disconnecting hoses; and (3) suit microenvironment (e.g., CO_2 levels). The seminar provided a fitting forum for participants to discuss their own experiences with BSL-4 suits and highlight advantages and disadvantages of suit design based on the type of work being performed (biosafety cabinet alone, small animal, or large animal work).

6. Conclusions

The productivity and growth of the BSL4ZNet emphasizes the value of a network bringing together high-containment agencies and laboratorians. Further supporting the merit of the network, in 2017, the BSL4ZNet was recognized by the CFIA President's National Award in Best Practices and Innovation. The Live Animal Handling Workshop, like previous workshops, provided a unique opportunity to link public health and animal health laboratories, facilitating knowledge transfer and building interagency collaborations. The range of expertise and experiences represented by the participants promoted a diverse array of discussions. The success of this workshop is due largely to the open discourse and collegiality demonstrated by participants. This and the other BSL4ZNet training opportunities would not be possible without the support of all partner organizations and BSL4ZNet members, especially the Training WG and the host institutions that support the workshops by providing facilities, supplies, and staff to ensure the success of the training program.

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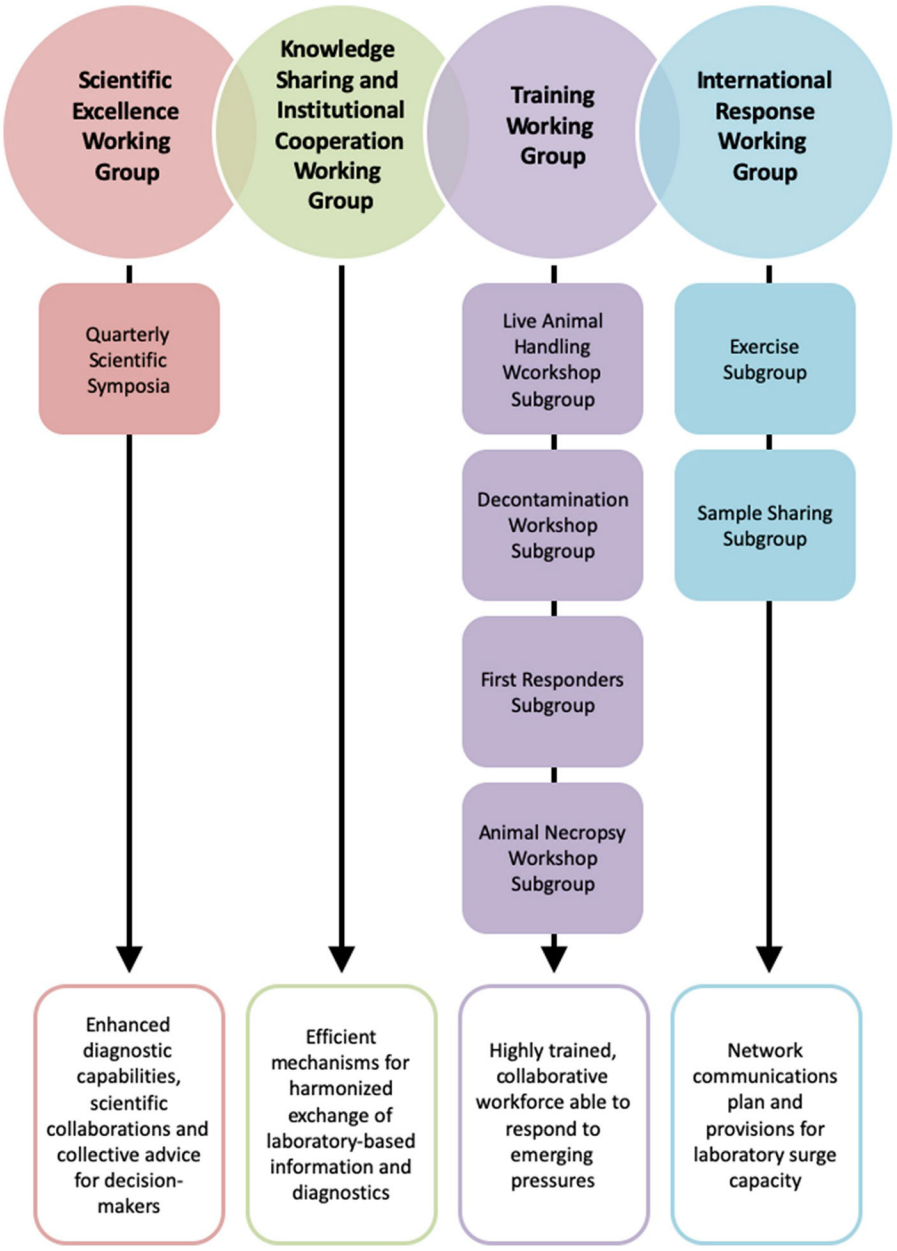

Fig. 1. Overview of the four BSL4ZNet working groups.

The working groups (circles) represent 4 key areas identified as the most beneficial to the network. Detailed are the activities (solid rectangles) and the desired outcomes (open rectangles) of the working groups.

Fig. 2. 2019 Live Animal Handling Workshop participants.

From left to right: Jessica Spengler (CDC), Cory Nakamura (CFIA), Brenton Rowe (CSIRO), Timm Konold (APHA), Charles Lewis (USDA), Antonia Dalziel (CSIRO), Fayna Diaz-San Segundo (USDA), Anne Balkema-Buschmann (FLI), Sandra Diederich (FLI), Brad Pickering (CFIA), Kevin Tierney (PHAC), Stephen Welch (CDC).

Table 1

BSL4ZNet partner organizations.

Organization	Acronym	Country	Point of Contact
Animal and Plant Health Agency	APHA	UK	Katja Voller
Canadian Food Inspection Agency	CFIA	Canada	Primal Silva
Centers for Disease Control and Prevention	CDC	United States	Inger Damon
Commonwealth Scientific and Industrial Research Organization	CSIRO	Australia	Trevor Drew
Department of Homeland Security	DHS	United States	Julie Brewer
Department of National Defence (Defence Research and Development Canada Centre for Security Science)	DND	Canada	Mark Williamson
Defence Science and Technology Laboratory	DSTL	UK	David Elliot
Friedrich-Loeffler-Institut	FLI	Germany	Martin Groschup
Global Affairs Canada	GAC	Canada	Ken Ugwu
Public Health Agency of Canada	PHAC	Canada	Steven Guercio
Public Health England	PHE	UK	Allen Roberts
Robert Koch Institut	RKI	Germany	Andreas Kurth
The Pirbright Institute	-	UK	Andrew White
United States Department of Agriculture (Animal and Plant Health Inspection Service and Agricultural Research Service)	USDA	United States	Elizabeth Lautner (APHIS); Jeff Silverstein (ARS)