International Network of High Containment Laboratories to Protect Human and Animal Health:
Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNet)
Current Biological Threat Environment

- Threats are **global**
- They occur through **both natural and deliberate** means
- Infectious agents are **continuously evolving**
- Over 60% of emerging infectious diseases are **zoonotic** (Jones *et al.*, 2008, Nature)
- Threats are **increasingly mobile** through travel and trade
- Pathogens of high consequence require unique considerations: **high containment environment and a specialized workforce** for diagnostics, research and countermeasure development
1980-2013: >44M humans cases affected globally by >12,000 infectious disease outbreaks (Smith et al. 2014 J R Soc Interface)

2014-2016: Ebola outbreak >28,000 human cases, >11,000 deaths, and $2.2B in foregone economic growth in Guinea, Sierra Leone, and Liberia in 2015 (World Bank)

80% of human BSL4/CL4 agents have animal reservoirs/vectors, a current focus world-wide is on animal health high-consequence pathogens (i.e. new and emerging threats).

2001: UK Foot and Mouth Disease outbreak
£3.1B loss to agriculture and food chain, >6M animal deaths (Thomson et al. 2002 Rev Sci Tech Off Int Epiz)

1997-2009: Six major outbreaks of fatal zoonotic agents*
Cost $80B (World Bank. 2012. People, Pathogens and Our Planet: The Economics of One Health)

*Nipah Virus (Malaysia), West Nile Fever (USA), SARS (Asia, Canada, other), Highly Pathogenic Avian Influenza (Asia, Europe), Bovine Spongiform Encephalopathy (US, UK), Rift Valley Fever (Tanzania, Kenya, Somalia)

Cost of a potential pandemic estimated $60B/year based on 1918 influenza pandemic (National Academies of Medicine. 2016. The Neglected Dimension of Global Security)
• Research and Knowledge Generation
• Subject Matter Experts
• Diagnostics and Surveillance
• Countermeasure Development
• Deploying Highly Trained Laboratory Personnel
• Capacity Building on the Ground
• Foresight
**Objective:** to strengthen international coordination, improve knowledge sharing and leverage partnering capacity to respond to current and emerging high consequence zoonotic bio-threats through animal health and public health laboratory partnerships.
BSL4ZNet is 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.

Member Organizations:

AUSTRALIA
Commonwealth Scientific and Industrial Research Organization

CANADA
Canadian Food Inspection Agency
Public Health Agency of Canada
Department of National Defence
Global Affairs Canada

GERMANY
Friedrich-Loeffler-Institut, National Research Institute for Animal Health

UNITED KINGDOM
Animal and Plant Health Agency
The Pirbright Institute
Public Health England

UNITED STATES
United States Department of Agriculture
Center of Disease Control and Prevention
Department of Homeland Security
Why We are Different

**Zoonotic:** BSL4ZNet seeks to link human and animal health high containment laboratories for a One-Health approach

**Global:** BSL4ZNet connects high containment laboratories from 5 countries around the world

**Laboratory Based:** BSL4ZNet seeks to address challenges faced by high containment scientists, facilities staff, operations and biosafety experts
Goals

1. To coordinate mechanisms of response for the provision of advice, research support and surge capacity with respect to threats of international concern.

2. To promote institutional cooperation through Canada’s leadership role as the secretariat for the Network.

3. To develop international competency through training and personnel exchange in order to meet the current and future demands for world class scientists.

4. To create trusted partnerships in strategic scientific collaborations, enhanced diagnostic capabilities and established expert advisory groups promoting scientific excellence.

Four working groups have been established to meet these Objectives:
The goals of the BSL4ZNet International Response Working Group are to:

- Strengthen laboratory preparedness and response during an outbreak by creating a communications protocol and hosting a table top exercise
- Explore ways to facilitate sample and personnel sharing to create a global workforce prepared for an international infectious disease incident
The goals of this working group are:

• To serve as a communication gateway for biosafety officers and high containment laboratory managers in order to foster collaboration among BSL4ZNet partners

• To identify common goals and synergies for BSL4ZNet partner high containment laboratories through strategic gathering of operational and programmatic information:
  o Operational Capabilities Benchmarking Survey
The goals of the BSL4ZNet Training Working Group are to:

- Strengthen BSL4 laboratory personnel training through identification and creation of training opportunities

- Build laboratory personnel by promoting cross-laboratory training opportunities and identify areas of training equivalencies
The goals of the BSL4ZNet Scientific Excellence Working Group are to:

- Facilitate research collaborations and serve as a communication gateway for the high containment (BSL4 and equivalent) community
  - Through symposia and workshops

- Discuss and share best practices in key areas of mutual interest

- Develop a shared awareness of new and emerging diagnostic technologies and platforms

- Create a space for the high containment community to develop interconnected networks
BSL4ZNet Impacts: Growing Canadian Capacity

- BSL4ZNet has **built capacity at the BSL4 laboratories (CFIA/PHAC)** through:
  
  - New containment suits purchased, equipment purchased to test the functionality of different suits and procedures
  
  - Facilitating upgrades to NCFAD’s internal procedures and processes
  
  - Funding 3 post-doctoral fellows, new research projects and training
  
  - Connecting laboratories with scientists, lab managers, biosafety officers, operations and management personnel, and lab directors from 9 other animal and public health high containment laboratories
BSL4ZNet Impacts: International Collaboration

- Facilitating and funding a **lab personnel exchange** between NCFAD and Australian Animal Health Laboratory (AAHL) – *March 2017*

- Developed an **international gap analysis** to assess the areas of need for international research on high containment pathogens – *November 2017*

- Developed **collaborative symposia:**
  
  To date features include:

  - High containment Decontamination
  - High containment Countermeasures
BSL4ZNet Impacts: International Collaboration

Lab personnel exchange

1. Training
2. BSL4 Suits
3. Operation—Daily work flow/Laboratory Procedures/Animal Work
4. Operations/Facilities/Mechanical
5. Validation Testing
6. Security
7. Onboarding/Training/Re-certification
8. Biosafety/Certification through Australian Government
Lab personnel exchange

An Example of Topics Covered—Training BSL4 AAHL

- AAHL has a specific training room housed in their containment area
  Specifically for onboarding and re-training of personnel in BSL4

- Head BSO spends a whole day with you before you are able to work in BSL4 alone.

- Everything from suit checks, BSC work, emergency procedures, etc. are covered in this training session.
Lab personnel exchange

- BSL4 Training Lab at AAHL
Facilitating information exchange: *Compare and Contrast Air Hose Connectors*

- Parker 60 Series Connectors (CFIA-Winnipeg)
- Swagelok Connectors (AAHL-Geelong)
- Staubli (alternate)
BSL4ZNet Impacts:
High Containment Training

- Developed a **workshop** to train animal handlers on safe practices to handle sharps inside high containment

**Objective:** Hands on workshop to share best practices in BSL4 animal pathology, post-mortem sampling, sharps handling training and further develop competencies in proper risk-assessment

**Outcomes of workshop**

  - Workshop report; best practices in BSL4 post-mortem sampling
  - Establishing a Community of Practice of animal handlers within BSL4
  - Opportunity for scientific collaborations
BSL4ZNet Impacts: High Containment Training

- Created a **workshop** to train animal handlers on safe practices to handle live animals inside high containment – *February 2019, Geelong Australia*

**Objective:** Hands on workshop to share best practices to handle live animals and further develop competencies in proper risk-assessment

**Outcomes of workshop**

- Workshop report; best practices in BSL4 live animal handling
- Establishing a Community of Practice of animal handlers within BSL4
- Opportunity for scientific collaborations
BSL4ZNet Impacts: High Containment Training

- Created a **workshop** to share best practices on decontamination and biosafety inside high containment

**Objective:** To share information, practices and experiences for decontamination of high containment spaces through discussion and demonstration of new technologies

**Outcomes of workshop**

- Workshop report; best practices in high containment decontamination
- Establishing a Community of Practice of decontamination within BSL4
- Opportunity for scientific collaborations

**Demonstration of Fumigants:**

*Ionized and Vaporized Hydrogen Peroxide, Dry Fog, Chlorine Dioxide*
BSL4ZNet Impacts:
High Containment Training

BSL4 Training Survey & Published Catalogue

- Includes high containment courses, custom training, fellowships, conferences and certifications
- Widely distributed as a BSL4ZNet product

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Objective: To capture best practices in biosafety, operations, and management of high containment laboratories

- Topics Surveyed:
  - Costs of High Containment Facilities
  - Scalability and Capacity
  - Sustainability
  - Evaluation framework
  - Capacity and Governance Structure
  - Computerized Maintenance Management System
  - Biosafety

- Outcomes:
  - Common lexicon and list of abbreviations
  - Identified best practices
  - Actionable recommendations for all participating organizations
Actionable Recommendations for Biological Safety:

- Risk Assessment models based on a management systems approach (CWA 15793*)
  
  *CWA 15793- An agreement document for guidance on activities involving biorisk threat pathogens developed by the European Committee for Standardization

- Suggested Improvements to Infrastructure:
  - Air Exchange improvement
  - Containment lab consolidation “under one roof”
  - Defining inactivation methods for liquid effluents
  - Review room isolation requirements for improved decontamination processes

- Suggested improvements to Operations:
  - Initiate inactivation studies to move samples to lower level of containment
  - Inter-Institutional collaboration on suit breathing air lines
Evaluation of Nine Positive Pressure Suits for Use in the BSL4 Laboratory

- 2 of the nine suits were associated with lower levels of CO₂ accumulation
- Construction materials were highly resistant to Microchem treatment when mechanical properties were compared to untreated controls
- The same 2 suits were highly preferred by volunteer test subjects

For more details see publication:

S. Kasloff et. al 2018 Applied Biosafety Evaluation of nine positive-pressure suits for use in the Biosafety Level-4 Laboratory
High Containment pathogens:
- Highly contagious
- Severe consequences to animal and human health

BSL4ZNet Impacts:

Research

- Ebola
- Rift Valley Fever
- MERS
- Nipah
- Crimean Congo Hemorrhagic Fever
- Unknown
EBOLAVIRUS

BSL4ZNet Impacts:
Research

Ebola across Africa

Sierra Leone
EBOV Cases: 913
Fatalities: 48
Case Fatality Rate: 5.3%
Health Exp: $60

Guinea
EBOV Cases: 390
Fatalities: 279
Case Fatality Rate: 71.8%
Health Exp: $132

Côte d’Ivoire
TaFV Cases: 1
Fatalities: 0
Case Fatality Rate: 0%
Health Exp: $0

Gabon
EBOV Cases: 214
Fatalities: 146
Case Fatality Rate: 68.4%
Health Exp: $57

Gambia
EBOV Cases: 61
Fatalities: 34
Case Fatality Rate: 55.7%
Health Exp: $65

* Ongoing *

South Sudan
EBOV Cases: 239
Fatalities: 160
Case Fatality Rate: 66.1%
Health Exp: $37

Uganda
Total Cases: 605
Sudan 457 & EBOV 148
Fatalities: 203
Case Fatality Rate: 17.1%
Health Exp: $44

Most outbreaks of Ebola Zaire (6)

Source: CDC, DHRMP, WHO, Steve Leete WHL, UN

STOPPING EBOLA

 Médécins Sans Frontières/Doctors Without Borders Canada (MSF) presents:

MSF’s experience on the front lines of a historic epidemic
Ebolavirus: Why look at animals

There are 5 different ebolavirus species:

Reston ebolavirus, Zaire ebolavirus, Sudan ebolavirus, Bundibugyo ebolavirus, Tai Forest ebolavirus, plus (Bombali ebolavirus)

2009 Reston ebolavirus identified in swine (Philippines) – workers developed antibodies

doi:10.1126/science.aan6899
Ebolavirus: Why look at animals

Replication, Pathogenicity, Shedding, and Transmission of Zaire ebolavirus in Pigs

Gary P. Kobinger,1,2 Anders Leung,1 James Neufeld,2 Jason S. Richardson,1 Darryl Falzarano,1,2 Greg Smith,3 Kevin Tierney,3 Ami Patel,1,2 and Hana M. Weingart1,3

1Special Pathogens Program, National Microbiology Laboratory, Public Health Agency of Canada; 2Department of Medical Microbiology, University of Manitoba; and 3National Centre for Foreign Animal Disease, Canadian Food Inspection Agency, Winnipeg, Manitoba

2017 Democratic Republic of the Congo, potential exposure of index case to wild boar
Nipah virus

• Earlier this summer an outbreak of Nipah virus occurred in Kerala State, India.

• Nipah virus can be transmitted to humans from animals (such as old world bats or pigs), contaminated fruit or directly from human-to-human.

• Nipah virus infection in humans may present as asymptomatic (subclinical) to an acute respiratory infection including fatal encephalitis.

• The case fatality rate is estimated at 40% to 75%, with no current treatment or vaccine available.

• The 2018 annual review of the WHO R&D Blueprint list of priority diseases indicates an urgent need for accelerated research and development for the Nipah virus.
Pathogenesis of Nipah virus Bangladesh (NiV-B) in Pigs (S. Kasloff)

Research Questions

1. Are pigs susceptible to NiV-B? Difference in pathogenesis vs NiV-Malaysia?
2. Do current NiV-Malaysia diagnostic protocols detect NiV-B in pig samples?
3. Assays for differential diagnosis?

Deliverables:

✓ Validation of NiV nucleoprotein qRT-PCR assay for detection of NiV-B
✓ Design of polymerase gene-based conventional RT-PCR assay for confirmatory sequencing
✓ Design and validation of NiV-B-specific qRT-PCR assay for differential genotyping
✓ Addressed knowledge gap on susceptibility of pigs to NiV-Bangladesh
Rift Valley Fever Virus

• Rift Valley fever (RVF) is a viral zoonosis primarily affecting animals, however does pose a threat individuals coming into close contact, primarily through the blood and tissues of infected animals.

• RVFV is a vector borne disease, with transmission between animals through bites of infected mosquitoes.

• RVFV has been identified in many countries throughout Africa; importantly many countries including North America harbour the vectors capable of promoting proliferation. Further, a recent study show white tail deer are susceptible to RVFV infection.
Research Questions

1. Can we create a pathogenic goat model for RVFV?
2. What is the response of dendritic cells and monocytes to RVFV infection?

Deliverables:

- Intranasal infection of goats with RVFV.
- Nubian goats as a model for RVFV.
- Information regarding viral pathogenesis and onset of disease.
- Requests for collaboration with industry for vaccine efficacy testing.
Secure and Open Borders: Strengthening operational capabilities at the One Health interface

- Ensure BSL4 laboratory sustainability can thrive through shared best practices in biosafety, operations, and management across agencies
- Creating strong partnerships between international animal health and public health BSL4 laboratories through joint activities

Connected partners: Establishing direct and efficient communication lines between BSL4 professionals

- 5 countries, 12 organizations, 60+ active members, >750 participant hours in teleconferences, 200+ documents shared through 4 working groups
Conclusions and Impact

High containment Science is Collaborative: Strengthening operational capabilities at the Science-Biosafety interface

- Ensure BSL4 laboratory sustainability can thrive through shared best practices in biosafety, operations, and management across agencies

Emphasis on Scientific Perception: Safe Science is Science Well done

- The public must have confidence that high containment science is being done with the highest standards of safety in mind
- Biosafety and Scientific staff must work collaboratively and effectively to get good science done
Incorporation of Biosafety into High Containment Training:

- Adding the understanding of biosafety and operations protocols and procedures to the high containment laboratory science curriculum will increase the collaboration and coordination between biosafety and scientific sectors.

Incorporation of Scientific input into biosafety standards: “Reverse Biosafety”

- Scientists and Biosafety regulators need to work together to figure out acceptable levels of risk with respect to protocols, procedures, equipment and emergency procedures.
Biosafety operators and scientists have a joint responsibility and shared accountability to ensure safe and effective lab practices.
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