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

The Cost of an Outbreak

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)

Value of High Containment Laboratories for Infectious Disease Preparedness and Response

- Research and Knowledge Generation
- Subject Matter Experts
- Diagnostics and Surveillance
- Countermeasure Development
- Deploying Highly Trained Laboratory Personnel
- Capacity Building on the Ground
- Foresight

Biosafety Level 4 Zoonotic Laboratory Network (BSL4ZNet)

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

Biosafety Level 4 Zoonotic Laboratory Network

Who We Are

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

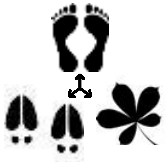
UNITED KINGDOM
Animal and Plant Health Agency
The Pirbright Institute
Public Health England

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

UNITED STATES
United States Department of Agriculture
Center of Disease Control and Prevention
Department of Homeland Security

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

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

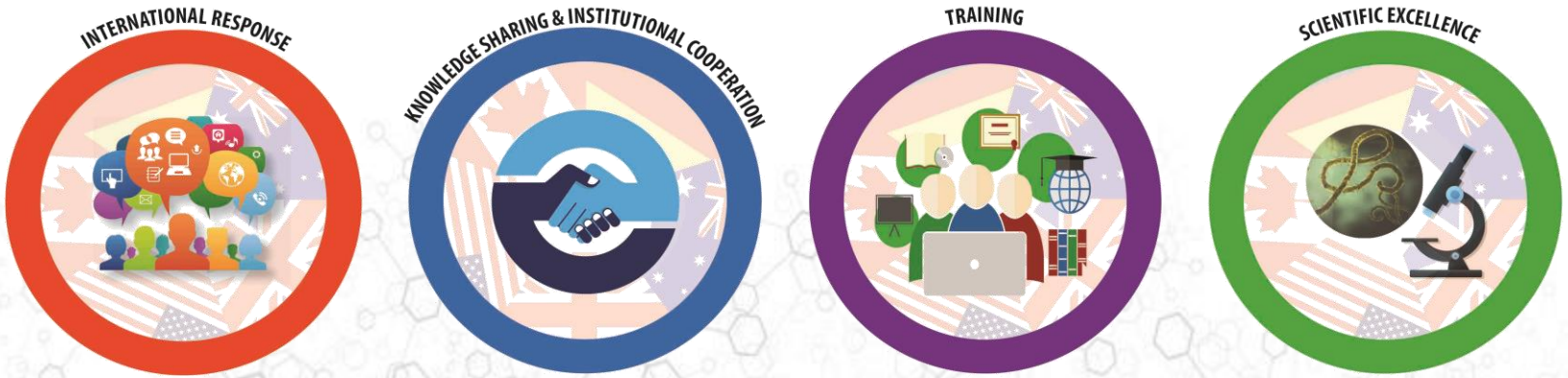
1. To coordinate mechanisms of **response** for the provision of advice, research support and surge capacity with respect to threats of international concern.

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:



Coordinated International Response

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

Fostering Knowledge Sharing and Institutional Cooperation

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:
    - Operational Capabilities Benchmarking Survey

Promoting High Containment Training

The goals of the BSL4ZNet Training Working Group are to:

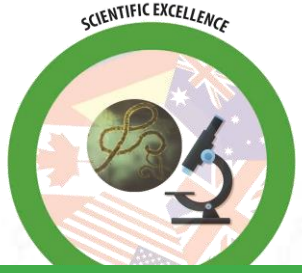
- Strengthen BSL4 laboratory personnel training through identification and creation of training opportunities
- Build laboratory personnel by promoting cross-laboratory training opportunities and identify areas of training equivalencies

Training

Fostering Scientific Excellence

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



Scientific Excellence

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

Biosafety Level 4 Zoonotic Laboratory Network

High Containment Decontamination Symposium

featuring

Jay Krishnan

"Containment Level 4 Fumigation at the Canadian Science Centre"

Senior Biosafety Officer
National Microbial Laboratory, Public Health Agency of Canada

Peter Krug, PhD

"Development of Alternative Methodologies to Inactivate High Consequence Pathogens: When Standards Refuse to Apply"

Foreign Animal Disease Research Unit, US Department of Agriculture

Samantha Kasloff, PhD

"Evaluation of 5% Micro-Chem Exposure on Mechanical Resistance of Positive-Pressure Suits"

National Center for Foreign Animal Diseases, Canadian Food Inspection Agency

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

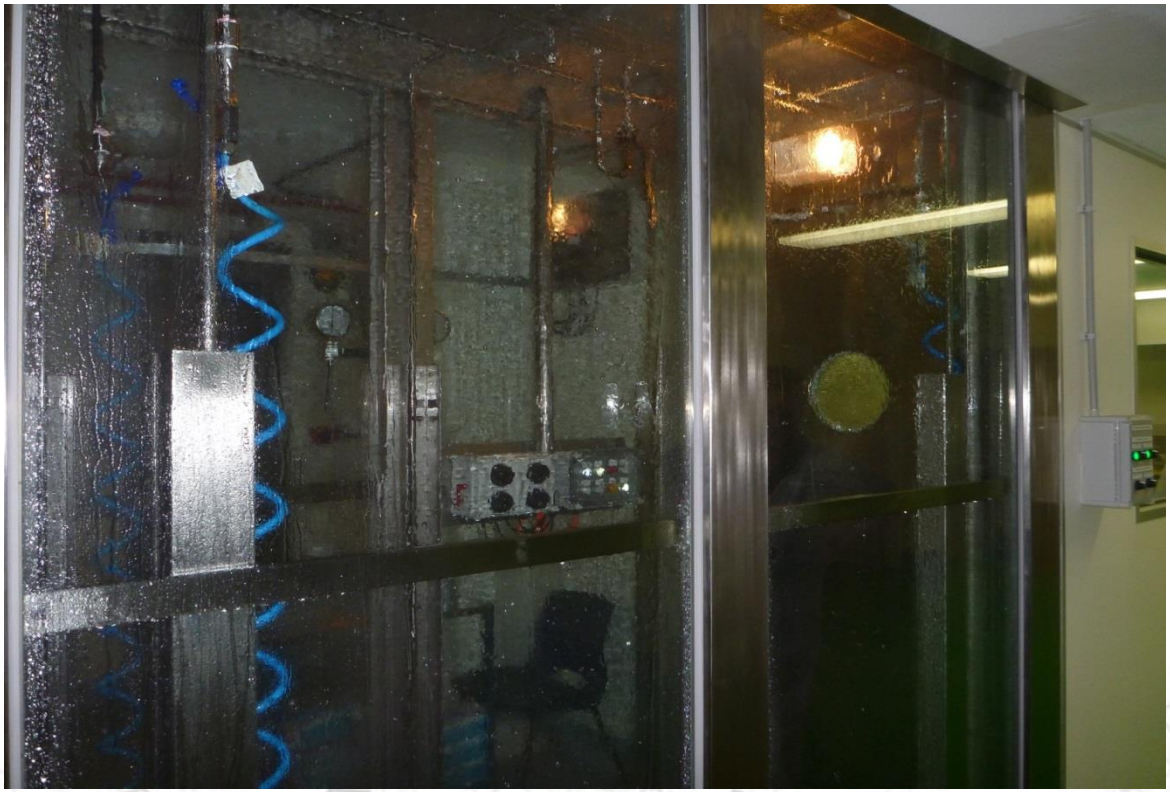
An Example of Topics Covered—Training BSL4 AAHL

- 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.

BSL4ZNet Impacts: International Collaboration

Lab personnel exchange

- BSL4 Training Lab at AAHL



BSL4ZNet Impacts: International Collaboration

- 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





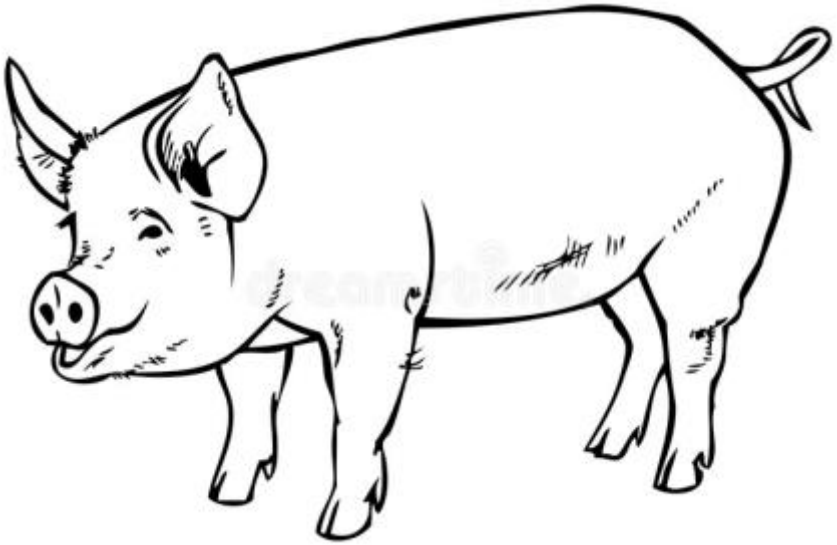
BSL4ZNet Impacts: High Containment Training

- 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 Hyrdogen Peroxide, Dry Fog, Chlorine Dioxide

Ionized Hydrogen Peroxide

Dry Fog

Fumigant Demonstration Chamber

Public Health Agency of Canada

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

Table of Contents

BSL4ZNet Impacts: International Benchmarking

<u>Objective:</u> 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
  - Biosaftey

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

BSL4ZNet Impacts: International Benchmarking

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 CO_2 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

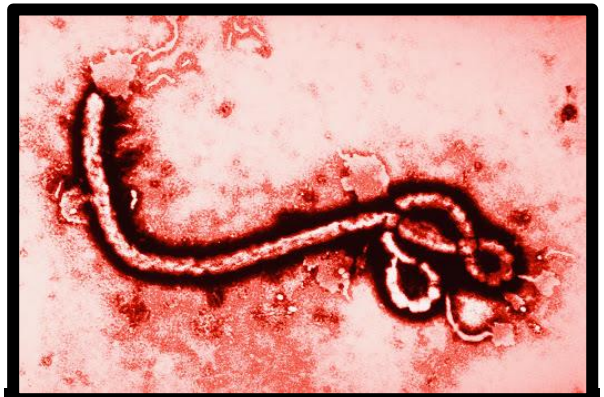
For more details see publication:

S. Kasloff *et. al* 2018 Applied Biosafety *Evaluation of nine positive-pressure suits for use in the Biosafety Level-4 Laboratory*

BSL4ZNet Impacts: Research

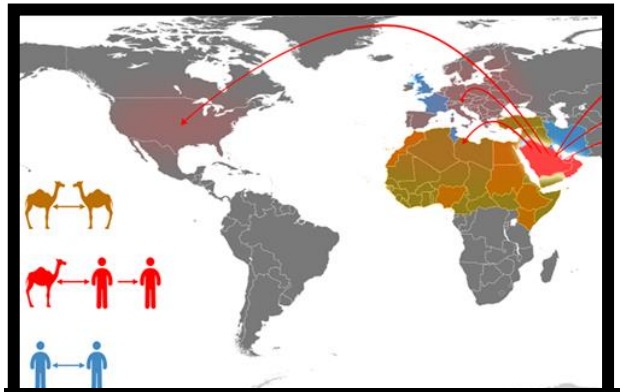
High Containment pathogens:

- Highly contagious
- Severe consequences to animal and human health



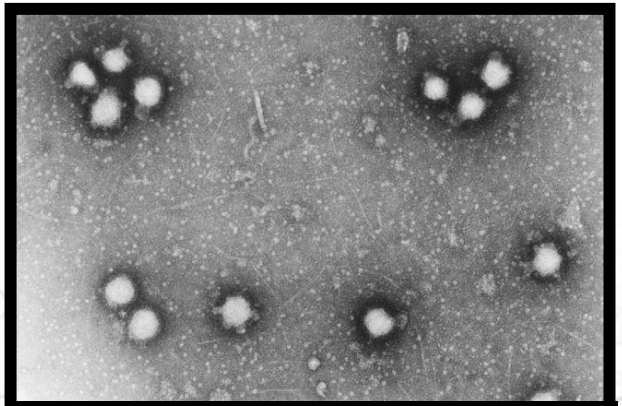
Ebola

Rift Valley Fever



MERS

Nipah

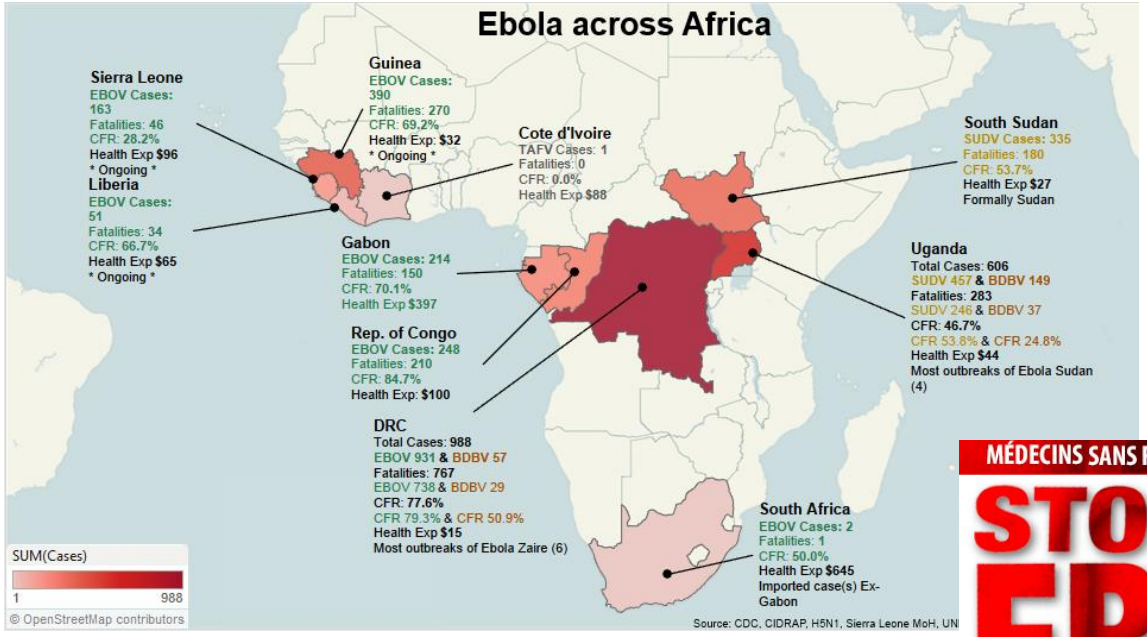


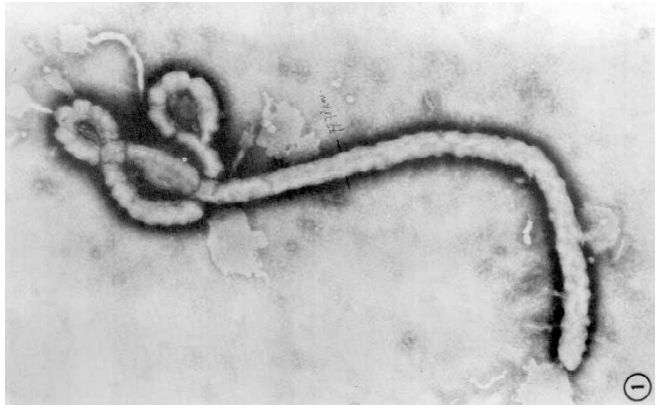
Crimean Congo Hemorrhagic Fever

Unknown

BSL4ZNet Impacts: Research

Ebolavirus





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

BSL4ZNet Impacts: Research

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,[3] Jason S. Richardson,[1] Darryl Falzarano,[1,2] Greg Smith,[3] Kevin Tierney,[3] Ami Patel,[1,2] and Hana M. Weingartl[2,3]

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

2017 Democratic Republic of the Congo, potential exposure of index case to wild bore

BSL4ZNet Impacts: Research

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.

BSL4ZNet Impacts: Research

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

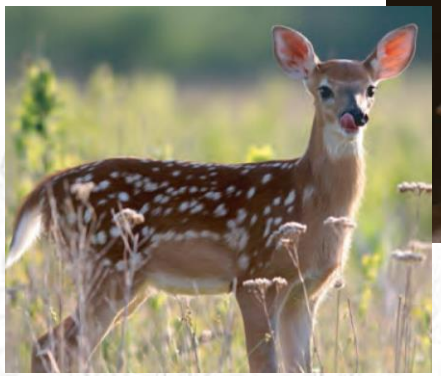
BSL4ZNet Impacts: Research

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.



BSL4ZNet Impacts: Research

Novel Animal Model for and innate immune responses to Rift Valley Fever Virus (A. Kroeker)

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

Conclusions and Impact

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
- Biosaftey and Scientific staff must work collaboratively and effectively to get good science done

Mutually Beneficial Relationship:
Science and Biosafety

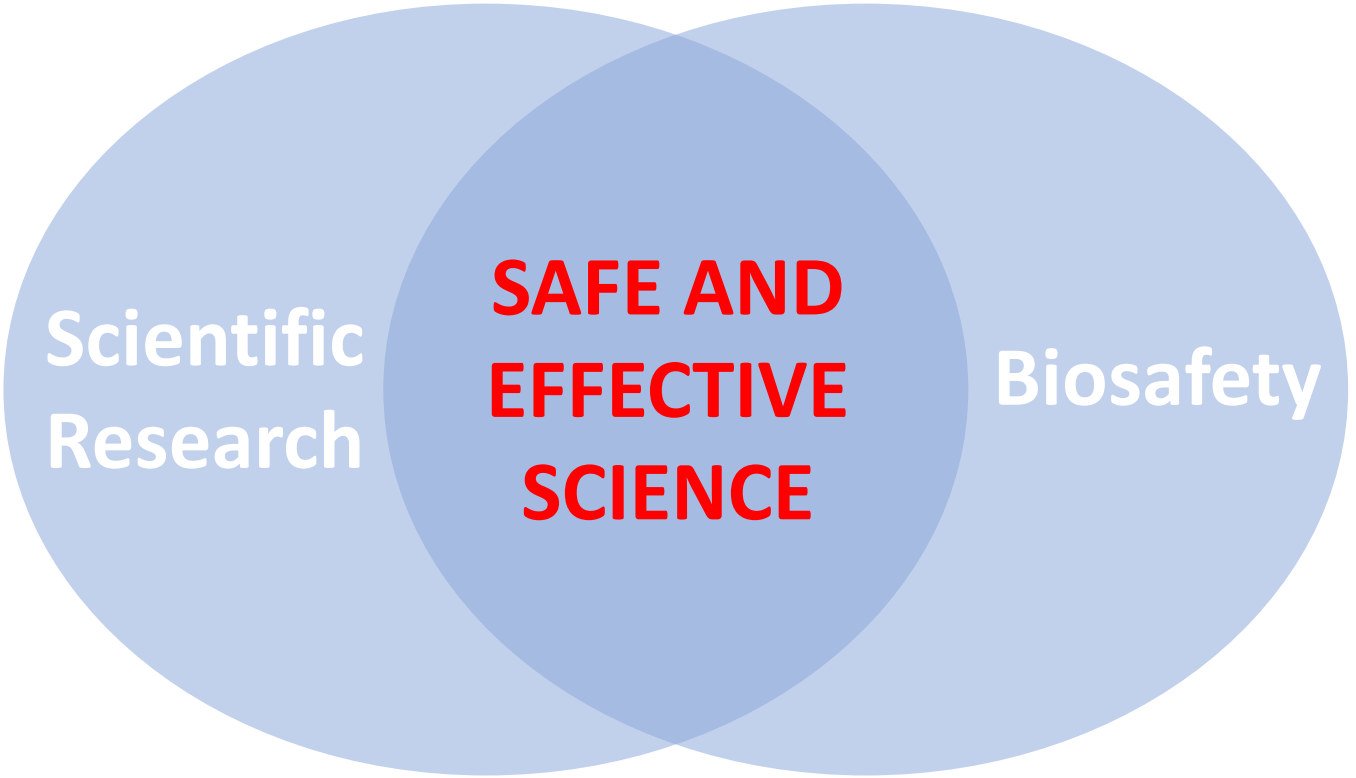
Incorporation of Biosafety into High Containment Training:

- 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

Joint Responsibility, Shared Accountability



Biosafety operators and scientists have a joint responsibility and shared accountability to ensure safe and effective lab practices

Acknowledgements

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