Select Agents and Toxins: What the Clinical Laboratory Needs to Know

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PH Safety Compliance Chief
10/27/16
Presenter Disclosure Statement:

The presenter has no financial arrangements or affiliations with any entities whose products, research or services that may be discussed during this presentation.

I have no actual or potential conflict of interest in relation to this program/presentation.

The information in this presentation referring to select agents is for instructional purposes only.
Objectives:

At the conclusion of this program, the participant will be able to:

1. Locate the select agent regulations and forms
2. Outline the responsibilities for notification of select agents and toxins
3. Outline the safety and security requirements and records keeping involved in the identification of select agents and toxins
Focus On Biosafety and Biosecurity:

**LAST WEEK**

Old, forgotten vials of Smallpox were found in a storage room near D.C. They've been moved to the CDC's secure labs in Atlanta.

**THIS WEEK**

An investigation reports the CDC transferred Anthrax using Ziploc bags.

They're in safe hands now!

You'd think.

Joe Heller, www.hellertoon.com
Biosafety and Biosecurity:

**Biosafety** is defined as: containment principles, technologies and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release.

**Biosecurity** is defined as: containment principles, technologies, and practices which are implemented to prevent intentional misuse or release of pathogens.

World Health Organization (WHO)
Laboratory Response Network (LRN)-Biological
Laboratory Response Network (LRN)-Chemical
Sentinel Clinical Laboratories:

- All laboratories capable of analyzing or referring specimens or samples that may contain microbial agents, biological toxins, chemical agents, chemical agent metabolites, or radiological agents function as sentinels in the public health laboratory system.
- This includes environmental, food, veterinary, agriculture, military, public health and clinical laboratories.

https://www.asm.org/index.php/guidelines/sentinel-guidelines

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Sentinel Clinical Laboratories in Vermont:

- Are the first line of defense for public health preparedness and response
- Vermont has 15 Clinical Hospital Laboratories
- 13 of the 15 meet the LRN Sentinel Clinical Laboratory Definition provided by the American Society for Microbiology (ASM)
Sentinel Clinical Laboratory Definition

The laboratory is certified to perform high complexity testing under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) by the Centers for Medicare & Medicaid Services (CMS) for the applicable Microbiology specialty or the laboratory is a Department of Defense (DoD) Laboratory certified under the DoD Clinical Laboratory Improvement Program or the laboratory is a veterinary medical diagnostic laboratory that is fully accredited by the American Association of Veterinary Laboratory Diagnosticians (AAVLD). Laboratory in-house testing includes Gram stains and at least one of the following: lower respiratory tract, wound or blood cultures.

Note: If your laboratory does not meet the definition above, please refer to items 1, 2, and 3 in the Responsibilities of the Sentinel Clinical Laboratory Laboratory section below.
Sentinel Laboratory Responsibilities: #1

• The laboratory is familiar with reportable disease guidelines in its jurisdiction
• Has policies and procedures in place to refer diagnostic specimens or isolates suspected to contain agents of public health significance to the public health laboratory in its jurisdiction
Sentinel Laboratory Responsibilities: #2

- The laboratory ensures personnel have met the applicable federal regulations for packing and shipping of infectious substances.
Sentinel Laboratory Responsibilities: #3

- The laboratory has policies and procedures for referral of suspect biothreat agent specimens and/or isolates to the LRN Reference Lab in its jurisdiction that reflect the ASM Sentinel Level Clinical Microbiology Laboratory Guidelines for Suspected Agents of Bioterrorism and Emerging Infectious Diseases: http://www.asm.org/index.php/guidelines/sentinel-guidelines

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Sentinel Laboratory Responsibilities: Continued

• The laboratory maintains the capability to perform testing outlined in the ASM Sentinel Clinical Microbiology Laboratory Guidelines for Suspected Agents of Bioterrorism and Emerging Infectious Diseases

• The laboratory has a Class II or higher certified biological safety cabinet (BSC)

• The laboratory complies with Biosafety Level II (BSL-2) practices (outlined in the Biosafety in Microbiological and Biomedical Laboratories 5th edition), e.g. use of BSCs
Sentinel Laboratory Responsibilities: Continued

• The laboratory complies with applicable Occupational Safety and Health Administration (OSHA) regulations for a respiratory protection program.

• The laboratory complies with the rules and regulations of the Select Agent Program (http://www.selectagents.gov/)
Select Agent Program

- The Federal Select Agent Program is comprised of the CDC: Division of Select Agents and Toxins and the Animal and Plant Health Inspection Services: Agriculture Select Agent Services
- Oversees the possession, use and transfer of biological select agents and toxins, which have the potential to pose a severe threat to public, animal or plant health or to animal or plant products
Select Agent Regulations

- Keep select agents and toxins out of the possession of individuals who might intend to misuse them
- Restrictions identified in the USA PATRIOT Act

http://www.selectagents.gov/
The Vermont Department of Health

HHS and USDA Select Agents and Toxins
7CFR Part 331, 9 CFR Part 121, and 42 CFR Part 73

HHS SELECT AGENTS AND TOXINS
Afrin
Botulinum neurotoxins
Botulinum neurotoxin producing species of Clastidium
Crototidin [short, paralytic alpha crototoxins containing the following amino acid sequence: CCKCCX(CXX)(CXX)(CXX)]
Coxiella burnetii
Crimean-Congo hemorrhagic fever virus
Diancetoxysdipenol
Eastern Equine Encephalitis virus
Ebola virus
Francisella tularensis
Lassa fever virus
Lujo virus
Marburg virus
Monkeypox virus
Reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments (reconstructed 1918 influenza virus)
Rlcn
Rickettsia prowazekii
SARS-associated coronavirus (SARS-CoV)
Saxitoxin
South American Hemorrhagic Fever viruses:
Chapare
Guaranile
Junin
Maracho
Sabbia
Staphylococcal enterotoxins A, B, C, D, E subtypes
T-2 toxin
Tetrodotoxin
Tick-borne encephalitis complex (flavi) viruses:
Far Eastern subtype
Siberian subtype
Kyasat Forest disease virus
Omsk hemorrhagic fever virus
Variola major virus (Smallpox virus)
Variola minor virus (Alastrim)
Yersinia pestis

OVERLAP SELECT AGENTS AND TOXINS
Bacillus anthracis
Bacillus anthracis Fasete strain
Brucella abortus
Brucella melitensis
Brucella suis
Burkholderia mallei
Burkholderia pseudomallei
Hendra virus
Nipah virus
Rift Valley Fever virus
Venezuelan equine encephalitis virus

USDA SELECT AGENTS AND TOXINS
African horse sickness virus
African swine fever virus
Avian influenza virus
Classical swine fever virus
Foot-and-mouth disease virus
Goat pox virus
Lumpy skin disease virus
Mycoplasma capricolum
Mycoplasma mycoides
Newcastle disease virus
Peste des petits ruminants virus
Rinderpest virus
Sheep pox virus
Swine vesicular disease virus

USDA PLANT PROTECTION AND QUARANTINE (PPQ)
SELECT AGENTS AND TOXINS
Peronosclerospora philipinensis
(Peronosclerospora sacchari)
Phoma glycines (formerly Pyrenochaeta glycines)
Ralstonia solanacearum
Ratilgobacter toxius
Sclerophthora rayesiae
Synchytrium endobioticum
Xanthomonas oryzae

Fitzsimmons Army Medical Center slide file.

CDC image
Summary and Utilization of Select Agent Forms by LRN Sentinel Level Laboratories

- LRN Sentinel Laboratories are not required to be registered with the Select Agent Program
- Must be compliant under specific conditions
- Completion of specific forms related to select agents
- Utilization of Forms 2, 3, and 4A as directed by an LRN Reference Laboratory or following authorization by CDC

http://www.selectagents.gov
Form 4: Report of the Identification of a Select Agent or Toxin

- Clinical/Diagnostic Identification (Form 4A)
- Proficiency Testing Identification (Form 4B): Any clinical or diagnostic laboratory, having identified a select agent or toxin contained in a specimen or sample presented for proficiency testing is required to report this identification by submitting a completed and signed APHIS/CDC Form 4B within 90 days of PT receipt
- Federal Law Enforcement Seizure (Form 4C)
- Form 4: http://www.selectagents.gov/CDForm.html
Form 4: Report of the Identification of a Select Agent or Toxin

- There are four parts to Form 4A.
- After select agent confirmation, the LRN Reference Lab must complete Parts A and B and send it to the CDC Select Agent Program (within 7 days).
- The CDC Select Agent Program calls the Reference Lab and provides a Case Identification Number.
- The Sentinel Lab completes Parts C and D and Form 3 if there was an occupational exposure.
- Form 4: [http://www.selectagents.gov/CDForm.html](http://www.selectagents.gov/CDForm.html)
In addition to completing a Form 4, the following select agents are required to be immediately (within 24 hours) reported to the Select Agent Program (via telephone, fax, or email):

- *Bacillus anthracis*
- Botulinum neurotoxins
- Botulinum neurotoxin producing species of *Clostridium*
- *Burkholderia mallei*
- *Burkholderia pseudomallei*
- Ebola virus
- Foot-and-mouth disease virus
- *Francisella tularensis*
- Marburg virus
- Rinderpest virus
- Variola major virus (Smallpox virus)
- Variola minor virus (Alastrim)
- *Yersinia pestis*
Form 4: Report of the Identification of a Select Agent or Toxin

• If there is any possibility that personnel handled the sample containing a select agent or toxin outside of primary containment (e.g., working with culture on open bench), it must be indicated on the Form 4 and an APHIS/CDC Form 3 must be submitted.
Form 3: Report of Theft, Loss, or Release of Select Agents and Toxins

- All laboratories must complete Form 3 if there is a theft, loss or release of a select agent or toxin (submitted within 7 days)
- A release is an occupational exposure or release of an agent outside of the primary barriers of the biocontainment area (e.g. biosafety cabinet)
- This form is also used to capture any laboratory exposures
- The discovery of a theft, loss, or a release of a select agent or toxin is required to be immediately reported (within 24 hours)
Form 3: Report of Theft, Loss, or Release of Select Agents and Toxins

Page 1
Section 3 - To be completed by all entities only for release of select agents and toxins or occupational exposure

26. An internal review of laboratory procedures and policies has been initiated to lessen the likelihood of recurrences of theft, loss or release of select agents and toxins at this entity.

☐ No  ☐ Yes  If yes, please provide additional details.

27. What were the hazards posed to humans by the extent of the release or occupational exposure?

28. What is the estimated extent of the release or exposure in relation to the proximity of susceptible humans, animals, and plants?

29. Provide a brief summary of how the laboratory and work surfaces were decontaminated after the release.

30. In select agents and toxins posing a risk to humans, please state how many laboratorians were potentially exposed and provide a brief summary of the medical surveillance provided (do not provide names or confidential information).

Certification: I hereby certify that the information contained on this form is true and correct to the best of my knowledge. I understand that if I knowingly provide a false statement on any part of this form, or its attachments, I may be subject to criminal fines and/or imprisonment. I further understand that violations of the select agent regulations may result in civil or criminal penalties, including imprisonment. 7 CFR 331.9, 9 CFR 121.42, 42 CFR 73.

Signature of Respondent: ___________________________  Title: ________________

Typed or printed name of Respondent: ___________________________  Date: ________________
Form 3: Report of Theft, Loss, or Release of Select Agents and Toxins

<table>
<thead>
<tr>
<th>APPENDIX A</th>
<th>ADDITIONAL SHEET FOR CONTINUATION OF INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue Form 3 comments here. State which block from the Form 3 the continuation is from. (Example: The following statement is a continuation of block 25).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APPENDIX B</th>
<th>IF THE INCIDENT OCCURRED DURING TRANSFER, COMPLETE SECTIONS 1 AND 2 OF FORM 3 AND PROVIDE THE FOLLOWING INFORMATION (INCLUDE A COPY OF THE RELEVANT APHIS/CDC FORM 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Transfer authorization number from APHIS/CDC Form 2:</td>
<td>2. Date Shipped:</td>
</tr>
<tr>
<td>3. Name of Carrier:</td>
<td>4. Airway bill number, bill of lading number, tracking number:</td>
</tr>
<tr>
<td>5. Package Description (size, shape, description of packaging including number and type of inner packages; attach additional sheets as necessary):</td>
<td></td>
</tr>
</tbody>
</table>

6. Package with select agents and toxins received by request: 7. Package with select agents and toxins appears to have been opened:

- No
- Yes

If yes, date of incident:

8. Sender was contacted regarding incident:

- No
- Yes

If yes, include explanation in box 5 above.

9. Carrier/consignee was contacted regarding incident:

- No
- Yes

Certification: I hereby certify that the information contained on this form is true and correct to the best of my knowledge. I understand that if I knowingly provide a false statement or any part of this form, or its attachments, I may be subject to criminal fines and/or imprisonment. I further understand that violations of the select agent regulations may result in civil or criminal penalties, including imprisonment. 7 CFR 331, 9 CFR 121, 42 CFR 73.

Signature of Respondent: ____________________________  Title: ____________________________

Typed or printed name of Respondent: ____________________________  Date: ____________________________

Pilot reporting burden: Public reporting burden of providing this information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and you are not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to OCCUPATIONAL Reports Clearance Officer, 1900 E. Dillon Road NE, MS CPR, Atlanta, Georgia 30309; OMB: 0920-0679.
Form 2: Request to Transfer Select Agents

- Rule Out or Refer: specimens or proficiency samples suspected of containing a select agent must be referred to the nearest LRN Reference Laboratory for confirmatory identification.
- Within 7 calendar days following notification that the agent/specimen was a select agent, it must be destroyed on-site by a recognized sterilization method.
- Completion of Form 2 would not normally be required of Sentinel Laboratories unless the sample/specimen had to be transferred.
- Form 2: [http://www.selectagents.gov/TransferForm.html](http://www.selectagents.gov/TransferForm.html)
Form 2: Request to Transfer Select Agents

Page 1

Detailed instructions are available at http://www.selectagents.gov/form2.html. Answer all items completely and type or print in ink. This request must be signed and submitted to either APHIS or CDC:

APHIS/CDC AUTHORIZATION NUMBER: ___________________________  EXPIRATION DATE: __________

SECTION 1 – TO BE COMPLETED BY RECIPIENT

1. Entity name: ____________________________  2. Entity registration number: __________
7. Principal Investigator name: ____________________________  First: __________  Last: __________  8. APHIS Permit #: __________
9. Responsible Official (RO) name: ____________________________  First: __________  Last: __________  10. RO telephone #: __________
11. RO fax #: __________  12. RO e-mail address: ____________________________

SECTION B – SENDER INFORMATION

13. Entity name: ____________________________  14. Entity registration number: __________
20. Responsible Official (RO) or facility director: ____________________________  First: __________  Last: __________  21. RO/Facility Director telephone #: __________
22. RO/Facility Director fax #: __________  23. RO/Facility Director e-mail address: ____________________________

SECTION C – LIST OF SELECT AGENTS AND TOXINS REQUESTED

24. This transfer request is for a select agent or toxin that was identified in a clinical or diagnostic sample:  Yes ☐  No ☐
   If yes, please ensure that an APHIS/CDC Form 4, "Report of the Identification of a Select Agent or Toxin," is submitted to APHIS or CDC within 7 calendar days.

25. Is the agent a product of a restricted experiment, as defined in section 13 of the select agent regulations?  If yes, provide the description used in the Federal Select Agent Program approval letter for the restricted experiment that produced the agent:  Yes ☐  No ☐

I hereby certify that the information contained in Section 1 on this form is true and correct to the best of my knowledge. I understand that if I knowingly provide a false statement on any part of this form, its attachments, I may be subject to criminal fines and/or imprisonment. I further understand that violations of 7 CFR 351, 8 CFR 121, and 42 CFR 73 may result in civil or criminal penalties, including imprisonment.

Signature of Responsible Official: ____________________________  Title: ____________________________
Typed or printed name of Responsible Official: ____________________________  Date: __________
Form 2: Request to Transfer Select Agents

Page 2

The Vermont Department of Health

Section 2 - To be completed by sender

Section D - List of select agents and toxins shipped (attach additional sheets if necessary)

27. Select agents and/or toxins:

28. Characterization of agent:

29. Number of items (e.g., viable, viable plant, etc.):

30. Form (powder/liquid, plant):

31. Total volume or weight of item contents (e.g., mL, mg, mg):

Section E - Recipient notification information

32. Name of individual at recipient entity notified of expected shipment:

33. Date of notification:

34. Type of notification: [ ] E-mail, [ ] Fax, [ ] Telephone

Section F - Shipping information

35. Name of individual who packaged shipment:

36. Name of individual who packaged shipment:

37. Number of packages shipped:

38. Package description (size, shape, description of packaging including number and type of inner packages):

39. Name of place of origin:

40. Airway bill number, bill of lading number, tracking number:

I hereby certify that the selected agents and/or toxins were packaged, labeled, and shipped in accordance with all federal and international regulations and information contained in Section 2 of this form is true and correct to the best of my knowledge. I understand that if I knowingly provide a false statement on any part of this form, or its attachments, I may be subject to criminal fines and/or imprisonment. I further understand that violations of 7 CFR 331, 9 CFR 121, and 42 CFR 73 may result in civil or criminal penalties, including imprisonment.

Signature of sender:

Type or printed name of sender:

Section 3 - To be completed by recipient

41. Name of individual who received shipment:

42. Transfer did not occur [ ] Yes, [ ] No

43. The agent[s] or toxin[s] listed in Section 2 were received:

44. Shipment was packaged, labeled, and shipped in accordance with regulations: [ ] Yes, [ ] No

I hereby certify that the information contained in Section 3 of this form is true and correct to the best of my knowledge. I understand that it is knowingly provide a false statement on any part of this form, or its attachments, I may be subject to criminal fines and/or imprisonment. I further understand that violations of 7 CFR 331, 9 CFR 121, and 42 CFR 73 may result in civil or criminal penalties, including imprisonment.

Signature of responsible official:

Type or printed name of responsible official:
Biosafety & Security Requirements

• Any laboratory identifying select agents (presumptive or confirmed) must secure the specimen, isolate or toxin against theft, loss or release from time of identification to time of transfer or destruction

• Chain-of-Custody: The laboratory is encouraged to follow its institutional policy

• All plates, tubes, and clinical material that contain the organism should be autoclaved, incinerated on-site or submitted to the designated LRN Reference Laboratory for disposal

• Alternatively, contaminated items should be soaked in 10% bleach or 10% formalin for 24 hours

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Records Keeping

- Record the destruction of all plates, tubes and clinical material:
  - List the number and type of each item destroyed
  - Include the date
  - The method used
  - The name of the individual
- All records must be maintained for 3 years and kept where they are easily accessible
Select Agents Identified in Vermont

- *Francisella tularensis* identified in an isolate sent to the Vermont Department of Health Laboratory: July 4, 2014
- Etiological agent of Tularemia

Humans can become infected through several routes, including:

- Tick and deer fly bites
- Skin contact with infected animals
- Ingestion of contaminated water
- Inhalation of contaminated aerosols or agricultural dusts
- Laboratory acquired infections
- Acts of bioterrorism

CDC
Vermont *F. tularensis* Case

- *Francisella tularensis*:
  - Subspecies *F. t. tularensis* (or type A) is found predominantly in North America
  - Subspecies *F. t. holarctica* (or type B) is found predominantly in Europe and Asia
Questions?