



Laboratory Diagnostics for Future Public Health Infectious Disease Threats

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Agenda

- Background – Questions from November, 2017 CLIAC to CDC
- Response
 - Laboratory Response Network (LRN) Perspective
 - Background on LRN
 - LRN Assay Prioritization Work Group
 - Prioritizing agents
 - Prioritizing assays
- Other considerations

Background – Request from November 2017 CLIAC

Considering the risk of emerging and re-emerging infectious disease –

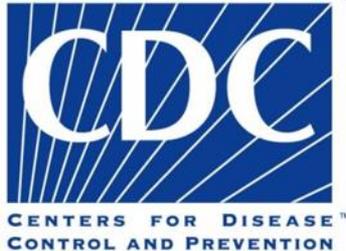
1. How does CDC – working with its partners – determine priorities for development of new diagnostic tests for deployment to public health laboratories and the health care system?
2. How does CDC assure that the tests which it deploys conform to laboratory quality standards?

Response from the Laboratory Response Network (LRN) Perspective



LRN Founding Partners

LRN established in 1999 as collaboration among:



LRN Mission



To provide timely, accurate laboratory test results
to inform public health decisions

LRN Tests for Two Types of Threats



- **Biological threats**

- Biological warfare or bioterrorism agents (smallpox, anthrax, plague, Ebola)
- Emerging infectious diseases (SARS, MERS, Zika, Ebola)



- **Chemical threats**

- Mustard gas, sarin

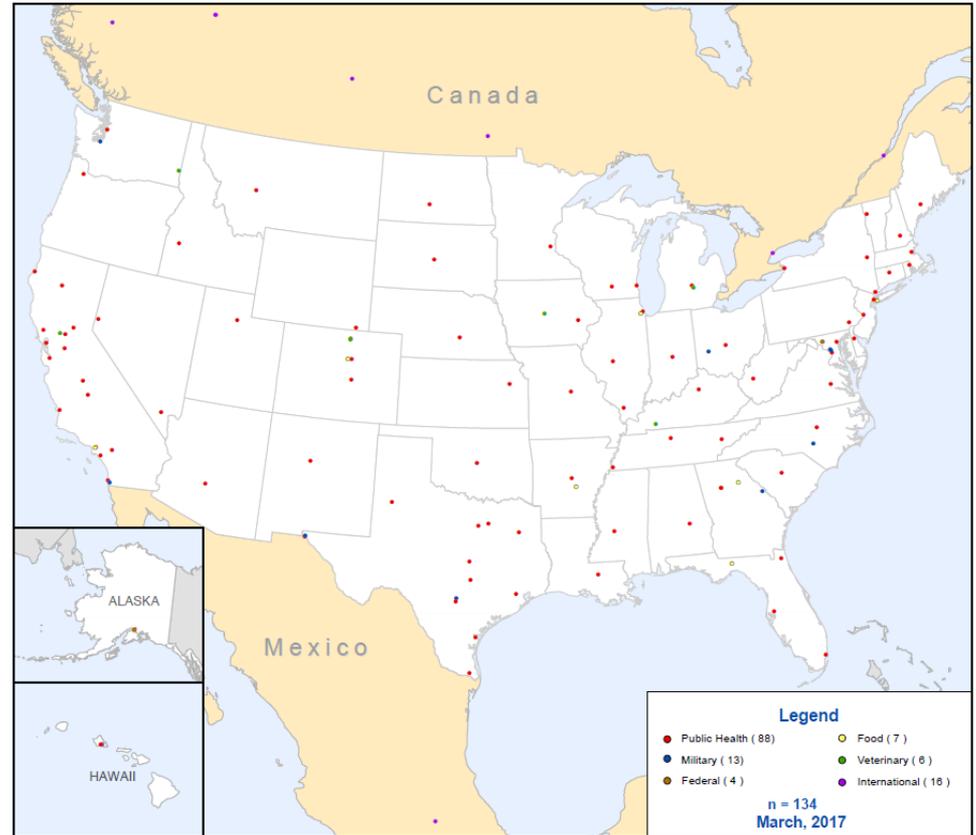
LRN-B

The remainder of the presentation describes the LRN for
Biological Threats (LRN-B) only

LRN Reference Laboratories Across the US

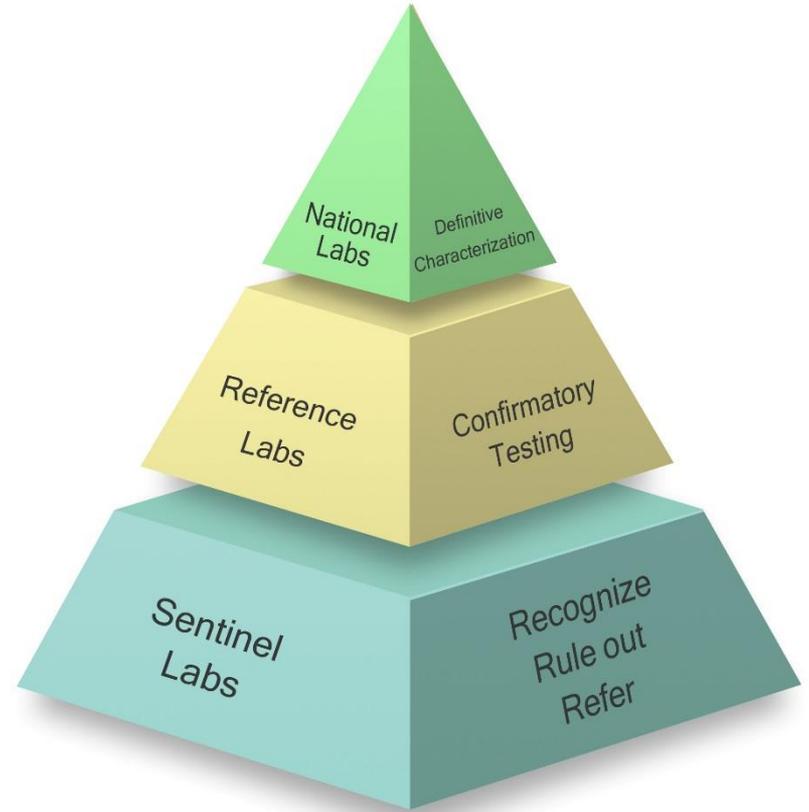
Includes many types of laboratories

- Federal
- State and local
- Military
- Food testing
- Environmental
- Veterinary



LRN Structure

- **National:** 3 laboratories
 - Highest technical capabilities & isolation
 - Test development & deployment
- **Reference:** ~135 laboratories
 - Perform standardized tests
 - Accurate, reliable testing
- **Sentinel:** 1,000s of laboratories
 - Hospital and clinical laboratories
 - Suspect and refer to reference laboratories



CDC's role in LRN

- Scientific and laboratory expertise for biological threats and emerging diseases
- Primary reference and surge capacity testing
- Development, manufacture, distribution, regulatory approval, and quality assurance of assays
- 365/24/7 technical and scientific support
- Funding for operation of LRN laboratories in U.S. states, territories, & cities
- Coordination of LRN



How does CDC prioritize assays for the LRN?

LRN Assay Development Working Group

- Chaired by Branch Chief, Laboratory Preparedness and Response Branch, Division of Preparedness and Emerging Infections
- Membership: CDC, APHL, FBI, & other agencies
- Prioritizes new assays for LRN, improvements to existing assays, adoption of new technologies
- Considers:
 - Risk (likelihood of outbreak X size of outbreak)
 - Value of assay in decreasing risk
 - Technological readiness level of assay
 - Development and sustainment costs
 - Potential sources of assays

Considerations for Agent Prioritization

- US government terrorism risk assessments and determinations
- Health and Human Services (HHS) Tier 1 Select Agents & Toxins List
- World Health Organization (WHO) Blueprint for R&D Preparedness
- National Institutes of Allergy and Infectious Diseases (NIAID) Priority Pathogen list



WHO R&D Blueprint Priority Agents, 2018

Given their potential to cause a public health emergency and the absence of efficacious drugs and/or vaccines, there is urgent need for accelerated research and development for:

- Crimean-Congo Hemorrhagic Fever (CCHF)
- Ebola Viral Disease and Marburg Viral Disease
- Lassa Fever
- MERS-CoV, SARS
- Nipah and henipaviral diseases
- Rift Valley Fever (RVF)
- Disease X

Terrorism Assessments & Risk Determination for Biological Warfare Agents

The Department of Homeland Security is responsible for processes that inform the US government's acquisition of medical countermeasures for biological warfare agents that include:

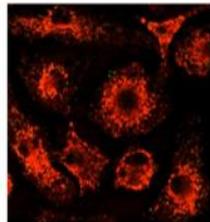
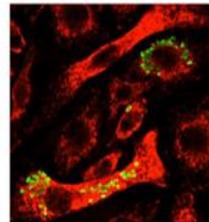
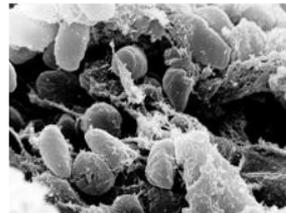
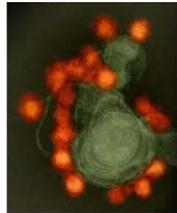
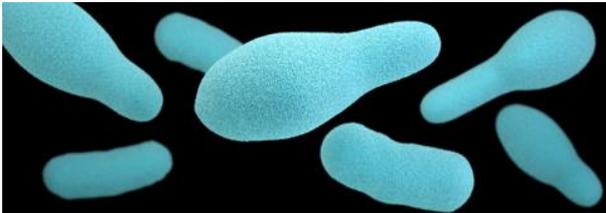
- Biological Terrorism Risk Assessment (BTRA)
- Integrated Terrorism Risk Assessment (ITRA)
- Material Threat Assessment (MTA)
- Material Threat Determination (MTD)
 - Enables use of Project Bioshield Reserve Funds

Considerations for Assay Prioritization

- However high the agent's priority, WG also must consider
 - Current state of development of the assay
 - Technology Readiness Level (TRL)
 - Availability of commercial assay or reagents
 - Availability of assay from Department of Defense
 - Suitable platform for testing in LRN
 - Is testing at CDC sufficient? Do we need a deployable assay?
 - Cost of acquisition or development
 - Cost of deployment and sustainment in LRN

LRN Assays Currently Under Development

- Botulism Neurotoxin Endopep-Mass Spectrometry Assay
- Ricin Mass Spectrometry Activity and Structure Assay
- Updated *F. tularensis* and *Y. pestis* Real-time PCR Assays
- Triplex Real-time multiplex PCR Assay for chikungunya, dengue & Zika
- Resazurin microbroth dilution for rapid antimicrobial susceptibility testing
- Evaluation of new instrumentation (as older equipment is phased out by industry), new chemistries, new reagents



How does CDC assure that new LRN assays conform to laboratory quality systems?

Creating an LRN Assay

- The LRN Assay Prioritization Workgroup reviews and determines the agents and assays to be prioritized for LRN assay development and evaluation.
- A CDC laboratory developed test (LTD) is often the starting point
- Funding is solicited and obtained, usually from CDC Preparedness funds, but sometimes from Biomedical Advanced Research and Development Agency (BARDA) or Department of Homeland Security
- Assays for both environmental and clinical samples are developed under design control processes.
- Clinical assays must conform to FDA and CMS/CLIA regulatory requirements

What it Takes to Get a CDC LDT to a FDA-authorized Assay for LRN Distribution

Collaboration with FDA Assay must be developed under design control; additional studies and data sometimes needed	Documentation Required documentation must be in place for distribution (details in protocol, FDA cleared labeling)	Manufacturing Need for controlled manufacture of reagents, controls, verification and proficiency testing materials
Instrumentation Assay must be performed on instrumentation that can be standard in LRN laboratories	Training LRN scientists must have proper instruction, training, & competency assessment	Quality Control Adding proficiency testing & verification panels made under a quality system to assist with CLIA requirements

Challenges to LRN Assay Development

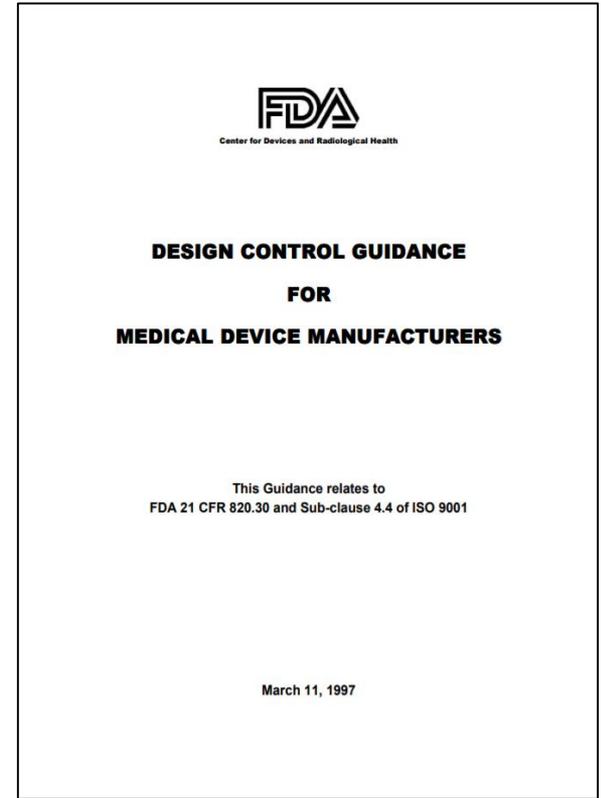


- Often lack agent samples and clinical materials
- Sometimes lack understanding clinical course of disease
- Difficult to do clinical studies
- Working with Tier 1 select agents

Design Control

- FDA Design Control Guidance for Medical Device Manufacturers: March 11, 1997
- Regulation does not prescribe the practices that must be used
- Establishes a framework to be used when developing and implementing design controls
- Based on quality assurance and engineering principles

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070642.pdf>



Design Control Process for LRN Assays

- Products must meet user needs, intended uses, and specific requirements
- Phases of design control include:
 - Concept
 - Design plan and input (requirements)
 - Analytical verification
 - Design validation
 - Design transfer
- Each phase requires documentation and leadership sign-off
 - OPHPR, NCEZID, DPEI, CDC laboratory and epidemiology SMEs



Assay Requirements

- Assay characteristics
- Intended use
- End users
- Test algorithm
- Results reporting
- Sample collection and processing
- Ancillary reagents and instrumentation
- Manufacturing
- Packaging, shipping, and storage



Emergency Use Authorization

- Countermeasure for a public health emergency is needed urgently
- CDC subject matter expert has an in-house assay (LTD) that may be developed for distribution
 - Protocol must be locked
 - Abbreviated analytical and clinical studies are conducted
 - Consideration must be made to available instrumentation in PHLs
 - Manufacturing strategy must be quickly decided and implemented
 - Laboratory safety risks must be considered and addressed
 - Discussions with the FDA begin immediately to determine strategy

LRN Assays Have Special Controls



- **Highly trained, qualified laboratories in the LRN**
 - Limited distribution
 - Proficiency testing program
 - Trained scientists performing similar tests daily
- **Standardized instrumentation & protocols**
- **Manufacturing capability and quality control testing**
- **Data reporting to CDC**
- **LRN Help Desk**
- **CDC subject matter experts available for interpretation**

Other Considerations

Other Considerations

- What about influenza?
- What about Disease X?
- What about pre-EUAs?
- What about testing to support clinical care?
- Role of Biomedical Advanced Research and Development Authority (BARDA)

Questions and Discussion

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

