Biodefense / Human Threats and Mass Spectrometry Applications

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CDC Biological Diseases/Agents List

Category A
- Anthrax (Bacillus anthracis)
- Botulism (Clostridium botulinum toxin)
- Plague (Yersinia pestis)
- Smallpox (Varioila major)
- Tularemia (Franciscella tularensis)
- Viral hemorrhagic fevers (Filoviruses [e.g., Ebola, Marburg] and Arenaviruses [e.g., Lassa, Machupo])

Category B
- Brucellosis (Brucella species)
- Epsilon toxin (Clostridium perfringens)
- Food safety threats (e.g., Salmonella species, Escherichia coli O157:H7, Shigella)
- Glanders (Burkholderia mallei)
- Melioidosis (Burkholderia pseudomallei)
- Psittacosis (Chlamydia psittaci)
- Q fever (Coxiella burnetii)
- Ricin toxin from Ricinus communis (castor beans)
- Staphylococcal enterotoxin B
- Typhus fever (Rickettsia prowazekii)
- Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])
- Water safety threats (e.g., Vibrio cholerae, Cryptosporidium parvum)

Category C
- Emerging infectious disease threats such as Nipah virus and hantavirus.
SARS (Severe Acute Respiratory Syndrome)

GLOBAL REACH

More than 4,500 cases of severe acute respiratory syndrome (SARS) had been reported to the World Health Organization by last week. More than 250 people had died, most of them in China and Southeast Asia.

Colera
Colera

- Gram negative bacteria causes severe watery diarrhea.
- Severe dehydration.
- Incubation period 24 hours
- January 1991 to September 1994 - Outbreak in South America, apparently initiated when a ship discharged ballast water. Beginning in Peru there were 1.04 million identified cases and almost 10,000 deaths.

Plague: The Black Death
Ebola / Marburg

Cases And Deaths From the Ebola-Zaire Virus, 1976-2003

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
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<tbody>
<tr>
<td>1976</td>
<td>209</td>
<td>318</td>
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<tr>
<td>1977</td>
<td>30</td>
<td>49</td>
</tr>
<tr>
<td>1994</td>
<td>12</td>
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<td>1995</td>
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<td>93</td>
</tr>
<tr>
<td>1996</td>
<td>97</td>
<td>122</td>
</tr>
<tr>
<td>2001-2002</td>
<td>128</td>
<td>142</td>
</tr>
</tbody>
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No. of Human Cases
No. of Deaths Among Cases
Smallpox
- Eradicated: 05/1980
- Last case Birmingham, England after which all isolates were sent to reference labs for destruction.
- In 2003 Smallpox scabs found in Civil War Medicine book in Santa Fe, New Mexico, no cases reported.
- Used as biological weapon in French and Indian wars, American Revolutionary war and perhaps World War II (research).
- Incubation period 10 days, if severe disease death may happen in 3-5 days.
- Vaccine available but hypothesized that virus might be genetically modified for use as bioweapon.

DETECTION OF BIOATTACK OR OUTBREAK

RELEASE ➔ PROGRESSION

**Human:**
- **Syndrome**
  - BioSense
  - ProMed
- **Disease Surveillance**

**Bug:**
- **Pathogen in Air**
  - BioWatch
- **Pathogen in People**
DETECTION OF BIOATTACK OR OUTBREAK

RELEASE

PROGRESSION

SYNDROME

Disease SURVEILLANCE

BioSense

ProMed

PATHOGEN in AIR

PATHOGEN in PEOPLE

PRE-SYMPTOMATIC

HOST-BASED DETECTION

Advantages of Host-Based Pre-Symptomatic Detection

- Treat to Prevent
- Containment of Outbreak
- Triage Based on Diagnosis
- Solution to AGENT X Problem
- DUAL USE TECHNOLOGY
Biosignature Pattern Recognition in Human Diseases

Host-based Presymptomatic Detection of Events

Genes
Environment
Age
Sex

Serum/Cell components

State of Health

Center for Innovations in Medicine

Doc In Box: BioSignatures

Diagnostic Device

signal

ILL

NOT ILL

prognosis
treatment strategy
diagnosis
Presymptomatic Diagnosis
clinical validation
drugs/vaccines

ILL

NOT ILL

Center for Innovations in Medicine
Upper Respiratory Disease Incubation Periods

Rhinoviruses: 5 Days
Influenza: 1-4 Days
Parainfluenza: 4 Days
Respiratory Syncytial Virus (RSV): 7 Days
Pertussis: 7-10 Days
Adenovirus: 5-8 Days
Epstein-Barr virus (EBV): 4-5 Weeks

Sources:
- http://www.cdc.gov/flu/professionals/diagnosis/
Goal:
Characterize the pathogen and/or host cell proteome, identifying proteins associated with biology of microbes, mechanisms of microbial pathogenesis, and host response to infection.

Discover targets for potential candidates for the next generation of vaccines, therapeutics, and diagnostics.

Proteomic Technology Development

- Albert Einstein College of Medicine
  PI: Ruth Angeletti
  Pathogens: Toxoplasma gondii, Cryptosporidium parvum

- Myriad Genetics, Inc
  PI: Jerry Lanchbury
  Pathogens: Bacillus anthracis, Yersinia pestis, Francisella tularensis, vaccinia, varicella

- The Scripps Research Institute
  PI: Peter Kuhn
  Pathogens: SARS-CoV

- University of Michigan
  PI: Philip Hanna
  Pathogen: Bacillus anthracis

- Harvard Medical School
  PI: Joshua LaBaer
  Pathogens: Bacillus anthracis, V. cholerae

- Caprion Pharmaceuticals, Inc
  PI: Eustache Paramithiotis
  Pathogen: Brucella abortus

- Pacific Northwest National Laboratory
  PI: Richard Smith
  Pathogens: Orthopox (vaccinia and monkeypox), Salmonella typhimurium and Salmonella typhi

- Administrative Resource Center
  PI: Margaret Moore

www.niaid.nih.gov/dmid/genomes/prc/default.htm
Overall Summary—May 2006

Proteins Identified:
- 6 structures solved for SARS-CoV; 282 human proteins that interact with Y. pestis (60), B. anthracis (50), and vaccinia (172) proteins; 176 novel proteins identified from B. abortus, and 360 from T. gondii.

Genes Identified:
- 493 differentially expressed murine macrophage genes found upon infection with anthrax

Reagents Generated
- 2983 V. cholerae Gateway entry clones made and deposited in an NIAID repository for use by the community

Progress Achieved—May 2006

Proteins Identified
- 360 membrane and cytoskeletal proteins identified in T. gondii
- 176 outer membrane proteins associated with virulence identified in B. abortus
- 282 human proteins found to interact with vaccinia (172), B. anthracis (50), and Y. pestis (60) proteins
- 6 SARS-CoV structures solved
- 2121/2343 proteins identified in virulent/avirulent S. typhimurium
- 263 early response and 329 late response proteins identified in murine macrophages infected with anthrax
18% of GNP on Health Care in 2006
Projected to be 25% - 30% by 2015
Average annual healthcare

Total Population vs. 65+ Population, 1950-2050

Source: U.S. Bureau of the Census, Multiple Census years.

*Only 8.1% of the total population in 1950 was over 65 years old.

What are the Costs of Medicine?

$2.26T/Year*

Drugs
Diagnostics
Care

*Estimated health expenditures for 2007


The Cost of Post-symptomatic Medicine

~$2 Trillion in Direct Medical Costs per Year

Two Options to Solve HC Crisis

- REDUCE CARE PROVIDED

or

- TRANSITION TO PRE-SYMPOTOMATIC DIAGNOSIS AND PREVENTATIVE MEDICINE
Changing Spectrum of BioThreat Risk

Tuberculosis
TB Timeline

- 1876: Discovery of M. tuberculosis
- 1876-82: Koch's postulates: general concept of medical bacteriology
- 1884-82: Bacterial response to prevent waterborne diseases
- 1890-91: Tuberculosis as diagnostic tool (success) and remedy (failure)
- 1892-1905: Tropical diseases
- 1905: Nobel Prize in Physiology
- 1993: World Health Organization declares tuberculosis a global emergency

Today:
- 2 million deaths annually due to tuberculosis
- 30% of global population infected with M. tuberculosis
- 17 million screened for HIV and M. tuberculosis
- 10 million infected with multi-resistant M. tuberculosis

M. tuberculosis
H37Rv
4.411.529 bp
Exposure to Infectious patients

- No infection (70%)
- Infection (30%)
  - Early progression (5%)
  - Immunologic defenses
  - Containment (95%)
- Immuneologic defenses
  - Late progression (5%)
  - Continued containment (90%)

Diagrammatic representation of the consequences of exposure to M. tuberculosis. The percentages shown are derived from epidemiologic data in persons without recognized immune response.
Three important steps:
- Phagosome formation
- Granuloma formation
- Failure of containment

TB Pathogenesis in a “Nutshell”

Cytokine / Chemokine Storm

- Recruitment of cells induced by CC and CXC production.
- TNF-α dominant CC. Produced by infected macrophages and induced production of other CC and CXC.
- Subsequent recruitment of cells and production of IFN-γ
Cell Mediated Immunity

Tuberculosis and Proteomics
Normalized Relative Intensities

Control  
TB  
TB/HIV

m/z
“If it were not for the great variability among individuals, medicine might be a science, not an art”

Because of our new ability to measure variability among individuals, medicine now can become a science rather than an art.
Thank you