The Program on Science and Global Security
The Biodefense Challenge:
How Should the Life-Science Research Community Respond?

Princeton University

Technical, economic and legal obstacles to the development of vaccines and other therapeutics for potential bioterrorism agents

Adel Mahmoud, MD, PhD
Merck & Co., Inc.
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Technical, economic and legal obstacles to the development of vaccines and other therapeutics for potential bioterrorism agents

Outline

• Infection: a biological reality
• Intent to harm
• Elements of response
  – Vaccines: • Discovery ⇒ Deployment
    • The smallpox case
    • Anthrax and others
  – Therapeutics
• Bioshield
• Perspective summation
The Convergence Model

- Social, Political and Economic Factors
- Physical Environmental Factors
- Genetic and Biological Factors
- Ecological Factors
- Microbe
- Human
## Leading Infectious Causes of Death Worldwide, 2001

<table>
<thead>
<tr>
<th>Cause</th>
<th>Rank</th>
<th>Estimated Number of Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory infections</td>
<td>1</td>
<td>3,871,000</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2</td>
<td>2,866,000</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>3</td>
<td>2,001,000</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>4</td>
<td>1,644,000</td>
</tr>
<tr>
<td>Malaria</td>
<td>5</td>
<td>1,124,000</td>
</tr>
<tr>
<td>Measles</td>
<td>6</td>
<td>745,000</td>
</tr>
<tr>
<td>Pertussis</td>
<td>7</td>
<td>285,000</td>
</tr>
<tr>
<td>Tetanus</td>
<td>8</td>
<td>282,000</td>
</tr>
<tr>
<td>Meningitis</td>
<td>9</td>
<td>173,000</td>
</tr>
<tr>
<td>Syphilis</td>
<td>10</td>
<td>167,000</td>
</tr>
</tbody>
</table>
Examples of Emergence

- Vancomycin-resistant Staphylococcus aureus
- Cryptosporidiosis
- Cyclosporiasis
- E. coli O157:H7
- Hepatitis C
- Whitewater Arroyo virus
- Hantavirus pulmonary syndrome
- Diphtheria
- Typhoid fever
- Rift Valley fever
- HIV
- Marburg virus
- Plague
- Ebola hemorrhagic fever
- Yellow fever
- Cholera
- Lassa fever
- Enterovirus 71
- Human monkeypox
- Hendra virus
- Nipah virus
- Marburg virus
- E. coli O157:H7
- H5N1 avian influenza
- Vancomycin-resistant Staphylococcus aureus
- V-CJD
- Whitewater Arroyo virus
- Typhoid fever
- Rift Valley fever
- Hantavirus pulmonary syndrome
- Plague
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Intent to Harm
Intent to Harm
## Organisms

### Highest priority (category A)

<table>
<thead>
<tr>
<th>Microbe or toxin</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacillus anthracis</em></td>
<td>Anthrax</td>
</tr>
<tr>
<td>Variola virus</td>
<td>Smallpox</td>
</tr>
<tr>
<td><em>Yersinia pestis</em></td>
<td>Plague</td>
</tr>
<tr>
<td><em>Clostridium botulinum</em></td>
<td>Botulism</td>
</tr>
<tr>
<td><em>Francisella tularensis</em></td>
<td>Tularemia</td>
</tr>
<tr>
<td>Filoviruses</td>
<td>Ebola hemorrhagic fevers, Marburg disease</td>
</tr>
<tr>
<td>Arenaviruses</td>
<td>Lassa fever, South American hemorrhagic fevers</td>
</tr>
<tr>
<td>Bunyaviruses</td>
<td>Rift Valley fever, Congo-Crimean hemorrhagic fevers</td>
</tr>
</tbody>
</table>
## Organisms

### Moderately high priority (category B)

<table>
<thead>
<tr>
<th>Microbe or toxin</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Coxiella burnetti</em></td>
<td>Q fever</td>
</tr>
<tr>
<td><em>Brucella</em> spp.</td>
<td>Brucellosis</td>
</tr>
<tr>
<td><em>Burkholderia mallei</em></td>
<td>Glanders</td>
</tr>
<tr>
<td>Alphaviruses</td>
<td>Viral encephalitides</td>
</tr>
<tr>
<td>Ricin</td>
<td>Ricin intoxiciation</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> enterotoxin B</td>
<td>Staphylococcal toxin illness</td>
</tr>
<tr>
<td><em>Salmonella</em> spp., <em>Shigella</em> dysenteriae, <em>Escherichia coli</em> 0157:H7, <em>Vibrio cholerae</em>, <em>Cryptosporidium parvum</em></td>
<td>Food- and water-borne gastroenteritis</td>
</tr>
</tbody>
</table>
### Organisms

<table>
<thead>
<tr>
<th>Category C</th>
<th>Microbe or toxin</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hantaviruses</td>
<td>Viral hemorrhagic fevers</td>
</tr>
<tr>
<td></td>
<td>Flaviviruses</td>
<td>Yellow fever</td>
</tr>
<tr>
<td></td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>Multidrug resistant tuberculosis</td>
</tr>
</tbody>
</table>
Organisms

**Miscellaneous**

Genetically engineered vaccine- and/or antimicrobial-resistant category A or B agents
HIV-1
Adenoviruses
Influenza
Rotaviruses
Hybrid pathogens (e.g. smallpox-plague, smallpox-ebola)
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Elements of Response

- Anticipation
- Surveillance
- Antimicrobials
- Vaccines
- Control
Select Aspects of Response – Vaccines

1. Technical challenges
   – Discovery
   – Development
   – Manufacturing
Select Aspects of Response – Vaccines

2. Economics
   – Industrial Base
   – Government Roles
   – Coverage
The setting of National Vaccine Policy – IOM Report 2003

- Government is deeply involved in the immunization enterprise, a role that reflects the public-good and spillover characteristics of vaccines.
- Government policy toward vaccine R&D is inconsistent: it both promotes and discourages the development of new vaccines.
- While states continue to take principal responsibility for immunization infrastructure and delivery, it can no longer be assumed that they will share responsibility for vaccine purchase with the federal government.
Select Aspects of Response – Vaccines

The setting of National Vaccine Policy – IOM Report 2003

– It cannot be assumed that private insurers will continue to share responsibility for covering immunizations.
– The assumption of a stable supply of vaccines produced by a healthy private sector can no longer be made.
– The current approaches to vaccine prioritization and immunization system planning are inadequate, as currently structured, to deal with the changing nature of vaccines and vaccine economics.
Select Aspects of Response – Vaccines

3. Legal Issues
   – Regulatory
   – Liability
The Smallpox Case I.

• Before 1980’s
• Virus destruction discussions 1990’s
• Vaccine supplies
• CDC contract 1999
The Smallpox Case II.

- September 11, 2001
  - Vaccines supplies
    - Dilution studies
    - Aventis stores
- New contract 2001
The Smallpox Case III.

- Vaccine challenges
  - New culture system
  - How to determine efficacy
  - Complications due to vaccination
  - Development of animal models
- The “new” vaccine
The Smallpox Case IV.

- Fundamental challenges
  - Protective antigens?
  - Evaluation methodology
    - in vitro
    - in vivo “animal models”
  - Human studies
Anthrax: The Other Case I.

- Before 1990’s
- Fall of 2001
- The current vaccine
- The response:
  - Antimicrobials
  - ? new vaccine
Anthrax: The Other Case II.

- B. anthracis toxins
- Cloning of protective antigen
- Biologicals and/or therapeutics for toxins
- Contract for procurement issued
What About Other Pathogens?

- Lack of basic biological knowledge
- Lack of definition of protective antigens
- No good evaluation systems
- Who will make these products?
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Bioshield

- Principal assumptions
- Basic research – development – procurement
- Purchase agreements
- Liability
Perspective Summation

• Infection: medical and public health implications
• Intent to harm
• The challenge:
  – Long term: science and containment
  – Immediate: prioritization
    R&D
    political will