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Potential Bio-threat Agents, Recognition & Diagnosis

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1st Qatar workshop for the "Assessing the Threats to Public Health
2-3 November 2016

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We Must Address an Unpredictable Future

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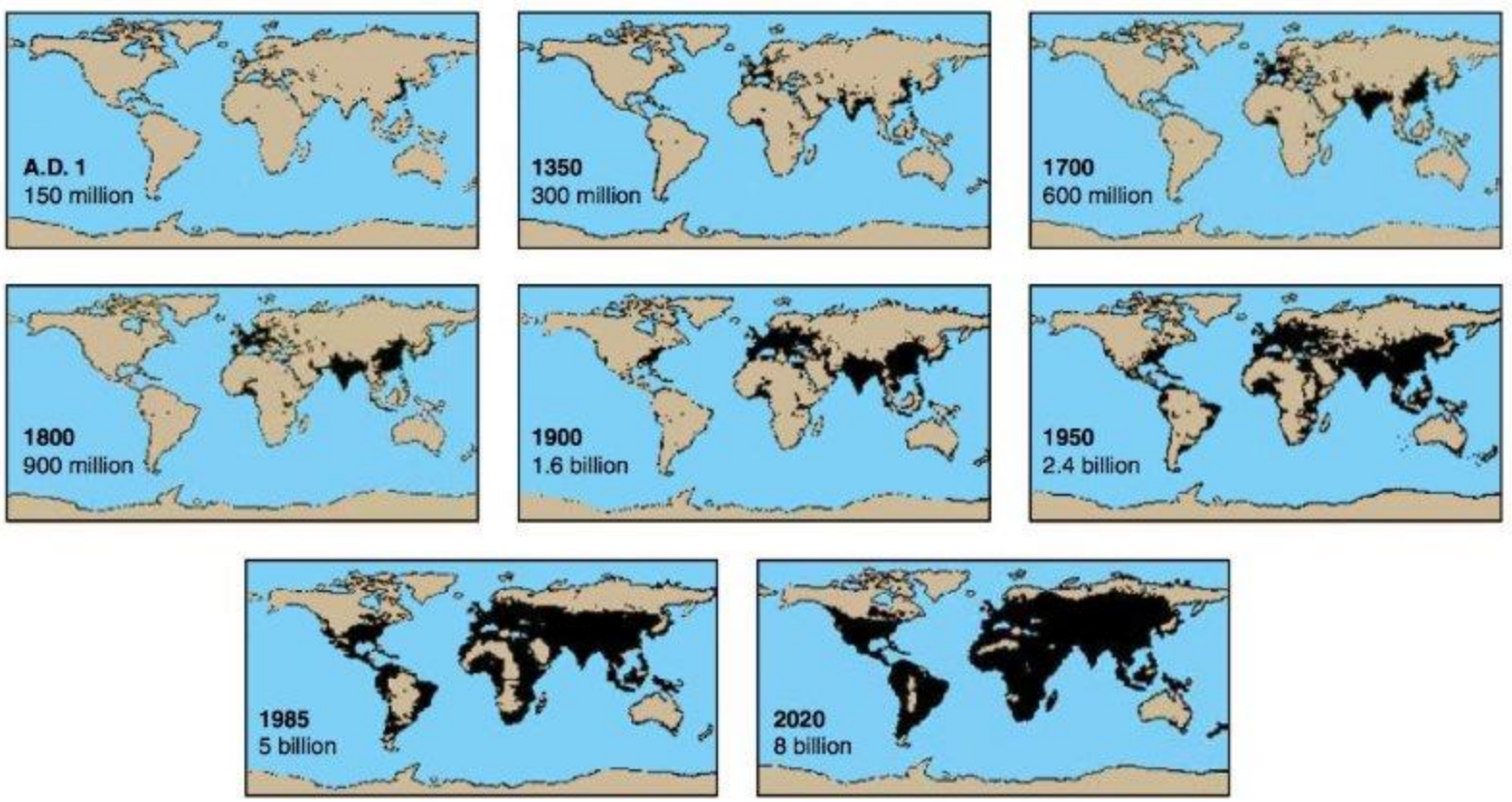
Human Population Throughout History, A.D. 1 to 2020



Emerging Threats & Trends

- States with poor governance; ethnic, cultural, or religious tensions; weak economies; and porous borders can become prime breeding grounds for terrorism
  - In such states, domestic groups will challenge the entrenched government, and transnational networks seeking safehavens
- The trend is moving away from state-supported political terrorism and toward more diverse, free-wheeling, transnational networks—enabled by information technology—will continue
  - Some of the states that actively sponsor terrorism or terrorist groups today may decrease or even cease their support as a result of regime changes, rapprochement with neighbors, or the conclusion that terrorism has become counterproductive
  - But weak states also could drift toward cooperation with terrorists, creating de facto new state supporters
- Between now and 2020 terrorist tactics will become increasingly sophisticated

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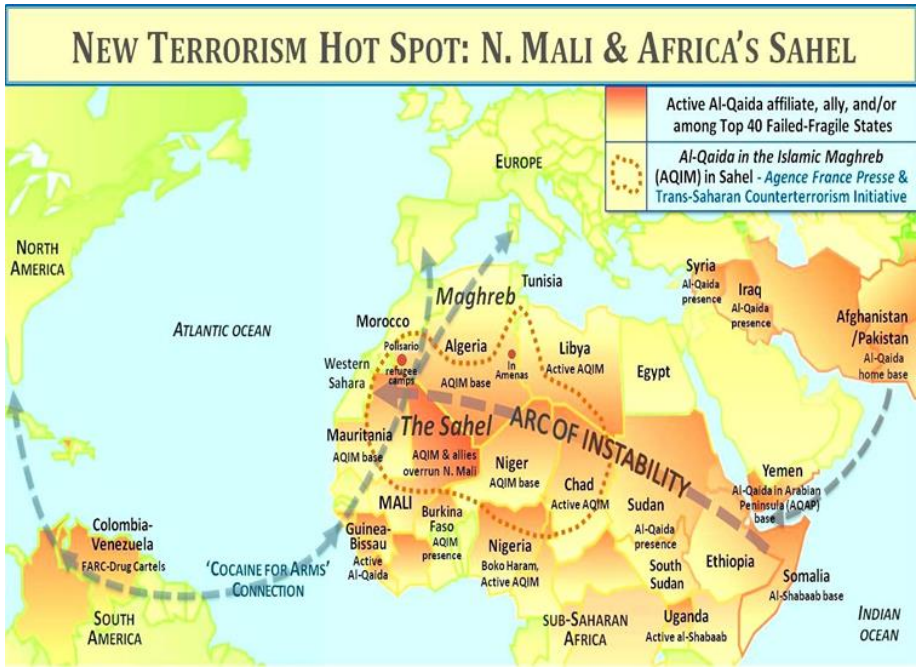
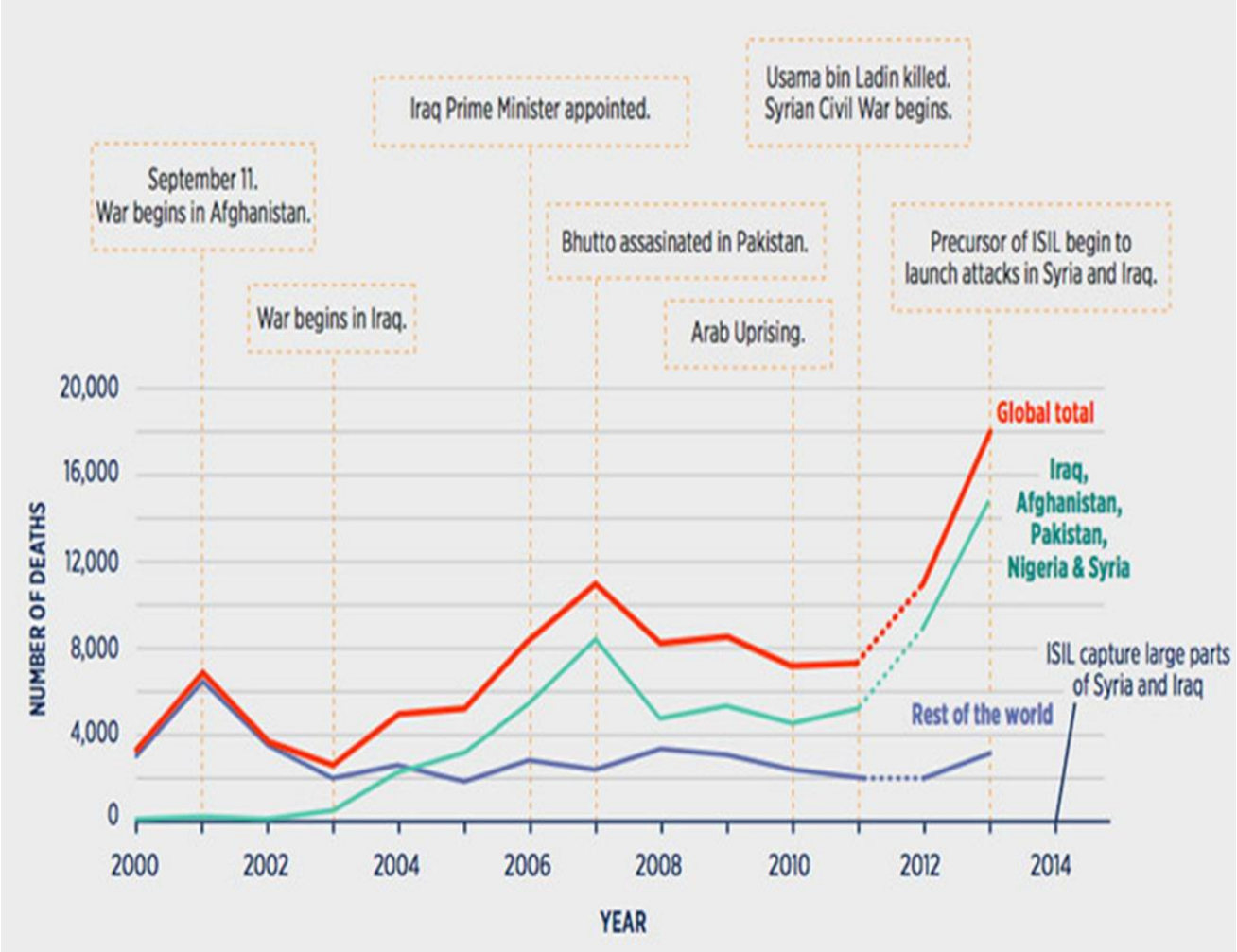
Terrorism

- Most terrorism is now based on perceived ethnic, religious or cultural grievances
- Terrorist groups will continue to find ways to attack US/Allies military and diplomatic facilities abroad
- These attacks are likely to expand increasingly to include US companies and American citizens in other countries
- Middle East, African and Southwest Asian-based terrorists organizations will most likely be the aggressors



Deaths from Terrorism, 2000-2013



The number of people who have died from terrorism activity has increases 5-folds since 2000

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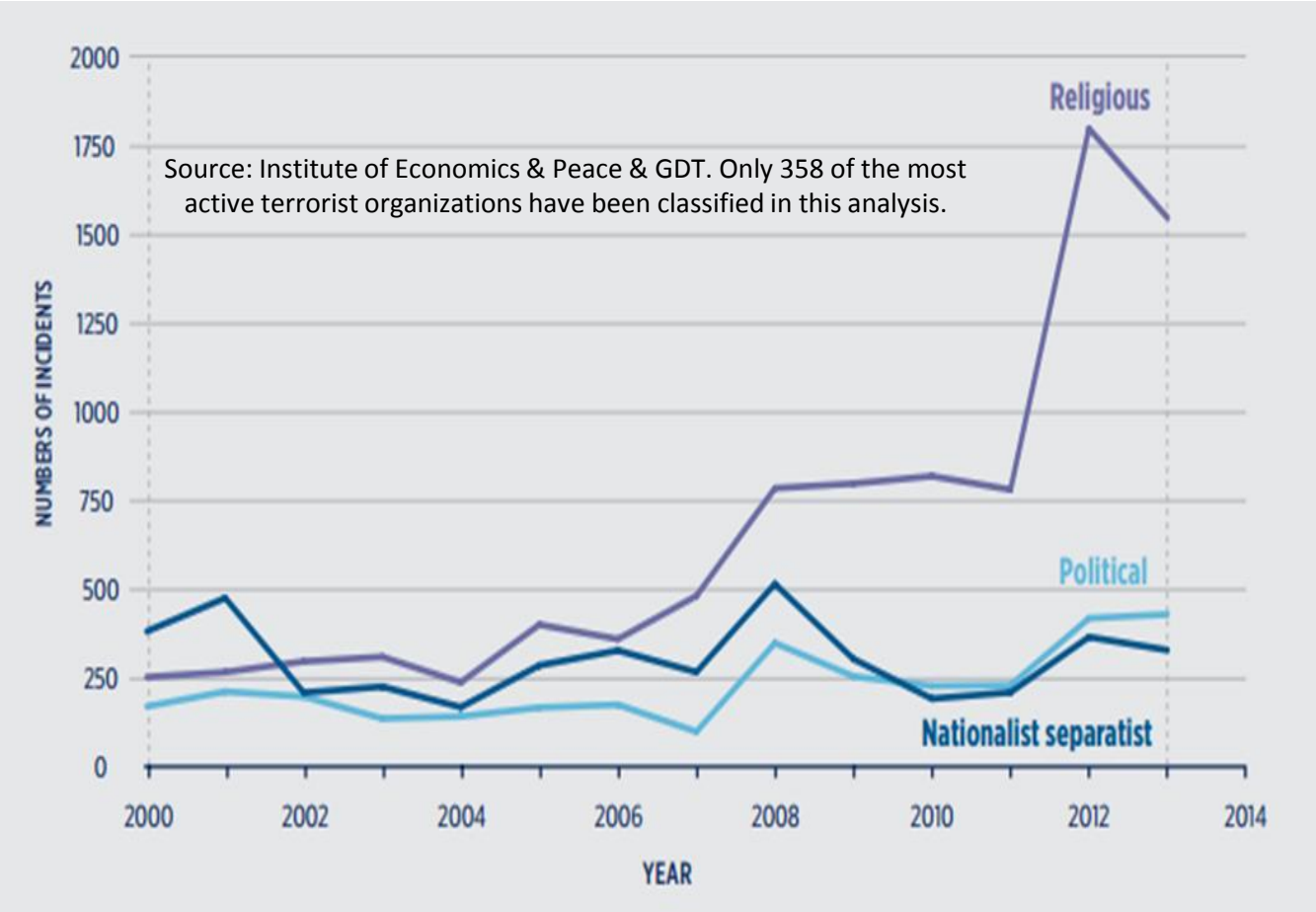
Deaths from Terrorism, 2000-2013



Religion as a driving ideology for terrorism has dramatically increased since 2000. However, in 2000 Nationalist Separatist movements were more prominent. Political and National Separatist movements are still significant in 2013 but have seen little change in activity over the period.

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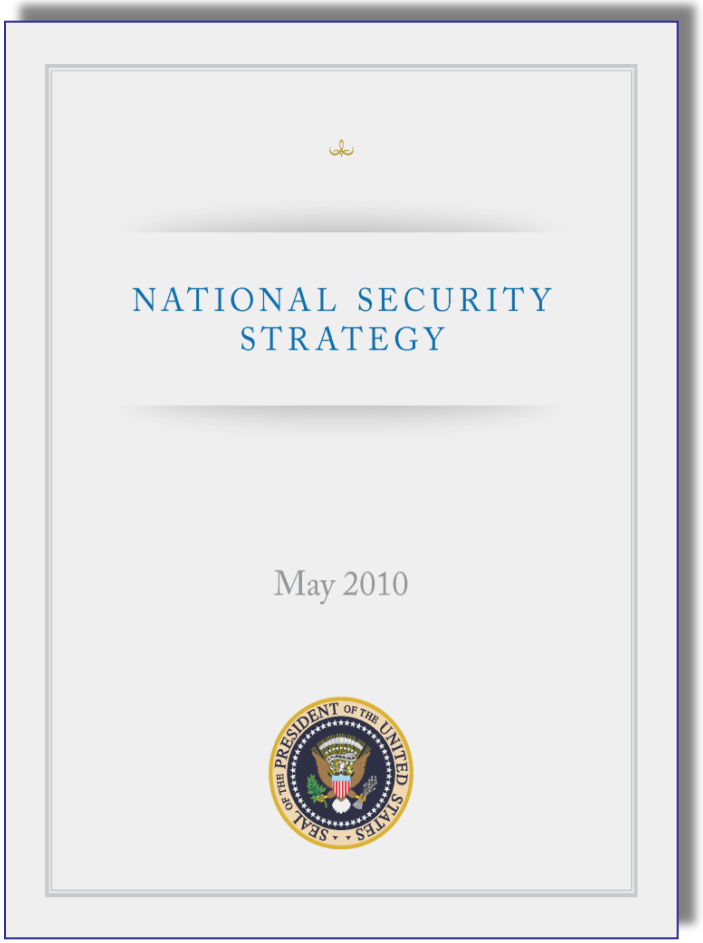
Countering Weapons of Mass Destruction (C-WMD) is a US National Priority



"…[T]here is no greater threat to the American people than weapons of mass destruction."

pg 4, National Security Strategy, May 2010

"The effective dissemination of a lethal biological agent within a population center would endanger the lives of hundreds of thousands of people and have unprecedented economic, societal, and political consequences."

pg 24, National Security Strategy, May 2010

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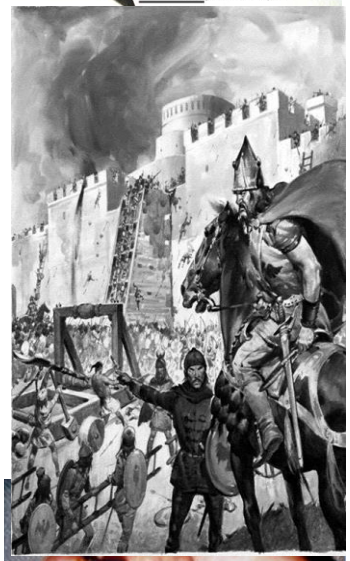
Bioterrorism

- **History**
  - **6th Century BC – Assyrians poison the wells of their enemies with rye ergot**
  - 6th Century BC – Solon of Athens poisons the water supply with hellebore (skunk cabbage) an herb purgative, during the siege of Krissa
  - 184 BC – Hannibal forces hurled earthen pots filled with serpents upon enemy
  - **1346 – Tatar army hurls its plague ridden dead over the walls of the city (present day Ukraine); caused and epidemic, city surrendered; likely started the Black Death pandemic killing 1/3 of Europeans**
  - *1422 – Battle of Carolstein, bodies of plague ridden soldiers plus 2000 cartloads of excrement are hurled into the enemy* ranks



Bioterrorism

- **History**
  - 15th Century: Pizarrio's army presented South American natives clothing laden with the variola virus
  - 1763: Captain Ecuyer of the Royal Americans, under the guise of friendship, presents to the native Americans two blankets and a handkerchief contaminated with smallpox.
  - **1767: During the French and Indian War, the English general, Sir Jeffrey Amherst, gives blankets laced with smallpox to Indians loyal to the French. The epidemic decimates the tribes, arguably, resulting in a successful British attack on Ft. Carillon.**

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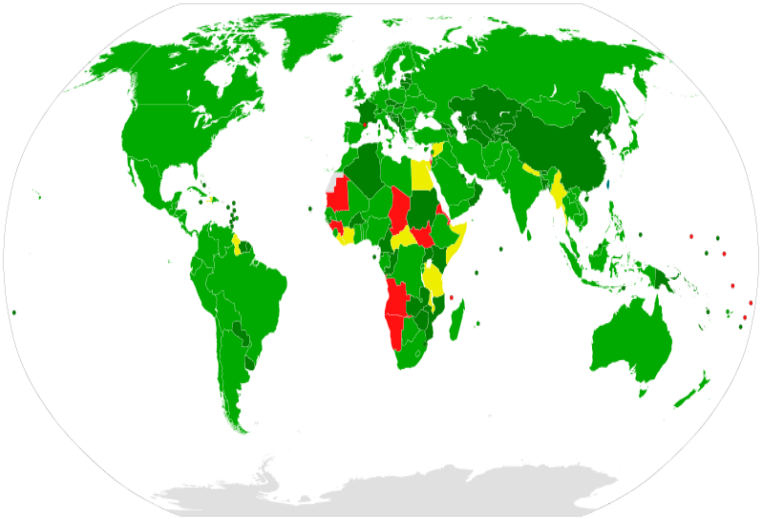
Bioterrorism

- **20th Century:**
  - US
    - 1943: USA Bio program launched
    - 1953: Bio Defensive program established
    - 1969: Bio Offensive program disbanded
  - Global
    - 1925 Geneva Protocol
    - 1972 Biological Weapons Convention signed by 103 nations
    - 1975 Geneva Conventions Ratified



Definition

The unlawful use, or threatened use, of microorganisms or toxins derived from living organisms to produce death or disease in humans, animals, or plants. The act is intended to create fear and/or intimidate governments or societies in pursuit of political, religious, or ideological goals.

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What makes the use of biological agents so attractive to the terrorist?

- **Ease of Acquisition**
  - Information readily accessible on World Wide Web
  - American Type Culture Collection, other sources
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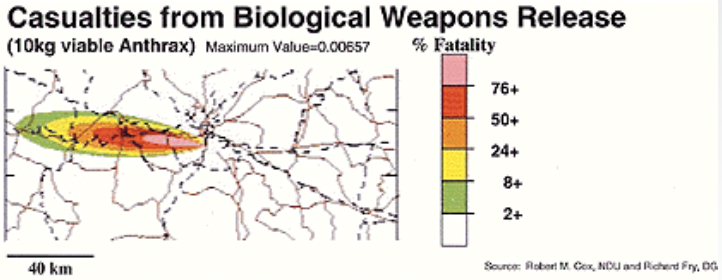
  - Information readily accessible on World Wide Web
  - American Type Culture Collection, other sources
- **Ease and Economy of Production**
  - Only basic microbiology equipment necessary
  - Small labs require no special licensing
  - Investment to cause 50% casualty rate per sq. km:
    - Conventional weapon $2000, nuclear $800, anthrax $1
- **Lethality**
  - 50 kg aerosolized anthrax = 100,000 mortality
  - Sverdlovsk experience, former USSR
- **Stability**
- **Infectivity**
  - Weaponized agents may be easily spread
  - Clinical symptoms days to weeks after release
- **Low Visibility**
- **Ease and Stealth of Delivery**
  - Remote, delayed, undetectable release
  - Difficult/impossible to trace origin of agent



Routes of Delivery for Biological Agents

- **Aerosol is most likely method of dissemination**
  - Easy, silent dispersal
  - Maximum number of victims exposed
  - Inhalation is most efficient and contagious route of infection

- **Food/Water-borne dispersal less likely**
  - Less stable, ineffective for some agents
  - Inefficient compared to aerosol

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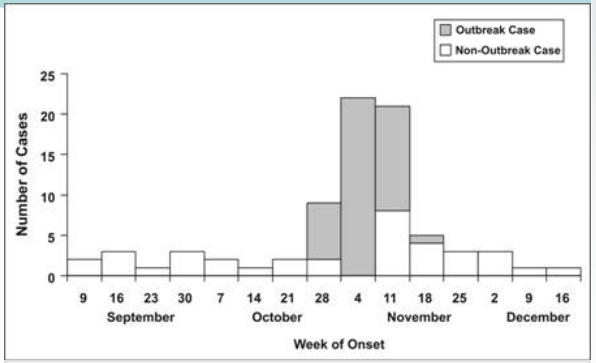
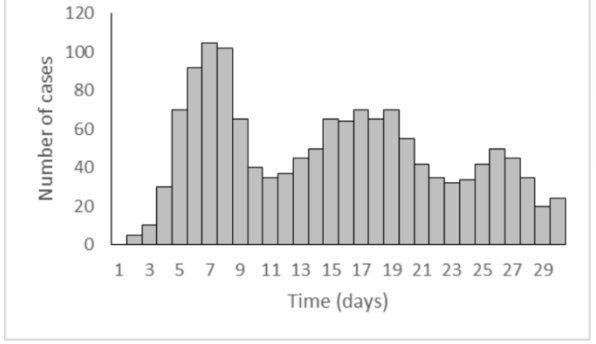
Events Suggesting the Release of a Bioweapon

- Multiple people ill at the same time (epidemic)
- Previously healthy persons affected
- High morbidity and mortality among affected individuals
- Identification of diseases and pathogens unusual particular region
- Recent terrorist claims or activity
- Unexplained epizootic of sick or dead animals
- Severe respiratory disease in a healthy host
- An epidemic curve rising and falling rapidly
- Increase in fever, respiratory, and GI symptoms
- Lower attacks rates in people working indoors vs. outdoors
- Seasonal disease during a different time of year
- Known pathogen with unusual antimicrobial resistance pattern
- Genetically-identical pathogen in different areas





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What Can We Do As Medical Professionals?

- Maintain a high index of suspicion by including biological agents in differential diagnoses
- Learn to recognize historical and physical examination findings suggestive of bioweapon exposure
- Stay informed of local, regional and national epidemiologic trends
- Be knowledgeable about treatment and prophylaxis of patients exposed to biological agents
- Know whom to report suspected biological agent exposures and illnesses to (Police, State Intelligence agency, Infectious Disease Specialists, Local and State Health Officials)

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Agents of Bioterrorism

- Bacterial Agents
  - *Bacillus anthracis* (Anthrax)
  - *Yersinia pestis* (Plague)
  - *Francisella tularensis* (Tularemia)
  - *Brucella spp.* (Brucellosis)
  - *Coxiella burnetii* (Q Fever)
  - *Burkholderia mallei* (Glanders)
  - *Vibrio cholerae* (Cholera)
- Viral Agents
  - Variola virus (Smallpox)
  - Venezuelan Equine Encephalitis Virus (VEE)
  - Hemorrhagic Fever Viruses: Ebola, Marburg, Lassa Fever, Argentine and Bolivian Hemorrhagic Fever Viruses, Hantavirus, Congo-Crimean Virus, Rift Valley Fever Virus, Yellow Fever Virus, Dengue Virus
- Biological Toxins
  - Botulinum Toxins
  - Staphylococcal Enterotoxin B
  - Ricin
  - Mycotoxins (T2)

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Source: CDC

Characteristics of BT Agents

Agent	Type	Minimum Dose	Incubation period	Initial Symptoms	Duration of illness	Lethality	Animal Indicator
Anthrax	Bacteria	8,000 (spores)	1-6 days	Flu-like	3-5 days	High 90%	Yes
Plague	Bacteria	100 organisms	2-3 days	Pneumonia / Flu-like	1-6 days	High 90-100%	Yes
Tuleramia	Bacteria	10 organisms	2-10 days (avg. 3-5)	Flu-like	>=2 weeks	Moderate 5-30%	Yes
Brucellosis	Bacteria	10 organisms	5-60 days	Flu-like	Weeks to months	Low 2-10%	Yes
Q Fever	Rickettsia	1 organisms	10-40 days	Flu-like	2-14 days	Low 4%	Yes
Smallpox	Virus	10 organisms	7-17 days (avg. 12)	Flu-like	4 weeks	High 30%	Animal Varients
Encephalitides VEE, EEE, WEE	Virus	10 organisms	2-6 days	Flu-like	days to weeks	low	Yes
Hemorrhagic Fevers: Ebola, Marburg	Virus	1 organism	4-21days	Flu-like	7-16 days	High Marburg 25% Ebola 50-90%	Yes
Botulinum	Toxin	100 ng	1-5 days	muscle weakness	24-72 hours	High 30%	Yes

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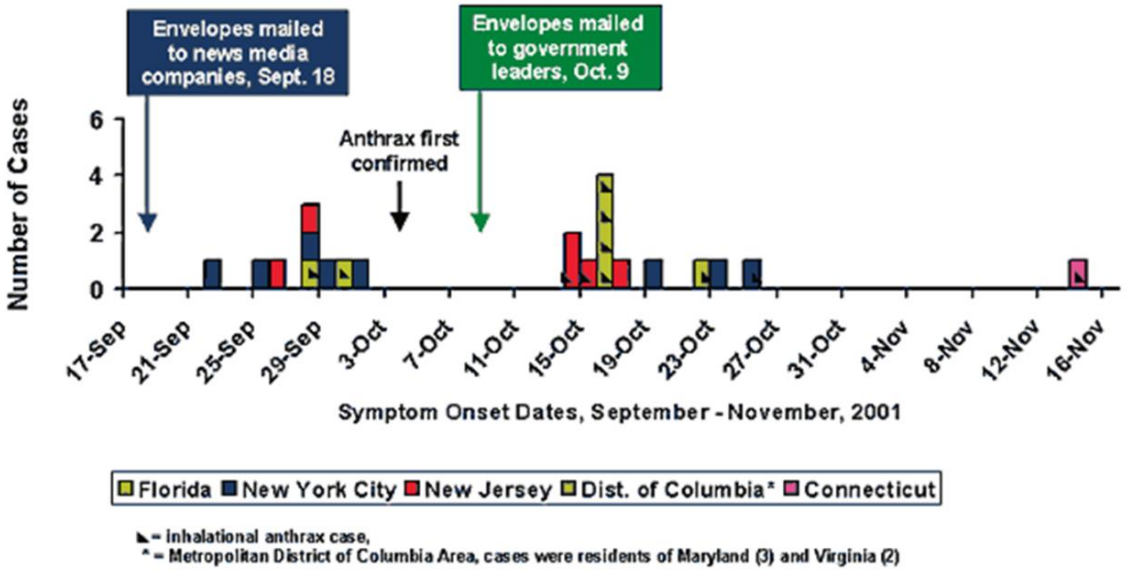
Anthrax

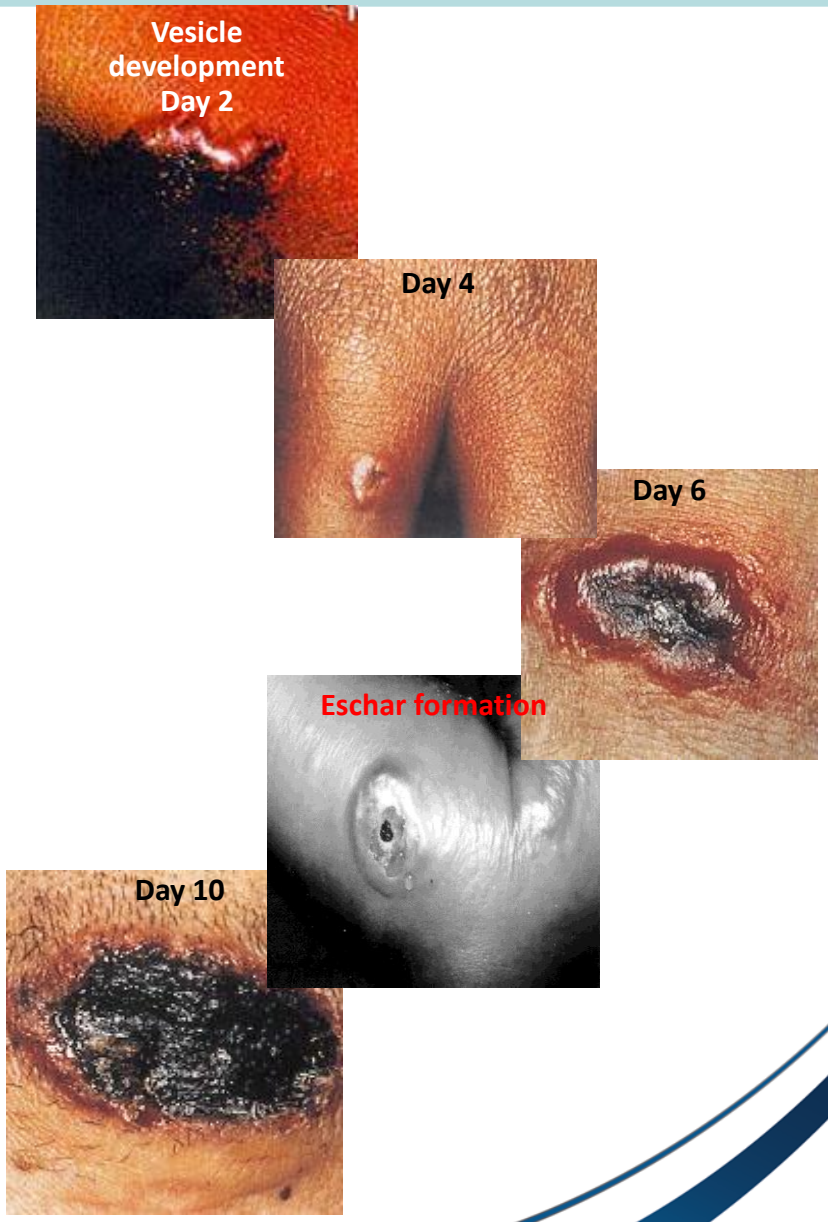
- Caused by contact with spores of *Bacillus anthracis*, a spore-forming, gram-positive rod
- Three distinct forms of clinical illness:
  - Cutaneous by inoculation of skin lesions with spores; common, easily recognized and treated
  - Inhalation by inhalation of spores into the lower respiratory tract; rare, difficult to recognize, > 80% mortality (classic description - Woolsorter's disease)
  - Gastrointestinal by ingestion of spores in contaminated meat; rarely encountered but highly lethal



Source: CDC

Cutaneous Anthrax

- A nondescript, painless, pruritic papule develops 3 to 5 days after introduction of B. anthracis endospores
- In 24 to 36 hours, the lesion forms a vesicle that undergoes central necrosis and drying, leaving a characteristic black eschar surrounded by edema and a number of purplish vesicles: resolves without scarring
- 80-90% resolve without treatment, but mortality can approach 20%, so cases usually treated



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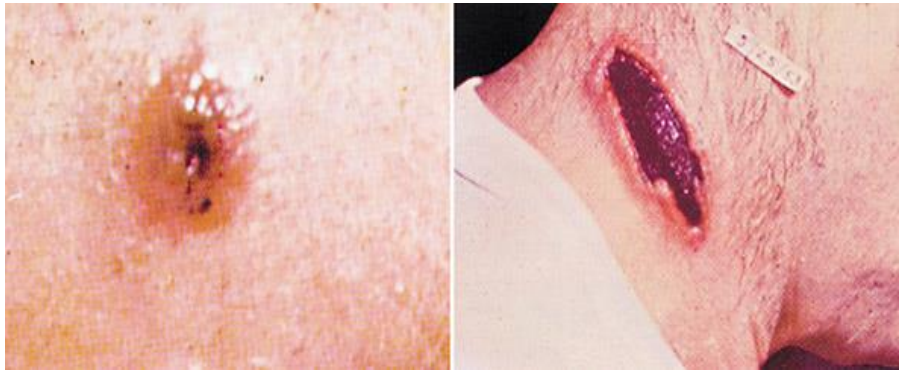
Cutaneous Anthrax



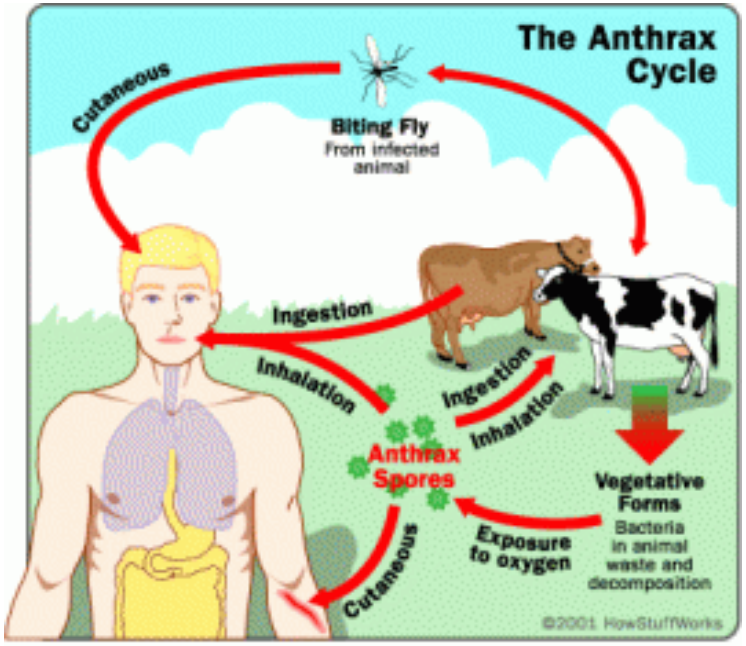
Left, **Forearm lesion on day 7**—vesiculation and ulceration of initial macular or papular anthrax skin lesion. Right, **Eschar of the neck on day 15** of illness, typical of the last stage of the lesion. From Binford CH, Connor DH, eds. *Pathology of Tropical and Extraordinary Diseases.* Vol 1. Washington, DC: AFIP; 1976:119. AFIP negative 71-1290–2.

Notice the edema and typical lesions

NEJM 1999; 341: 815– 826

Cutaneous Anthrax: Diagnosis

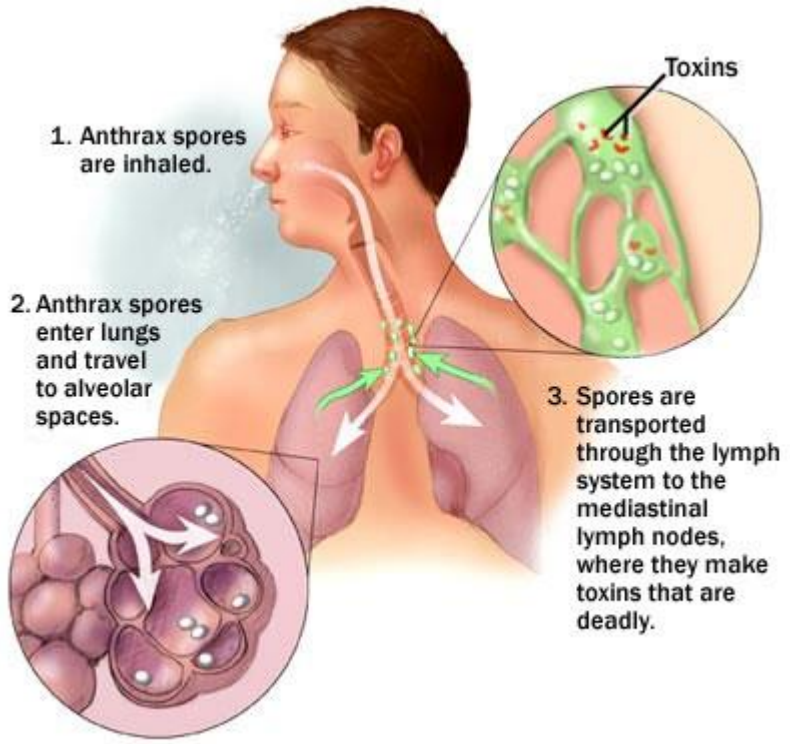
- CGram stain, polymerase chain reaction (PCR), or culture of vesicular fluid, exudate, or eschar
- Blood culture if systemic symptoms present
- Biopsy for immunohistochemistry, especially if person taking antimicrobials
- Differential Diagnosis
  - Spider bite
  - Ecthyma gangrenosum
  - Ulceroglandular tularemia
  - Plague
  - Staphylococcal or streptococcal cellulitis
  - Herpes simplex virus



Inhalational Anthrax

Pathogenesis

- 1-5 micron Anthrax spore size is optimal for deposition into alveoli
- Inhaled spores are ingested by alveolar macrophages and transported to mediastinal and peribronchial lymph nodes, spores germinating en route
- Anthrax bacilli multiply in lymph nodes, causing hemorrhagic mediastinitis, and spread throughout the body in the blood



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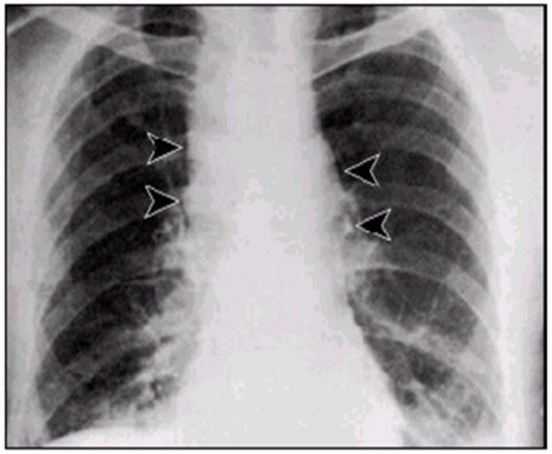
Clinical Presentation

- 10 days to 6 weeks after inhalation of spores, infected patients develop fever, non-productive cough, myalgia and malaise
- Early in the course of the disease, chest radiographs show a widened mediastinum, which is evidence of hemorrhagic mediastinitis, and marked pleural effusions
- After 1-3 days, the disease takes a fulminant course with dyspnea, strident cough, and chills, culminating in hypotension, shock, and death



Mediastinal widening
JAMA 1999;281:1735–1745

Diagnosis

- Chest X-ray—widened mediastinum, pleural effusions, infiltrates, pulmonary congestion
- Affected tissue biopsy for immunohistochemistry
- Any available sterile site fluid for Gram stain, PCR, or culture
- Pleural fluid cell block for immunohistochemistry
- Differential Diagnosis:
  - Mycoplasmal pneumonia
  - Legionnaires' disease
  - Psittacosis
  - Tularemia
  - Q fever
  - Viral pneumonia
  - Histoplasmosis (fibrous mediastinitis)
  - Coccidioidomycosis
  - Malignancy

Mediastinal Widening and Pleural Effusion

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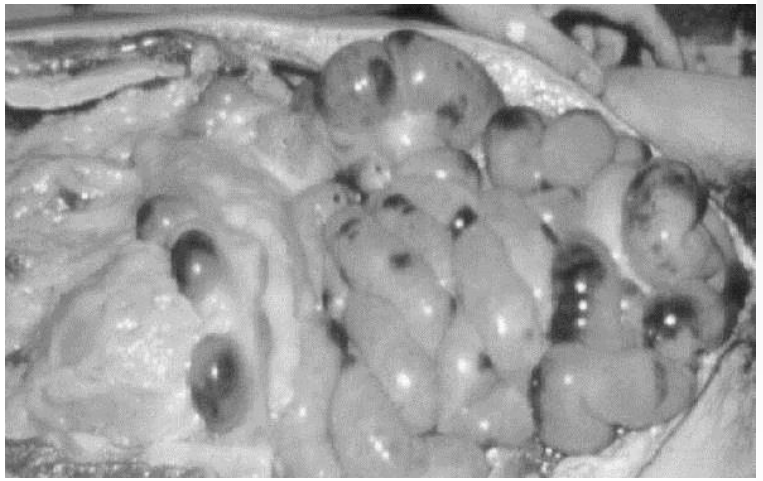
Source: CDC

Gastrointestinal Anthrax

- Fever and diffuse abdominal pain with rebound tenderness develop 2-5 days after ingestion of spores in contaminated meat
- Melenic or blood-tinged stools, blood-tinged or coffee-ground emesis, and ascites develop
- Death results from fluid and electrolyte imbalances, blood loss, shock, intestinal perforation or anthrax toxemia
- Diagnosis:
  - Blood cultures
  - Oropharyngeal (OP) swab collection



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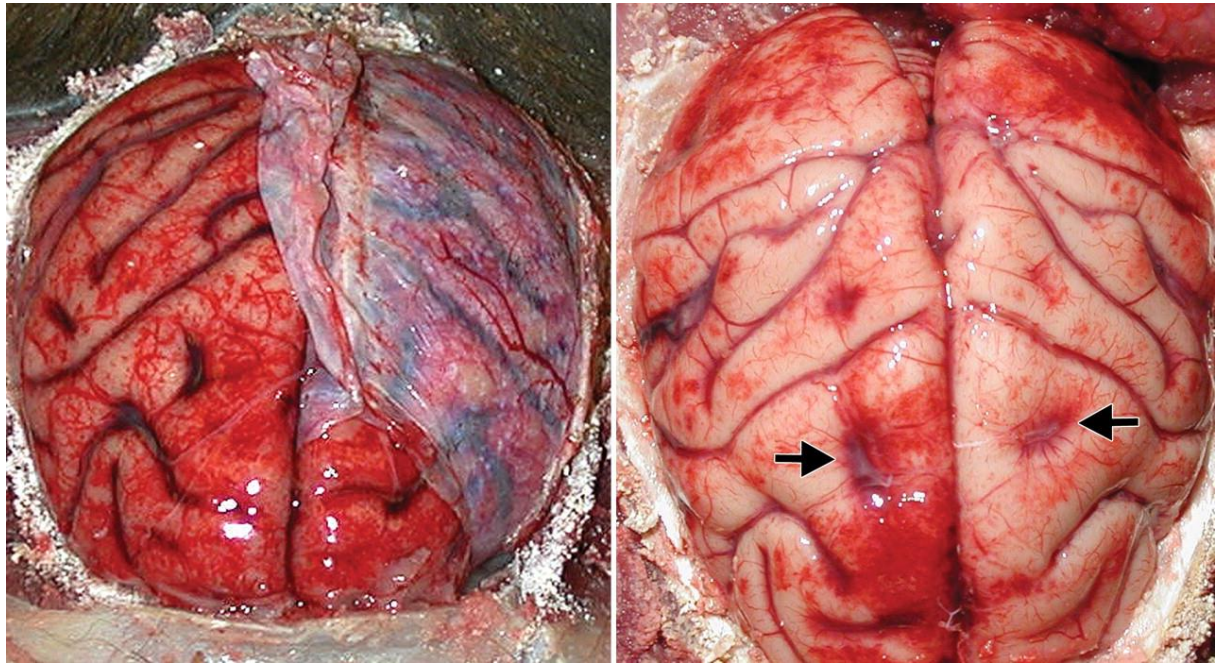
Source: CDC

Anthrax Meningitis

- Hemorrhagic meningitis is a potential complication of anthrax, and may accompany cutaneous, gastrointestinal, or inhalational anthrax (seen in 50% of inhalational cases)
- Death almost universal within 1-6 days after onset of illness
- Rare survivors have been treated using appropriate antibiotics in combination with antitoxin, prednisone or both



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Source: CDC

Laboratory Criteria for Identification of *B. anthracis*

- From clinical samples, such as blood, cerebrospinal fluid (CSF), skin lesion (eschar), or oropharyngeal ulcer
  - Encapsulated gram-positive rods on Gram stain
- From growth on sheep blood agar:
  - Large gram-positive rods
  - Nonmotile
  - Nonhemolytic
- Rapid screening assay (PCR- and antigen-detection based) for use on cultures and directly on clinical specimens
- Confirmatory criteria for identification of *B. anthracis*
  - Capsule production
  - Lysis by gamma-phage
  - Direct fluorescent antibody assay (DFA)
- Gram Stain Morphology of *B. anthracis*
  - Broad, gram-positive rod: 1–1.5 x 3–5 µ
  - Oval, central to subterminal spores: 1 x 1.5 µ with no significant swelling of cell
  - Spores usually NOT present in clinical specimens unless exposed to atmospheric O2

Gram Stain of Blood in Culture Media
Gram-positive bacilli in long chains (original magnification 20). Enlargement shows typical "jointed bamboo-rod" appearance of Bacillus anthracis (original magnification 100).

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Source: CDC

Smallpox

- Worst-case scenario biological agent
  - Highly contagious once rash present (not before)
  - World's population is largely susceptible
  - Up to 30% case fatality rate in non-immune
  - Secondary attack rate of 25-40% (10-20 secondary cases can be expected per index case)
  - No specific treatment available
- Globally very few physicians currently practicing have seen actual cases
- Virus has been weaponized by Soviets, uncertain who exactly owns viable stocks

Source: CDC

Smallpox

- Caused by Variola virus (Orthopox virus)
- Immunization of U.S. civilian population suspended in 1980, U.S. military recruits in 1989
- Virus is stable in environment
- Spread primarily by respiratory droplets, also by contact, fomites
- Two distinct types of smallpox:
  - Variola Minor (Alastrim): diminutive lesions and mild systemic toxicity
  - Variola Major: Ordinary (subtypes discrete, semi-confluent, confluent), Modified, Flat, Hemorrhagic

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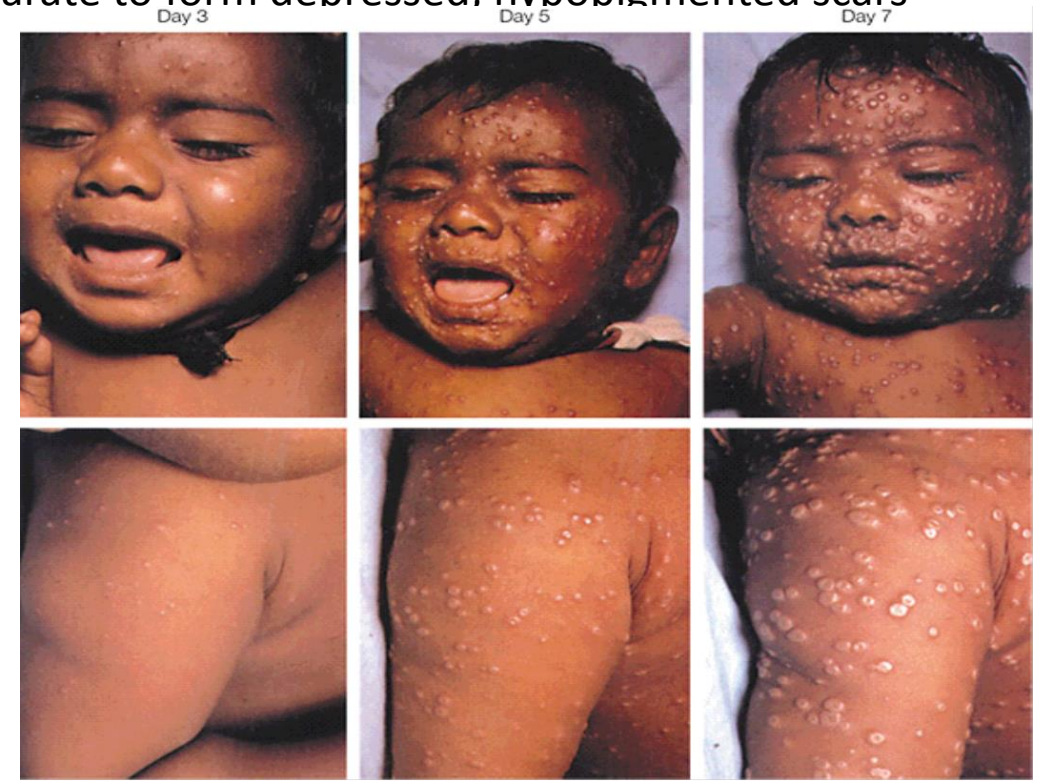
Source: CDC

Clinical Presentation

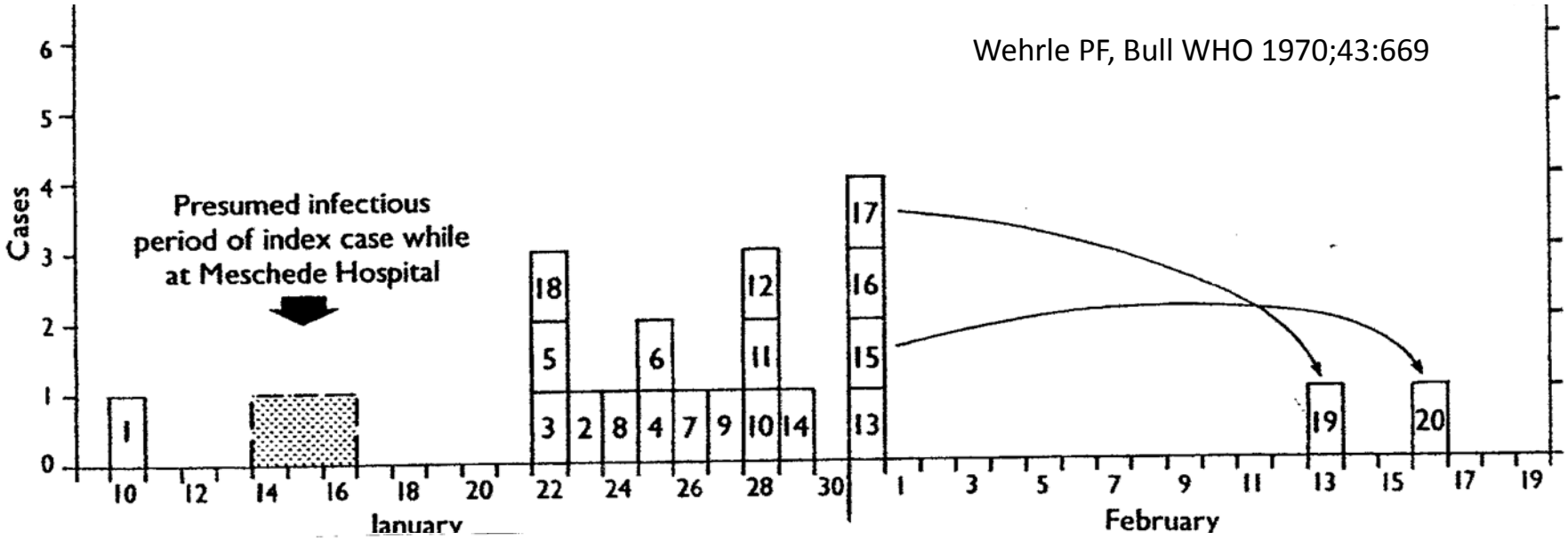
- 7-17 day incubation period
- Prodromal phase: 2-4 days of malaise, fever, rigors, headache, backache, delirium
- Rash then develops on face, hands, forearms and legs, including palms and soles (centrifugal distribution is important distinguishing feature).
- Initial rash is maculopapular. In 1-2 days, lesions become vesicular, then evolve into round, tense pustules deeply imbedded in the dermis. Crusts form on 8th to 9th day of rash
- Crusts separate to form depressed, hypopigmented scars

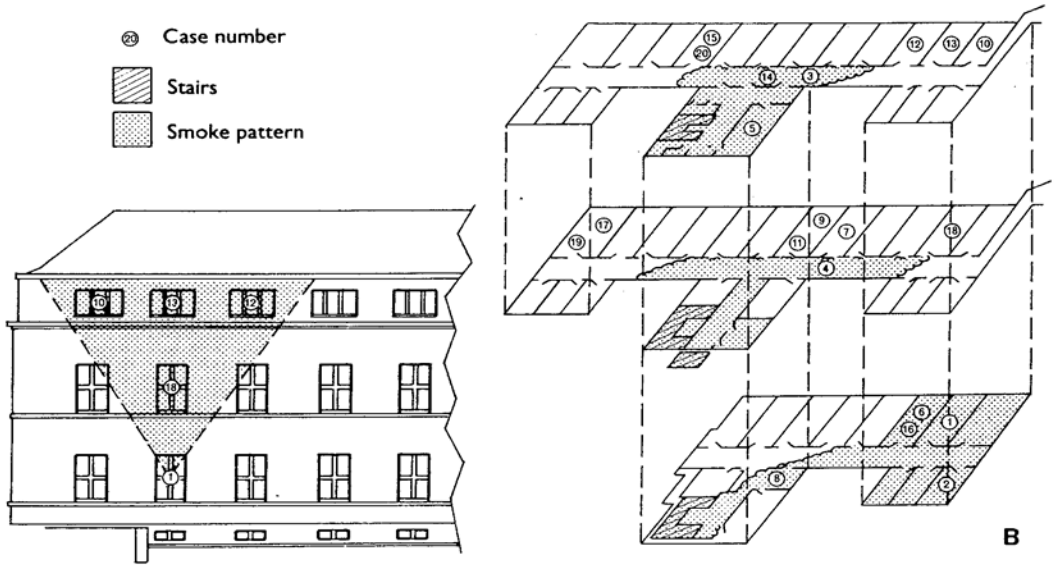


Source: CDC

Smallpox Outbreak, Meschede Hospital, Germany, 1970

Wehrle PF, Bull WHO 1970;43:669





Diagnosis & Management

- Diagnosis:
  - Recognition of clinical features in early index cases is key
  - Identification of a single case of smallpox constitutes an international medical emergency, and should be considered evidence of a bioterrorist attack
  - Confirmation of diagnosis is made by demonstration of characteristic virions on electron microscopy of vesicular scrapings
- Management:
  - Immediate quarantine of affected and exposed individuals for 17 days
  - Only supportive care is available. Cidofovir has demonstrated in vitro activity
  - Immediate vaccination of all exposed persons with Vaccinia virus vaccine by inoculation with a bifurcated needle (scarification)
  - Administration of Vaccinia Immune Globulin (VIG), 0.6 ml/kg intramuscularly, concomitant with vaccination
  - Active and passive immunization is effective at preventing disease and death if given within 7 days of exposure

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Source: CDC

Biosurveillance Initiatives

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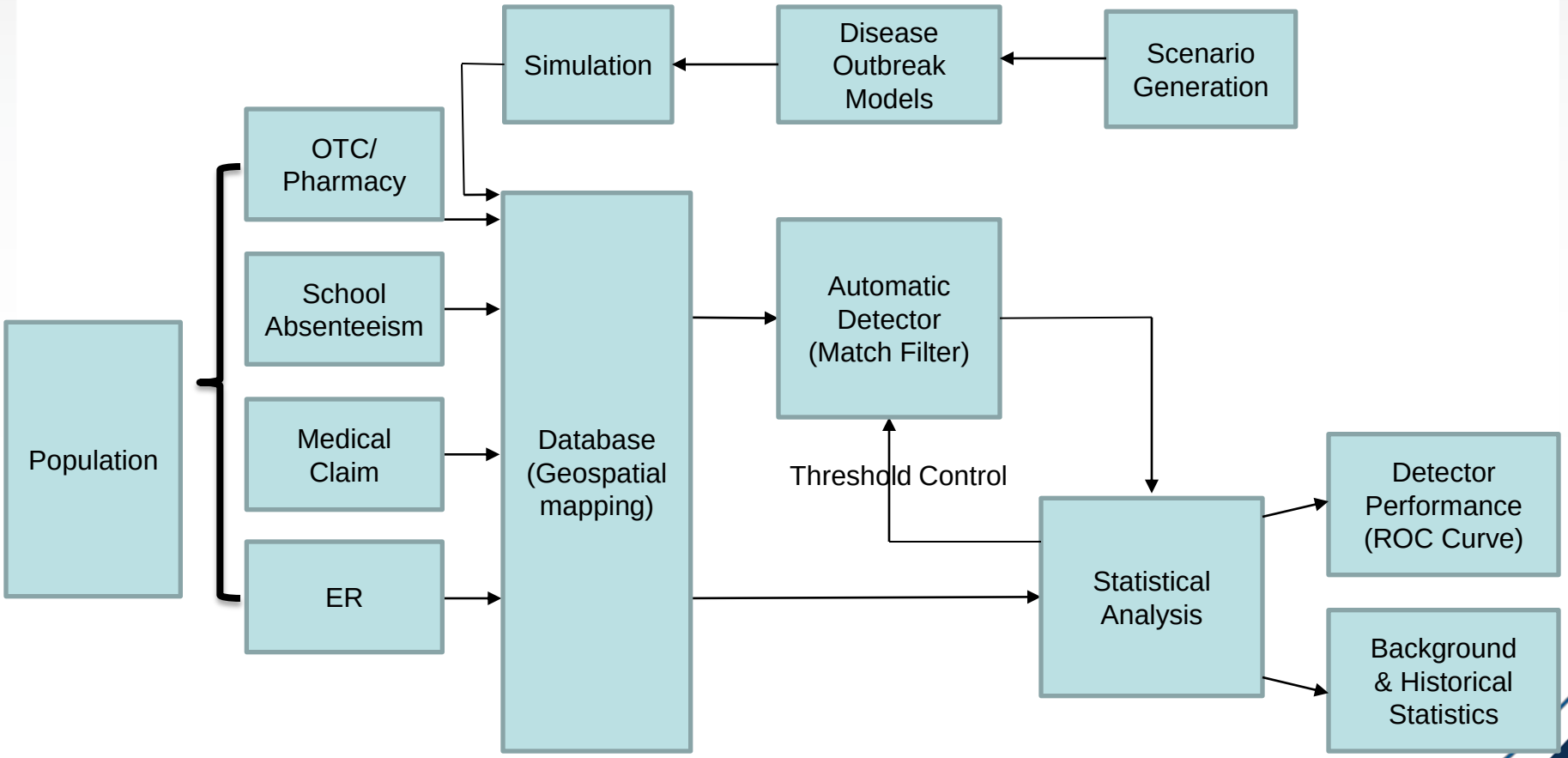
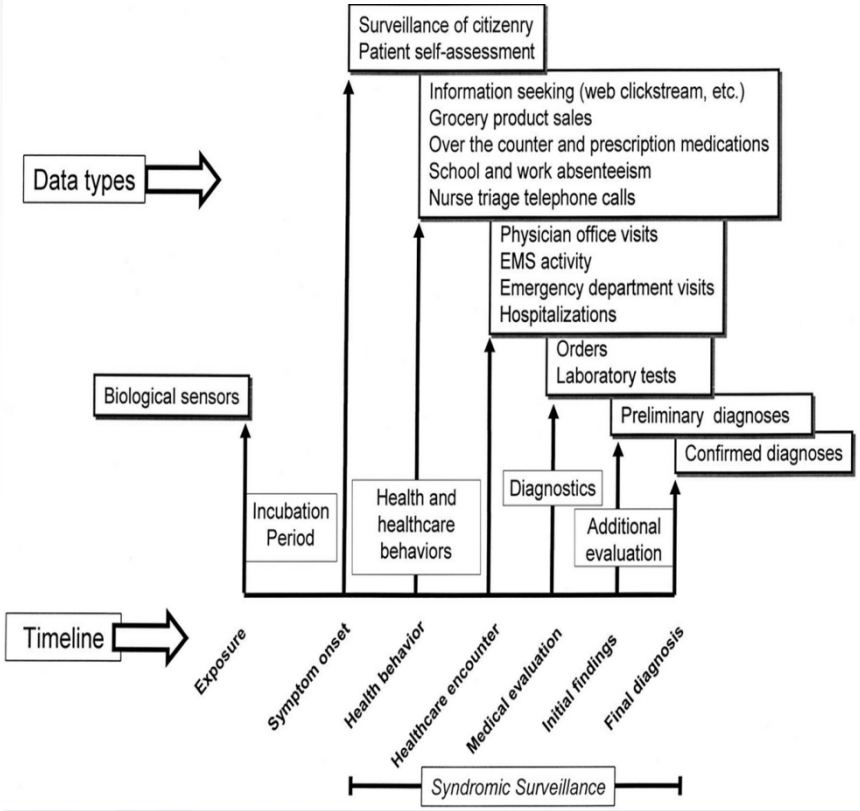
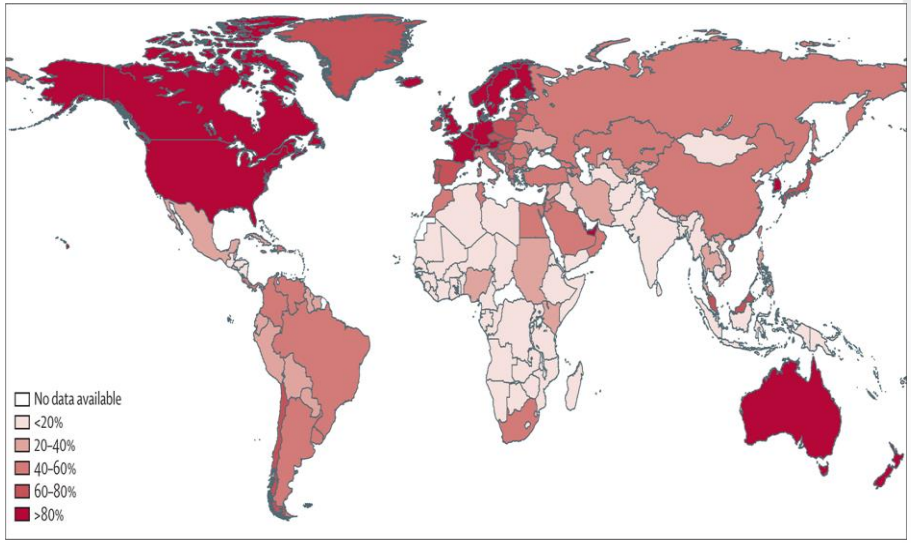
Biosurveillance Initiatives

Method and System for Bio-surveillance Detection and Alerting
(1999-2000 Post doctorate DARPA Challenge) for Bio-threat Agents

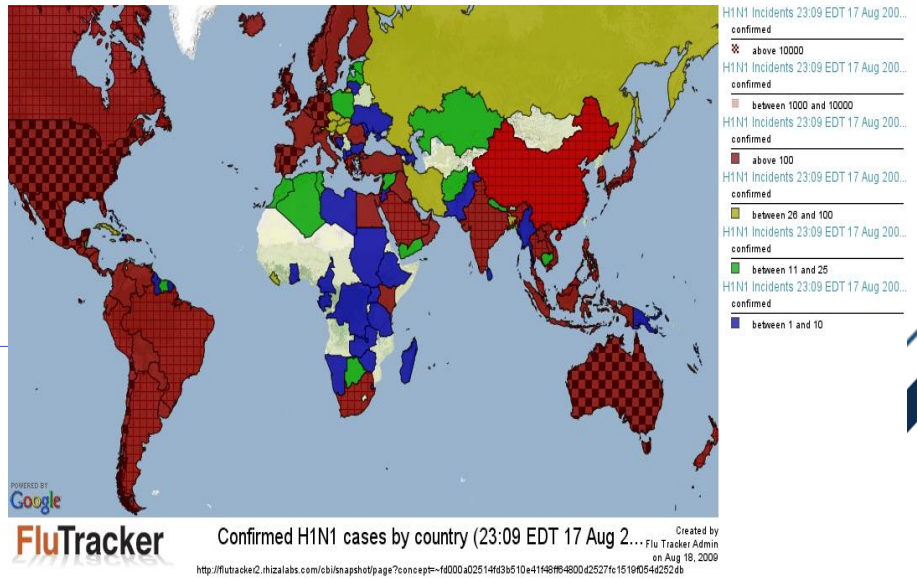


Biosurveillance Potential Data Sources





Internet-based surveillance systems for monitoring emerging infectious diseases. Milinovich et al. Lancet



Biosurveillance covers a broad complex space

- “Integration of biosurveillance elements and other data (including human health, animal health, agricultural, meteorological, environmental, intelligence, and other data) will provide a comprehensive picture of the health of communities and the associated threat environment for incorporation into the national “common operating picture.” (ref. HSPD-21)
- Requires collecting, analyzing, producing information, then disseminating to decision-makers to mitigate or reduce the effects of biological events
- Should cover I&W, event situational awareness and forecasting
- Needed daily for:
  - Disease outbreak monitoring, health care resource allocations, community health situational awareness, national health security
- Necessary to manage a national event
  - Diseases such as influenza
  - Food Contamination Events – Salmonella outbreaks, E coli outbreaks, intentional adulteration events
  - Animal diseases and impacts – BSE, Foot and Mouth Disease, zoonotic diseases
  - Events with biological impact
    - Haiti earthquake → dengue fever outbreak
    - Gulf Oil Spill → marine, plant, human health impacts
    - Fukishima earthquake nuclear disaster → personnel radioactive contamination

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Take Home Message

- Early Detection:
  - Epidemiology capacity
  - Critical and comprehensive biosurveillance program and strategy
  - Laboratory capability and capacity for detection of bio-threat agents

- Preparedness, planning and readiness assessment
  - Education & Training for HCW for identification of bio-threat agents
  - Health alert network
  - Conducting Exercises and Drills for Consequence Management
  - Having a robust National Stockpile Program
  - Building hospitals capability and capacity for surge in case of a public health disaster

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Take Home Message

- The intentional use of biothreat agents can cause panic, disease, and death.
- Whether a biological attack is well orchestrated causing mass causalities or involves an unsophisticated delivery system with a limited number of true cases, the outcome is frightening.
- **As Qatar mobilizes to address an array of overlapping foreign policy, infectious disease, and national security threats, it must make sure that a comprehensive program to counter and prevent bioterrorism ranks high on the priority list.**

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For the past half-century the main concern was a nuclear Armageddon caused by atomic weapons. However, with the discovery of various offensive biological warfare programs around the globe, the concern regarding intentional use of viruses and microorganisms as weapons of mass destruction increased during the past decade. The threat of biological warfare is real. It is now widely acknowledged that the biological weapons, in terms of destructiveness and in the generation of panic and civil disorder could produce an effect that is equivalent to that of a nuclear weapon.

Medical professionals globally should make sure that the world does not suffer a catastrophe as a result of the use of biowarfare pathogens

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Chotani, 2003