RECOGNITION AND MANAGEMENT OF AGENTS OF BIOTHREATS AND EXOTIC DISEASES

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TERRORISM TODAY

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Time, Special Edition

LECTURE TOPICS

- Potential exposures to rare and exotic diseases
- Major biologic warfare agents
- For most likely BW agents (anthrax, smallpox): Pre-exposure prophylaxis, post-exposure prophylaxis, therapy
- Recognizing a biologic warfare attack
- Review of anthrax and smallpox

EMERGING INFECTIOUS DISEASES SINCE 1990

- 1993 (US) - Hantavirus pulmonary syndrome (Sin nombre virus)
- 1994 (US) – Human granulocyte ehrlichiosis
- 1994 (Australia) – Hendra virus
- 1995 (Worldwide) - Kaposi sarcoma (HHV-8)
- 1996 (England) – Variant Creutzfeld-Jakob disease (vCJD)
- 1997 (Japan) – Vancomycin-intermediate *S. aureus*
- 1999 (US) - West Nile encephalitis (West Nile virus)
- 2001 (US) - Anthrax attack via letters
- 2001 (Netherlands) – Human metapneumovirus
- 2002 (US) – Vancomycin-resistant *S. aureus*
- 2003 (China → worldwide) - Severe acute respiratory syndrome (SARS)
- 2003 (US) - Monkeypox
- 2004 (Asia) – Avian influenza (H5N1) with human-to-human transmission
- 2005 (Africa) – Outbreaks of Ebola, Marburg, and Lassa fever
- 2006 (India) – Outbreak of Chikungunya fever (new variant)
- 2007 (Italy) – Outbreak of Chikungunya fever (first outbreak in Europe)
- 2009 (Worldwide) – Outbreak of 2009 H1N1
- 2012 (Middle East) – MERS-CoV

EMERGING DISEASES IN THE US

DISEASE (source)	CASES	OUTCOME	YEAR
West Nile virus (Israel)	Thousands	Endemic (US)	1999
SARS (China)	8096 (8 US, 1 UNC)	Controlled	2003
Monkeypox (Africa)	71 US	Controlled	2003
Novel flu, H1N1 (Mexico)	Millions	Endemic (Worldwide)	2009
MERS-CoV (Arabian Peninsula)	Thousands (2 US)	Epidemic	2014-15
Enterovirus D68 (US)	Hundreds (18 UNC)	Epidemic	2014
Ebola (West Africa)	Thousands (4 US)	Epidemic	2014-15

COUNTRIES WITH LAB-CONFIRMED MERS CASES

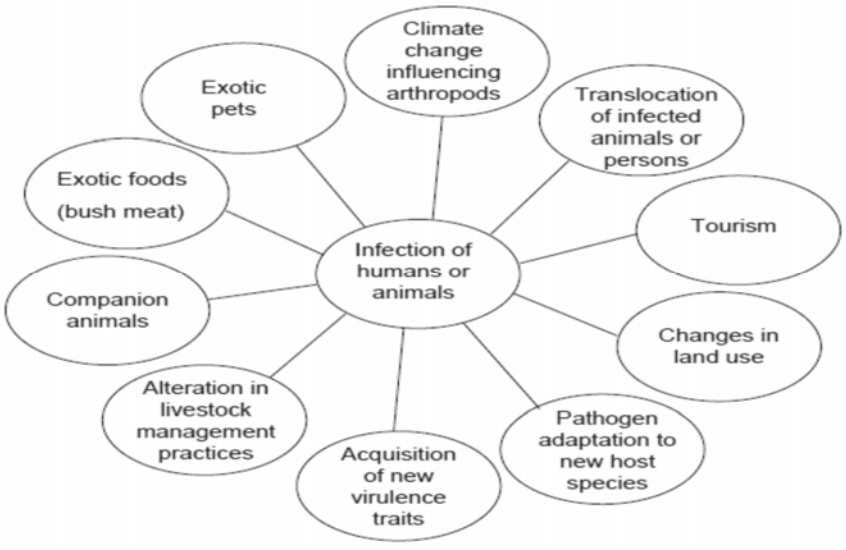
- Countries in the Arabian Penisula with Cases
  - Saudi Arabia
  - United Arab Emirates (UAE)
  - Qatar
  - Oman
  - Jordan
  - Kuwait
  - Yemen
  - Lebanon
  - Iran
- Countries with Travel-Associated Cases
  - United States
  - Europe: United Kingdom (UK), France, Italy, Greece, Germany, Netherlands, Austria, Turkey
  - Africa: Tunisia, Egypt, Algeria
  - Asia: Malaysia, Philippines China, South Korea
- Cases (as if 2 Dec. 2014, WHO)
  - 927 lab confirmed cases
  - At least 338 deaths

http://www.cdc.gov/coronavirus/mers/index.html
http://www.who.int/csr/don/2-december-2014-mers/en/

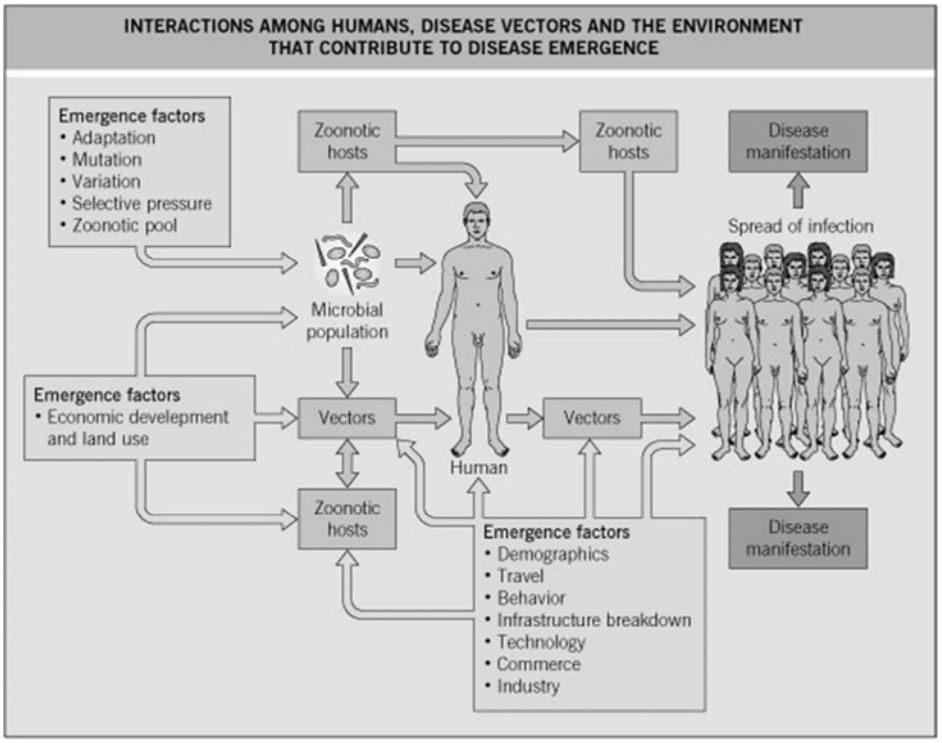
NOVEL INFLUENZA VIRUSES

- Avian influenza A (H7N9)
  - First reported in China, March 2013; spread to Malaysia in February 2014
  - Source: Infected poultry or contaminated environment
  - Clinical illness: Severe respiratory illness; mortality ~33%
- Influenza A (H3N2v)
  - First detected in US pigs in 2010 and human in 2011
  - Source: Prolonged exposure to pigs at agricultural fairs
  - Similar to seasonal flu
- Influenza A (H5N2), (H5N8), (H5N1)
  - Multiple reports of birds in US infected with these viruses (Asian origin) in CA, ID, OR, UT, WA in backyard flocks, wild birds, and wild aquatic birds
- Influenza A (H5N1)
  - Ongoing poultry and human cases in Asia, Europe and North Africa

FACTORS INFLUENCING NEW AND REEMERGING ZOONOSES



Cutler SJ et al. Emerg Infect Dis 2010;16:1-7



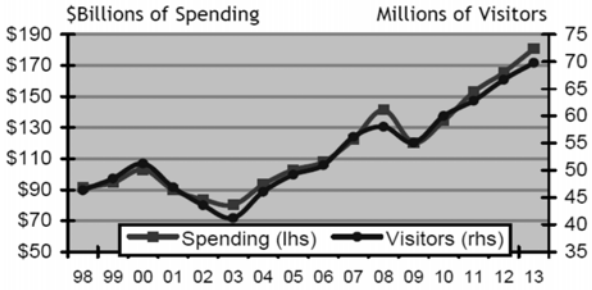
SOURCES OF EXOTIC DISEASES

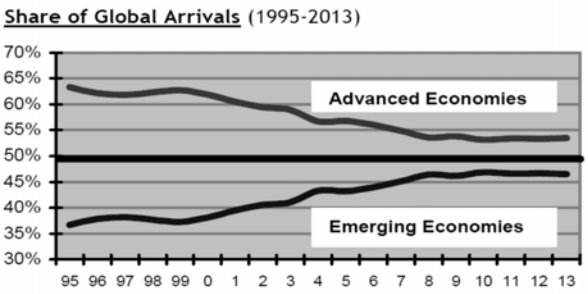
- Travel
- Animal exposure (zoonotic diseases)
  - Exposure via travel, leisure pursuits (hunting, camping, fishing), occupation (farming), pets
- Bioterrorist agents
- Research
  - Exposure via laboratory work (e.g., SARS, West Nile) or animal care

Speed of Global Travel in Relation to World Population Growth

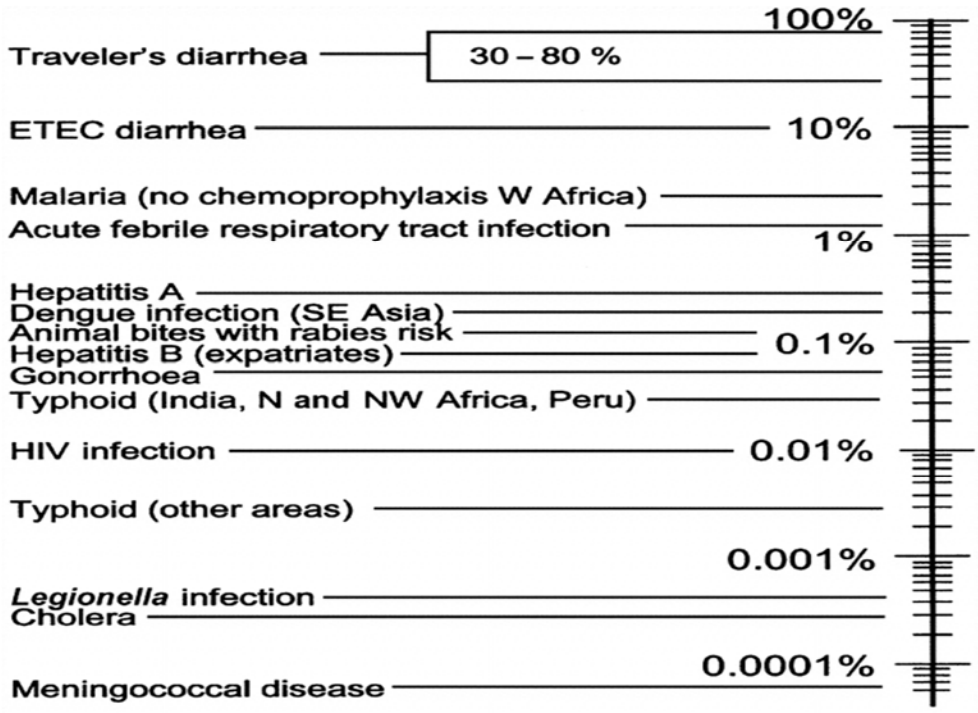
VISITORS TO THE US, 2013

Country	Visitors (millions)
Canada	23.4
Mexico	14.3
UK	3.8
Japan	3.7
Brazil	2.1
Germany	1.9
China	1.8
France	1.5
S. Korea	1.4
Australia	1.2
TOTAL	69.8





Tinet.ita.doc.gov/outreachpages/download_data_table/Fast_Facts.pdf



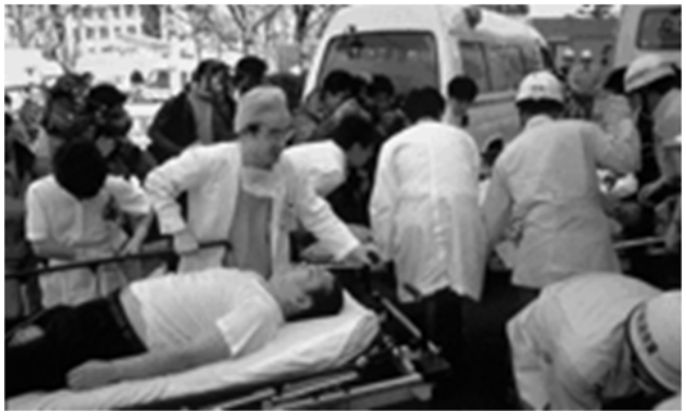
Stiffen R, Ericsson CD. CID 2000;30:809.

BIOLOGIC WARFARE: HISTORY

- 300 BC: Greeks pollute wells and drinking water with animal corpses
- 1346, Kaffa: Attacking Tatar force catapulted cadavers of plague victims into city – outbreak of plague led to defeat
- 1763, Fort Pitt, North America: Blankets from smallpox hospital provided to Native Americans – resulted in epidemic of smallpox among tribes in Ohio River valley
- 1932-45, Manchuria: Japanese military physicians infected 10,000 prisoners with biological agents (*B. anthracis, Y. pestis, V. cholerae, Salmonella* spp., *Shigella* spp.) – 11 Chinese cities attacked via food/water contamination, spraying via aircraft

Attack in Northern Iraq by former Government using nerve and mustard gas

Sarin gas attack in Tokyo subway

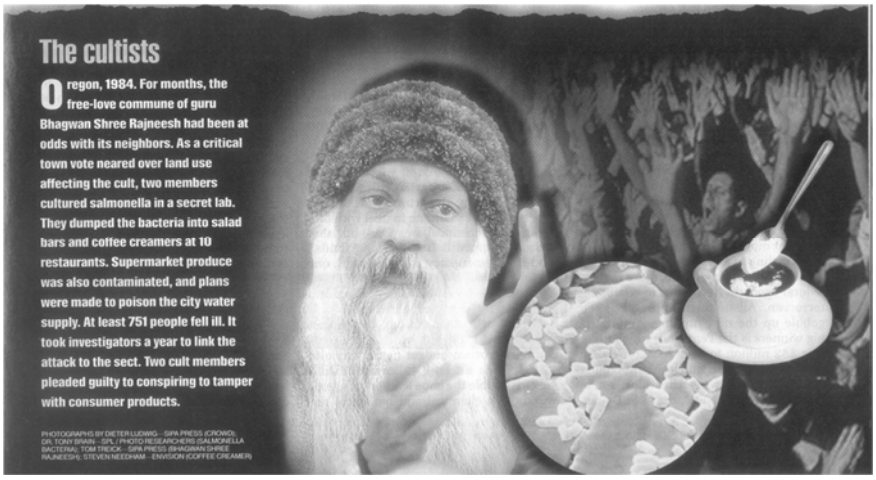


USE OF BIOLOGICAL AGENTS: US

- Site: The Dalles, Oregon, 1984
- Agent: *Salmonella typhimurium*
- Method of transmission: Restaurant salad bars
- Number ill: 751 (45 hospitalized)
- Responsible party: Members of a religious community had deliberately contaminated the salad bars on multiple occasions (goal to incapacitate voters to prevent them from voting and thus influence the outcome of the election)

Torok TJ, et al. JAMA 1997;278:389-395

GURU BHAGWAN SHREE RAJNEESH



USE OF BIOLOGICAL AGENTS: US

- Site: Large medical center, Texas, 1997
- Agent: *Shigella dysenteriae*
- Method of transmission: Ingestion of muffins/doughnuts
- Number ill: 45 (4 hospitalized)
- Responsible party: Disgruntled lab employee? *S. dysenteriae* identical by PFGE from stock culture stored in laboratory

Kolavic S, et al. JAMA 1997;278:396-398.

BIOTERRORISM: WHY NOW?

- SecDef William Cohen, March 1998, Heritage Foundation
  - Our American military superiority presents a paradox…because our potential adversaries know they can't win in a conventional challenge to the U.S. forces, they're much more likely to try unconventional or asymmetrical methods, such as biologic or chemical weapons
- Richard Betts, Council on Foreign Relations
  - Nuclear arms have great killing capacity but are hard to get; chemical weapons are easy to get but lack such killing capacity; biological agents have both qualities.

TRENDS FAVORING BIOLOGICAL WEAPONS

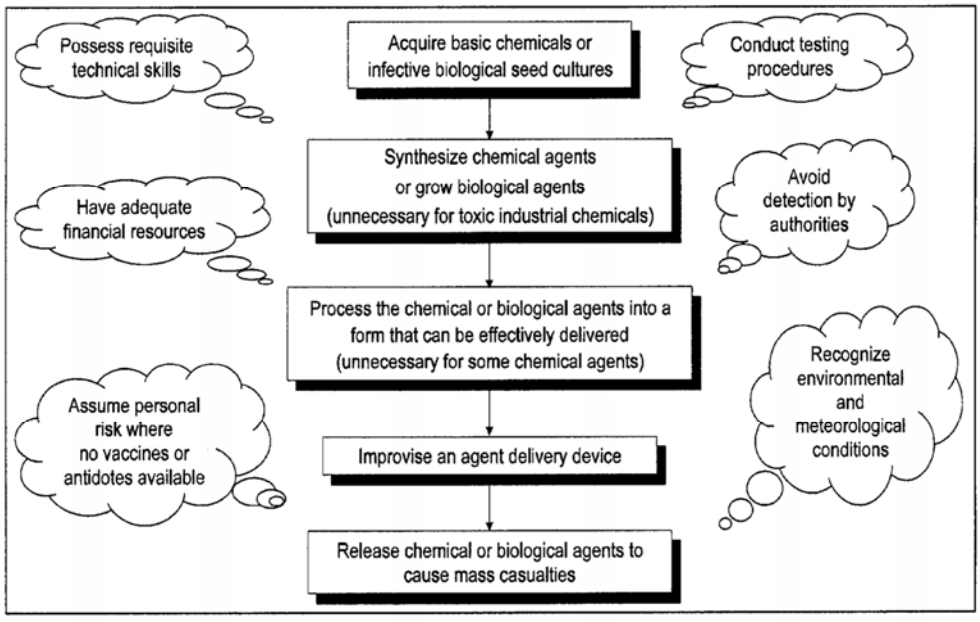
- Biological weapons have an unmatched destructive potential
- Technology for dispersing biologic agents is becoming more sophisticated
- The lag time between infection and appearance of symptoms generally is longer for biological agents than with chemical exposures
- Lethal biological agents can be produced easily and cheaply
- Biological agents are easier to produce clandestinely than are either chemical or nuclear weapons

Heritage Foundation

TRENDS FAVORING BIOLOGICAL WEAPONS

- Global transportation links facilitate the potential for biological terrorist strikes to inflict mass casualties
- Urbanization provides terrorists with a wide array of lucrative targets
- The Diaspora of Russian scientists has increased the danger that rogue states or terrorist groups will accrue the biological expertise needed to mount catastrophic terrorist attacks
- The emergence of global, real-time media coverage increases the likelihood that a major biological incident will induce panic

Figure 1: Stages and Obstacles for Chemical and Biological Terrorism



Source: GAO, on the basis of analysis of technical data and discussions with chemical and biological warfare experts.

CENTERS FOR DISEASE CONTROL BIOTERRORIST AGENTS: CATEGORY A

- Easily disseminated or transmitted person-to-person
- High mortality, with potential for major public health impact
- Might cause public panic and social disruption
- Require special action for public health preparedness .
- Viruses: Variola major (smallpox), filoviruses (e.g., Ebola, Marburg), arenaviruses (e.g., Lassa, Machupo)
- Bacteria: *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *Francisella tularensis* (tularemia)
- Toxins: *Clostridium botulinum* toxin (botulism)

http://emergency.cdc.gov/agent/agentlist-category.asp

CLASS A AGENTS OF BIOTERRORISM

Disease	Agent	Incubation period	Transmission	Clinical symptoms and signs	Treatment
Anthrax	*Bacillus anthracis*	2–4 d	Direct contact, inhalation, or ingestion	Cutaneous eschar, fever, mediastinitis with widened mediastinum on chest radiograph	Doxycycline or ciprofloxacin plus one or two other agents (see text)
Smallpox	Smallpox virus	10–12 d	Airborne droplets and direct contact	Fever followed by vesicular rash in centrifugal distribution	Supportive treatment, consider early vaccination
Hemorrhagic fever viruses	Four families of viruses (see text)	2–21 d	Airborne droplets, bite of infected carrier, or direct contact	Virus dependent (see Table 2); fever, petechiae, bleeding, disseminated intravascular coagulation	Consider ribavirin
Plague	*Yersinia pestis*	2–4 d	Flea bite (most common), airborne droplet, and direct contact	Buboes, fever, pneumonia, acute respiratory distress syndrome, sepsis	Streptomycin or gentamicin
Botulism	*Clostridium botulinum*	12–36 h	Airborne droplet, ingestion, or contaminated wound	Descending paralysis with diplopia, dysphagia, dysarthria, and dysphonia	Supportive treatment and botulinum antitoxin
Tularemia	*Francisella tularensis*	3–5 d	Arthropod bite, airborne droplets, or ingestion	Fever, dry cough, pneumonia, pulse-temperature dissociation	Streptomycin, gentamicin, ciprofloxacin, doxycycline

Kman NE, Nelson RN. Emerg Med Clin NA 2008;26:517-547

HEMORRHAGIC FEVER VIRUSES

Virus	Family	Key clinical features	Vector	Person-to-person transmission	Incubation period (d)	Mortality (%)	Treatment
Ebola	Filoviridae	Sudden onset fever, weakness, muscle pain, headache, sore throat and maculopapular rash by day 5 Bleeding and disseminated intravascular coagulation common	Unknown (possibly bat)	Yes	2–21	50–90	Supportive
Marburg	Filoviridae	High fever, myalgia Nonpruritic maculopapular rash may develop Bleeding and disseminated intravascular coagulation common	Unknown (probably bat)	Yes	2–14	23–70	Supportive
Lassa fever	Arenaviridae	Early gradual fever, nausea, abdominal pain, pharyngitis, cough, conjunctivitis, cervical lymphadenopathy Late pleural and pericardial effusions Hemorrhage less common	Rodent	Yes	5–16	15–20	Ribavirin, supportive
New World arenaviruses	Arenaviridae	Gradual fever, myalgia, nausea, abdominal pain, conjunctivitis, facial flushing and generalized lymphadenopathy Possible petechiae, bleeding, and central nervous system dysfunction	Rodent	Yes	7–14	15–30	Ribavirin, supportive
Rift Valley fever	Bunyaviridae	Fever, retro-orbital headache, photophobia, jaundice, and retinitis (up to 10%) Hemorrhagic fever or encephalitis rare (>1%)	Mosquito	No	2–6	<1	Ribavirin, supportive
Yellow fever	Flaviviridae	Fever, myalgia, facial flushing, and conjunctival injection Patients either recover or experience fever, bradycardia, jaundice, renal failure, and hemorrhagic complications after short remission	Mosquito	No	3–6	20	Supportive

CENTERS FOR DISEASE CONTROL BIOTERRORIST AGENTS: CATEGORY B

- Moderately easy to disseminate
- Moderate morbidity and low mortality
- Require improved diagnostic capacity & enhanced surveillance .
- Viruses: Alphaviruses (VEE, EEE, WEE)
- Bacteria: *Coxiella burnetii* (Q fever), *Brucella spp*. (brucellosis), *Burkholderia mallei* (glanders) , *B. pseudomallei* (melioidosis), *Rickettsia prowazekii* (typhus fever), Chlamydia psittaci (psittacosis)
- Toxins: *Rinus communis* (caster beans) ricin toxin, *Clostridium perfringens* episolon toxin, *Staphylococcus* enterotoxin B
- Food/waterborne pathogens: *Salmonella spp*., *Vibrio cholerae*, *Shigella dyseneriae*, *E. coli* O157:H7, *Cryptosporidium parvum*, etc.

CENTERS FOR DISEASE CONTROL BIOTERRORIST AGENTS: CATEGORY C

- Availability
- Ease of production and dissemination
- Potential for high morbidity and mortality and major public health impact
- Emerging agents such as Nipah virus and hantavirus

CDC FACT SHEETS AVAILABILITY

- Anthrax
- Botulism
- Brucellosis
- Plague
- Smallpox
- Tularemia
- Viral hemorrhagic fevers

http://emergency.cdc.gov/bioterrorism/factsheets.asp

CHARACTERISTICS* OF PRIORITY AGENTS

- Infectious via aerosol
- Organisms fairly stable in aerosol
- Susceptible civilian populations
- High morbidity and mortality
- Person-to-person transmission
- Difficult to diagnose and/or treat
- Previous development for BW

* Priority agents may exhibit all or some of the above characteristics

Sample Biological Agent Ratings

	Public Health Impact		Dissemination Potential		Special	Pubic
Disease	Morbidity	Mortality	Stable/Produce/Distribute	Transmissable	Preparedness	Perception
Smallpox	+	++	++	+++	+++	+++
Inhalational anthrax	++	+++	+++	-	+++	+++
Pneumonic plague	++	+++	++	++	+++	+++
Tularemia	++	++	++	-	+++	++
Botulism	++	+++	++	-	+++	++
VHF	++	+++	+	+	+++	+++
Glanders	++	+++	++	-	++	+
VE	++	+	++	-	++	+
Q fever	+	+	++	-	++	+
Brucellosis	+	+	++	-	++	+
Toxins	++	++	+	-	++	+
HPS	++	++	+	++	-	+
Nipah encephalitis	++	++	-	-	+	+

CHEMICAL AGENTS

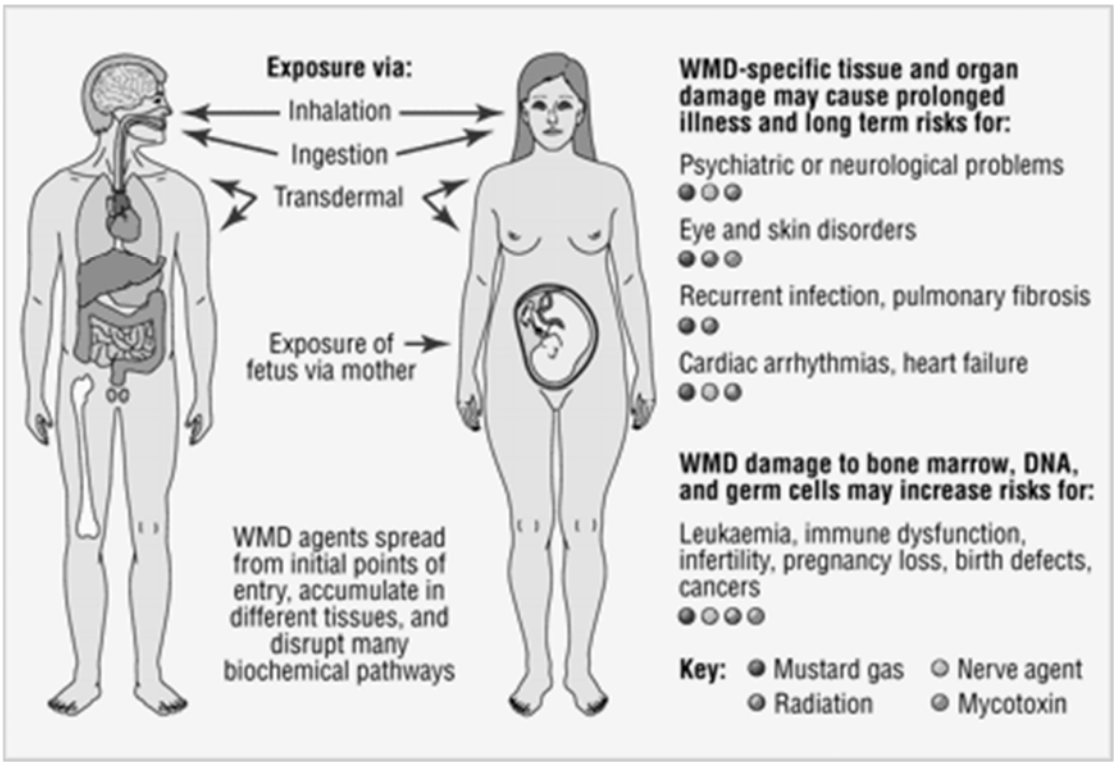
- Biotoxins
  - Abrin
  - Brevetoxin
  - Colchicine
  - Digitalis
  - Nicotine
  - Ricin
  - Saxitoxin
  - Tetrodotoxin
  - Trichotecene
- Blood agents
  - Arsine (SA)
  - Carbon monoxide
  - Cyanogen chloride (CK)
  - Hydrogen cyanide (AC)
  - Potassium cyanide (KCN)
  - Sodium cyanide (NaCN)
  - Sodium monfluoracetate

CHEMICAL AGENTS

- Blister agents/vesicants
  - Mustards
  - Phosgene (CX)
- Caustics (acids)
  - Hydrofluoric acid
- Incapacitating agents
  - BZ
  - Fentalyls & other opioids
- Choking/lung agents
  - Ammonia
  - Bromine, Chlorine
  - Hydrogen chloride
  - Methyl bromide
  - Methyl isocynante
  - Osmium tetroxide
  - Phosgene, Disphosgene
  - Phosphine, Phosphorus
  - Sulfuryl fluoride

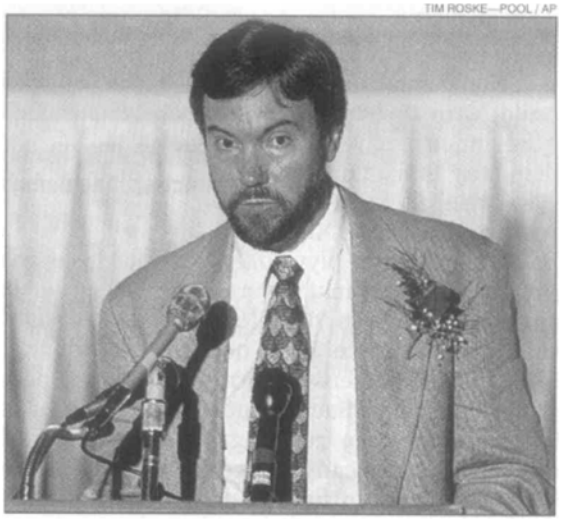
CHEMICAL AGENTS

- Riot control agents
  - Bromobenzylcyanide
  - Chloracetophenone
  - Chlorobenzyl-idenemalononitrile
  - Debenzoxazepine
- Nerve agents
  - G agents
  - Sarin (GB)
  - Soman (GD)
  - Tabun (GA)
  - VX
- Metals
  - Arsenic
  - Barium
  - Mercury
  - Thallium



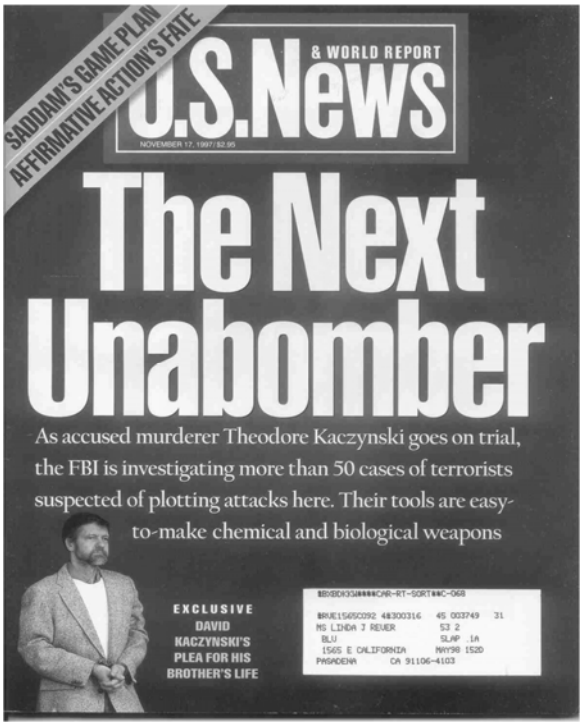
SOURCES OF BIOTERRORISM

- Biological warfare
- State sponsored terrorism
- International terrorist groups
- National cults
- The deranged “loner”



Kaczynski's mailbox near Lincoln, Mont. Says one trial expert: "He was never able to have any social interaction except through the mail."

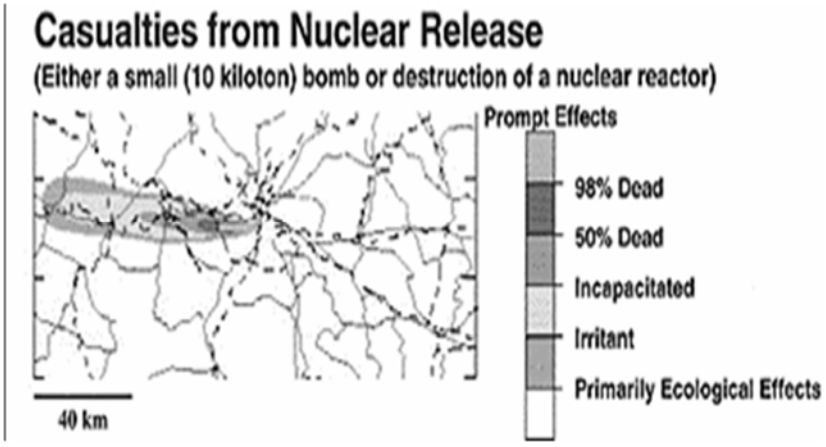
ELAINE THOMPSON—AP



BIOTERRORISM: IMPACT

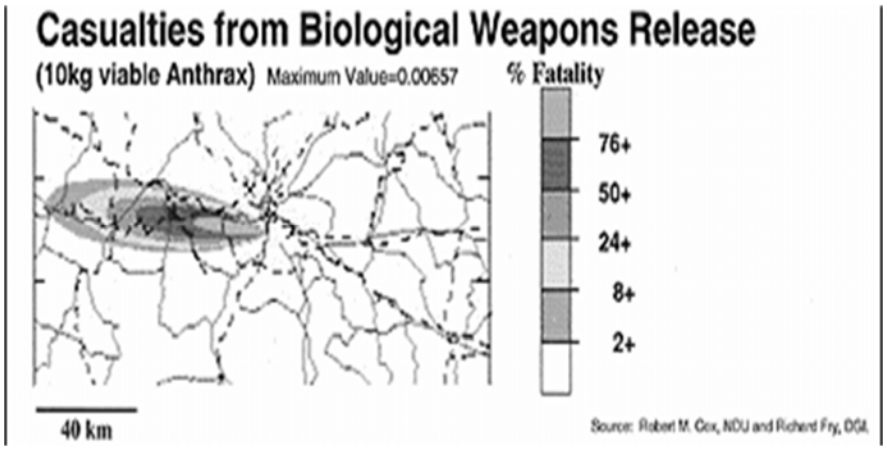
- Direct infection: Mortality, morbidity
- Indirect infection: Person-to-person transmission, fomite transmission
- Environmental impact: Environmental survival, animal infection
- Other: Social, political, economic

EFFECTS OF A NUCLEAR WEAPONS RELEASE



Siegrist, Emerging Infectious Diseases 1999

EFFECTS OF A BIOLOGICAL WEAPONS RELEASE



Siegrist, Emerging Infectious Diseases 1999

BIOLOGICAL WARFARE: IMPACT

[release of 50 kg agent by aircraft along a 2 km line upwind of a population center of 500,000 – Christopher et al., JAMA 278;1997:412]

Agent	Downwind reach, km	No. dead	No. incapacitated
Rift Valley fever	1	400	35,000
Tick-borne encephalitis	1	9,500	35,000
Typhus	5	19,000	85,000
Brucellosis	10	500	125,000
Q fever	>20	150	125,000
Tularemia	>20	30,000	125,000
Anthrax	>20	95,000	125,000

CHARACTERISTICS OF BIOWARFARE

- Potential for massive numbers of casualties
- Ability to produce lengthy illnesses requiring prolonged and intensive care
- Ability of certain agents to spread via contagion
- Paucity of adequate detection systems
- Presence of an incubation period, enabling victims to disperse widely
- Ability to produce non-specific symptoms, complicating diagnosis
- Ability to mimic endemic infectious diseases, further complicating diagnosis

US Army, Biologic Casualties Handbook, 2001

STEPS IN MANAGEMENT

1. Maintain an index of suspicion
2. Protect thyself
3. Assess the patient
4. Decontaminate as appropriate
5. Establish a diagnosis
6. Render prompt therapy
7. Practice good infection control
8. Alert the proper authorities
9. Assist in the epidemiologic investigation
10. Maintain proficiency and spread the gospel

US Army, Biologic Casualties Handbook, 2001

INFECTION CONTROL ISSUES FOR SELECTED AGENTS OF BIOTERRORISM			
Disease	**Incubation period (days)**	**Person-to-person transmission**	**Infection control precautions**
Inhalational anthrax (see Chapter 185)	2–43*	No	Standard
Botulism (see Chapter 25)	12–72 hours	No	Standard
Primary pneumonic plague (see Chapter 176)	1–6	Yes	Droplet
Smallpox (see Chapter 151)	7–17	Yes	Contact and airborne
Tularemia (see Chapter 177)	1–14	No	Standard
Viral hemorrhagic fevers (see Chapter 183)	2–21	Yes	Contact and airborne
Viral encephalitides (see Chapter 23)	2–14	No	Standard
Q fever (see Chapter 235)	2–14	No	Standard
Brucellosis (see Chapter 180)	5–60	No	Standard
Glanders	10–14	No	Standard

* Based on limited data from human outbreaks; experimental animal data support clinical latency periods of up to 100 days

BW AGENT PROPHYLAXIS AND TREATMENT

Disease	Vaccine Efficacy*	PEP	Treatment
Anthrax**^	Effective, 1,000 LD_{50} monkeys	Antibiotics	Antibiotics
Smallpox	Effective, high dose primates	Vaccine, VIG	Cidofovir?
Plague**^	Ineffective, 118 LD_{50} monkeys	Antibiotics	Antibiotics
Q fever#	94%, 3500 LD_{50} guinea	Antibiotics	Antibiotics
Tularemia#	80%,1-10 LD_{50}	Antibiotics	Antibiotics
VHF+	No vaccine	None	Ribavirin@

VHF-viral hemorrhagic fevers, PEP-postexposure prophylaxis

*Aerosol exposure; **Pneumonic form; ^FDA approved vaccine (not available); #IND

+ IND BHF, RVF; @ CCHF, Lassa *US Army, Biological Casualties Handbook, 2001*

FOMITE ACQUISITION

- Agents acquired from contaminated clothes
  - Variola major (smallpox)
  - *Bacillus anthracis* (anthrax)
  - *Coxiella burnetii* (Q fever)
  - *Yersinia pestis* (plague)
- Management
  - Remove clothing, have patient shower
  - Place contaminated clothes in impervious bag, wear PPE
  - Decontaminate environmental surfaces with EPA approved germicidal agent or 0.5% bleach (1:10 dilution)

Bioterrorism Agents: Laboratory Risk

Agent	BSL	Laboratory Risk
B. anthracis	2	low
Y. pestis	2	medium
F. tularensis	2/3	high
Brucella spp.	2/3	high
Botulinum toxin	2	medium
Chlaymdia pittaci	2/3	medium
Smallpox	4	high
Viral Hemorrhagic fever	4	high

http://www.cdc.gov/od/biosfty/bmbl/BMBL_5th_Edition.pdf

DETECTION OF OUTBREAKS

- Epidemiologic clues
- Medical clues
- Syndromic surveillance
- Other
  - Intelligence reports
  - Claims of release
  - Discovery of munitions or tampering
  - Increased numbers of pharmacy orders for antibiotics
  - Increased number of 911 calls

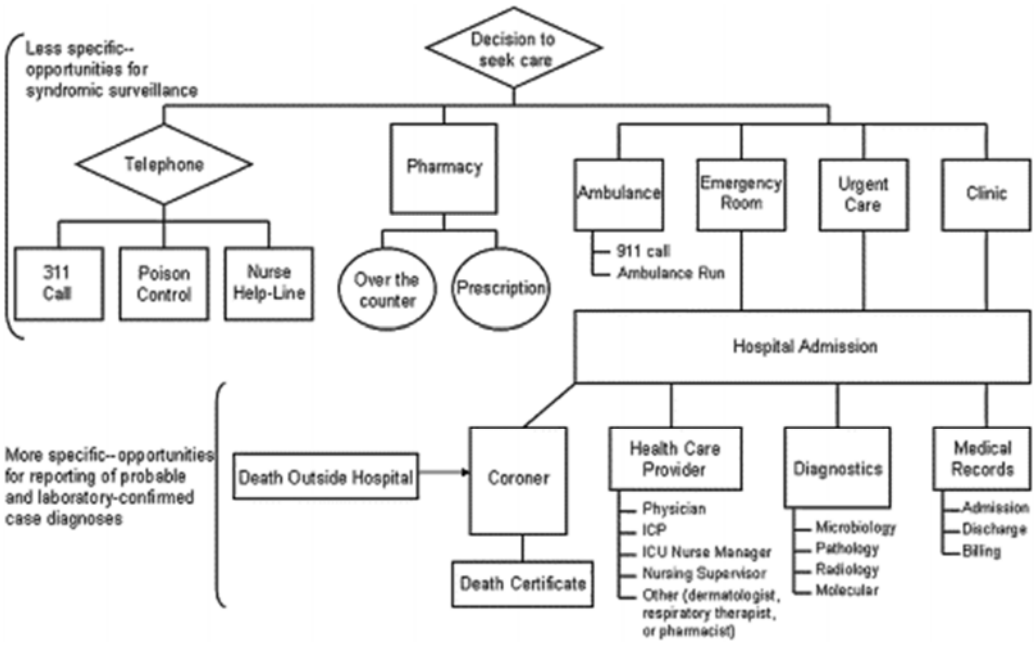
ID Clinics NA 2006;20:179-211

DETECTION OF BT OUTBREAKS: EPIDEMIOLOGIC CLUES

- A rapidly increasing disease incidence
- Unusual clustering of disease for the geographic area
- Disease occurrence outside of the normal transmission season
- Simultaneous outbreaks of different infectious diseases
- Disease outbreak in humans after recognition of disease in animals
- Unexplained number dead animals or birds
- Disease requiring for transmission a vector previously not seen in the area
- Rapid emergence of genetically identical pathogens from different geographic areas

DETECTION OF BT OUTBREAKS: MEDICAL CLUES

- Unusual route of infection
- Unusual age distribution or clinical presentation of common disease
- More severe disease and higher fatality rate than expected
- Unusual variants of organisms
- Unusual antimicrobial susceptibility patterns
- Any patient presenting with a disease that is relatively uncommon and has bioterrorism potential



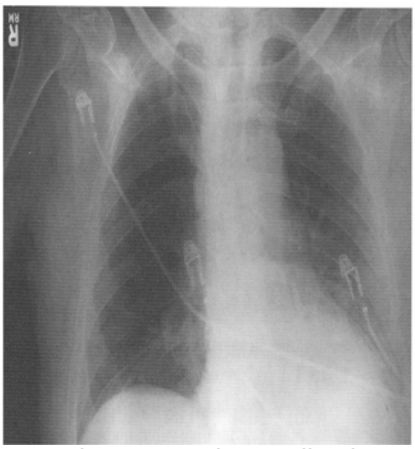
An unusual increase in the number of people seeking care, esp. with fever, respiratory, or gastrointestinal symptoms

ANTHRAX IN THE US, 2001

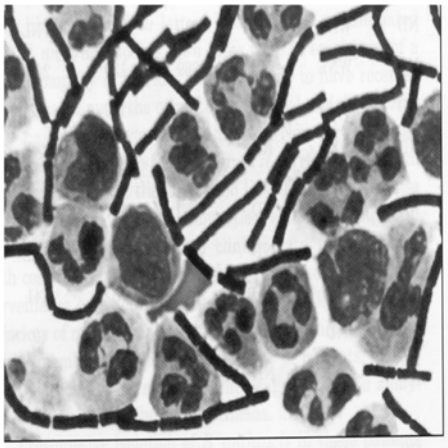
- Locations: FL, NY, DC, NJ, CT, VA
- Mechanism: Via the mail (4 letters positive)
- Infections: 22 cases
  - Cutaneous anthrax: 11 (fatality rate = 0)
  - Inhalation anthrax: 11 (fatality rate = 45%)
- Prophylaxis
  - Initiated: ~32,000
  - 60 day course recommended: ~5,000

EID 2002;8:1019

INHALATION ANTHRAX, US: CASE 1



Prominent superior mediastinum,
?small left pleural effusion

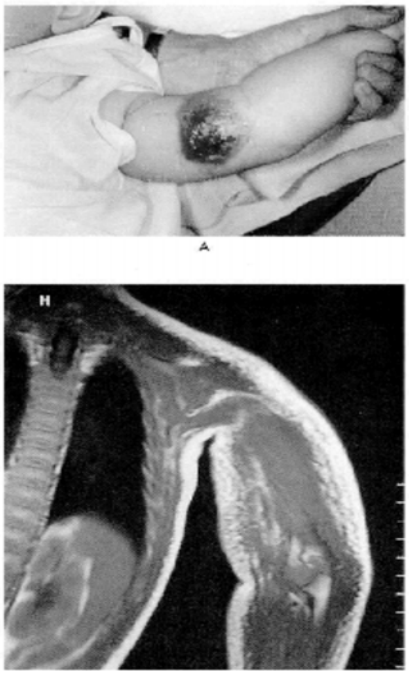


CSF Gram stain

Cutaneous Anthrax, US

7 mo male infant hospitalized with 2 day history of swelling left arm and weeping lesion at left elbow. Patient had been at his mother's office at a TV network. Biopsies yielded *B. anthracis.*

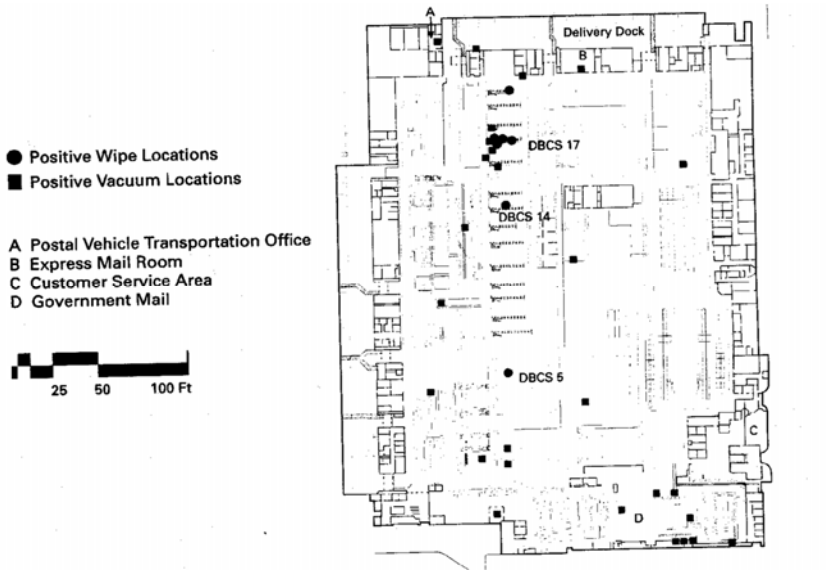
Roche KJ, et al.
NEJM 2001;345:1611



UNEXPECTED FEATURES OF ATTACK

- Targets (news media)
- Vehicle (US mail)
- Source of strain (US, probably weaponized)
- Translocation of spore through envelope
- Airborne acquisition in mail facilities
- Wide spread contamination in mail facilities
- Transmission via mail-to-mail contamination
- No person or group has claimed responsibility

MAIL PROCESSING CENTER, DC, OCT. 2001



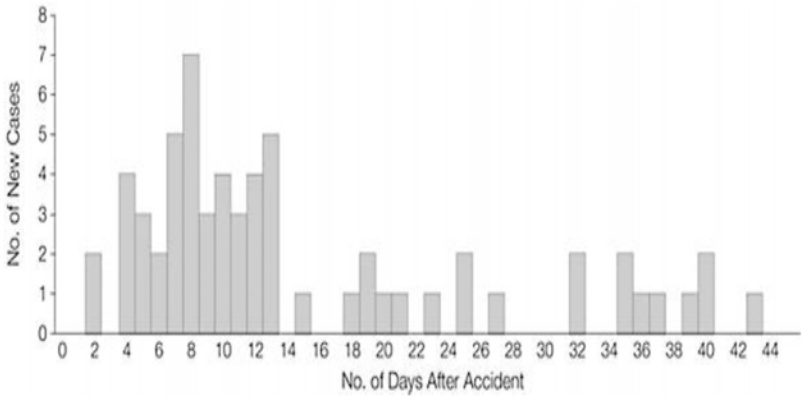
CDC. MMWR 2001;50:1130

SVERDLOVSK ANTHRAX OUTBREAK

- Site: Sverdlovsk, USSR
- Year: 1979
- Cause: Accidental release from military microbiologic facility – Military report noted: “Filter clogged so I’ve removed it. Replacement necessary”
- Transmission: Airborne
- Impact: 68 human deaths, 79 human cases, multiple animal deaths (sheep, cows)

ANTHRAX Sverdlovsk

The Sverdlovsk Anthrax Outbreak of 1979
Day of Onset of Inhalational Anthrax



Inglesby: JAMA, 281;1999:1735-1745

Sverdlovsk Anthrax Outbreak of 1979
Probable locations of patients when exposed

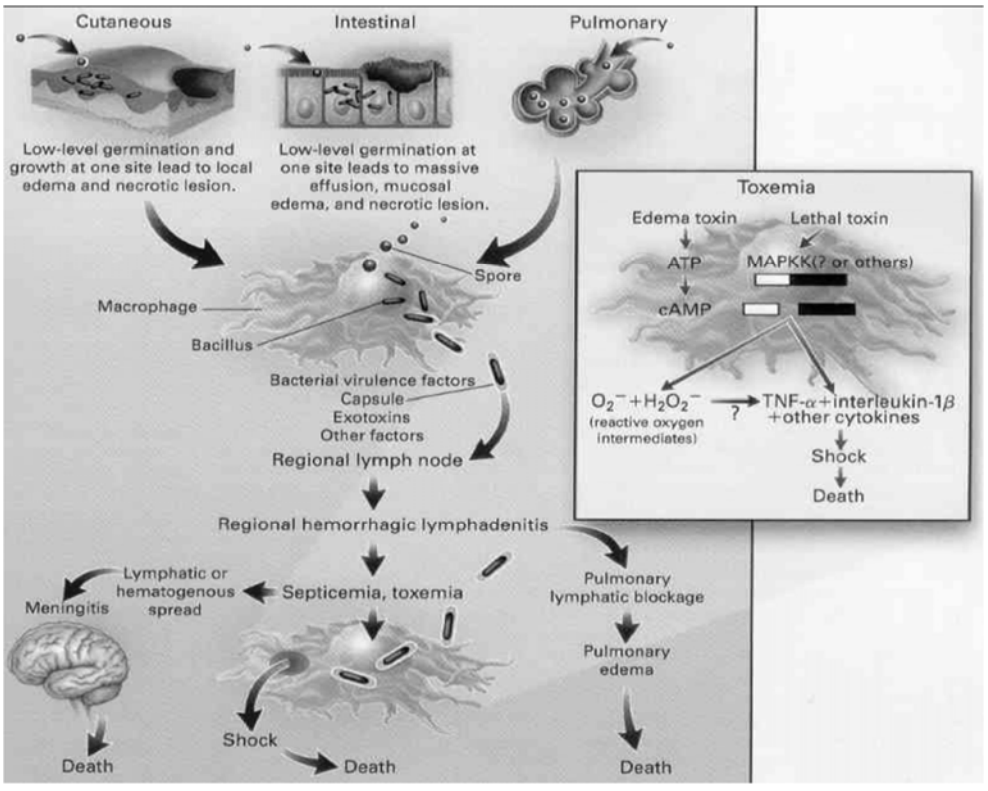
Meselson : Science 266;1994:1202-1207

ANTHRAX: EPIDEMIOLOGY

- Agent: *Bacillus anthracis*, a Gram-positive, spore forming non-motile bacillus (straightforward lab identification)
- Reservoir: Herbivores (cattle, goats, sheep), capable of surviving in the environment for prolonged periods
- Transmission
  - Contact, ingestion, or inhalation of infective spores
  - Sources of infection: Contaminated hides, wool, hair, bone, meat, or other animal products

ANTHRAX: CLINICAL FEATURES

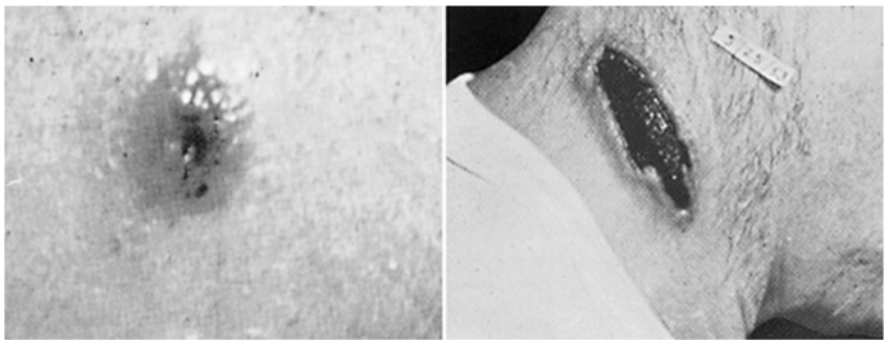
- Incubation period: 1-7 days (1-60 days)
- Clinical syndrome(s): Cutaneous ulcer, respiratory (rare), gastrointestinal (rare), oropharyngeal (very rare)
- Inhalation anthrax = main threat
  - Spores may germinate up to 60 days after exposure
  - LD_{50} (human): 2,500 to 55,000 spores
  - Bronchopneumonia not a component (hemorrhagic lymphadenitis and mediastinitis)
  - Early diagnosis difficult



CUTANEOUS ANTHRAX

Forearm lesion, day 7

Neck eschar, day 15

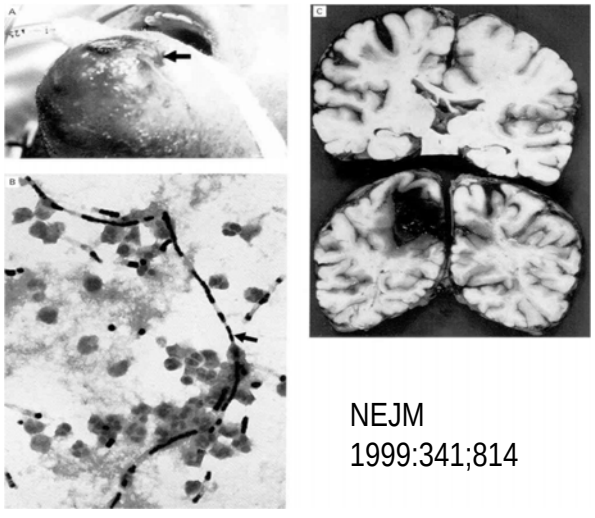


Inglesby T, et al. JAMA;281:1735

B. ANTHRACIS MENINGITIS

Lesion on chin

CSF



NEJM
1999:341;814

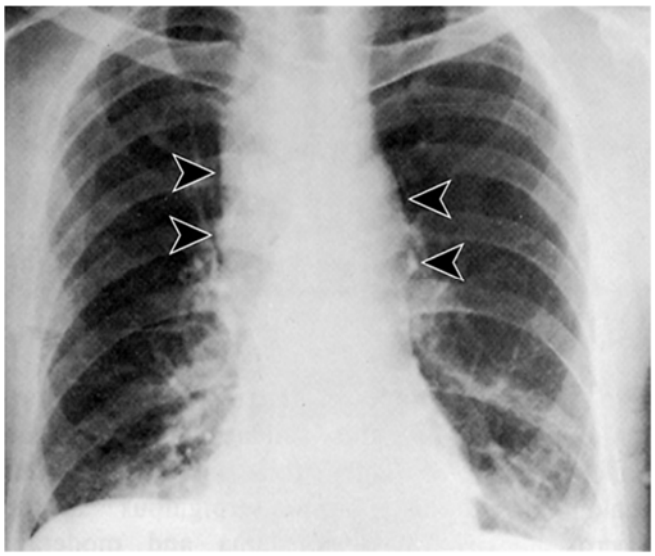
INHALATION ANTHRAX: DIAGNOSIS

- Epidemiology
  - Sudden appearance of multiple cases of severe flu illness with fulminant course and high mortality
- Clinical symptoms
  - Non-specific prodrome of flu-like symptoms
  - Possible brief interim improvement
  - Abrupt onset of respiratory failure and hemodynamic collapse 2-4 days after initial symptoms, possibly accompanied by thoracic edema and a widened mediastinum on CxR

INHALATION ANTHRAX: DIAGNOSIS

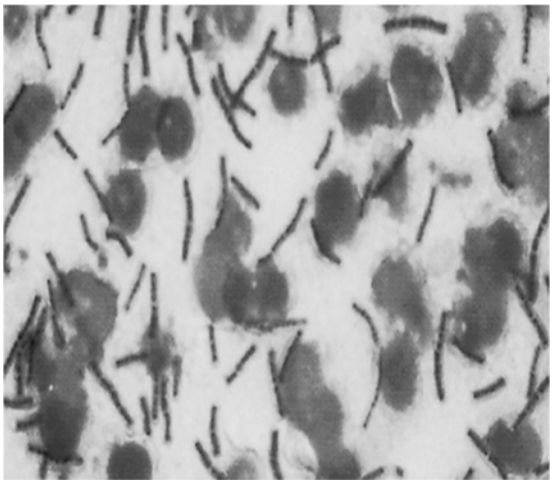
- Diagnostic studies
  - Chest radiograph with widened mediastinum
  - Peripheral blood smear with gram (+) bacilli on unspun smear
- Microbiology
  - Blood culture growth of large gram (+) bacilli with preliminary identification of *Bacillus spp*.
- Pathology
  - Hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, hemorrhagic meningitis

INHALATION ANTHRAX: CxR



Inglesby: JAMA, 281;1999:1735-1745

B. ANTHRACIS: PERIPHERAL BLOOD SMEAR



Inglesby T, et al.
JAMA;281:1735

DIFFERENTIAL DIAGNOSIS: ESCHAR AND ULCERATION

- Anti-phospholipid antibody syndrome ulcers
- Aspergillosis
- Brown recluse spider bite
- Coumadin necrosis
- Cutaneous leishmaniasis
- Cutaneous tuberculosis
- Ecthyma gangrenosum
- Glanders
- Heparin necrosis
- Leprosy
- Mucormycosis
- Orf/Milker's nodule
- Plague
- Rat bite fever
- Rickettsialpox
- Staphylococcal/streptococcal infection
- Tropical ulcer
- Tularemia
- Typhus, scrub and tick

DIFFERENTIAL DIAGNOSIS: ULCEROGLANDULAR SYNDROMES

- Cat scratch disease
- Chancroid
- Glanders
- Herpes simplex infection
- Lymphogranuloma venereum
- Melioidosis
- Plague
- Staphylococcal/streptococcal infection
- Tuberculosis
- Tularemia

TABLE 324-2 Considerations for Evaluation and Management of Suspected Inhalational Anthrax

1. Obtain blood cultures before any antibiotics if anthrax is suspected.
2. Notify microbiology laboratory of concern for anthrax to expedite evaluation of specimens. Blood cultures are usually positive in < 24 hours.
3. Obtain history to include any epidemiologic link to known or suspected anthrax. Attention to respiratory complaints, neurologic or cognitive problems, GI complaints, fever, profuse diaphoresis, or new skin lesions.
4. Physical examination with attention to any respiratory abnormalities, neurologic or cognitive deficits, tachycardia, GI abnormalities, or skin lesions.
5. Obtain chest radiograph or noncontrast chest CT scan looking for a widened mediastinum due to hemorrhagic adenopathy, or pleural effusions.
6. If a suspicion of meningitis, examine CSF for characteristic large boxcar-shaped gram-positive rods.
7. If symptomatic and there is known or possible epidemiologic exposure to anthrax, give initial intravenous doses of at least two antibiotics to which the circulating *Bacillus anthracis* isolate is sensitive, including either ciprofloxacin or doxycycline as soon as possible in the ER before admitting to the ward. Combine with other antibiotics recommended by Department of Health or CDC, if information is available. Include antibiotics that penetrate CSF.

CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; CT, computed tomography; ER, emergency room; GI, gastrointestinal.

ANTHRAX: CONTROL

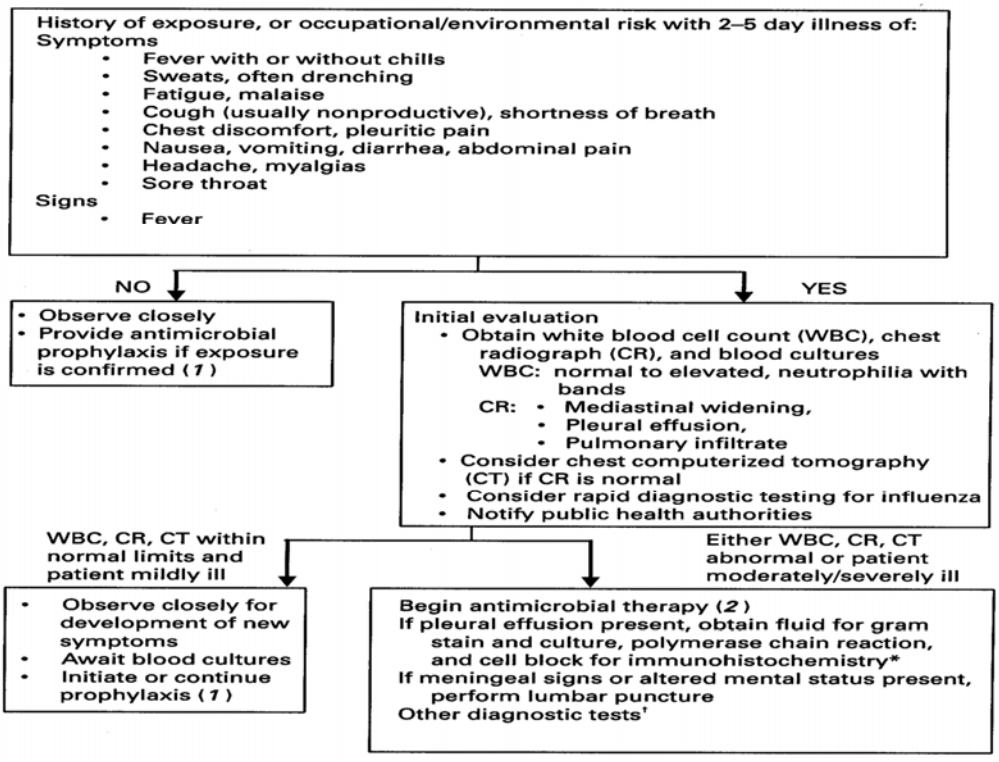
- Laboratory precautions: BSL 2
- Prophylaxis
  - Pre-exposure: Vaccine (0.5 ml SC at 0 & 4 wks; 6, 12, & 18 mo; annual booster){Manufacturer = BioPort Corp, Lansing, MI)
  - Post-exposure: Ciprofloxacin (or other quinolone) or doxycycline (+/- vaccine if available)
- CDC isolation guideline: Standard
- UNC recommended isolation: Contact if cutaneous lesions present

TABLE 324-6 Comparison of Anthrax Vaccine for Pre-exposure and Post-exposure Use

Clinical Setting	*No. of Doses*	*Schedule*	*FDA-Licensed*	*IND Required*[a]
Pre-exposure	6	Weeks 0, 2, 4 Months 6, 12, 18	Yes	No
Post-exposure	3	Weeks 0, 2, 4	No	Yes

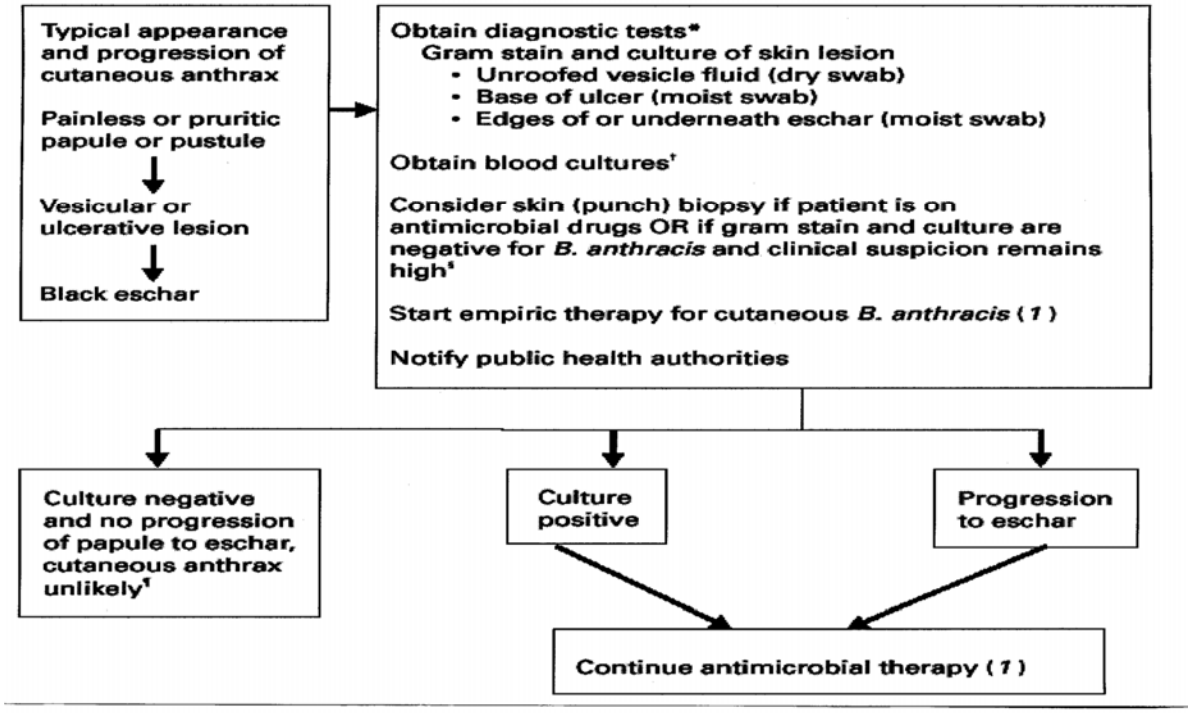
[a]IND, investigational new drug. An IND is required by the Food and Drug Administration (FDA) in the post-exposure setting for this vaccine for two reasons: (1) the vaccine was approved for pre-exposure use but not for post-exposure use; (2) a total of three doses of vaccine over 1 month is recommended for post-exposure vaccination, unlike the six-dose vaccine schedule given for pre-exposure vaccination as part of the FDA licensure.

FIGURE 2. Clinical evaluation of persons with possible inhalational anthrax



CDC. MMWR 2001;50:941

FIGURE 3. Clinical evaluation of persons with possible cutaneous anthrax



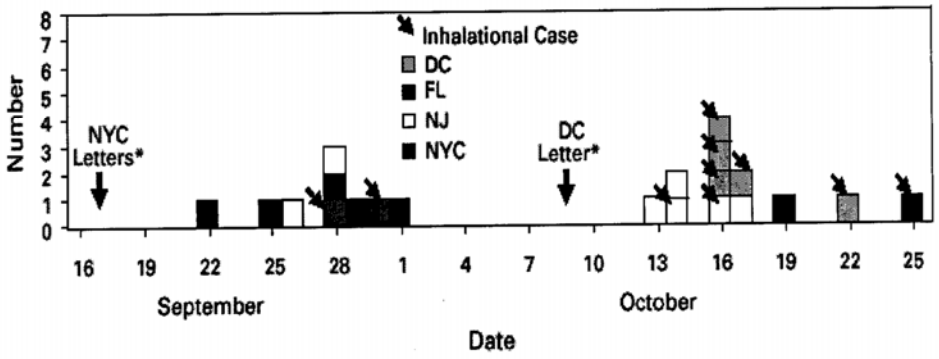
CDC. MMWR 2001;50:941

PROPHYLAXIS AND TREATMENT

- Prophylaxis
  - Ciprofloxacin or doxycycline x 60 days
- Treatment: Cutaneous
  - Ciprofloxacin or doxycycline x 60 days
- Treatment: Inhalation
  - Ciprofloxacin or doxycline PLUS
  - 1 or 2 other drugs (e.g., vancomycin, imipenem)
  - Initial Rx should be IV then switch to PO for total 60 days
- Same treatment for children and pregnant women
- Use of vaccine may allow shorted period of antibiotic post-exposure prophylaxis

ANTHRAX CASES, US

FIGURE 1. Number of bioterrorism-related anthrax cases, by date of onset and work location — District of Columbia (DC), Florida (FL), New Jersey (NJ), and New York City (NYC), September 16–October 25, 2001



CDC. MMWR 2001;50:941

INHALATION ANTHRAX: US CASES: FIRST 10 CASES

- Risk factors
  - Postal employee: 7
  - Media employee: 2
    - ◆Received contaminated mail: 1, sorted mail: 1
  - Unknown (NY): 1 (probably via mail){additional case CT}
- Median age: 56 (43-73)
- Male: 7
- Incubation period: 4d (4-6d)

Jernigan JA, et al. Emerg Infec tDis 2001;7:933

INHALATION ANTHRAX, US: FIRST 10 CASES

Symptoms at initial presentation

- Fever or chills: 10
- Fatigue, malaise, or lethargy: 10
- Minimal or nonproductive cough: 9 (with bloody sputum 1)
- Nausea or vomiting: 9
- Dyspnea: 8
- Sweats, often drenching: 8
- Chest discomfort or pleuritic pain: 7
- Others: myalgias 6, headache 5, confusion 4, abdominal pain 3, sore throat 2, rhinorrhea 1

INHALATION ANTHRAX, US: FIRST 10 CASES

Physical findings

- Fever (>37.8 ^{o}C): 7/10
- Tachycardia (heart rate >100/min): 8/10
- Hypotension (systolic BP <110 mm Hg): 1/10

Laboratory results

- WBC (median, range): 9.8 x 10^3/mm^3 (7.5 – 13.3)
  - Neutrophils (>70%): 7/10, bands (>5%): 4/5
- Elevated transaminases (SGOT or SGPT >40): 9/10
- Hypoxemia (alveolar-arterial O_2 gradient >30 mm): 6/10
- Metabolic acidosis: 2/10
- Elevated creatinine (>1.5 mg/dL): 1/10

INHALATION ANTHRAX, US: FIRST 10 CASES

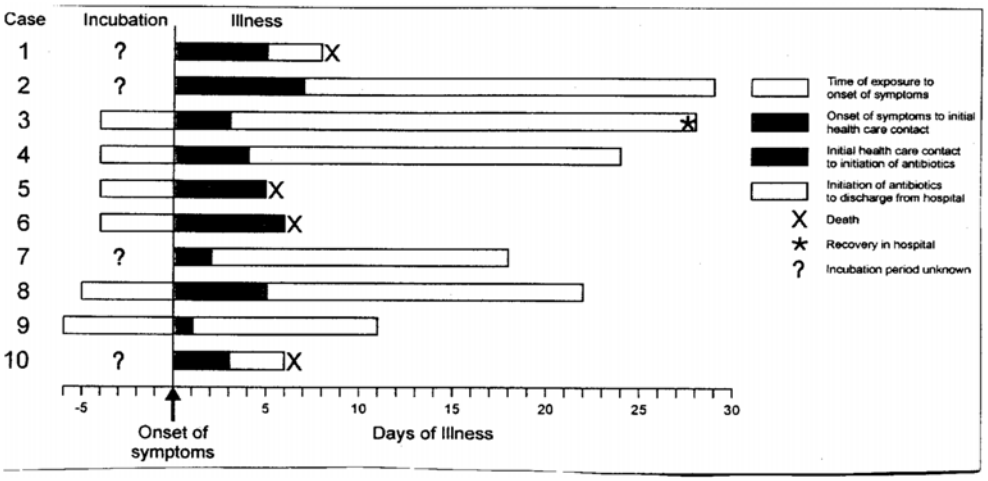
Chest radiographic findings

- Any abnormality: 10/10
- Mediastinal widening: 7/10
- Infiltrates, consolidation: 7/10
- Pleural effusion: 8/10

Chest CT

- Any abnormality: 8/8
- Mediastinal widening: 7/8
- Pleural effusion: 8/8
- Infiltrates, consolidation: 6/8

INHALATION ANTHRAX, US: FIRST 10 CASES (TIMELINE)



INHALATION ANTHRAX, US: FIRST 10 CASES

- Bacterial cultures
  - All blood cultures positive if obtained prior to antibiotics: 7/7
- Only one case developed meningitis
- All patients received combination antimicrobial therapy
  - Rx with fluoroquinolone plus one other active drug

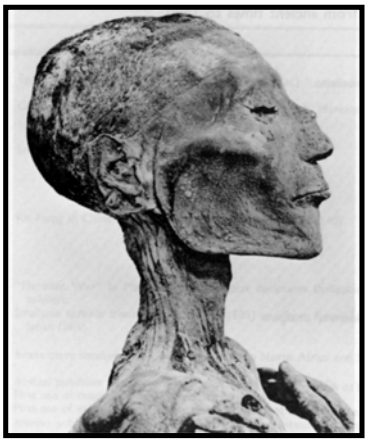
ADVERSE EVENT WITH POST-EXPOSURE PROPHYLAXIS

Adverse Event	Day 10 Cipro	Day 10 Doxy	Day 30 Cipro	Day 30 Doxy
≥1 adverse event	45%	49%	77%	71%*
GI (nausea, vomiting, diarrhea, abdominal pain)	26%	26%	42%	49%
CNS (fainting, dizziness, seizures, light-headedness)	18%	11%	23%	18%*
Rash, hives, or itchy skin	7%	7%	14%	14%
Joint problem	8%	7%	25%	16%*

Shepard CW, et al. EID 2002;8:1125

SMALLPOX: HISTORY

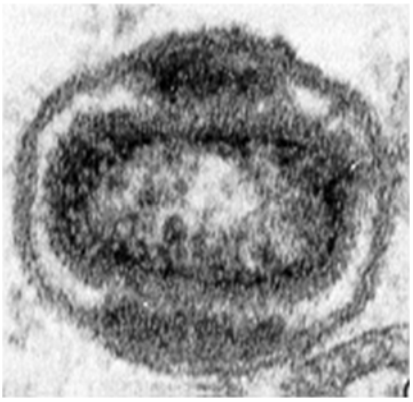
- Infections traced back >10,000 years
- 1754-67: Biological weapon French and Indian wars
- 1796: Edward Jenner uses vaccinia for immunization
- 1967: WHO global eradication campaign
- 1972: US ceases routine vaccination
- 1977: Last case endemic smallpox (Somalia)
- 1978: Last laboratory acquired case (UK)
- 1982: Worldwide cessation of vaccination



Three Egyptian Mummies
1570-1085 BC
Ramses the Vth, died 1157 BC

SMALLPOX: VIROLOGY

- Agent: Variola (family poxviridae)
  - 8 genera in family
- Human infectious agents
  - Orthopoxviruses: Variola, varicella (chickenpox)
  - Mullucipoxvirus: Mulluscum contagiosum virus
- Nonhuman orthopoxviruses: Monkeypox, cowpox, canarypox, rabbitpox, etc.



Large DNA virus,
Complex membranes

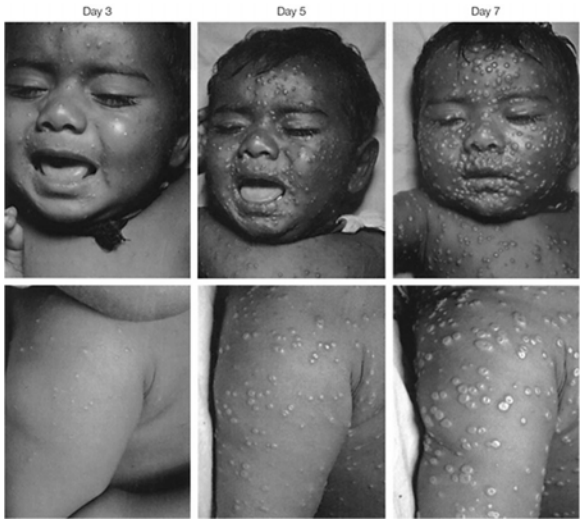
SMALLPOX: EPIDEMIOLOGY

- Agent: Variola virus
- Reservoir: Humans
- Transmission
  - Contact, droplet, and airborne (attack rate = 37-88%)
  - Transmission does not occur until the onset oral enanthema (may precede generalized rash by 24 hours)
  - Maximum infectiousness, days 7-10 of rash
  - Increased infectiousness if patient coughing or has a hemorrhagic form of smallpox

SMALLPOX: CLINICAL FEATURES

- Incubation period: 12 days (6-22 days)
- Clinical features
  - Non-specific prodrome (2-4 days) of fever, mylagias
  - Rash most prominent on face and extremities (including palms and soles) in contrast to truncal distribution of varicella
  - Rash scabs over in 1-2 weeks
  - Variola rash has a synchronous onset (in contrast to the rash of varicella which arises in crops)
- Mortality rate (unvaccinated) ~30% (15-50%)

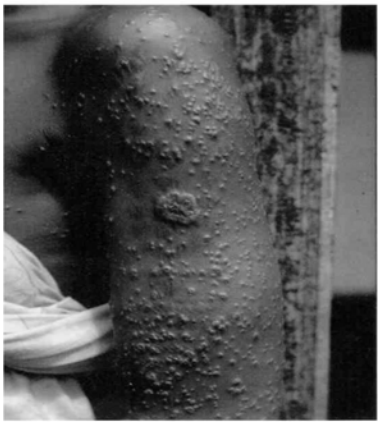
SMALLPOX IN A CHILD



Henderson
JAMA
281;1999:2127

Smallpox in an adult
Nigeria, 1970
27 yo female

Lesions have a peripheral distribution, Facial edema, and Uniform in terms of Stage of development



Herron C.
NEJM 1996;334:1304

SMALLPOX: DIAGNOSIS

- Appearance of rash
  - Hemorrhagic smallpox may be mistaken for meningococcemia or severe acute leukemia
- Culture of lesions
  - Should be obtained by immunized person; place specimen in vacutainer tube, tape juncture of stopper and tube, place in second durable, watertight container
  - Alert lab

DIFFERENTIATING CHICKENPOX FROM SMALLPOX

Features of chickenpox:

- No or mild prodrome
- Lesions are superficial vesicles
- Lesions appear in crops on any one part of the body there are lesions in different stages
- Centripetal distribution: Greatest concentration on trunk, fewest on distal extremities
- First lesions appear on face or trunk

DIFFERENTIATING CHICKENPOX FROM SMALLPOX

Features of chickenpox

- Patients rarely toxic or morbund
- Rapid evolution: lesions evolve from macules $\rightarrow$ papules $\rightarrow$ vesicles $\rightarrow$ crusts quickly (<24 hours)
- Palms and soles rarely involved
- Patient lacks history of varicella or varicella vaccination
- 50-80% recall an exposure to chickpox or shingles (10-21 days before rash onset)

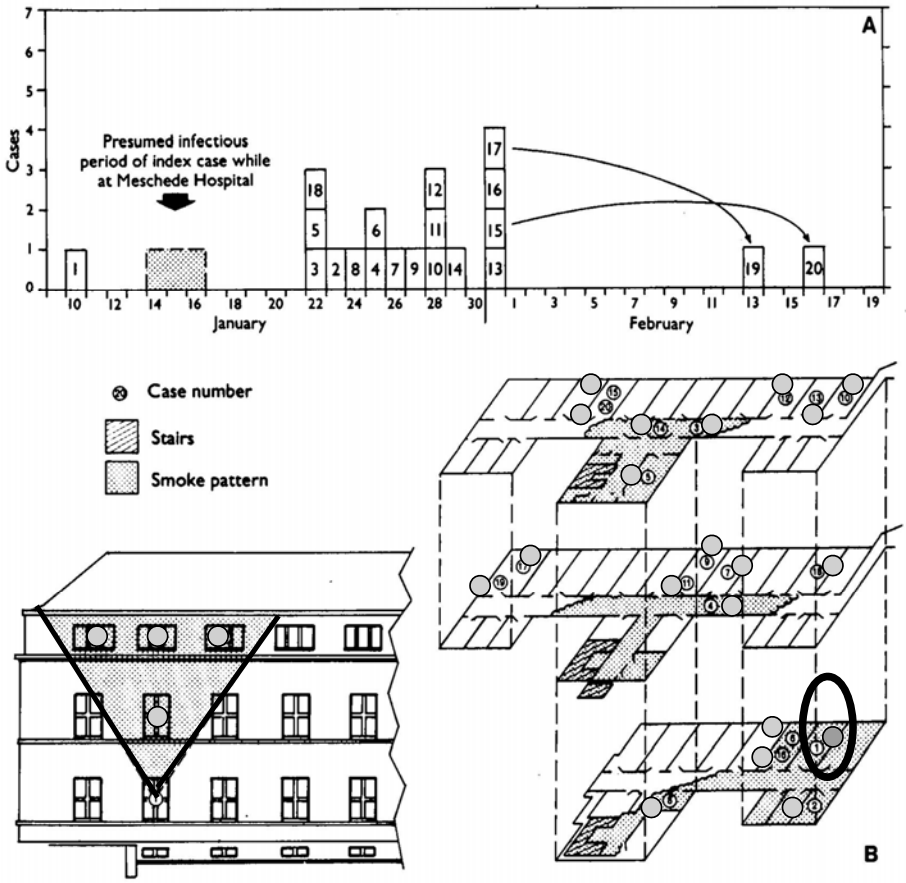
DIFFERNTIAL DIAGNOSIS OF VARIOLA

- Varicella
- Disseminated herpes zoster
- Impetigo (*Streptococcus pyogenes, Staphylococcal aureus*)
- Drug eruptions
- Contact dermatitis
- Erythema multiforme
- Enteroviral infections (esp., hand, foot and mouth disease)
- Disseminated herpes simplex
- Scabies
- Molluscum contagiosum

SMALLPOX: CONTROL

- Laboratory precautions: BSL 4
- Clothing/fomites: Decontaminate
- Prophylaxis
  - Pre-exposure: Vaccine
  - Post-exposure: Vaccine (within 4 days) or vaccine plus VIG (>4 days); potential role for cidofovir
- Isolation: Contact plus special airborne (eye protection)

Airborne Spread of Smallpox in the Meschede Hospital

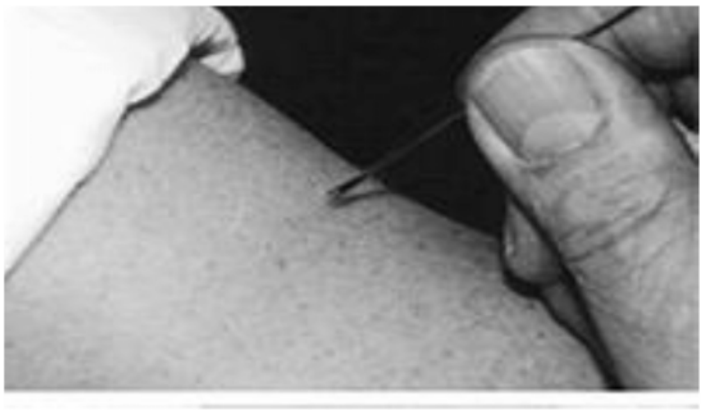


Fenner. 1988.Fig. 4.9

Portrait of Edward Jenner (1749-1823)

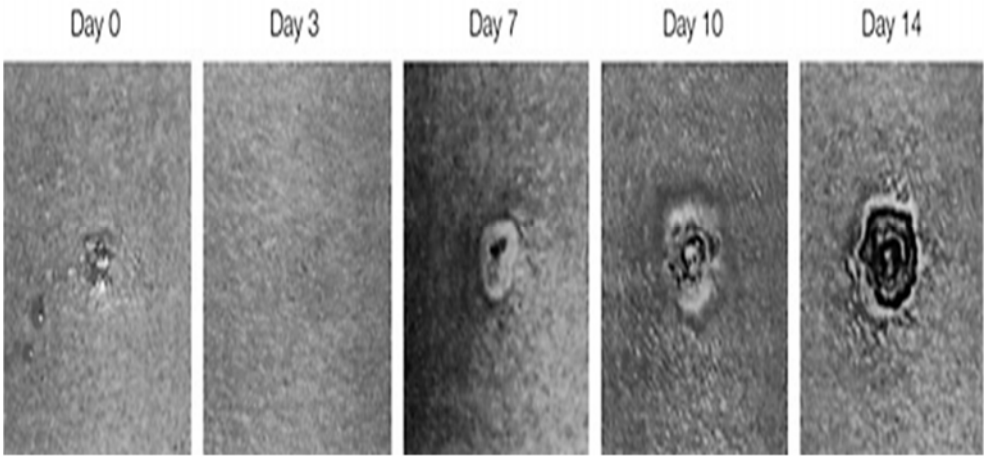
Ann Intern Med 1997;127:635-42

Vaccination With the Bifurcated Needle

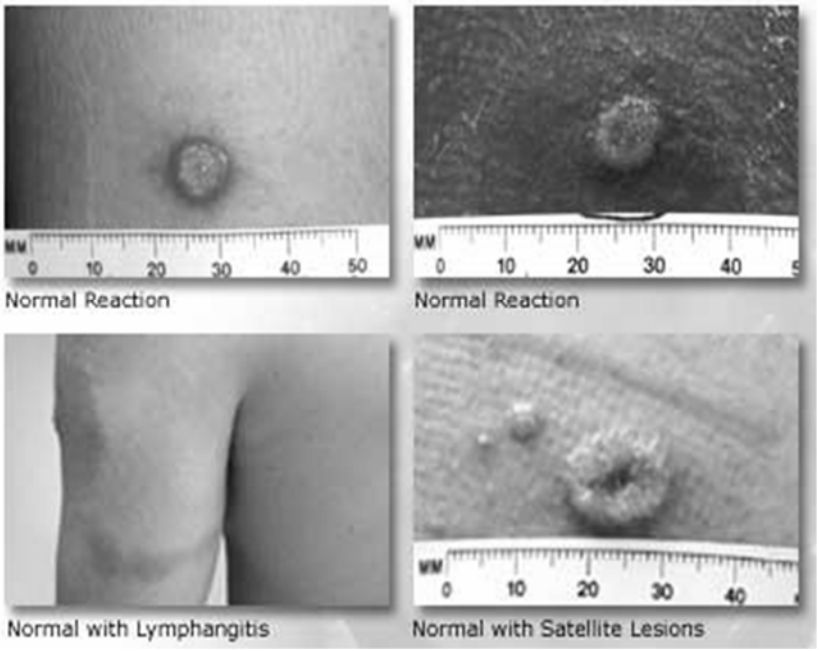


Henderson: JAMA 281;1999:2127-2137

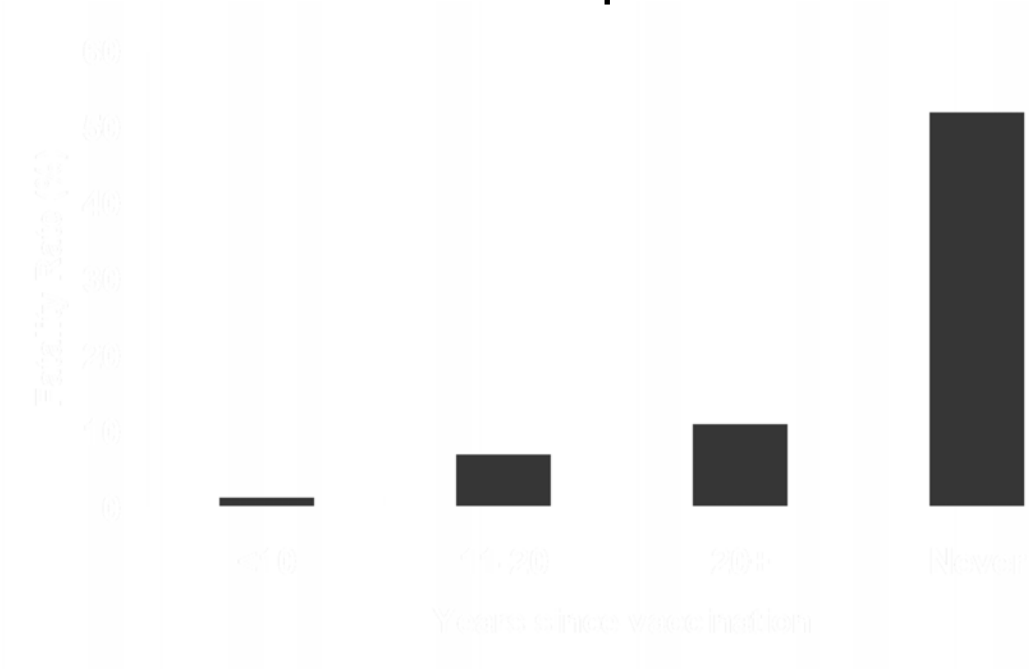
EVOLVING PRIMARY VACCINATION



Normal reactions include a wide spectrum of cutaneous presentations:

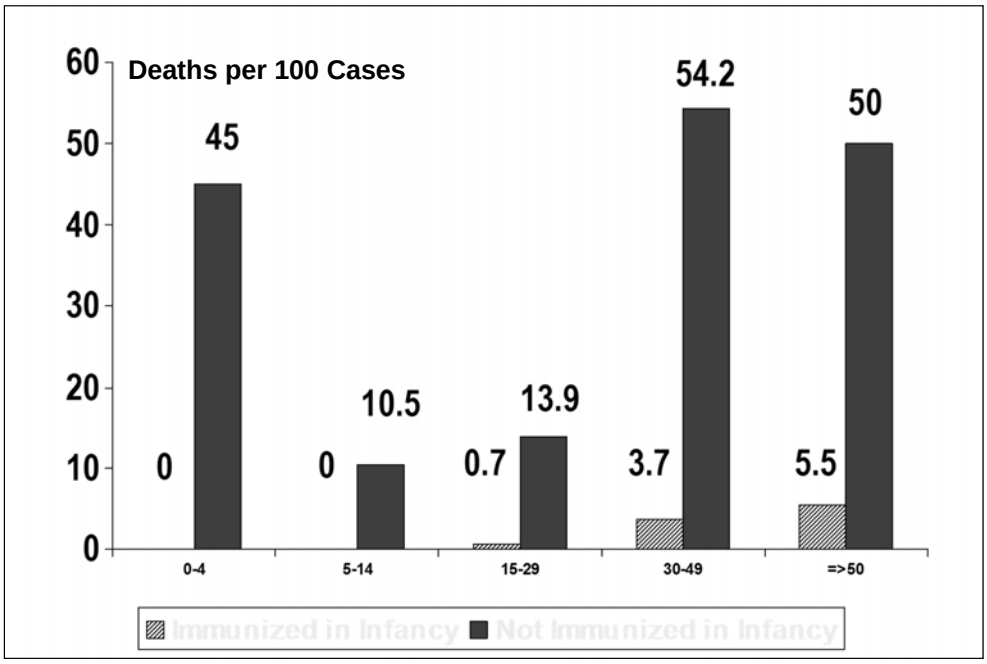


Smallpox Fatality Rate by Time Since Vaccination - Europe, 1950-1971*



*Mack TM. J Infect Dis 1972;125:161-9.

PROTECTIVE EFFECT OF INFANT IMMUNIZATION AGAINST MORTALITY BY AGE OF INFECTION



Hanna, W. 1913, Studies in smallpox and Vaccination. Bristol, Wright.

VACCINIA VACCINE: PRECAUTONS AND CONTRAINDICATIONS

- Severe allergic reaction to prior dose of vaccine
- History or presence of eczema, other skin conditions
- Pregnancy (children in the household is not a contraindication)
- Altered immocompetence
  - HIV, Leukemia, lymphoma, generalized malignancy
  - Solid organ transplant, BMT
  - Corticosteroids, alkylating agents, antimetabolites, radiation
  - Cardiac disease
- Allergies
  - Neomycin, polymyxin b, tetracyclines, streptomycin

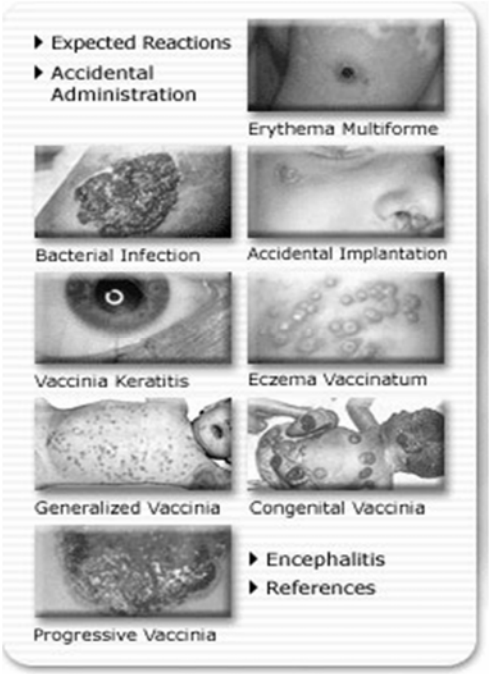
VACCINIA VACCINE: PREVENTION OF CONTACT TRANSMISSION

- Vaccinia virus can be cultured from primary vaccination site beginning at the time of development papule (2-5d after vaccination)
- Transmission via direct skin contact may occur
- Vaccination site should be covered with a porous bandage until scab has separated and underlying skin has healed (do not use an occlusive dressing)
  - Use impermeable bandage when bathing
- Vaccinated HCWs may continue to work (vaccination site covered with sterile gauze and semipermeable dressing, and practice of good handwashing)

Adverse Reaction Rates*

Reaction	Primary Vaccination	Re - vaccination
Inadvertent inoculation	1/1,700	1/24,000
Generalized vaccinia	1/5,000	1/111,000
Eczema vaccinatum	1/26,000	1/333,000
Progressive vaccinia	1/667,000	1/333,000
Postvaccinial encephalitis	1/80,000	1/500,000
Death	1/million	0.25/million

*Adapted from CDC.Vaccinia (smallpox vaccine): recommendations of the ACIP, 2001. MMWR 2001;50(RR-10)



ADVERSE EVENTS REPORT (AERs) FOLLOWING CIVILIAN SMALLPOX VACCINATIONS

Adverse Events	Suspected	Probable	Confirmed
Eczema vaccinatum	--	--	--
Fetal vaccinia	--	--	--
Generalized vaccinia	2	--	1
Inadvertent inoculation	12	--	8
Ocular vaccinia	1	--	2
Progressive vaccinia	--	--	--
Erythema multiforme major	--	--	--
Myo/pericariditis	17	4	--
Post-vaccinial encephalitis	1	--	--
Pyogenic infection (vaccine site)	--	--	--

N=37,802 immunizations

MMWR 2003;52:639

PRE-EVENT SMALLPOX PLANNING

- Each state should establish and maintain ≥1 smallpox response team
- Each acute-care hospital should identify HCWs who can be vaccinated and trained to provide direct medical care for the first smallpox patients requiring hospital admission
- Optimal infection-control practices and appropriate site care should prevent transmission of vaccinia virus from vaccinated HCWs to patients
- When feasible, HCP responsible for dressing changes for smallpox vaccine recipients should be vaccinated

CDC. MMWR 2003;52(RR07):1-16

DEVELOPING A BT PLAN

- Recognition of infection
- Incident command system
- Communication with public health
- Triage of patients
- Decontamination of patients
- Maintaining clean and contaminated areas
- Proper patient isolation
- Post-exposure prophylaxis
- Treatment
- Control/screening of visitors
- Immunization of HCWs
- Internal communications
- Availability of diagnostic tests
- Availability of PPE

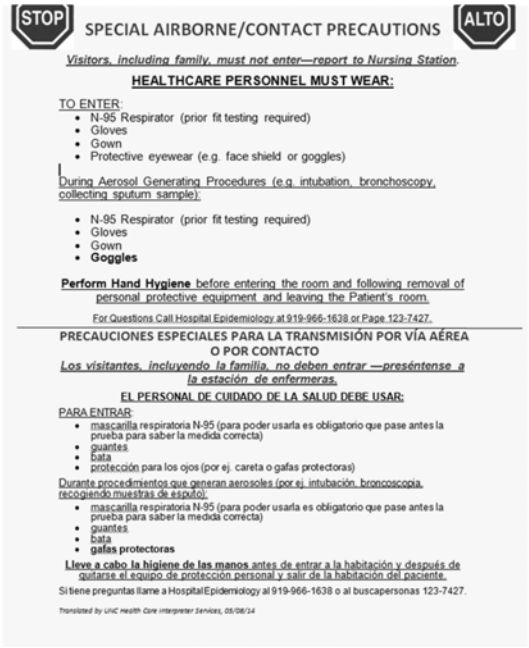
DEVELOPING A BT PLAN

- Have a written BT preparedness plan
- Assess the feasibility and viability of the plan
- Disseminate the plan and ensure familiarity by all key stakeholders
- Use elements of daily practice as the backbone of the plan
- Incorporate internal mechanisms for intensified surveillance
- Ensure appropriate internal and external mechanisms of communication
- Test the plan periodically through drills
- Incorporate flexibility and build redundancy for key components
- Address logistics involving surge capacity
- Emphasize community preparedness

Shaikh Z. ID Clinics NA 2006;20:433-453

SPECIAL AIRBORNE/CONTACT PRECAUTIONS

- New outpatient clinic constructed to see patients with highly contagious diseases
  - Direct entry from outside
  - All rooms have airborne isolation
- Representative pathogens
  - Monkeypox
  - SARS Co-V
  - Smallpox
  - Ebola



STOP SPECIAL AIRBORNE/CONTACT PRECAUTIONS ALTO

Visitors, including family, must not enter—report to Nursing Station.

HEALTHCARE PERSONNEL MUST WEAR:

TO ENTER:
- N-95 Respirator (prior fit testing required)
- Gloves
- Gown
- Protective eyewear (e.g. face shield or goggles)

During Aerosol Generating Procedures (e.g. intubation, bronchoscopy, collecting sputum sample):
- N-95 Respirator (prior fit testing required)
- Gloves
- Gown
- **Goggles**

Perform Hand Hygiene before entering the room and following removal of personal protective equipment and leaving the Patient's room.

For Questions Call Hospital Epidemiology at 919-966-1638 or Page 123-7427.

PRECAUCIONES ESPECIALES PARA LA TRANSMISIÓN POR VÍA AÉREA O POR CONTACTO

Los visitantes, incluyendo la familia, no deben entrar —preséntense a la estación de enfermeras.

EL PERSONAL DE CUIDADO DE LA SALUD DEBE USAR:

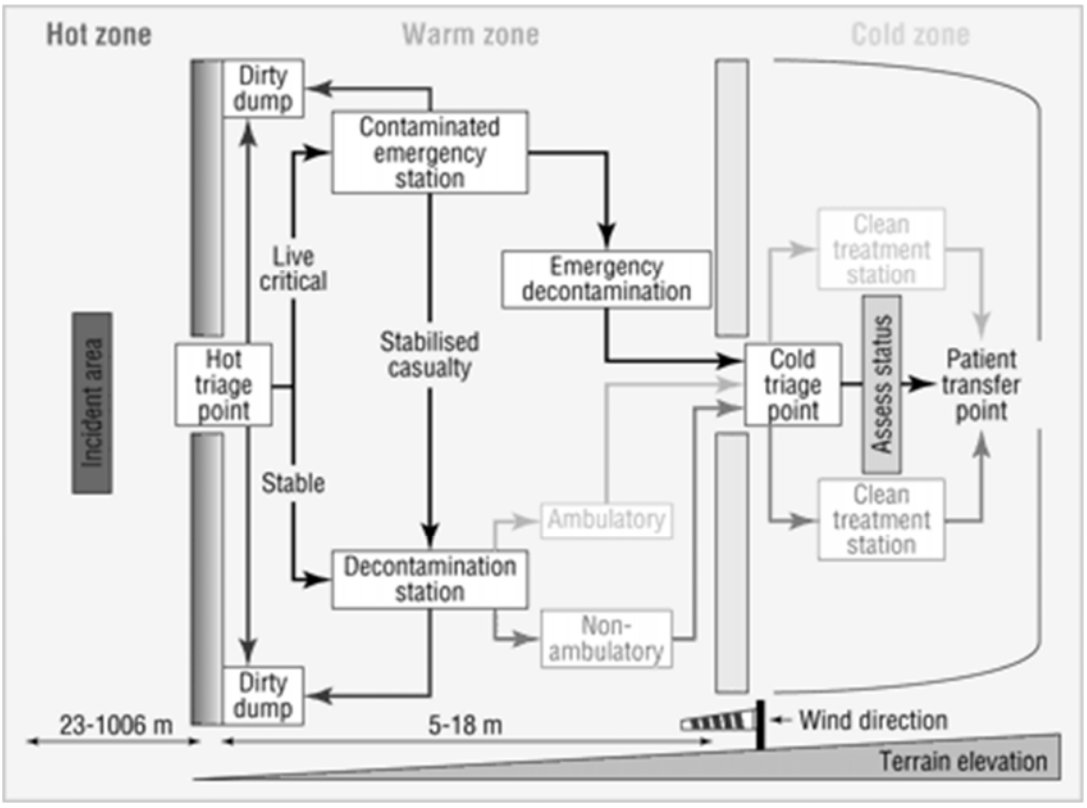
PARA ENTRAR:
- mascarilla respiratoria N-95 (para poder usarla es obligatorio que pase antes la prueba para saber la medida correcta)
- guantes
- bata
- protección para los ojos (por ej. careta o gafas protectoras)

Durante procedimientos que generan aerosoles (por ej. intubación, broncoscopia, recogiendo muestras de esputo):
- mascarilla respiratoria N-95 (para poder usarla es obligatorio que pase antes la prueba para saber la medida correcta)
- guantes
- bata
- **gafas protectoras**

Lleve a cabo la higiene de las manos antes de entrar a la habitación y después de quitarse el equipo de protección personal y salir de la habitación del paciente.

Si tiene preguntas llame a Hospital Epidemiology al 919-966-1638 o al buscapersonas 123-7427.

Translated by UNC Health Care Interpreter Services, 05/08/14



Gosden C, Gardner D. BMJ 2005;331:397

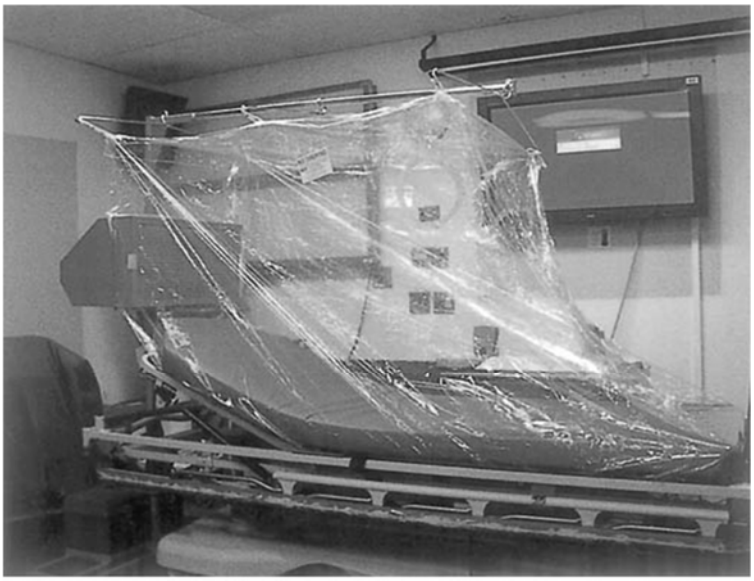
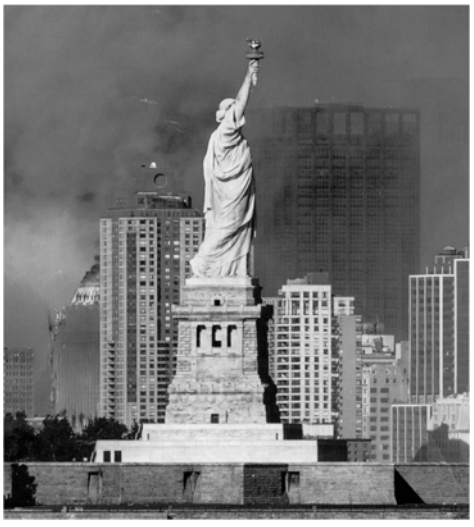


Figure 16-6 A high-efficiency particulate air (HEPA)–filtered mobile isolation device designed for transport of patients with contagious diseases.

(Demistifier, Peace Medical Inc., Orange, NJ.)

WORST CASE SENARIO

WE HAVE A DUTY TO BE PREPARED



- FBI (Richmond): 804-261-1044
- Local health department (911 after hours, ask for local health director)
- NC Dept. Health: 919-733-3419
- UNC Healthcare System, Infection Control: 966-4131 (ask for ICP on duty)
- CDC Emergency Response Coordinating Group: 770-488-7100
- USAMRIID: 301-619-2833