

Center for Disease Control & Prevention



Overview of Category A Bioterrorism Agents

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July 13, 2011

Acknowledgements

- New England Alliance for Public Health Workforce Development
- Boston University School of Public Health
- Massachusetts Association of Public Health Nurses (MAPHN)

Learning Objectives

- List properties of each agent
- Describe recommended response measures for each agent
- Explain agent-specific special considerations
- Identify additional resources

Category A Bioterrorism Agents

- **Anthrax**- *Bacillus anthracis*
- **Botulism**- *Clostridium botulinum*
- **Plague**- *Yersinia pestis*
- **Smallpox**- *Variola virus*
- **Tularemia**- *Francisella tularensis*
- **Viral Hemorrhagic Fever Viruses**

Properties of Category A Agents

- Can be easily disseminated or transmitted from person to person
- Result in high mortality with major public health impact
- Would cause panic and social disruption
- Require special action for public health preparedness

Categories B and C Agents

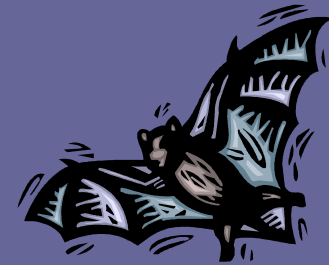
- Cat B Agents
 - Moderately easy to disseminate
 - Moderate morbidity, low mortality
 - Require enhancement of current diagnostic/laboratory capabilities and enhanced surveillance
- Cat C Agents
 - Emerging pathogens thought to have potential

Category B Examples

- Bacterial/rickettsial/protozoal agents
 - Brucellosis, Glanders, Melioidosis, Q Fever, Psittacosis, Typhus Fever
 - Cholera, Cryptosporidiosis (water threats)
- Toxins
 - Staphylococcus enterotoxin B, C. perfringens epsilon toxin, ricin toxin
- Viral agents
 - Viral encephalitides – Venezuelan, Western, and Eastern Equine Encephalitis

Category C Examples

- Emerging viral pathogens
 - Nipah virus
 - Hantavirus
 - Hantavirus pulmonary syndrome
 - Hantavirus hemorrhagic fever syndrome
- Currently not as well-developed as Cat B
- Higher mortality than Cat B Agents

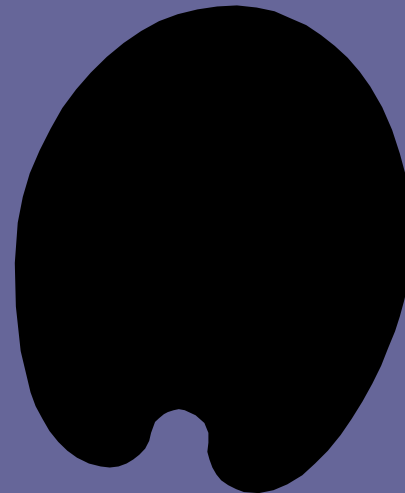
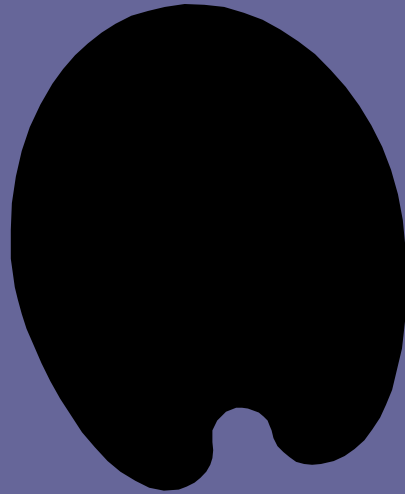


Detection of BT Release



- Claims by those who released the agent
- Observation of suspicious activity
- BioWatch alarm
- Clinical diagnosis by front-line health care providers – emergency depts. and doctors, school nurses, community health practitioners, pharmacists, veterinarians

“When you hear hoofbeats....”



“...consider some zebras.”



Important Points to Remember

- BT agents often behave differently from their naturally occurring counterparts.
- There is little epidemiological data on impact of BT agents in humans.
- Early diagnosis is critical.
- Rapid reporting is essential to containment.
- Response to contained and mass casualties will vary.

Prophylaxis/Treatment

- Oral antibiotics – tablet, capsule, liquid
 - doxycycline, ciprofloxacin
- Vaccines to be given intramuscularly
 - **Biothrax**; **Nuthrax** (anthrax vaccine)
- Vaccines to be given percutaneously
 - **ACAM 2000** (replicating live vaccinia vaccine)
 - **Imvamune** (nonreplicating live vaccinia vaccine)
- Antitoxins to be given intravenously
 - **HBAT** (Heptavalent Botulinum Antitoxin, eq.)
- Antivirals to be given by mouth, IM, IV



Anthrax ~ *Bacillus anthracis*

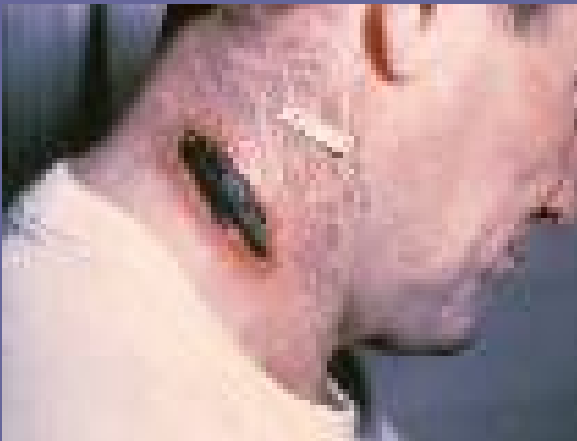
- Spore-forming bacteria; found naturally in soil worldwide

3 Types of disease:

- Cutaneous
 - most common naturally occurring form
 - skin inoculation with spores from infected animals, hides, wool, etc.
- Gastrointestinal
 - ingestion of undercooked, contaminated meat
- Inhalational
 - inhalation of spores in 1-5 micron particles
 - most deadly form and most likely in BT
 - odorless and invisible

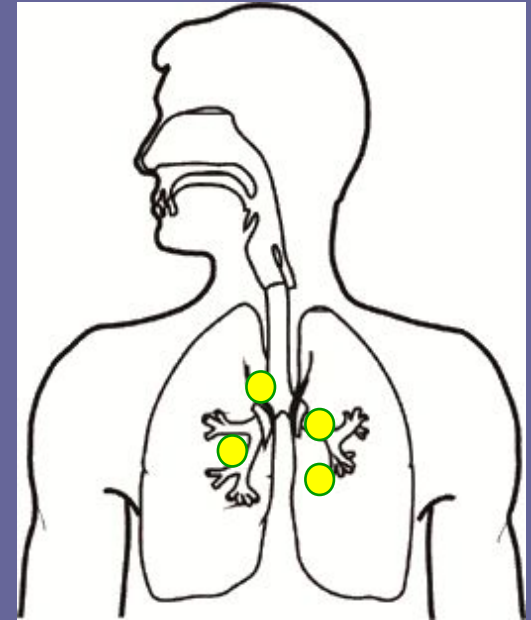
Cutaneous Anthrax

- Incubation period 1-10 days; (usually 5 days)
- Small macule or papule forms ulcer – (day 2)
- Vesicle appears and ruptures – (5-7 days)
- Ulcer dries into black eschar – (1-2 weeks)
- Malaise, low grade fever, lymphadenopathy
- Complications: toxic shock and death within 36 hours in 20% of untreated patients



Inhalational Anthrax

- Incubation period: 1-5 days (up to 60+)
- Inhalation of spores (1-5 microns)
- Infective dose may be quite low
- Fever, fatigue, cough, headache, and chest discomfort
- Severe dyspnea, chest pain, abdominal pain, nausea, vomiting, diaphoresis
- Hemorrhagic meningitis – 50%
- Toxic shock and death within 24-36 hrs





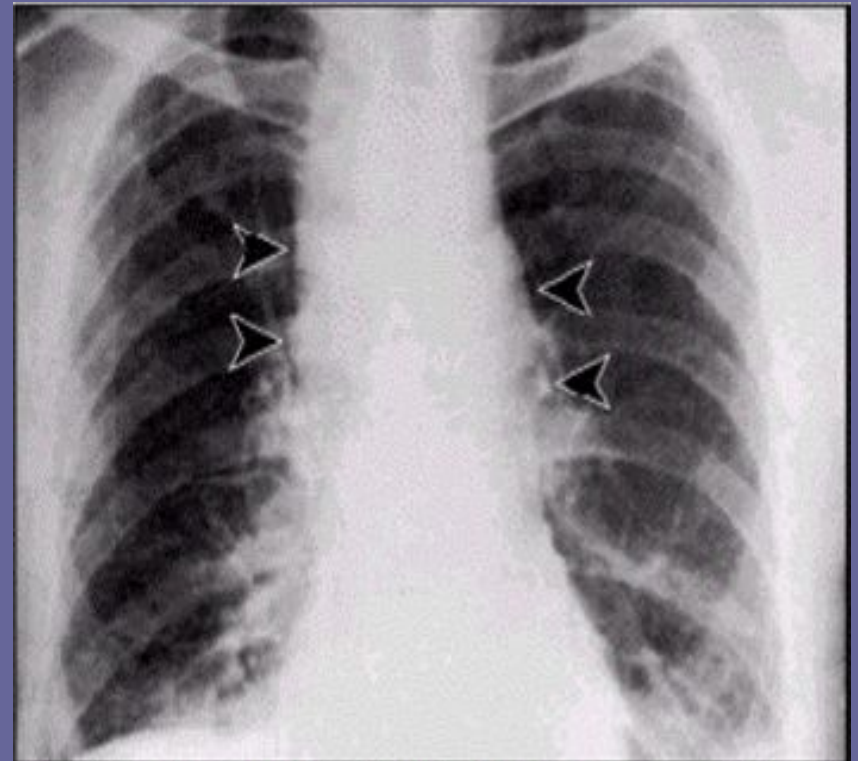
Pathophysiology of Inhalational Anthrax

- Spores are inhaled – taken up by alveolar macrophages which then move to lymph nodes
- Spores germinate, producing edema factor and lethal factor toxins
- Toxins produce local hemorrhagic lymphadenitis and necrosis in the chest (mediastinum)
- Septicemia can result, leading to sepsis and multi-organ failure
- Even with full ICU treatment, mortality is very high once symptoms develop

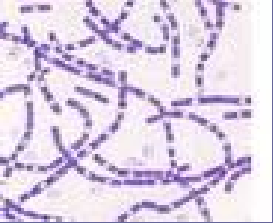
Inhalational Anthrax



Normal chest x-ray



Mediastinal widening with inhalation anthrax (JAMA 1999;281:1735-1745)



Diagnosing Inhalational Anthrax

- Possible history of exposure
- Differential diagnosis: tularemia, staph/strep
- Widened mediastinum/possible pleural effusion on chest xray
- Hemorrhagic mediastinal nodes on scan
- Gram positive bacteria (rods) on peripheral smear
- ELISA test – IgG for Protective Antigen -- rapid results
- Call your state epidemiologist for assistance with collection of specimens and diagnosis



Treatment for Inhalational Anthrax

- For symptomatic patients – IV therapy with two or more antibiotics, depending on sensitivity
- Supportive care (ICU – ventilator)
- Draw labs to confirm diagnosis and initiate therapy immediately – delayed treatment results in worse prognosis



Anthrax ~ Post-Exposure Prophylaxis (PEP)

CDC recommends combined therapy:

- 3 doses of vaccine - investigational new drug (IND)
- Oral antibiotics for 60 days:
 - ciprofloxacin
 - doxycycline
 - amoxicillin or penicillin (if susceptibility testing is supportive)
- Oral antibiotics – before symptom onset
- Vaccine alone is not protective for PEP
- **PEP may depend on numbers of people exposed**

Special Considerations - Anthrax

- Not spread person to person
 - No risk of spreading disease among clinic attendees
 - Minimal PPE needed to protect clinic staff
- Incubation period 1 to 60+ days
 - PEP must be started very early
- Inhaled spores may stay viable inside body for >60 days
 - PEP must be continued for at least 60 days

Special Considerations, Anthrax (cont.)

- Inhalation anthrax is a DEADLY disease
 - If PEP isn't begun before symptoms arise, prognosis is grave (“worst-case scenario”)
 - Need great risk communication to target pop.
- CDC recommendation: oral antibiotics x 60 days + series of 3 vaccinations
- Logistical challenges of delivering materiel on this scale



Botulism ~ Clostridium botulinum

- Spore-forming bacteria; found naturally in soil
- Produces most poisonous substance known
- Toxins are colorless, odorless, tasteless
- Inactivated by heat ($\geq 85^{\circ}\text{C}$ for 5 min)



Botulism ~ Types



- Infant (3–30 days)
 - toxin produced by organisms in intestinal tract
- Wound (4-14 days)
 - toxin produced by organisms contaminating wound
- Foodborne (12-36 hrs)
 - ingestion of pre-formed toxin from improperly processed or canned, low-acid foods
- Inhalation botulism (12-72 hrs)
 - inhalation of toxin, not natural occurrence, BT threat only



Pathophysiology of Botulism

- Toxin binds permanently to neuromuscular junction, preventing the release of neurotransmitter (acetylcholine)
- Muscles controlled by affected nerves are completely paralyzed
- Branches will grow around affected nerve axons, creating new pathways for neural impulses. Slowly, paralysis resolves... although this takes weeks to months



Infant Botulism (“floppy baby”)



CDC Image Library



Diagnosing Botulism

- History of possible exposure
- Sudden onset descending, bilateral, symmetrical, floppy paralysis, starting at top of head
- Double vision, drooping of eyelids, mumbling, hoarseness, difficulty swallowing, dry mouth/pharynx; increasing difficulty with secretions; also nausea and diarrhea; progresses downward
- Awake, alert, aware, oriented; no fever
- Diagnosis is primarily clinical. Lab tests can help confirm diagnosis, but they take time



Diagnosing Botulism (cont.)

- Differential diagnosis:
 - Myasthenia gravis (+ Tensilon® test)
 - Guillain-Barre syndrome (+ CSF protein; EMGs; ascending paralysis)
 - Paralytic shellfish poisoning (paresthesias)
 - Stroke (unilateral s/s, + findings on scans)
 - Other toxins or drugs (+ tox screens)
 - In New England, also consider tick paralysis (ascending paralysis; exposure to and presence of tick)

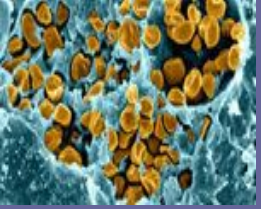


Botulism ~ Treatment

- Combined supportive care and antitoxin
- Consult with state public health officials to obtain antitoxin
- Botulinum antitoxin
 - New heptavalent product from CDC (**HBAT**, equine)
 - **BabyBIG** – human antitoxin for infant botulism, available from CA Health Dept.
- Recovery may be prolonged (many months)
- Monitor exposed persons for signs of illness

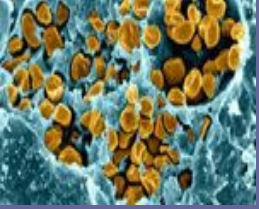
Special Considerations - Botulism

- Antibiotics won't help – toxin is preformed substance
- Antitoxin will stop but not reverse progression
- Antitoxin usually given IV as treatment
- Antitoxin = equine origin = ALLERGENIC
- Mass casualty prophylaxis/treatment will be determined by local, state, and federal public health officials at the time of the event.



Tularemia ~ *Francisella tularensis*

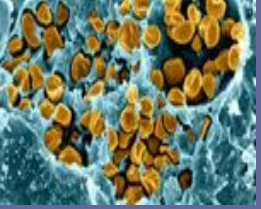
- Small, non-spore-forming bacteria
- Survives for weeks at low temps in water, soil, hay, straw and animal carcasses
- Extremely infectious; as few as 10 organisms can cause disease
- Small mammals (rabbits) – reservoirs
- Occurs in North America, Europe, Russia, China and Japan



Tularemia ~ Transmission & Types

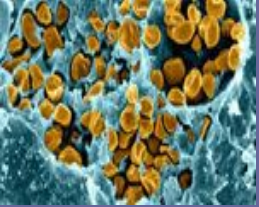
- Diverse transmission routes:
 - Insect bite, mammal bite, contact with infectious tissue, ingestion of contaminated food or water, and inhalation
- Diverse clinical presentations, dependent on route of transmission
- Incubation period
1-21 days (ave. 3-5 days)





Tularemia ~ Symptoms

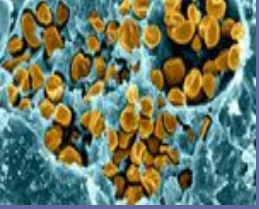
- **All forms - rapid onset of fever and inflamed lymph nodes**
 - “Influenza-like illness”
- **Pneumonic** - resembles plague
 - Inhalational tularemia is characterized by inflammation of upper and/or lower airways, including in some cases destruction of the air sacs in the lungs
- **Typhoidal** – rare, septicemia, abdominal pain, diarrhea, vomiting, gastrointestinal bleeding
- **Other forms** include: glandular and cutaneous



Tularemia Lesions

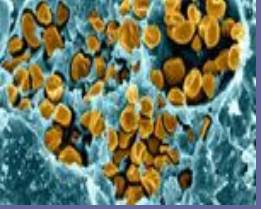


CDC Public Health Image Library



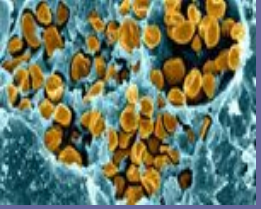
Pneumonic Tularemia -- Pathophysiology

- Organism hides, survives and replicates inside macrophages
- Pneumonic tularemia can develop secondarily after ulceroglandular or glandular disease



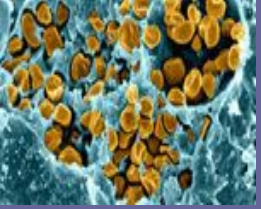
Diagnosing Pneumonic Tularemia

- Difficult to diagnose because of nonspecific signs and symptoms
- **Diagnosis may rely on epidemiologic evidence** (e.g., history of mowing lawn in endemic area)
- Some laboratory studies may be useful depending on stage of disease
- A large number of cases of pneumonic tularemia (or disease in a nonendemic area) would raise the level of concern for a BT release



Treating Tularemia

- Antibiotics -- mainstay of therapy
- Genetically engineered resistant strains may be used as BT weapons
- Contact your state health department for treatment guidance and protocols



Tularemia ~ Post Exposure Prophylaxis

- Mass casualty - oral antibiotics for 14 days
 - doxycycline or ciprofloxacin
- Potential exposure – place on fever watch and administer antibiotics if needed
- Vaccination – not recommended as PEP
 - Short incubation period
 - Incomplete protection for inhalational tularemia

Special Considerations -- Tularemia

- Not spread person to person
 - Antibiotic dispensing clinics do not pose risk of transmission to healthy staff or community members
- Incubation period variable, as short as 1 day
- Tularemia can usually be treated successfully *after* symptoms arise
 - Mass casualty response will probably include “fever watch” and treatment of those who develop symptoms if release is not detected immediately



Plague ~ *Yersinia pestis*

- Naturally occurring zoonotic infection
- Bacterial reservoir – small rodents, other mammals
- Transmitted by bite of an infected flea
- Occurs worldwide - 1,700 cases/yr
- Occurs in southwestern US; 12-14 cases/yr



Plague ~ Types

- **Bubonic** – most common type; painful swelling of lymph nodes
- **Pneumonic** – primary or secondary; inhalation of aerosolized bacilli into lungs or infection of lungs from bacteria
- **Septicemic** – primary or secondary; less common
- Meningitis or pharyngitis – less common
- Pneumonic and septicemic – approaching 100% fatal if untreated

Pathophysiology of Plague

- After a flea bite, bacteria travel to regional nodes, producing suppurative adenitis (buboes)
- Bacteremia can develop, seeding the lungs and/or resulting in sepsis
- Plague also spread in droplets expelled while coughing



Inguinal/Femoral and Axillary Buboes



Source: All photos from CDC Image Library

“The Black Death”



All photos taken from CDC Image Library



Pneumonic Plague Symptoms

- Incubation period 1-6 days (usually 2-4 days)
- Malaise, fever, chills, headache, muscle ache
- Cough, chest pain, difficulty breathing
- Rapidly progressing, severe pneumonia
- Copious bloody, watery, or purulent sputum presenting transmission danger
- Prominent gastrointestinal symptoms
- Death in 2-6 days after exposure without treatment – prognosis grim if treatment delayed



Diagnosing Pneumonic Plague

- History of exposure/endemic areas
- Chest x-ray – usually bilateral alveolar infiltrates
- Extensive, fulminant pneumonia with bloody sputum in an otherwise healthy, immunocompetent host, with Gram neg “safety-pin” rods in sputum
- DFA (direct fluorescent antibody) useful

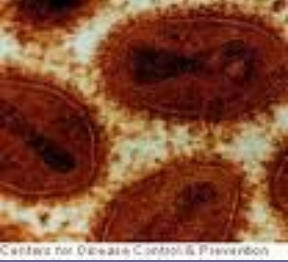


Pneumonic Plague ~ Treatment and Post-Exposure Prophylaxis

- Treatment – IV antibiotic therapy for 10 days with supportive treatment, as needed
- Mass casualty PEP – oral antibiotics for 7 days (doxycycline)
- Mass casualty – treatment instituted for fevers, new cough

Special Considerations – Plague

- Plague transmissible from person to person
 - Pneumonic plague is highly contagious
 - Precautions until 72 hrs after institution of effective antibiotic therapy
 - Bubonic plague also contagious
 - Precautions until 48 hrs after institution of effective antibiotic therapy
 - Pneumonic plague can develop secondarily
 - Clinic setting will pose risk to staff and community members
 - Pre-clinic screening and PPE necessary
 - Alternatives to “pull” clinic setting preferable
- Plague requires PEP before symptoms begin



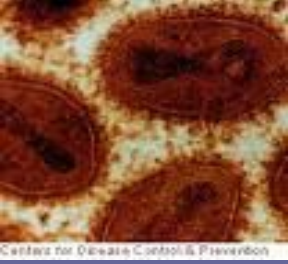
Smallpox- Variola

- Variola Virus
 - Variola Major (30% case fatality rate)
 - Variola Minor (variant with milder disease)
 - Hemorrhagic Smallpox (immunocompromised pts; approaching 100% mortality)
- Transmission:
 - Via respiratory droplets of the patient (airborne transmission)
 - Direct contact
 - Indirect contact with contaminated linens
- Small infectious dose
- Incubation period: 7-17 days (10-14 days)
- Aerosol release – virus inactive after 2 days



Smallpox

- No natural host outside of humans; does not currently exist in nature
- Last case in the US 1949
- Ceased routine vaccination in US 1972
 - Immunity wanes in 3-5 years
 - Immunity probably absent after 10 years
 - Most of US population = UNPROTECTED
- Last naturally occurring case 1977
- WHO declares eradicated 1980
- Virus destroyed except for two depots:
 - Atlanta
 - Moscow



Smallpox - Symptoms

- High fever, malaise, headache, backache
- Rash (about 15 days after exposure):
 - maculopapules, day 1-2 of rash
 - vesicles, day 4-5 of rash
 - pustules - round, firm, embedded in dermis, day 7
- Infectious from onset of fever – virus is shed from oral lesions preceding rash onset.
- Death from toxemia – 2nd week of illness
- Hemorrhagic and malignant smallpox – more severe, less common forms of smallpox

Smallpox rash progression





Diagnosing Smallpox

Rule out smallpox for any febrile rash illness



Smallpox vs. Chickenpox

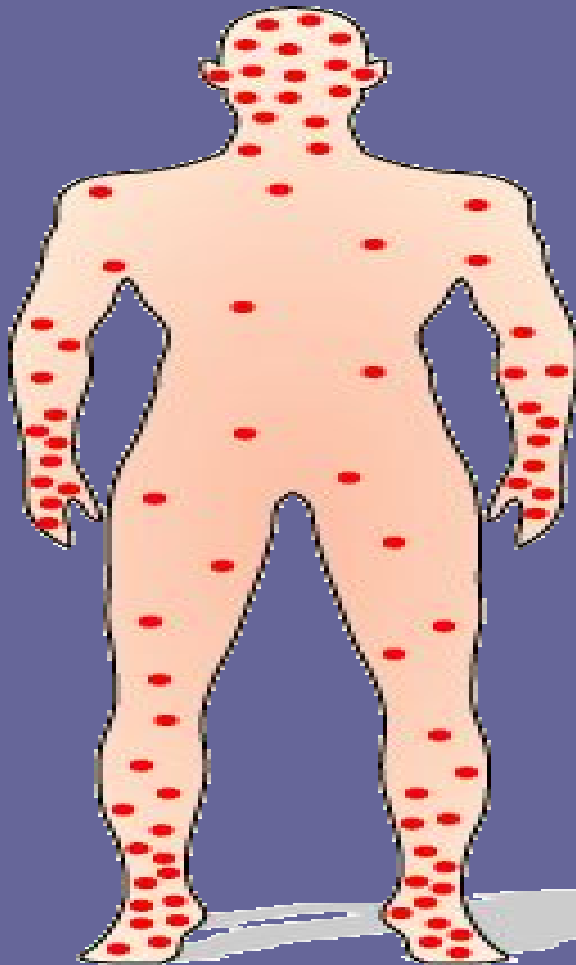
Smallpox

- Centrifugal Rash
- Pox over 1-2 day period, all evolve at same rate
- All pox at same stage
- Rash on palms and soles
- Lesions extend into dermis
- Pronounced prodrome and fever

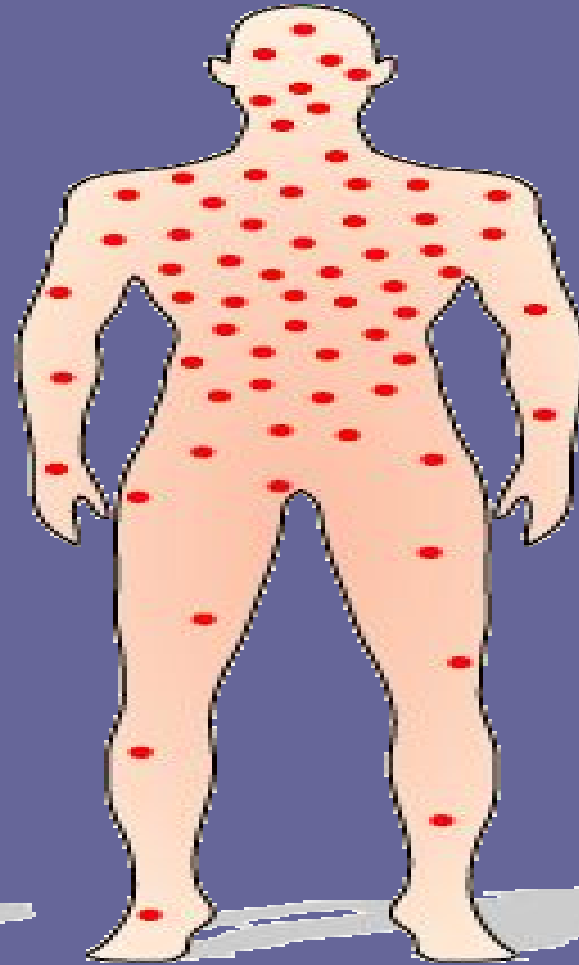
Chickenpox

- Centripetal Rash
- Crops of lesions at different stages of development
- Adjacent lesions at different stages
- Never on palms or soles
- Lesions not as deep
- Mild or no prodrome/fever

Smallpox vs. Chickenpox

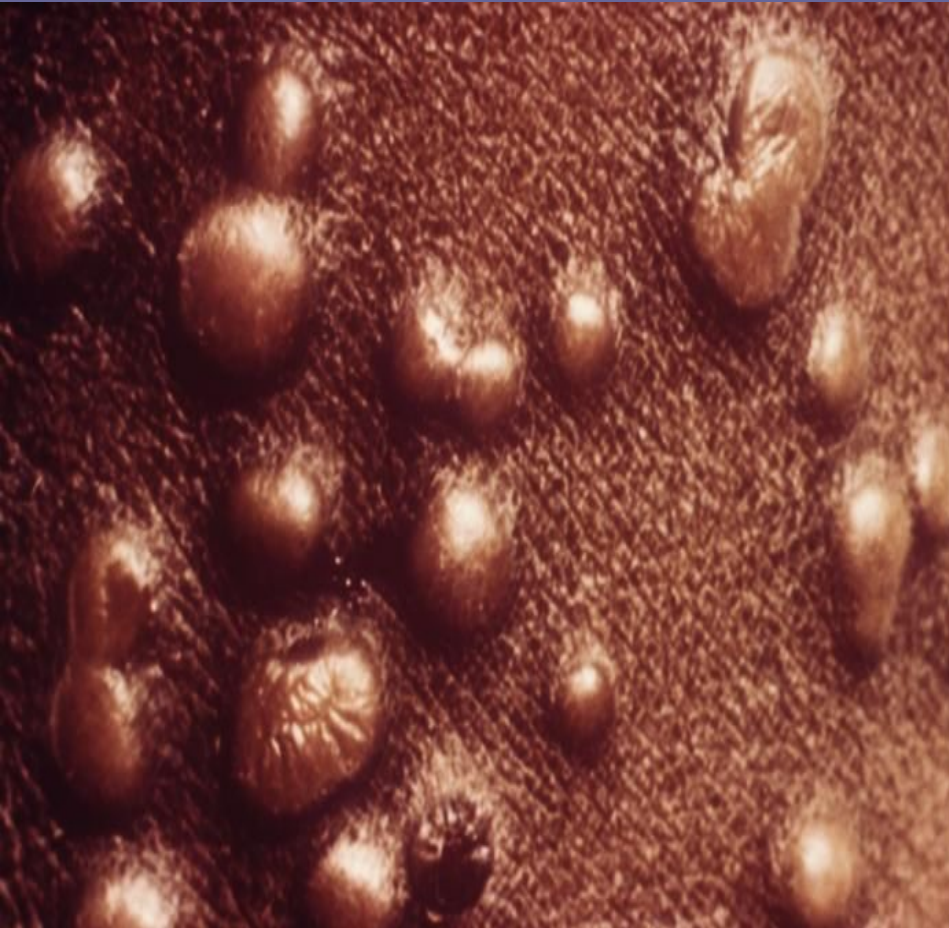


smallpox



chickenpox

Smallpox Rash



Chickenpox Rash



Source: www.fda.gov

Smallpox Rash



Source: CDC

Smallpox Rash



Photo: CDC Image Library



Smallpox- Treatment and Post Exposure Prophylaxis

- Supportive therapy for patients
- Afebrile contacts – under fever surveillance for 18 days (14 days, if vaccinated)
- Febrile contacts – isolated for 5 days
- General public: vaccination within 3 days
- VIG – to counter adverse reactions and for immunocompromised people

Special Considerations – Smallpox

- Smallpox is highly contagious – staff and clients may be at risk in clinic settings
 - Pre-screening and PPE may be needed
 - Alternate vaccine distribution may be preferable, but difficult
- It takes time to build immunity after vaccination
 - Those not vaccinated within a few days after exposure will get sick
 - Vaccination after a few days may mitigate if not prevent disease

Special Considerations – Smallpox (cont.)

- Smallpox mortality rate: 30% (may be much higher among immunocompromised)
- Vaccination technique requires training
- Live vaccine (vaccinia) requires “cold chain” and careful handling
- Vaccination site requires about 4 weeks of special care until scab falls off
 - Clients must be trained to care for vaccination site

Special Considerations – Smallpox (cont.)

- Vaccination site must be evaluated in 6 to 8 days after vaccination to check for a successful reaction called a “take”
- Standard vaccine has risk of adverse events
 - Limited amounts of nonreplicating vaccine soon available

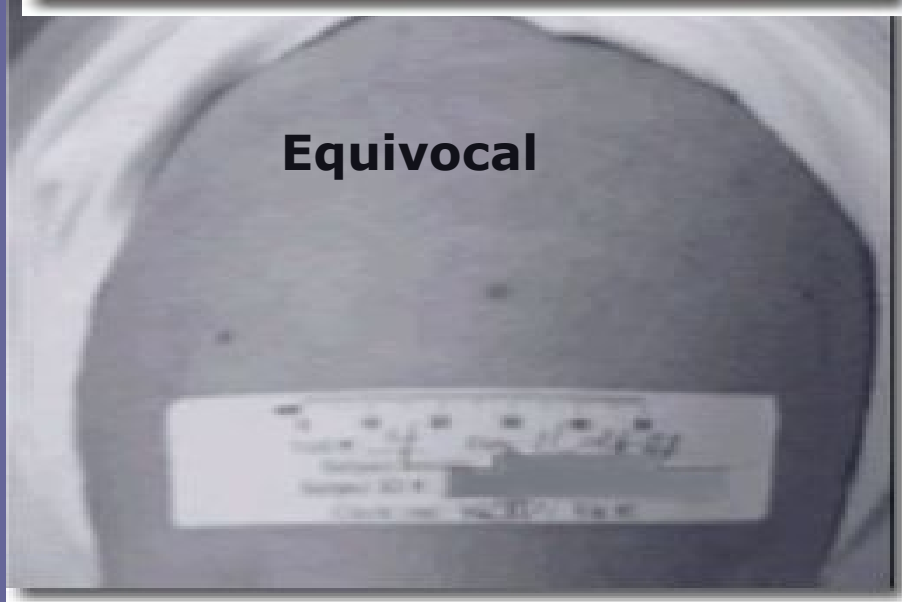
Vaccination Site Evaluation

Development of a major cutaneous reaction at the site

- Lesion evolves gradually
 - papule after 2-5 days
 - papule becomes vesicular, then pustular, and reaches its maximum size at 8-10 days after vaccination
 - pustule dries and forms a scab, which usually separates within 14-21 days, leaving a pitted scar.



Examples of Major Reactions (“Takes”) vs. Equivocal Reactions





Viral Hemorrhagic Fevers (VHFs)

- Severe multisystem syndrome - 4 virus families
- Arenaviruses and filoviruses are Cat A agents
 - Ex: Lassa, Argentine (Junin), Bolivian (Machupo), Ebola, Marburg
- Animals and insects – natural reservoir
- Geographically restricted to host environment
- Zoonotic with human to human transmission
- Outbreaks occur sporadically; not predictable
- Limited treatment options for all VHFs
- VHFs successfully aerosolized as bioweapons



Each virus has its own routes of transmission....

- Vectorborne:
 - mosquitoes or ticks (dengue hemorrhagic fever)
- Rapid spread via contact with:
 - Rodents (Junin, Machupo)
 - Rodents' urine or feces (hantaviruses)
 - Infected animal, person, blood or body fluids (Ebola, Marburg) including contaminated bedding or medical equipment
- Some airborne spread possible (e.g. aerosolized Ebola, arenaviruses)



VHF Symptoms

- Incubation period: 1-21 days; ave. 3-10 days
- Initial symptoms:
 - ILI
 - Filoviruses – characteristic red rash
- Severe symptoms:
 - Coagulation abnormalities
 - bleeding under the skin, in internal organs, or from body orifices
 - shock, nervous system malfunction, coma, delirium, and seizures, renal failure
- Duration of symptoms: few days to couple of weeks
- Fatality rates range 10% to 90%



Bolivian Hemorrhagic Fever

(source: JAMA 2002)



Hemorrhagic Fever

<http://creativecommons.org/licenses/by-sa/3.0/>

Viral Hemorrhagic Fever



Marburg Rash

(source: JAMA 2002)



VHFs Treatment & Infection Control

- No vaccines except for Argentine HF and yellow fever. Others in pipeline
- Don't transport patients; don't do unnecessary venipunctures
- Supportive care, careful IV fluid maintenance
- No cure or established drug treatment (? steroids, ribavirin, other antivirals, ? immune plasma? Treat coagulopathies if diagnosed. Dialysis if indicated)
- Standard, contact, droplet, and airborne precautions, patient isolation.
- Bedding and medical equipment - cleaned and sterilized
- Personal surveillance for close contacts

Special Considerations – Viral Hemorrhagic Fevers

- Antibiotics, antitoxins of no use
- Vaccines of very limited use (e.g., Junin)
- Oral antivirals probably of no use; IV antivirals may be helpful for some VHFs; in very short supply

Reporting Suspect BT Incidents

- Report all suspect cases of BT immediately to your state health department
- Find out now what the reporting protocols are in your jurisdiction or state

Resources

- **Arnon, S. et al. Botulinum Toxin as a Biological Weapon. *JAMA*. 2001;285;1059-1068.**
- **Dennis, D. et al. Tularemia as a Biological Weapon. *JAMA*. 2001;285;2763-2772.**
- **Henderson, D. et al. Smallpox as a Biological Weapon. *JAMA*. 1999;281;2127-2137.**
- **Inglesby, T. et al. Anthrax as a Biological Weapon, 2002. *JAMA*. 2002;287;2236-2250.**
- **Inglesby, T. et al. Plague as a Biological Weapon. *JAMA*. 2000;283;2281-2289.**

Resources

- **CDC website:**

<http://www.bt.cdc.gov/bioterrorism/training.asp>

- **Special Pathogens:**

www.cdc.gov/ncidod/dvrd/spb

- **MA Dept of Public Health. *Guide to Surveillance, Reporting and Control*. 2006; available online at www.mass.gov/dph; on left side of page, under *Key Resources*, click on *Infectious Disease Reporting and Requirements*. See following for updates.**

Resources

- MA Dept of Public Health. *Summary of Reportable Diseases, Surveillance, and Isolation and Quarantine Requirements*. Extracted from 105 CMR 300.000. MDPH, 2009. www.mass.gov/dph
- “The Blue Book” -- *Medical Management of Biological Casualties Handbook*, United States Army Medical Research Institute of Infectious Diseases (USAMRIID). Fort Detrick, Frederick, Maryland; 6th Edition; April 2005. Available on line for free at

<http://www.usamriid.army.mil/education/bluebookpdf/USAMRIID%20BlueBook%206th%20Edition%20-%20Sep%202006.pdf>

Resources

- ***Red Book: 2009 Report of the Committee on Infectious Diseases*, 28th ed. Elk Grove Village, IL; American Academy of Pediatrics; 2009 with 2011 updates <http://aapredbook.aappublications.org/>**
- **“The Pink Book” – Centers for Disease Control and Prevention. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. W. Atkinson et al; 12th edition (2011) free at**

<http://www.cdc.gov/vaccines/pubs/pinkbook/default.htm>

Resources

- **“The Yellow Book” – *CDC Health Information for International Travel 2012*. Atlanta: US Dept of Health and Human Services, Public Health Service;
<http://wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm>**
- **Iowa State University Center for Food Security and Public Health (veterinary pages):
<http://www.cfsph.iastate.edu/DiseaseInfo/>**
- **Lenhart, M., ed. *Textbooks of Military Medicine: Medical Aspects of Biological Warfare*. Borden Institute Press, Fort Sam Houston, TX, 2007. Available free online at
http://www.bordeninstitute.army.mil/published_volumes/biolo**

Resources

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Acknowledgements

- New England Alliance for Public Health Workforce Development
- Boston University School of Public Health
- Massachusetts Association of Public Health Nurses (MAPHN)

