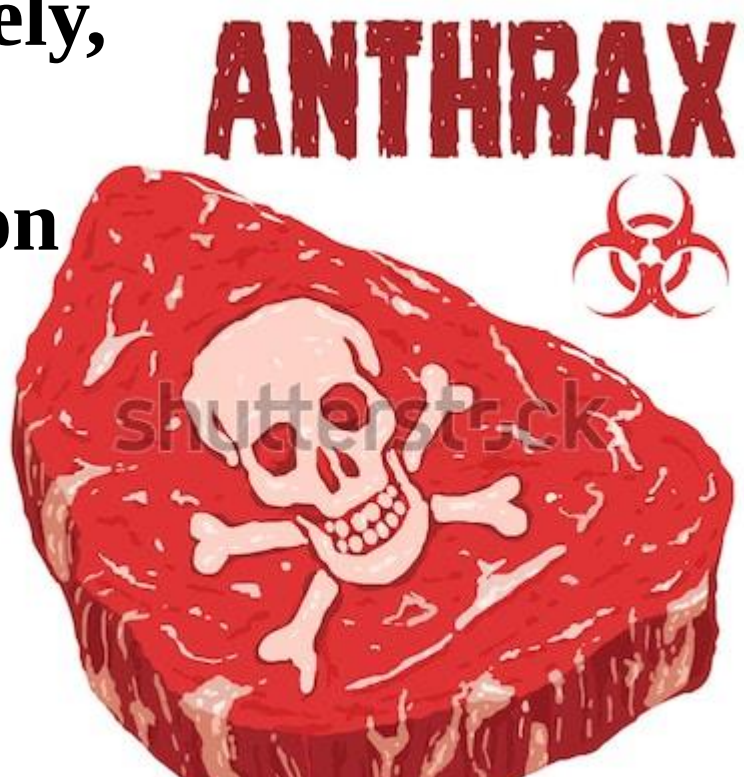
ANTHRAX

Anthrax is a worldwide disease of domesticated and wild animals that secondarily may occur in humans. Estimates of worldwide cases vary widely, but it is estimated by the World Health Organization that there are between 2000 and 20,000 human cases per year.

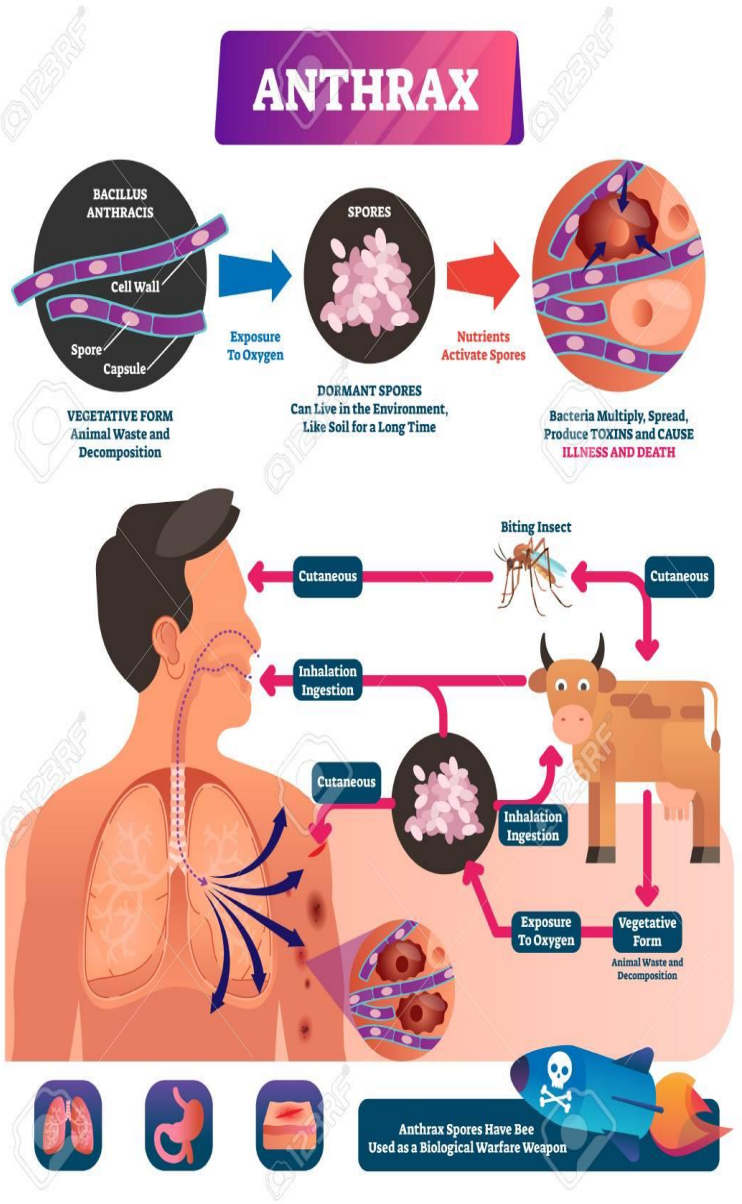


Anthrax is an acute disease caused by the bacterium *Bacillus anthracis*.

Most forms of the disease are lethal, and it affects mostly animals.

It is contagious and can be transmitted through contact or consumption of infected meat.

Effective vaccines against anthrax are available, and some forms of the disease respond well to antibiotic treatment.



History

Etymology

The English name comes from *anthrax* (ἄνθραξ), the Greek word for coal, because of the characteristic black skin lesions developed by victims with a cutaneous anthrax infection. The central, black eschar, surrounded by vivid red skin has long been recognised as typical of the disease.

The first recorded use of the word "anthrax" in English is in a 1398 translation of Bartholomaeus Anglicus' work *De proprietatibus rerum* (*On the Properties of Things*, 1240).

Anthrax has been known by a wide variety of names, indicating its symptoms, location and groups considered most vulnerable to infection. These include Siberian plague, Cumberland disease, charbon, splenic fever, malignant edema, woolsorter's disease, and even *la maladie de Bradford*.

Anthrax outbreaks occur in some wild animal populations with some regularity.

The disease is more common in countries without widespread veterinary or human public health programs.

In the 21st century, anthrax is still a problem in less developed countries.

In December 2009, an outbreak of anthrax occurred amongst heroin addicts in Glasgow, Scotland, resulting in 14 deaths.

The source of the anthrax is believed to be dilution of the heroin with bone meal in Afghanistan.

Anthrax is a rare disease in the EU/EEA countries.

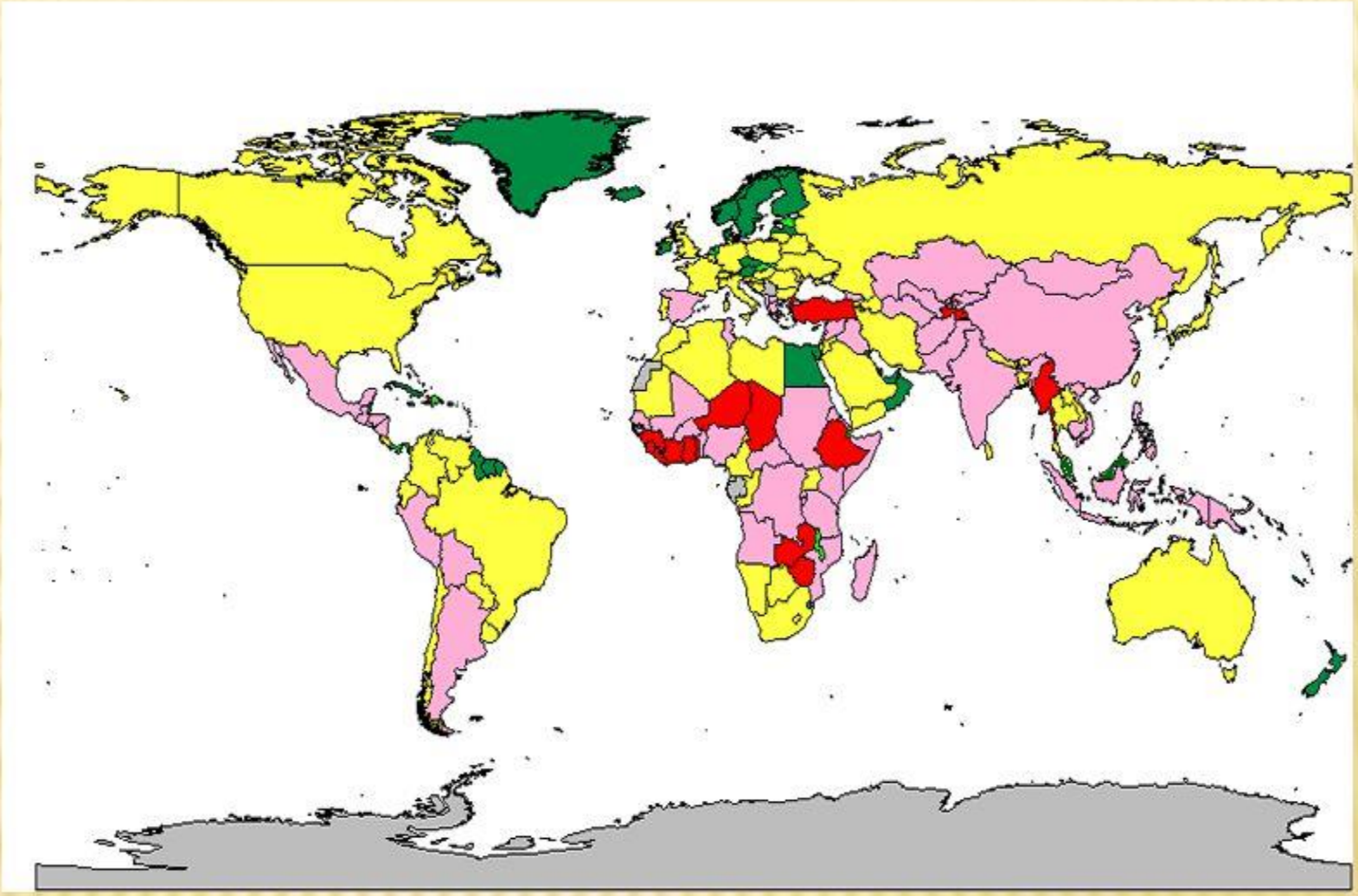
Between 2010 and 2014, 58 confirmed cases were reported via the European Surveillance System (TESSy) by EU/EEA countries, ranging from one to 32 per year.

A large proportion of these cases were reported in people who inject drugs and were part of European outbreaks affecting consumers of contaminated heroin in western and northern European countries.

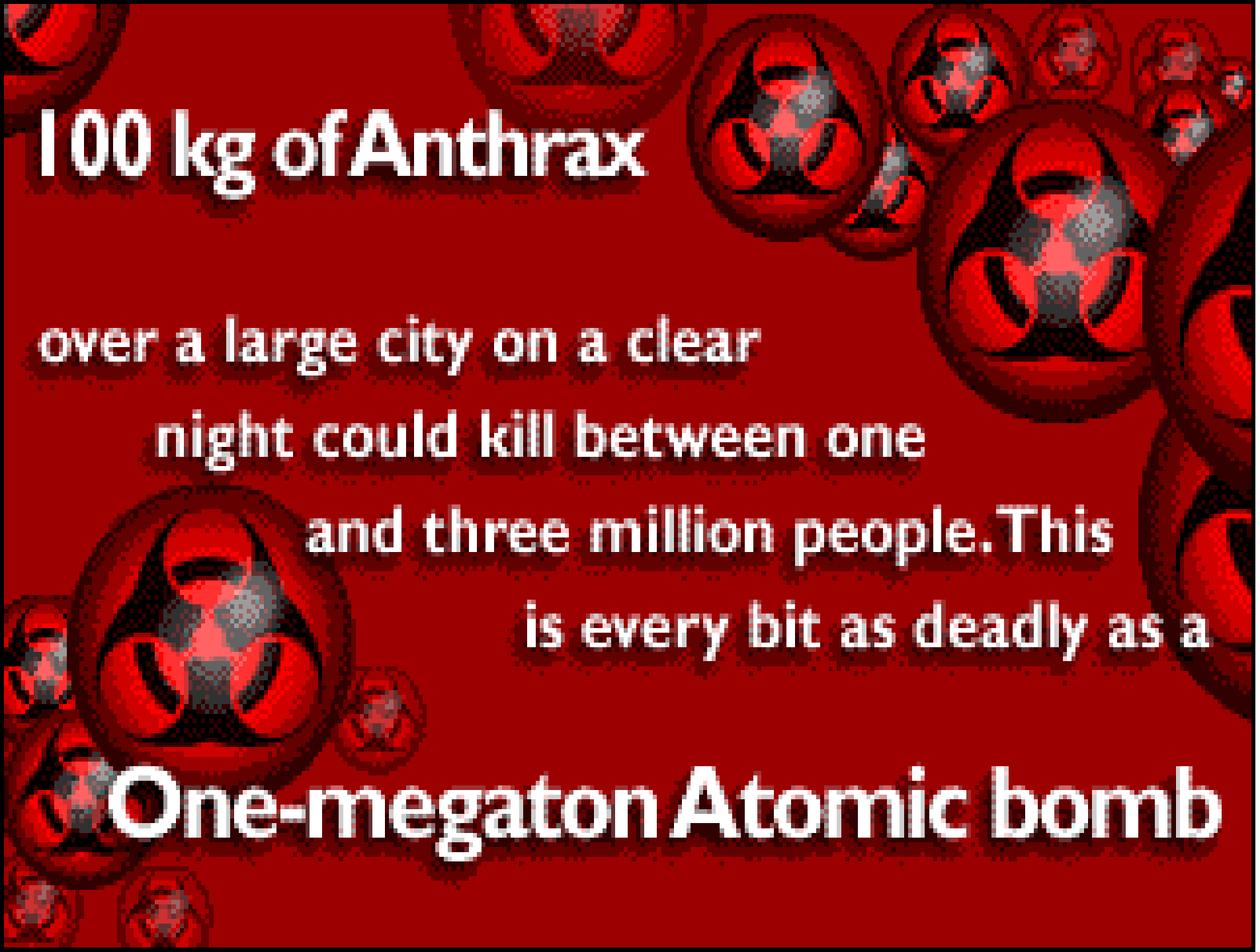
Since 2009, anthrax has emerged among heroin users in Europe, presenting a novel clinical manifestation, 'injectional anthrax', which has been attributed to contaminated heroin distributed throughout Europe.

Anthrax-contaminated heroin killed a user in Blackpool

Distribution of anthrax in the world

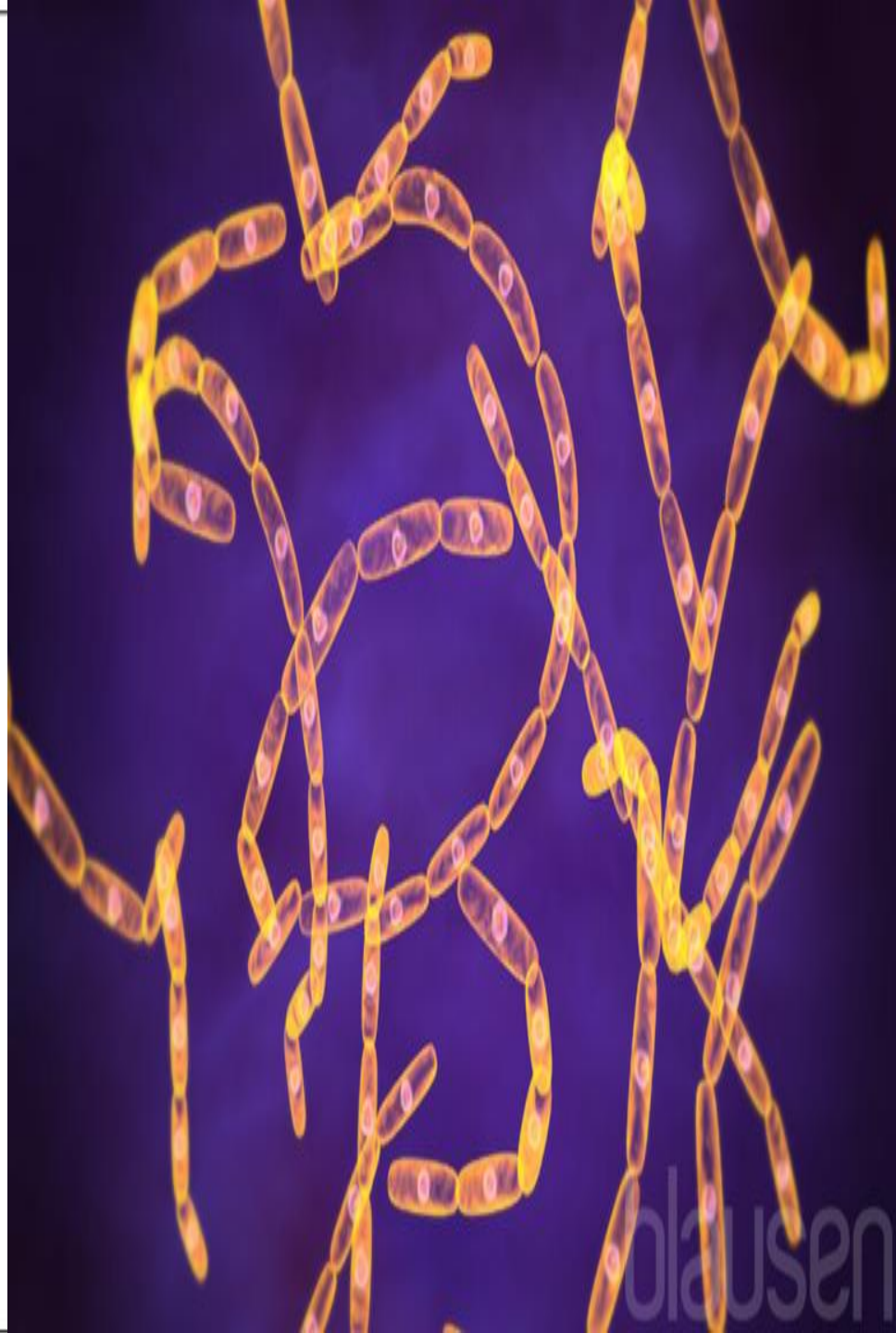


Anthrax does not spread directly from one infected animal or person to another; rather, it is spread by spores. These spores can be transported by clothing or shoes. The body of an animal that had active anthrax at the time of death can also be a source of anthrax spores. Owing to the hardiness of anthrax spores, and their ease of production *in vitro*, they are extraordinarily well suited to use (in powdered and aerosol form) as biological weapons. Such weaponization has been accomplished in the past by at least five state bioweapons programs — those of the United Kingdom, Japan, the United States, Russia, and Iraq — and has been attempted by several others.


100 kg of Anthrax
over a large city on a clear
night could kill between one
and three million people. This
is every bit as deadly as a
One-megaton Atomic bomb

Scientific classification

- Kingdom: **Bacteria**
- Phylum: **Firmicutes**
- Class: **Bacilli**
- Order: **Bacillales**
- Family: **Bacillaceae**
- Genus: ***Bacillus***
- Species: ***B. anthracis***



Bacillus anthracis -

the causative agent of anthrax, is a large (1-1.5 × 3-8 μm), gram-positive bacillus with rapid, non-hemolytic growth on blood agar that readily forms spores in the presence of oxygen.

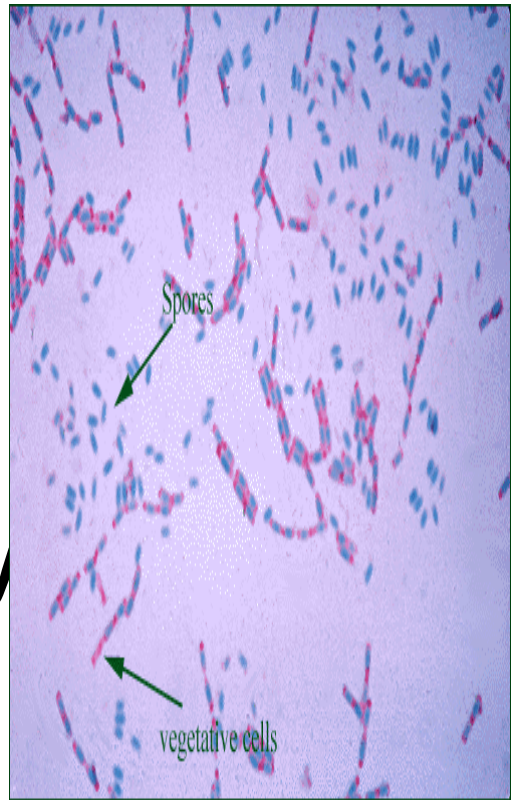
The spores are extremely hardy and may survive in certain soil conditions for decades.

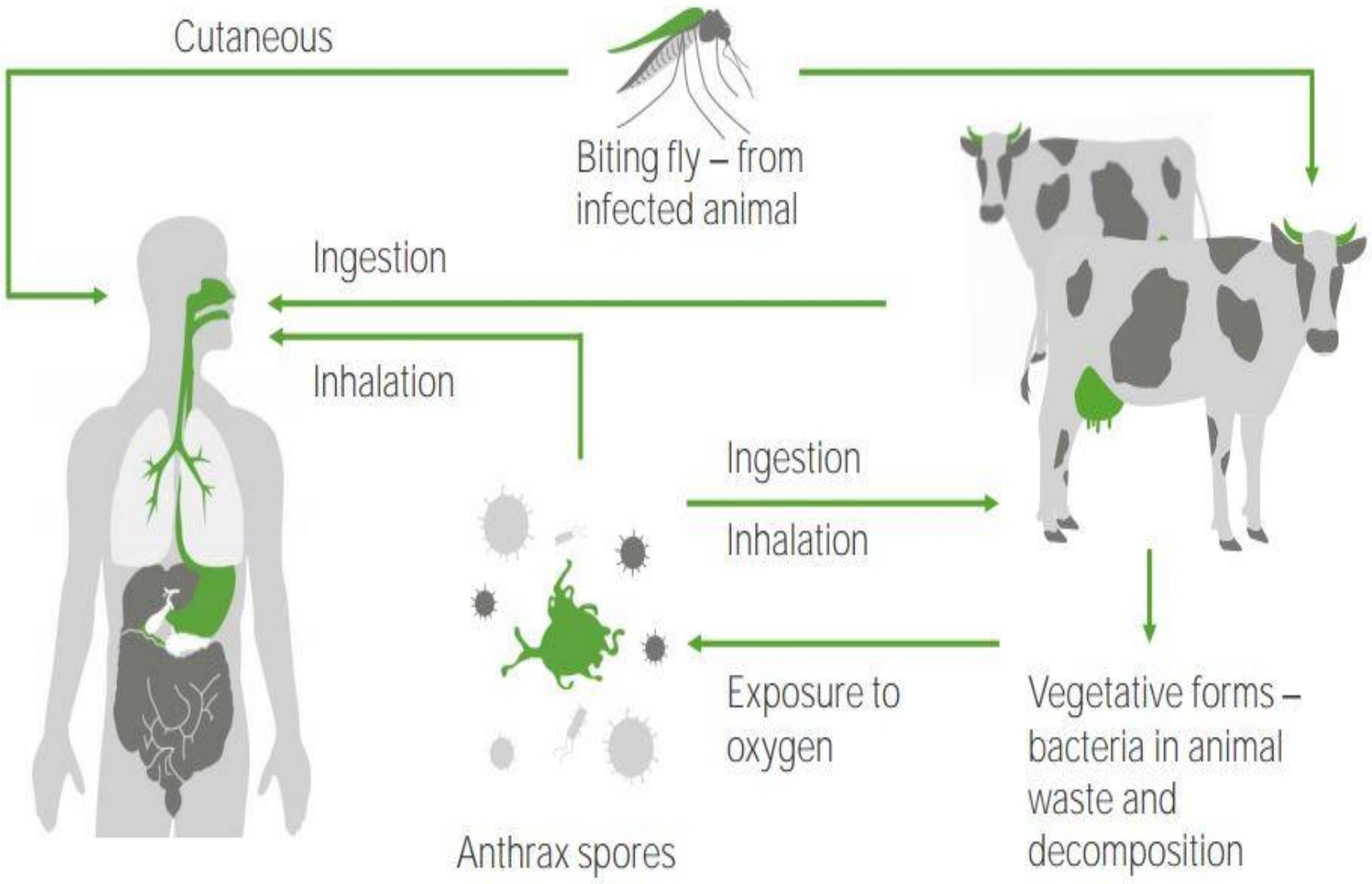
Although spores have demonstrated viability in soil for decades and even longer in bones from an archeological site, in most environments, where the organism must compete with other soil-dwelling bacteria, they typically survive only for months and rarely more than 4 years.

Like many other members of the genus *Bacillus*, *B. anthracis* can form dormant endospores (often referred to as "spores" for short, but not to be confused with fungal spores) that are able to survive in harsh conditions for decades or even centuries.

Such spores can be found on all continents, even Antarctica.

When spores are inhaled, ingested, or come into contact with a skin lesion on a host, they may become reactivated and multiply rapidly.



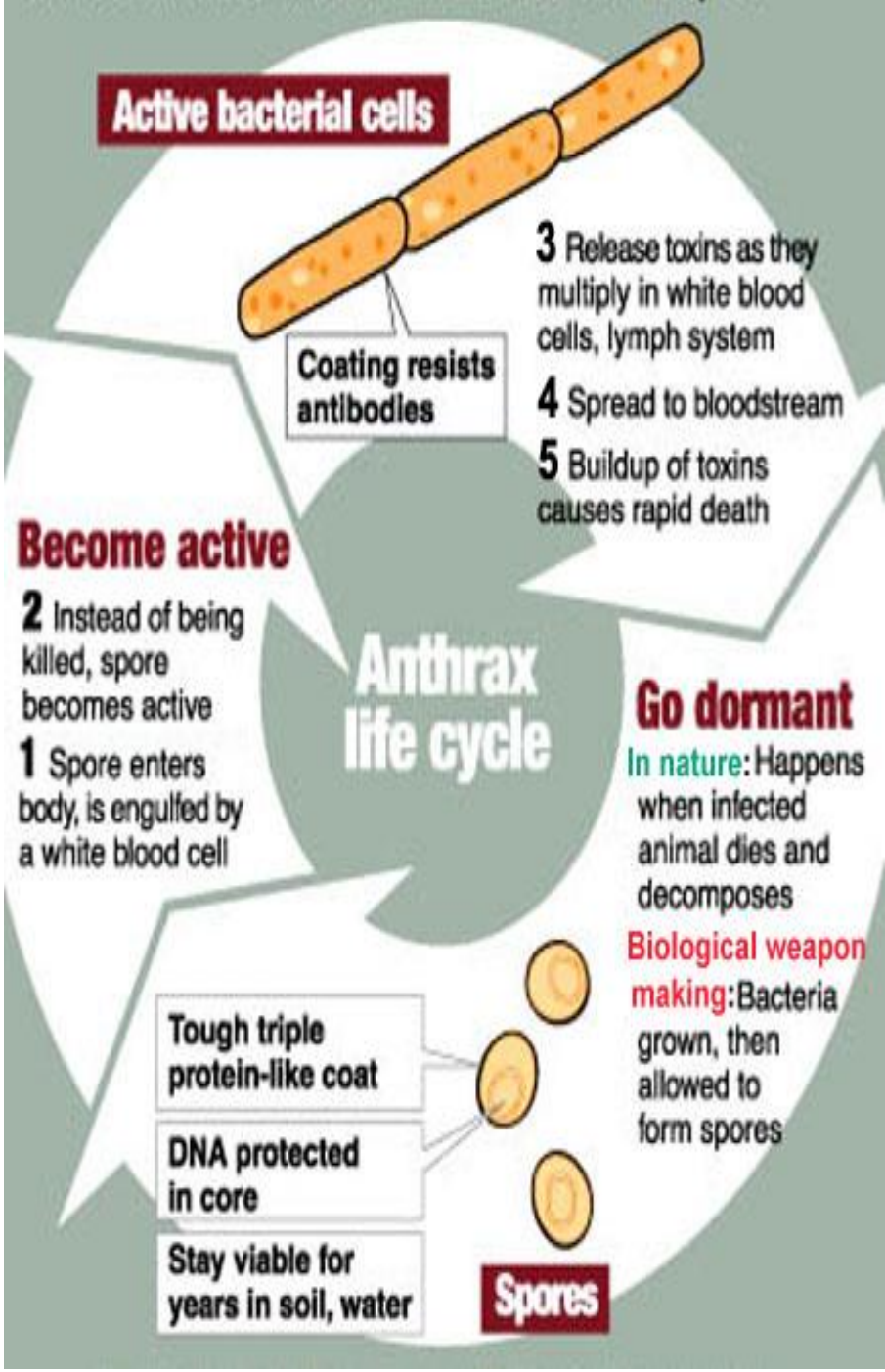

Cutaneous
Biting fly – from infected animal
Ingestion
Inhalation
Ingestion
Inhalation
Exposure to oxygen
Vegetative forms – bacteria in animal waste and decomposition
Anthrax spores

Animals are infected when they graze on fields or grain contaminated with spores or through the bites of flies that have fed on infected carcasses.

Human cases usually are associated with exposure to infected animals or contaminated animal products. Numerous products have been implicated in transmission to humans including wool, hair, bone and bone meal, meat, horns, and hides.

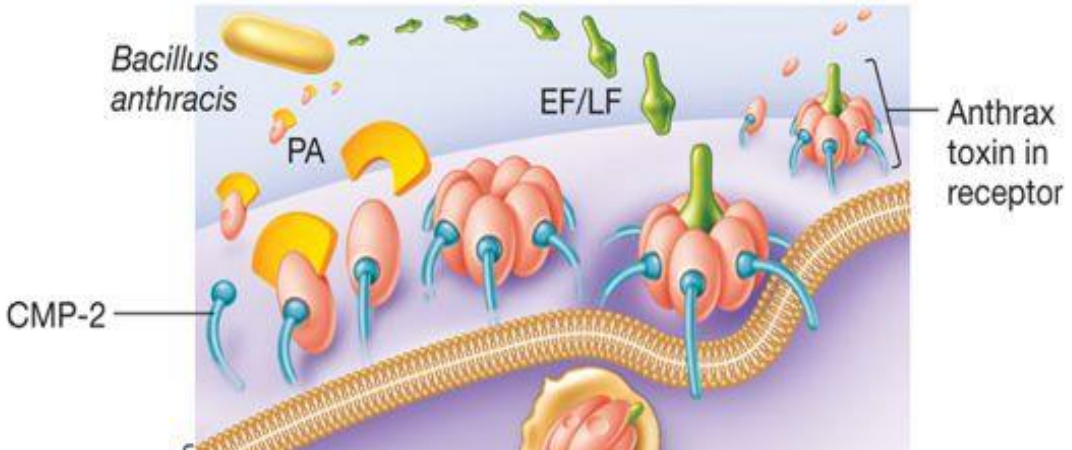
The source may not be readily evident as the animal product may have been processed, e.g., goat-skin drums, wool-based tapestries, and bone meal–based fertilizers. In developing countries, the major risk is with exposure to contaminated soil. Transmission from flies has also been documented.

The bacterium normally rests in endospore form in the soil, and can survive for decades in this state.
Herbivores are often infected whilst grazing, especially when eating rough, irritant, or spiky vegetation: the vegetation has been hypothesized to cause wounds within the gastrointestinal tract permitting entry of the bacterial endospores into the tissues, though this has not been proven.
Once ingested or placed in an open wound, the bacterium begins multiplying inside the animal or human and typically kills the host within a few days or weeks.
The endospores germinate at the site of entry into the tissues and then spread by the circulation to the lymphatics, where the bacteria multiply.



Anthrax Virulence

- *B. anthracis* evades immune system by
  - capsule which inhibits phagocytosis
  - synthesis of complex exotoxin
    - protective antigen – forms hole for entry of other toxins
    - edema factor – fluid release and edema
    - lethal factor – inhibits cytokine production
  - macrophages die, release toxic contents leading to septic shock, death



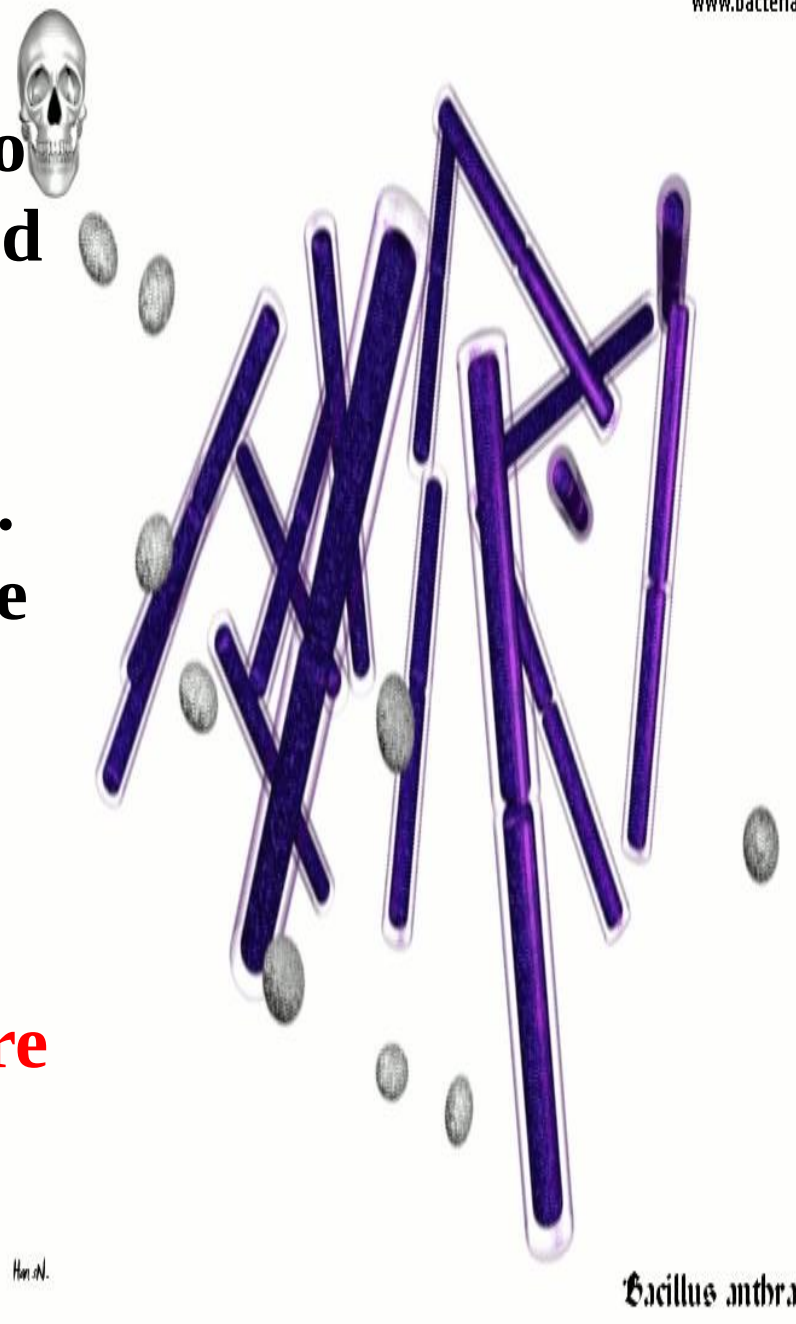
Pathogenesis.

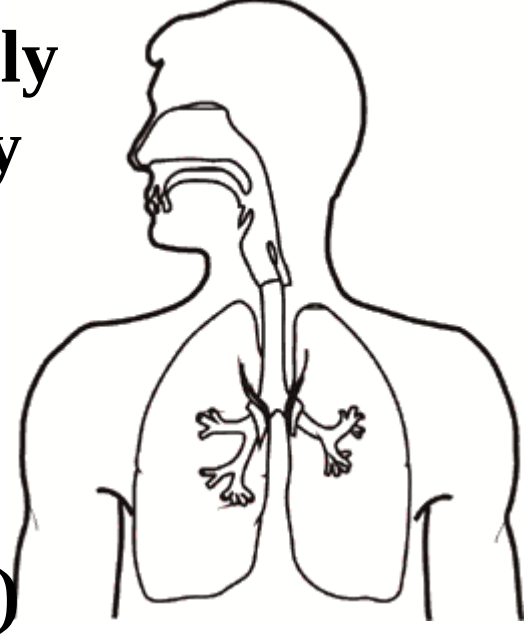
B. anthracis **spores introduced into the host are ingested at the exposed site by macrophages and then germinate into vegetative forms that produce the virulence factors.**

B. anthracis **has 3 known virulence factors:**

an antiphagocytic capsule and 2 protein toxins (known as edema factor and lethal factor).

Lethal factor and edema factor are named for the effects they induce when injected into experimental animals.





The infection of herbivores (and occasionally humans) by the inhalational route normally proceeds as follows: Once the spores are inhaled, they are transported through the air passages into the tiny air sacs (alveoli) in the lungs. The spores are then picked up by scavenger cells (macrophages) in the lungs and are transported through small vessels (lymphatics) to the lymph nodes in the central chest cavity (mediastinum). Damage caused by the anthrax spores and bacilli to the central chest cavity can cause chest pain and difficulty in breathing. Once in the lymph nodes, the spores germinate into active bacilli that multiply and eventually burst the macrophages, releasing many more bacilli into the bloodstream to be transferred to the entire body.

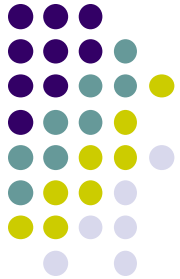
Once in the blood stream, these bacilli release three proteins named lethal factor, edema factor, and protective antigen.

The three are not toxic by themselves, but the combination is incredibly lethal to humans.-Protective antigen combines with these other two factors to form lethal toxin and edema toxin, respectively. These toxins are the primary agents of tissue destruction, bleeding, and death of the host. If antibiotics are administered too late, even if the antibiotics eradicate the bacteria, some hosts will still die of toxemia because the toxins produced by the bacilli remain in their system at lethal dose levels.

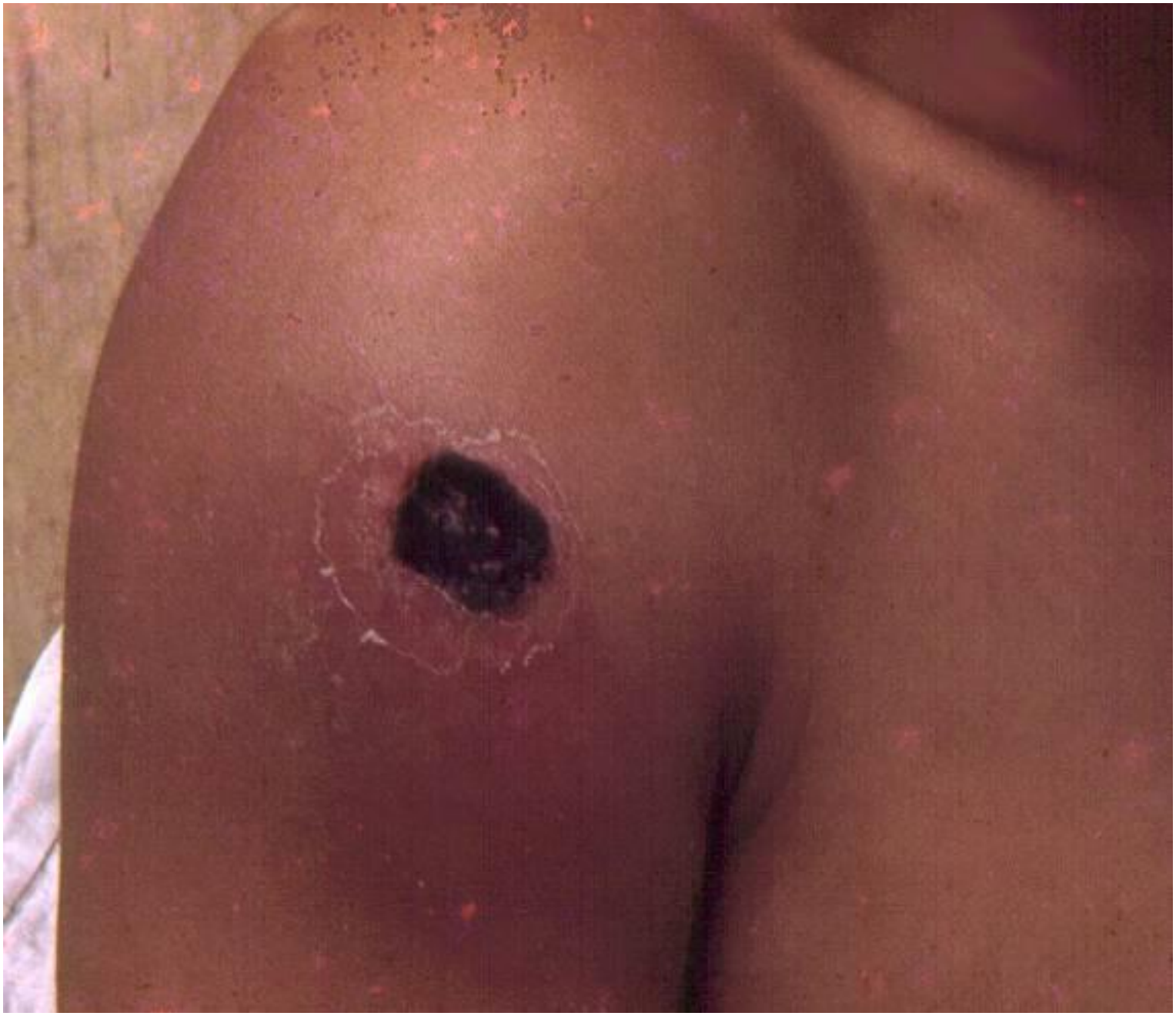
Malignant pustule

- Anthrax proper, Charbon
- In endemic areas, through contact with infected animals
- In industry, contact with hides, bones, wool, hair
- Occasionally, brushes, bone, ivory, clothes,etc.
- History in days: incubation of 3 to 4 days; then,
  - 1) Initial pimple or papule, single or multiple
  - 2) Vesicle ring around papule - initially, clear fluid
  - 3) Papule ulcerates, dries, becomes dark eschar
  - 3) Edema develops, becomes angry red
  - 3-on) No local pain, but local ganglia grow tender
  - 4) Eschar blackens, grows on vesicles, thickens

Site of Malignant pustule



- **Head: usually no complication**
- **Face: severe, superinfection; gangrene near eye**
- **Neck, breast or chest wall: massive edema, over thorax and sometimes involving scrotum**
- **Shoulders, arms: may be multiple, small lesions**
- **Forearms, fingers: atypical on palms**
- **General symptoms, fever, chills, depend on site.**
- **Weakness, hypotension are danger signs.**



Black eschar. Redness remains

Classification and clinical features

The three primary forms of anthrax are dependent on the route of exposure:

- **cutaneous,**
- **inhalational (pulmonary)**
- **gastrointestinal**

Bacteremia secondary to any of the primary forms of anthrax may lead to seeding of any site, including the central nervous system with the resulting hemorrhagic meningoencephalitis.

Three forms of Anthrax

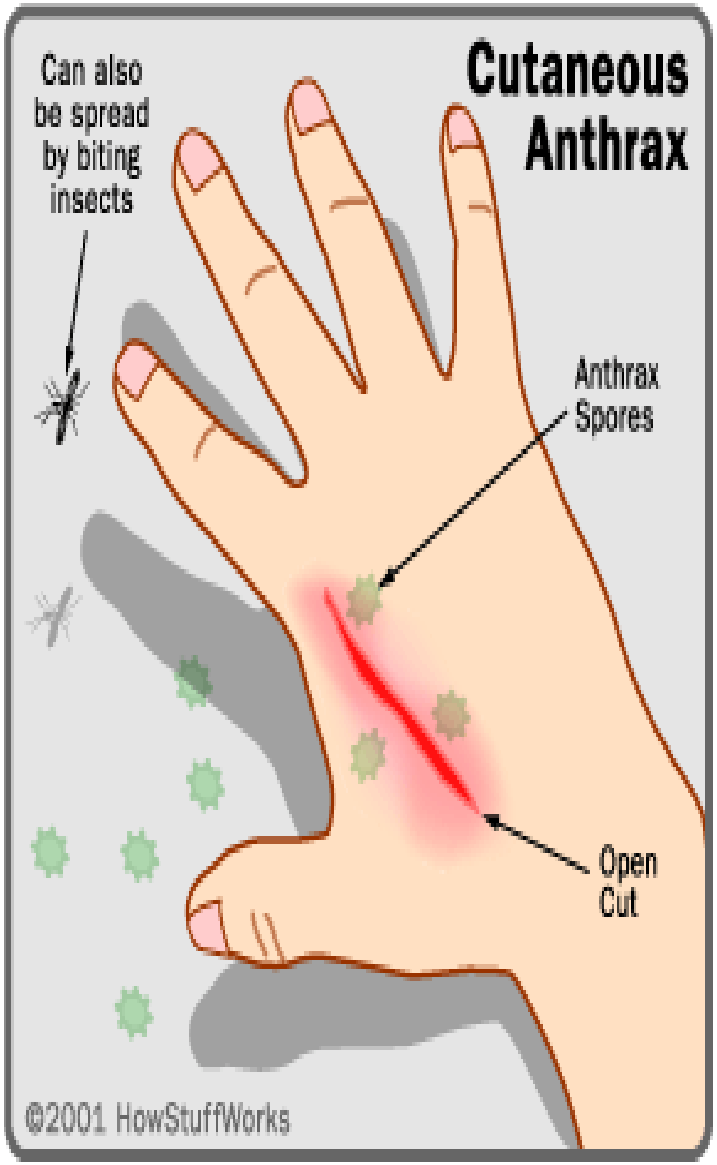
- **Cutaneous** anthrax
  - Skin
  - Most common
  - Spores enter to skin through small lesions
- **Inhalation** anthrax
  - Spores are inhaled
- **Gastrointestinal (GI)** anthrax
  - Spores are ingested
  - Oral-pharyngeal and abdominal

Cutaneous anthrax

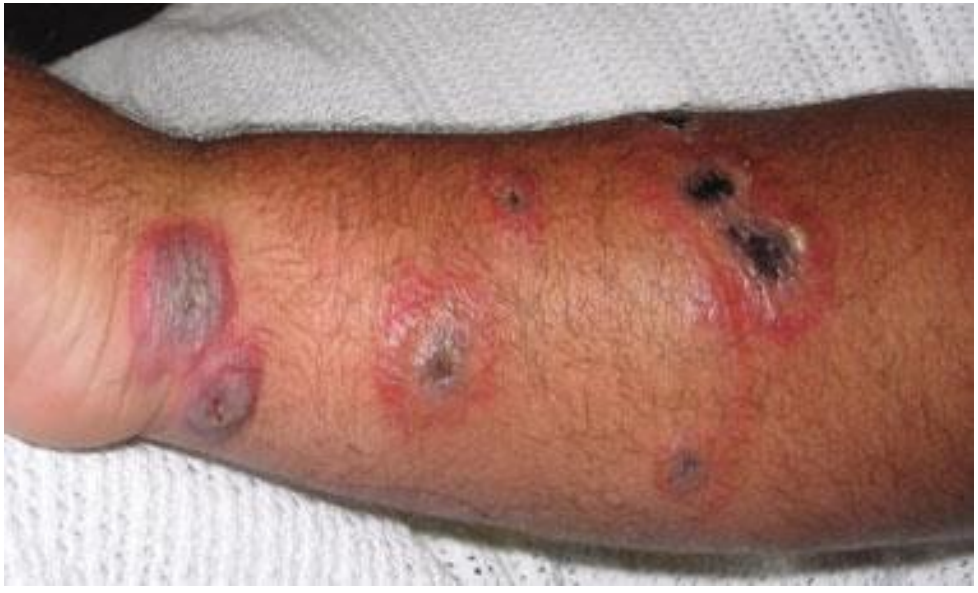
Naturally occurring anthrax infections in humans are, in more than 95% of cases, cutaneous disease, also known as Hide porter's disease.

After the introduction of anthrax spores into the skin, often with just trivial trauma, there is an incubation period of 1-10 (more commonly 3-5) days, leading to the development of a small, pruritic papule at the inoculation site. The majority of lesions are on exposed areas of the head, neck, and extremities.

A day or two after the formation of the papule,vesicles containing a clear to serosanguineous fluid form around the lesion and may become quite large, 1-2 cm in diameter. There is no purulence, and the lesions remain painless. The vesicles are thin roofed and easily rupture, leading to formation of a dark brown, turning to black, eschar at the base of a shallow ulcer.

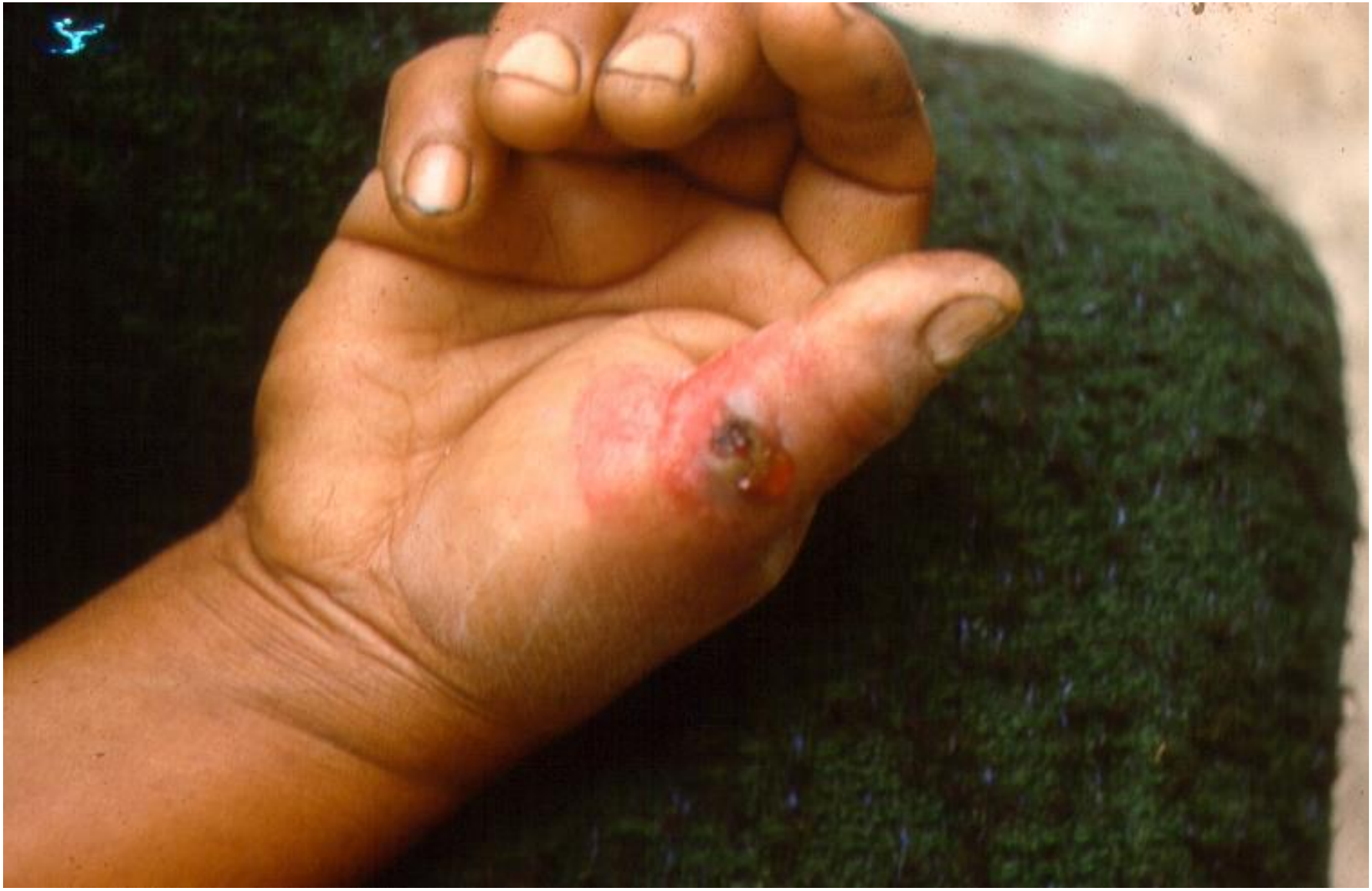


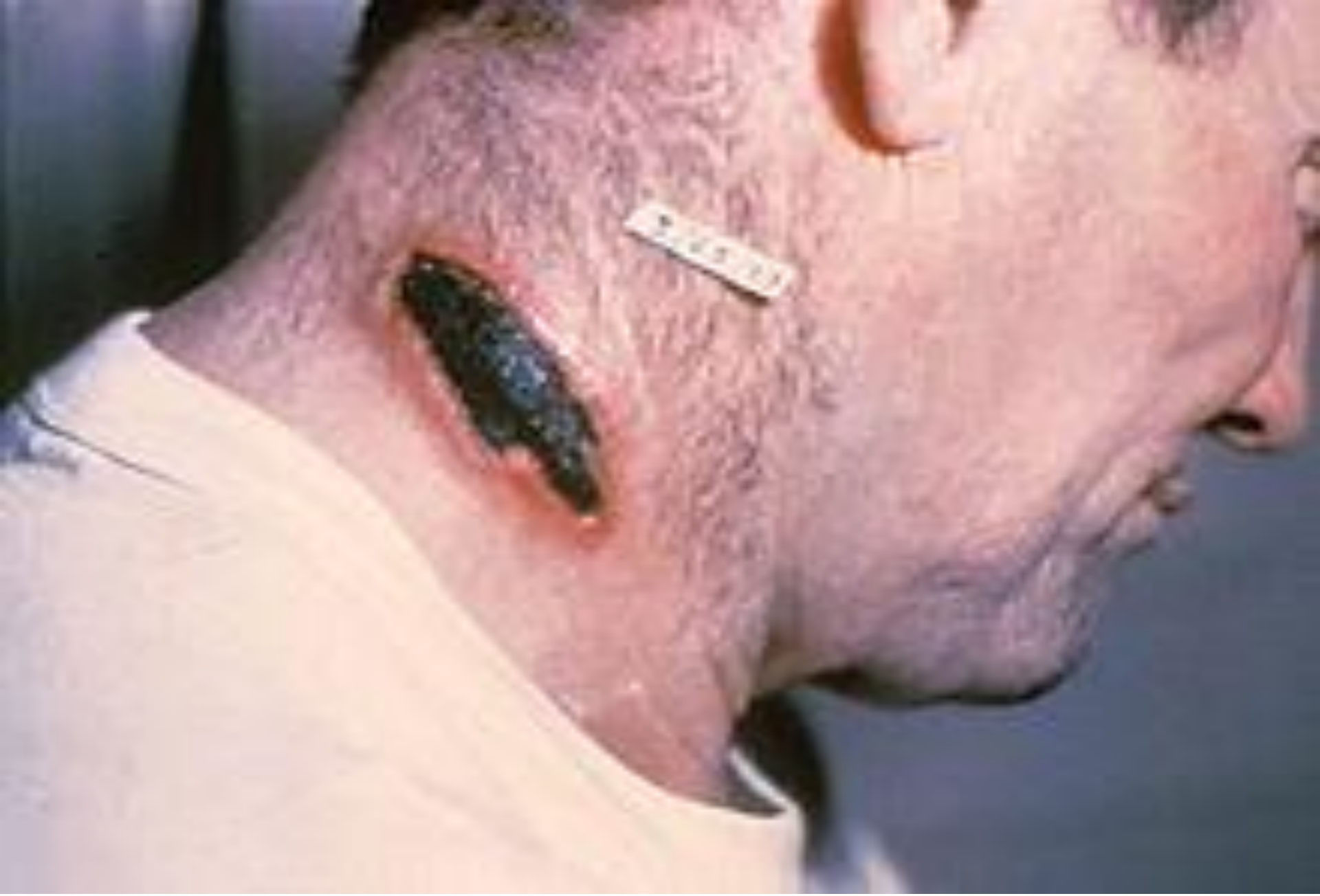
The ulcer is typically surrounded by an area of induration, and in some cases non-pitting edema may be marked.
In uncomplicated cases lesions slowly heal over a period of 1-3 weeks and the eschar loosens and falls off, typically without leaving a scar. Antibiotics do not affect the evolution of the skin lesions. In most cases, patients report associated headache, malaise. and low-grade fever even if the infection does not progress to bacteremia. Cutaneous anthrax is rarely fatal if treated, because the infection area is limited to the skin, preventing the lethal factor, edema factor, and protective antigen from entering and destroying a vital organ.
Without treatment, about 20% of cutaneous skin infection cases progress to toxemia and death.



Cutaneous anthrax-symptoms

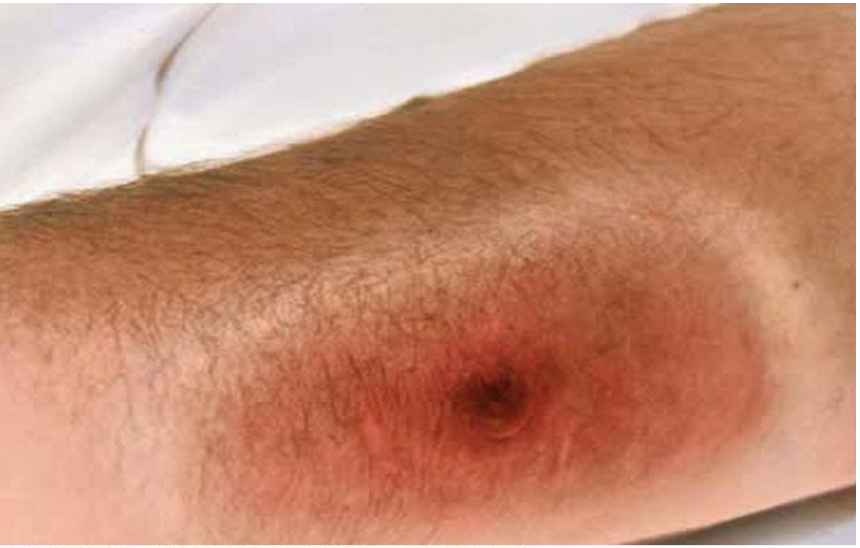
- Itching of skin
- Lesion - progression
  - spider bite-like pustule
  - Vesicle (blisters)
  - black lesion - eschar
- Lesion – location
  - Head
  - Arms
  - Hands
- Moderate to severe swelling around lesion
  - Lymph nodes
  - Secondary infection
- Fatalities can occur

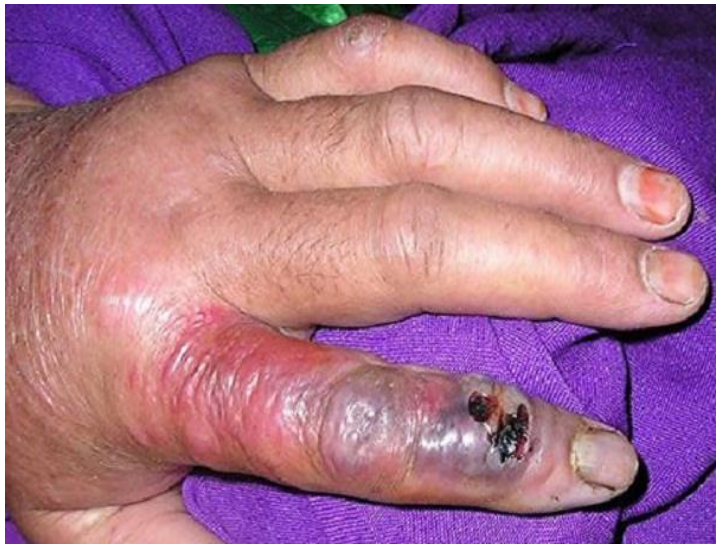


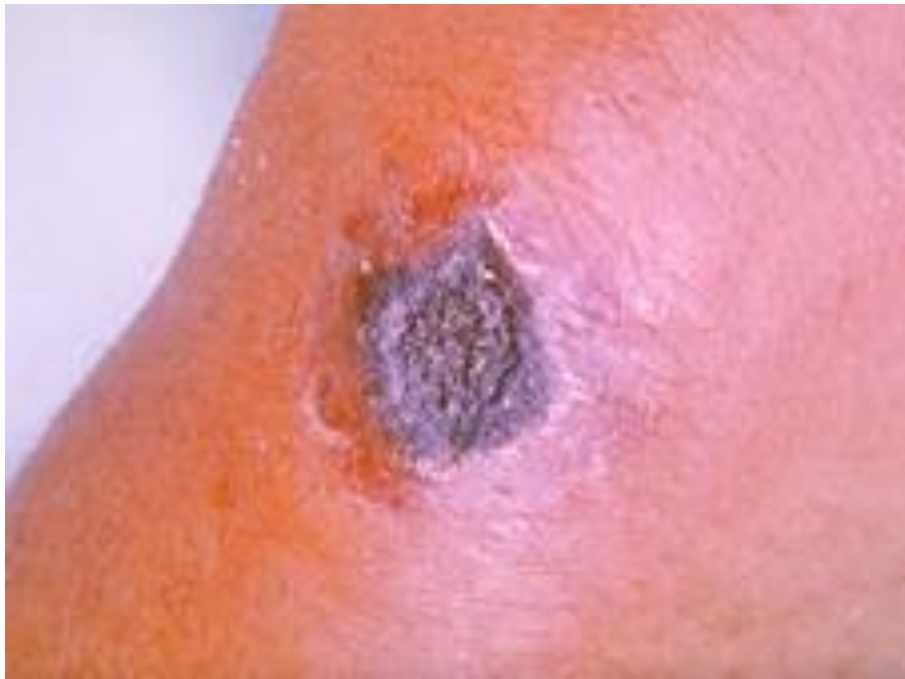


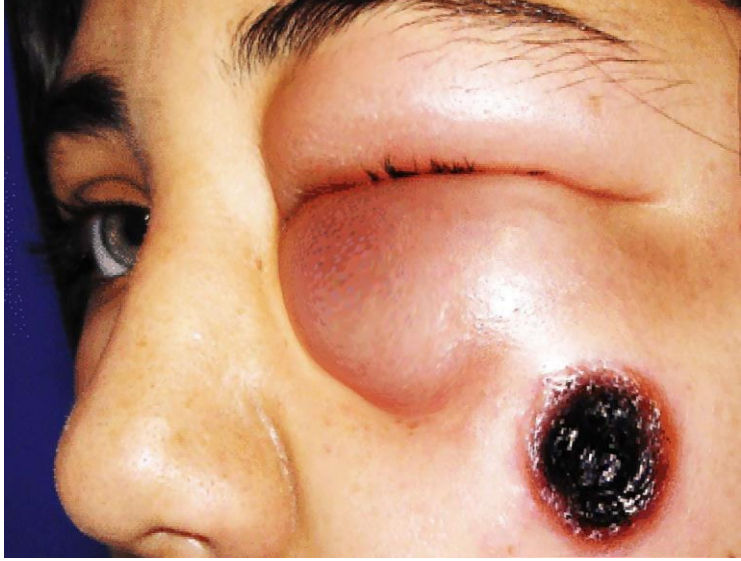
Skin anthrax lesion on the neck

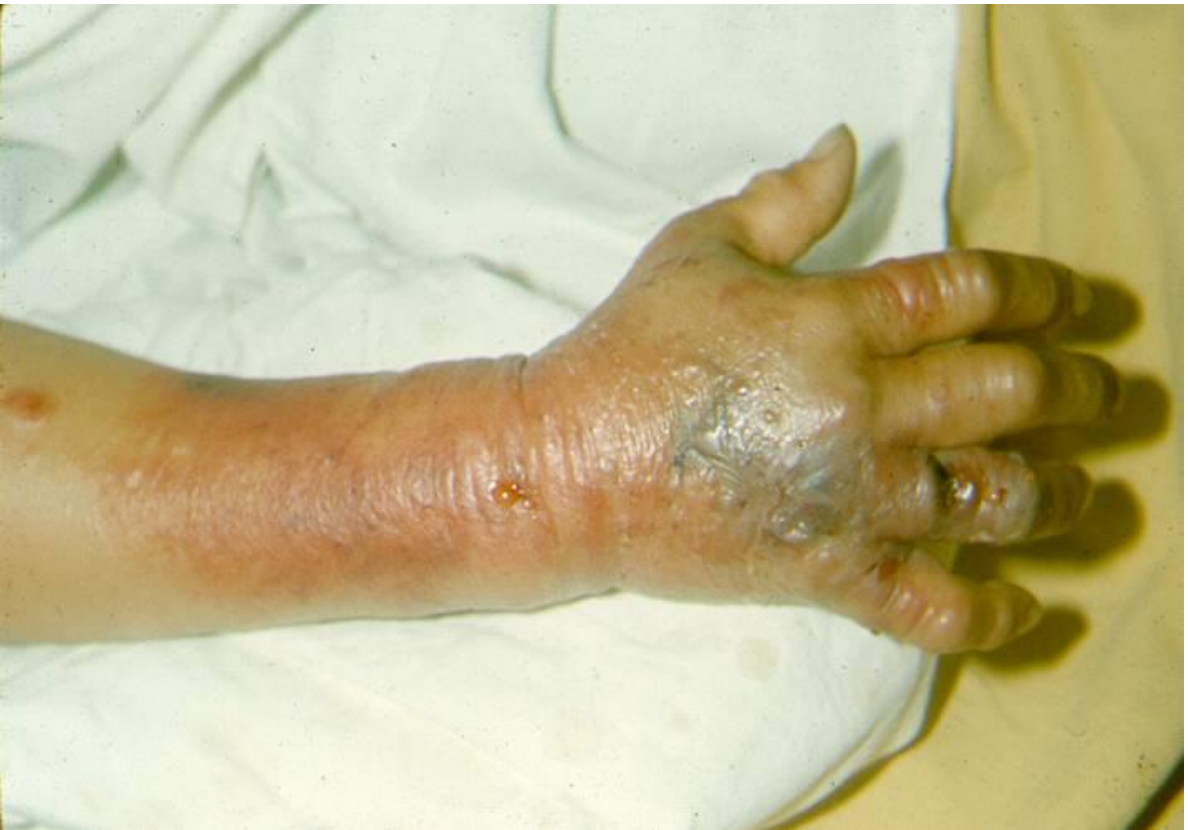
A large sore with a black center, caused by cutaneous anthrax



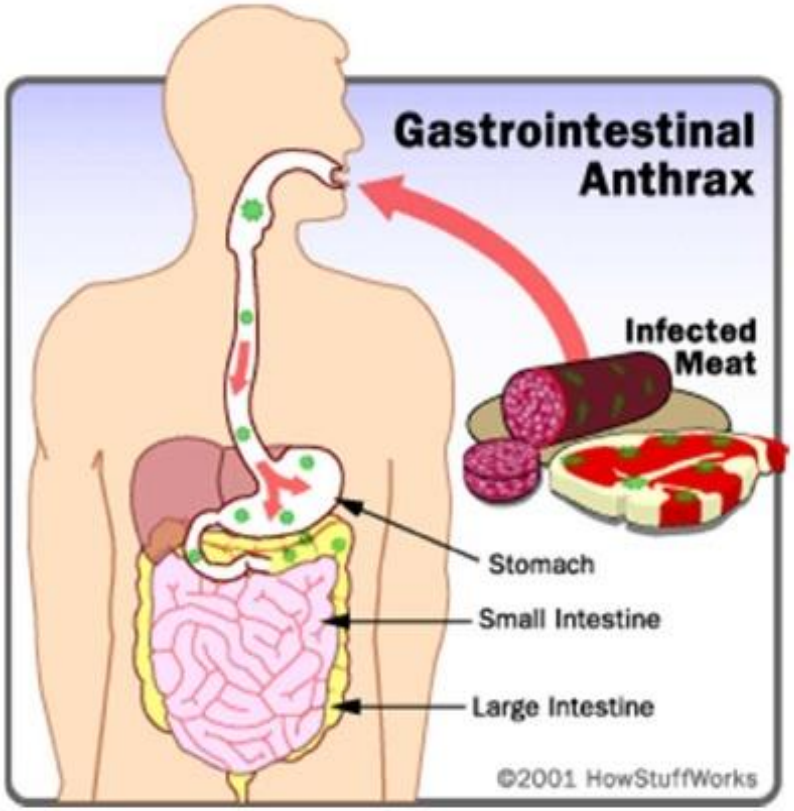






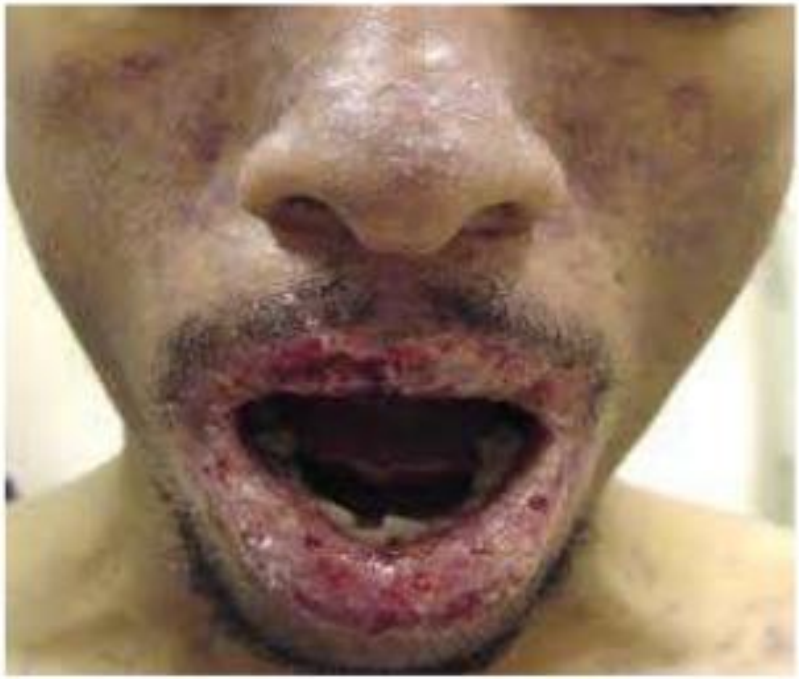


Gastrointestinal Anthrax



- GI anthrax may follow after the consumption of contaminated, poorly cooked meat.
- There are 2 different forms of GI anthrax:
  1) Oral-pharyngeal
  2) Abdominal
- Abdominal anthrax is more common than the oral-pharyngeal form.

Gastrointestinal anthrax :



- Abdominal pain
- Bloody diarrhea
- Diarrhea
- Fever
- Mouth sores
- Nausea and vomiting
  (vomit contain blood)
- acute inflammation of the intestinal tract, and loss of appetite

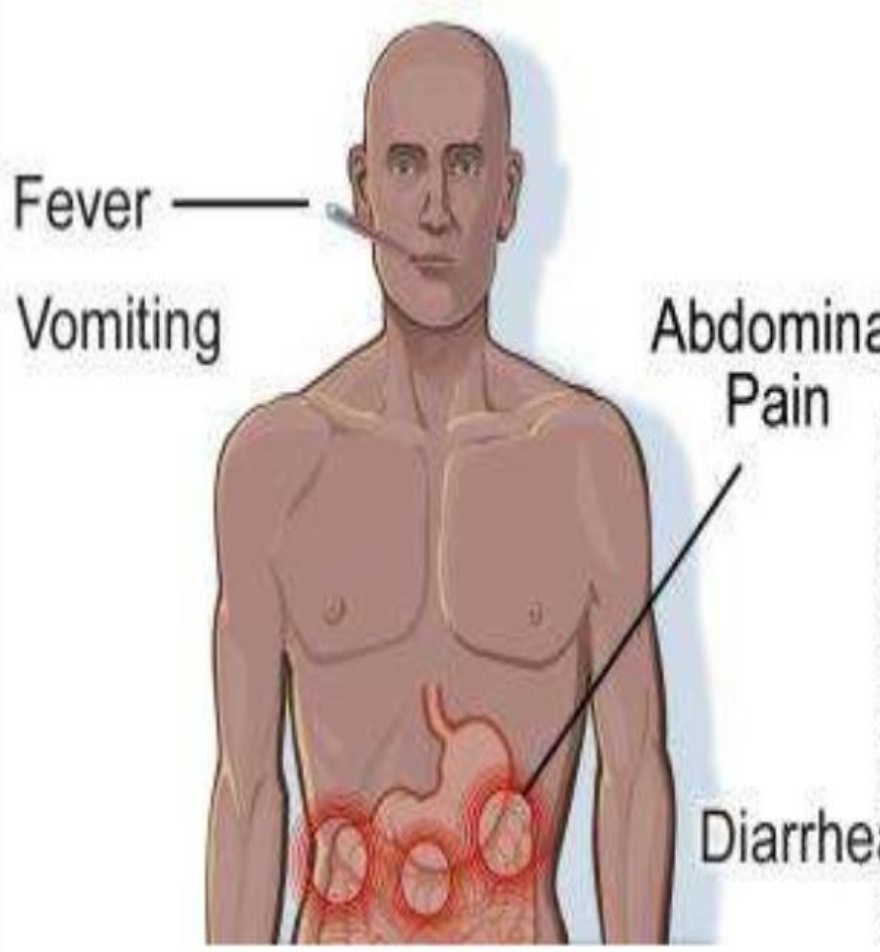
Gastrointestinal

Typically incubation period lasts 1-5 days.
Oropharyngeal anthrax demonstrates symptoms and signs at the site of inoculation in the mouth or pharynx of swelling, severe pharyngitis, dysphagia, odynophagia, fever, and in some cases, respiratory distress due to marked edema and lymphadenitis.
An ulcer may be observed in the mouth, the pharynx, the tonsil, or the tongue.
Pseudomembranes often form over the ulcer after the first week, bringing diphtheria into the differential diagnosis.
Although significant neck swelling is seen in all oropharyngeal cases, massive facial and neck edema is occasionally seen.

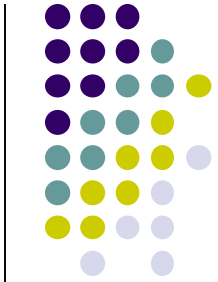
Intestinal disease occurs with infection of the stomach or bowel wall.

The patient presents with nausea, vomiting, and fever, followed by severe abdominal pain often manifested as a surgical abdomen.

Many cases will be associated with hematemesis, massive ascites, and bloody diarrhea.

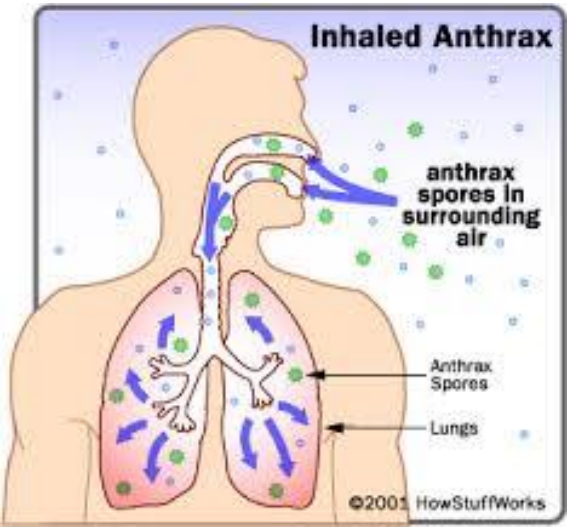


Inhalational anthrax

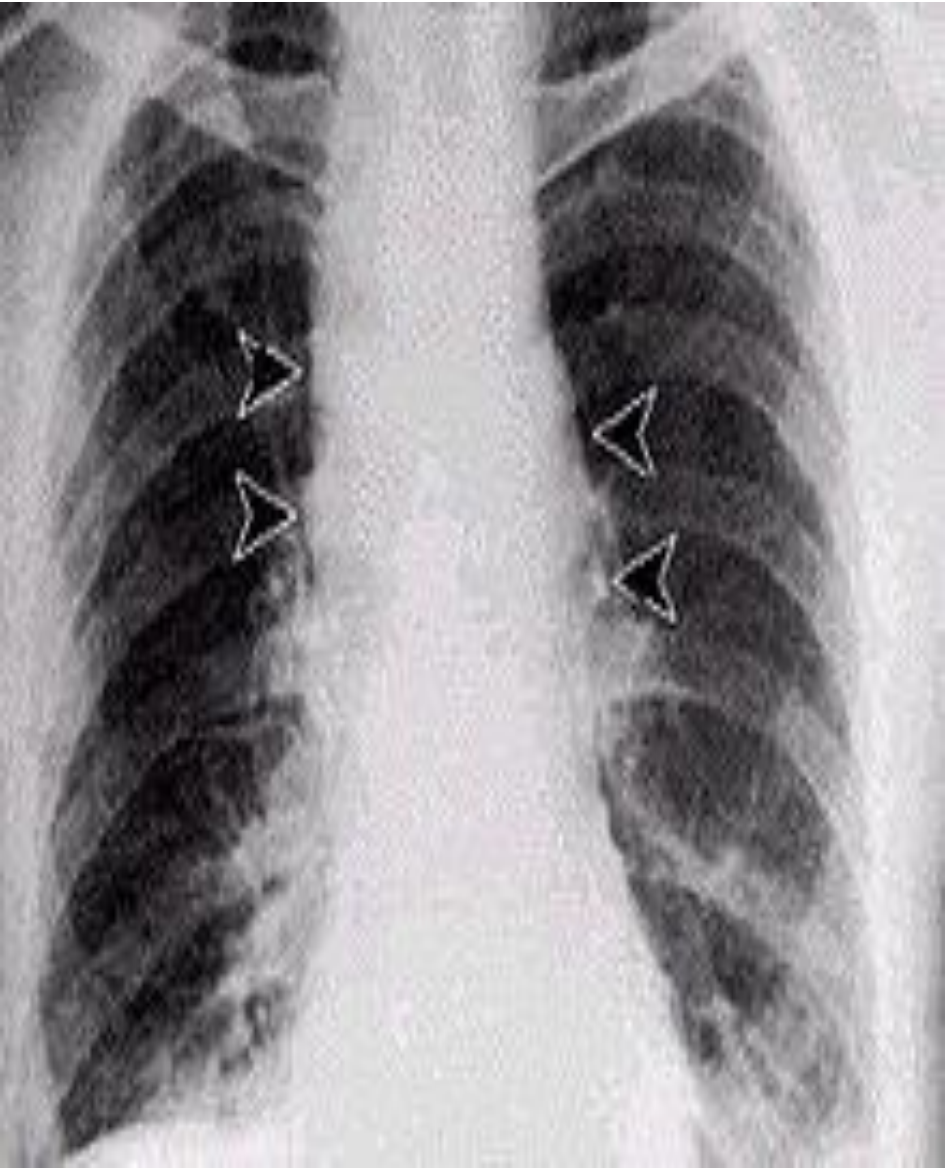


- **Initial symptoms**
  - **Mild, non-specific (e.g., "flu-like")**
  - **Fever**
  - **Malaise**
  - **Mild cough, chest pain**
- **Acute symptoms**
  - **Respiratory distress**
  - **Shock**
  - **Mediastinal widening on chest X-ray**
- **Fatalities can occur (80-90%)**

Pulmonary



Respiratory infection in humans is relatively rare and initially presents with cold or flu-like symptoms for several days, followed by pneumonia and severe (and often fatal) respiratory collapse. Historical mortality rates were over 85%, but, when treated early (seen in the 2001 anthrax attacks), observed case fatality rate dropped to 45%.

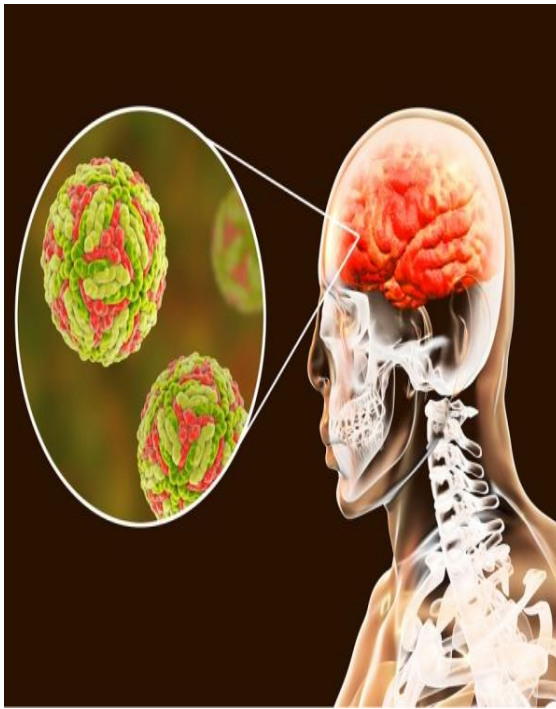


Distinguishing pulmonary anthrax from more common causes of respiratory illness is essential to avoiding delays in diagnosis and thereby improving outcomes. An algorithm for this purpose has been developed.

Inhalational anthrax, mediastinal widening

Anthrax Meningitis

- **Usually a complication of anthrax septicemia.**
- **Subarachnoid haemorrhage is a common feature**
- **Very often fatal**



Meningitis is an uncommon sequel of cutaneous anthrax but a frequent complication of the rarer inhalational or gastrointestinal disease, occurring in up to 50% of cases of the former. The hallmark of anthrax meningitis is its hemorrhagic component associated with large gram-positive bacilli. CNS involvement may also include parenchymal brain hemorrhage and subarachnoid hemorrhage possibly owing to a diffuse cerebral arteritis or necrotizing vasculitis. As might be expected from anthrax infections in other sites, cerebral edema may also be prominent.

Initial symptoms include abrupt onset of severe headache, malaise, fever, chills, nausea, and vomiting. Meningeal signs such as nuchal rigidity may be absent early in the course but develop as the patient deteriorates. Seizures, delirium, and coma usually follow within hours. Death was inevitable in the preantibiotic era but is currently estimated at approximately 95% of cases

Anthrax meningitis: Subarachnoid Haemorrhage

Anthrax:
Diagnosis

Inhalational

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

Diagnosis

Various techniques are used for the direct identification of *B. anthracis* in clinical material.

Firstly, specimens may be Gram stained. *Bacillus* spp. are quite large in size (3 to 4 μm long), they grow in long chains, and they stain Gram-positive. To confirm the organism is *B. anthracis*, rapid diagnostic techniques such as polymerase chain reaction-based assays and immunofluorescence microscopy may be used.

All *Bacillus* species grow well on 5% sheep blood agar and other routine culture media. Polymyxin-lysozyme-EDTA-thallous acetate can be used to isolate *B. anthracis* from contaminated specimens, and bicarbonate agar is used as an identification method to induce capsule formation.

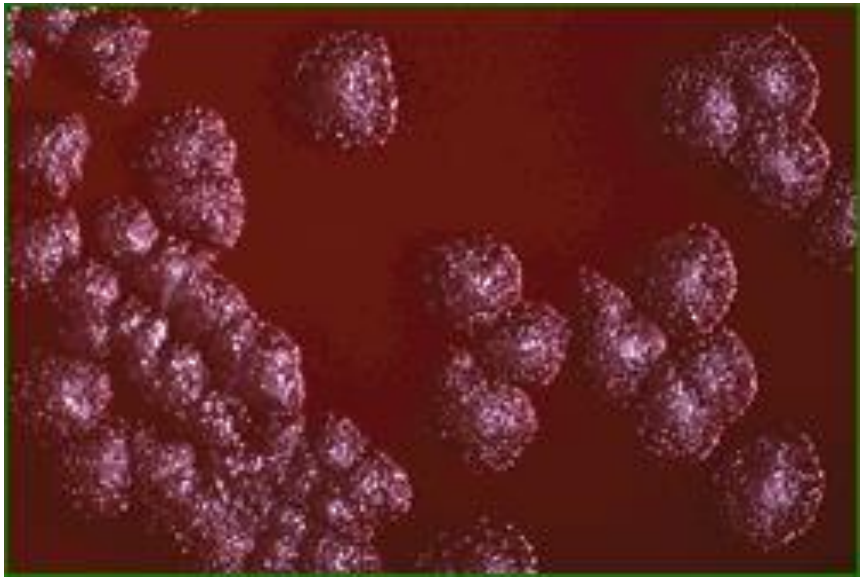
Tests for anthrax

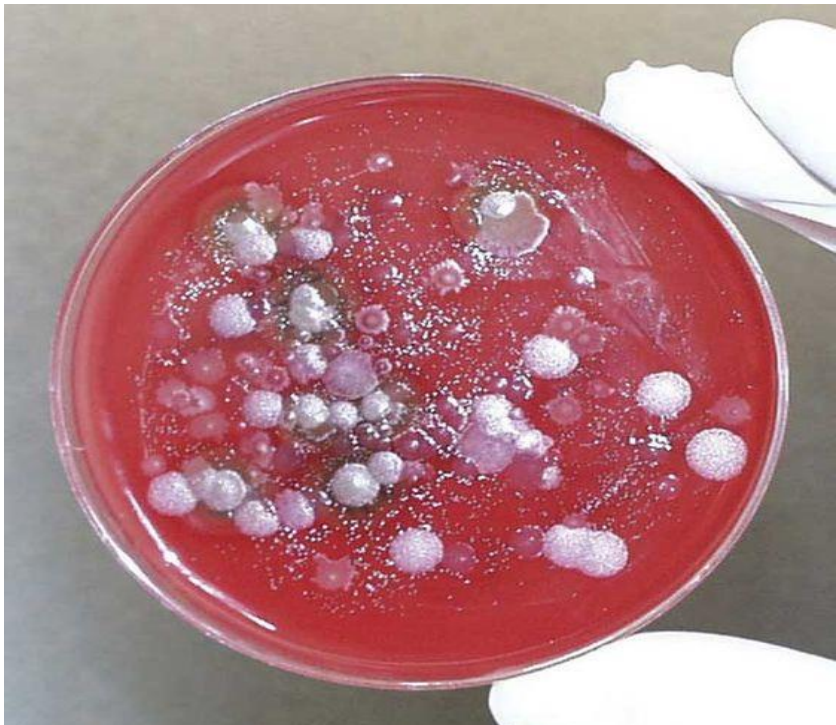
- Nasal swabs – epidemiological tool
  - Not diagnostic for disease
  - Determines “Zone(s) of Exposure”
- Cultures
  - Blood
  - Exudates
- Antibody tests – antibodies to anthrax
- Polymerase Chain Reaction (PCR)
  - DNA amplification
- Environmental tests
  - Swabs
  - Wipes

Tests for anthrax

- **Antibody tests**
  - **Quick antibody test strips**
  - **ELISA test (lab)**
  - **Blood test**
- **Microscopic analysis**
- **Bacterial culture**
- **DNA test – PCR**
- **Environmental samples**
  - **Swabs**
  - **Wipes**

B. anthracis on Blood Agar





The differential diagnosis

of cutaneous anthrax includes tularemia, scrub typhus, rat bite fever, blastomycosis, ringworm acquired from animals, and mycobacterial infection with *Mycobacterium marinum*. Gastrointestinal anthrax should be differentiated with Shigella, Yersinia or Campylobacter infections, pulmonary anthrax – wide array of bacterial and viral processes.

Treatment

- Penicillin continues to be the treatment of choice.
- iv treatment was adopted to provide enough.
- Do not incise lesions.
- Eschar is not dangerous after treatment.
- The patient must remain hospitalized until fully cured.

Treatment

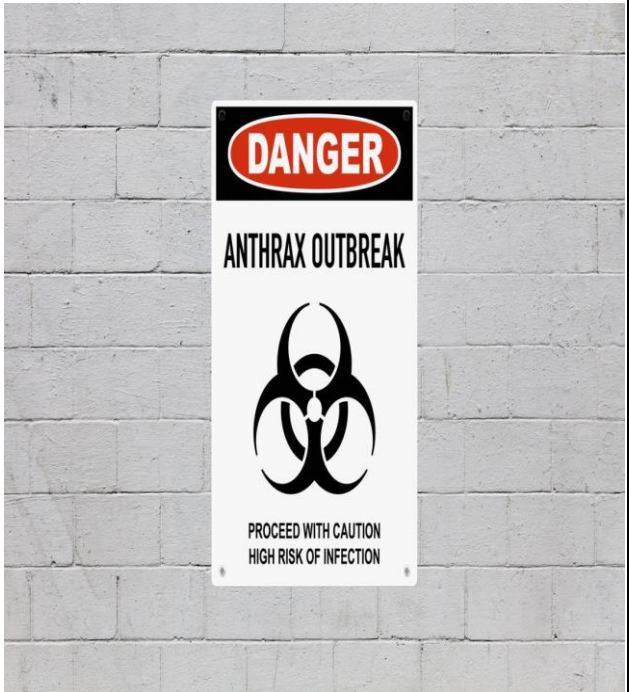
- All forms of anthrax
  - Floroquinolones-oral (Ciprofloxacin)*
  - Doxycycline-oral**
    - 100 mg BID for adults
    - 1mg/pound BID for children (less than 100 pounds)
  - Penicillin
  - Others available

Monoclonal antibodies

On 14 December 2012, the US Food and Drug Administration approved raxibacumab injection to treat inhalational anthrax. Raxibacumab is a monoclonal antibody that neutralizes toxins produced by *B. anthracis* that can cause massive and irreversible tissue injury and death. A monoclonal antibody is a protein that closely resembles a human antibody, and identifies and neutralizes foreign material such as bacteria and viruses.

Prevention

- **Industrial protection. Gloves, masks, disinfection of materials prior to handling. Mostly impractical!**
- **Information, charts, education for awareness.**
- **Reporting of sudden illness in risk areas, lesions.**



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**

Vaccines

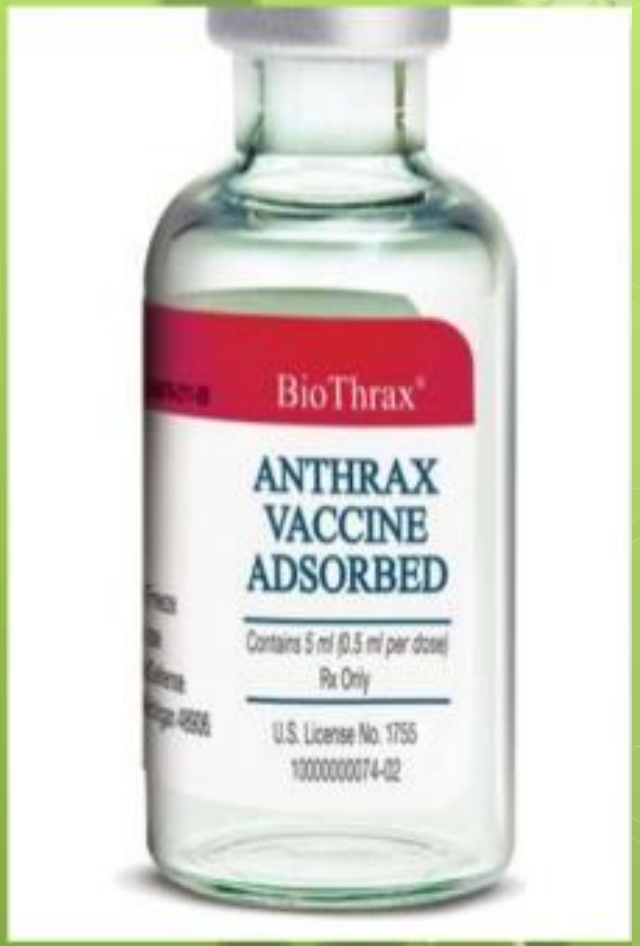
Vaccines against anthrax for use in livestock and humans have had a prominent place in the history of medicine, from Pasteur's pioneering 19th-century work with cattle (the second effective vaccine ever) to the controversial 20th century use of a modern product (BioThrax) to protect American troops against the use of anthrax in biological warfare. Human anthrax vaccines were developed by the Soviet Union in the late 1930s and in the US and UK in the 1950s. The current FDA-approved US vaccine was formulated in the 1960s.

Currently administered human anthrax vaccines include acellular (United States) and live spore (Russia) varieties. All currently used anthrax vaccines show considerable local and general reactogenicity (erythema, induration, soreness, fever) and serious adverse reactions occur in about 1% of recipients.-The American product, BioThrax, is licensed by the FDA and was formerly administered in a six-dose primary series at 0, 2, 4 weeks and 6, 12, 18 months, with annual boosters to maintain immunity. In 2008, the FDA approved omitting the week-2 dose, resulting in the currently recommended five-dose series.-New second-generation vaccines currently being researched include recombinant live vacciness and recombinant subunit vaccines.

ANTHRAX VACCINES

Vaccination Schedule

- ✓ Initial doses at 0, 2, and 4 weeks.
- ✓ Additional doses at 6, 12, and 18 months.
- ✓ Annual booster doses thereafter.
- ✓ Alternative schedules being investigated.



Prophylaxis

If a person is suspected as having died from anthrax, every precaution should be taken to avoid skin contact with the potentially contaminated body and fluids exuded through natural body openings. The body should be put in strict quarantine. A blood sample should then be collected and sealed in a container and analyzed in an approved laboratory to ascertain if anthrax is the cause of death. Then, the body should be incinerated. Microscopic visualization of the encapsulated bacilli, usually in very large numbers, in a blood smear stained with polychrome methylene blue (McFadyean stain) is fully diagnostic, though culture of the organism is still the gold standard for diagnosis. Full isolation of the body is important to prevent possible contamination of others.

Protective, impermeable clothing and equipment such as rubber gloves, rubber apron, and rubber boots with no perforations should be used when handling the body. No skin, especially if it has any wounds or scratches, should be exposed. Disposable personal protective equipment is preferable, but if not available, decontamination can be achieved by autoclaving. Disposable personal protective equipment and filters should be autoclaved, and/or burned and buried. *B. anthracis* bacillii range from 0.5–5.0 μm in size. Anyone working with anthrax in a suspected or confirmed victim should wear respiratory equipment capable of filtering this size of particle or smaller.