



MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
DEPARTMENT OF INFECTIOUS DISEASES, EPIDEMIOLOGY,
PARASITOLOGY AND TROPICAL MEDICINE

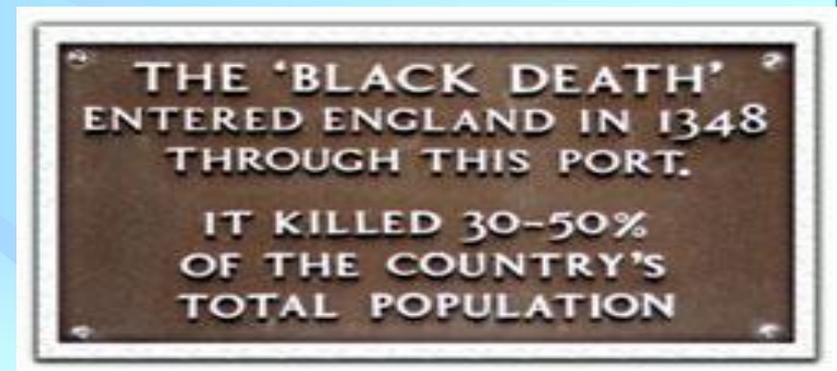
Lecture № 15-a

PLAGUE
LEPROSY

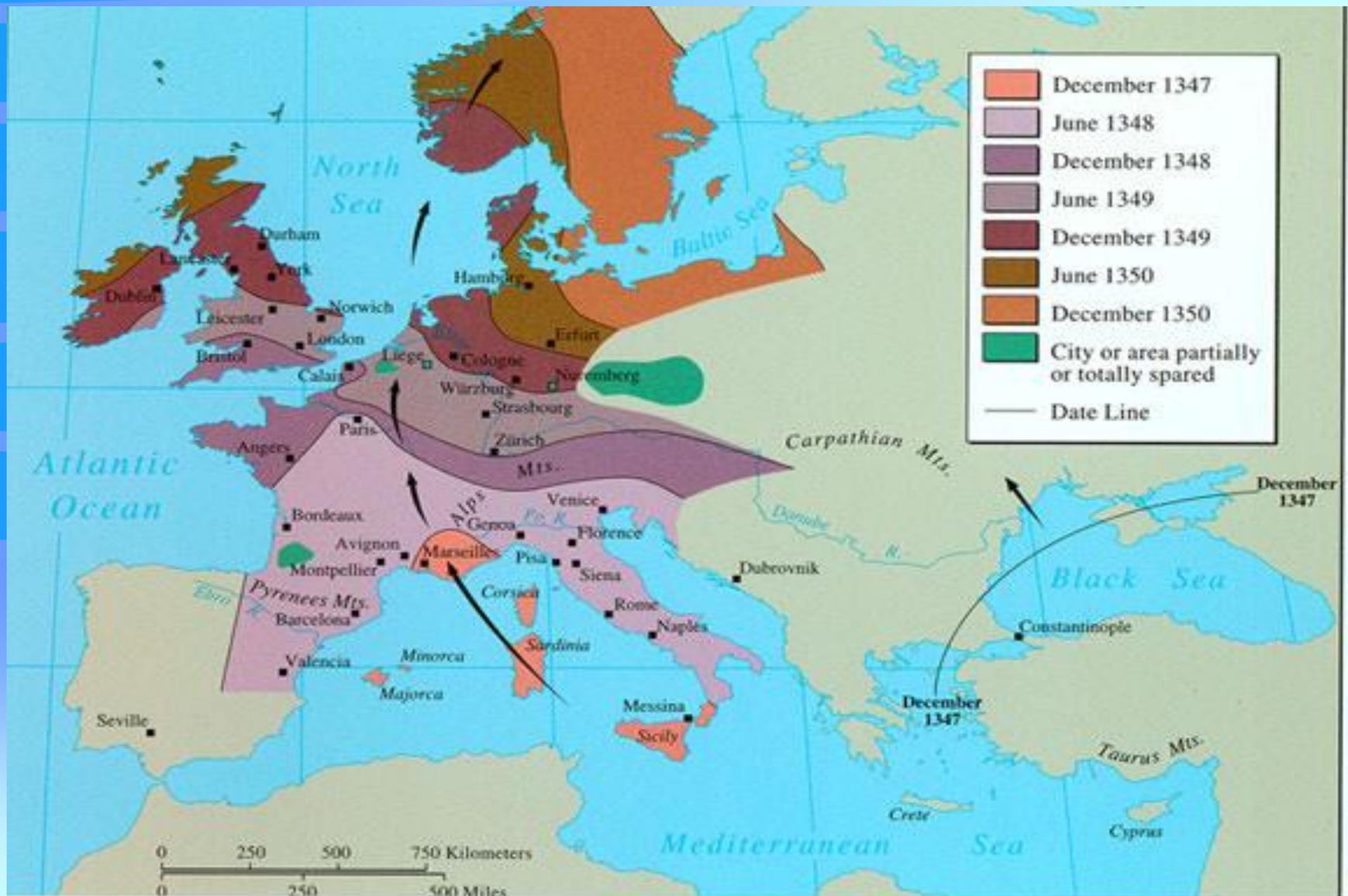
Assoc. Prof. Galya Gancheva, MD, PhD

Plague – history and significance

- Recorded since biblical times, many epidemics throughout history.
- Examples:
- 1st epidemic (Antiqua) – 541 AD; Mediterranean region, 50-60% of pop.
- 2nd epidemic (Medievalis) – “Black Death” – 1346-1351; 1/3 of the populaion of Europe died (20-30 million)
- 3rd epidemic (Orientalis) – 1855-1890; started in China, spread through Asia; 10 million died in India alone.



The Black Death Epidemic





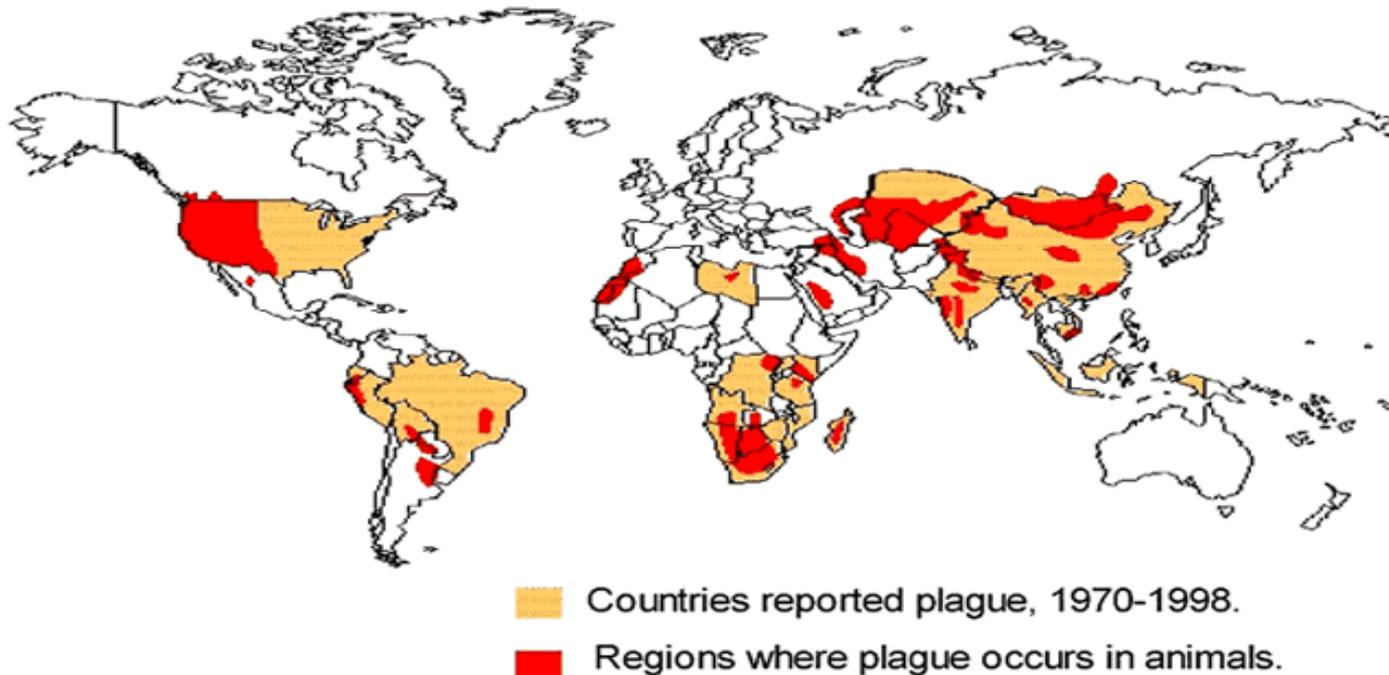
Anatomy of the Plague



The Modern Day Situation

- Studied by Soviet and, to a smaller extent, U.S. biological weapons programs.
- 1995: Larry Wayne Harris arrested for illicit procurement of culture via mail.
- Roughly 2000 cases and 200 deaths per year (WHO)
- Vast majority in Africa
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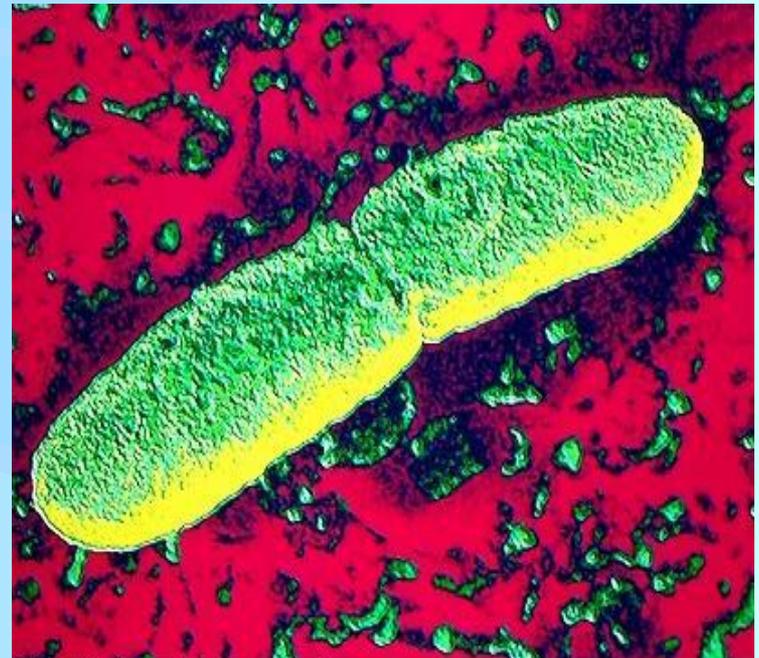
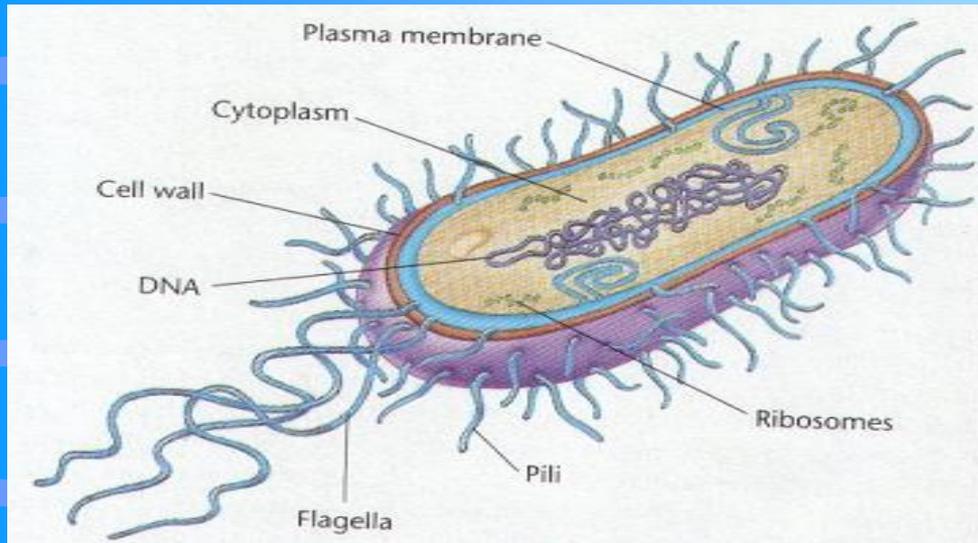
World Distribution of Plague, 1998



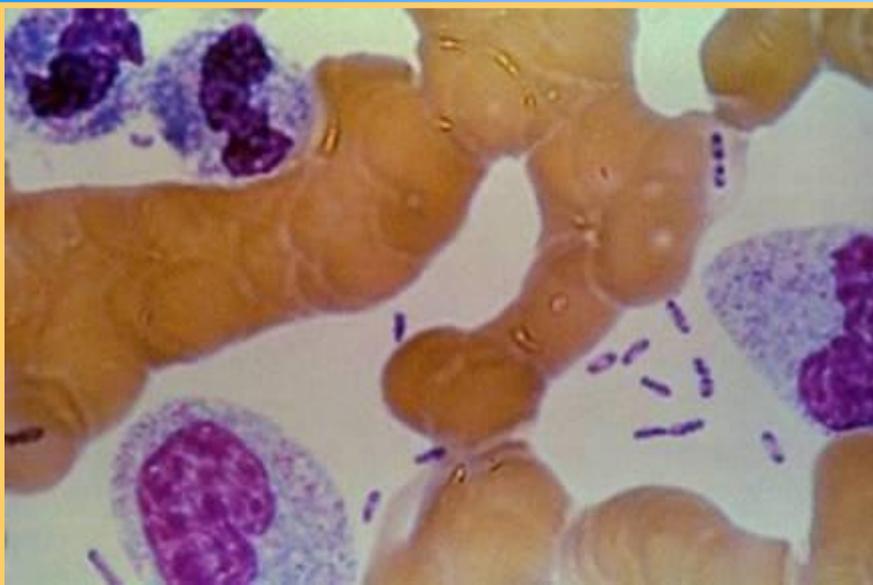
Plague – etiology

- Yersinia pestis is a Gram-negative, bipolar-staining bacillus that belongs to the bacterial family Enterobacteriaceae. It grows aerobically on most culture media, including blood agar and MacConkey agar.
- Like the other yersiniae, the plague bacillus produces V and W antigens, which confer a requirement for calcium to grow at 37°C. This property, mediated by a 45 MDa plasmid, is essential for virulence and plays a part in adapting the organism for intracellular survival and growth.
- Other important virulence factors include the production of lipopolysaccharide endotoxin, a capsular envelope containing the antiphagocytic principle fraction I antigen, the ability to absorb organic iron in the form of a haemin, and the presence of the temperature-dependent enzymes coagulase and fibrinolysin.

Yersinia pestis



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Plague – epidemiology

- Plague is primarily a **zoonotic infection**. It is transmitted among the natural animal reservoirs, which are predominantly urban and sylvatic rodents, by flea bites, or by ingestion of contaminated animal tissues.
- Throughout the world, the urban and domestic rats *Rattus rattus* and *Rattus norvegicus* are the most important reservoirs of the plague bacillus.
- These and other rodent reservoirs (rock squirrels, ground squirrels, prairie dog, mice, voles) tolerate plague infection and develop prolonged bacteraemia, giving their fleas ample opportunity to transmit infection.

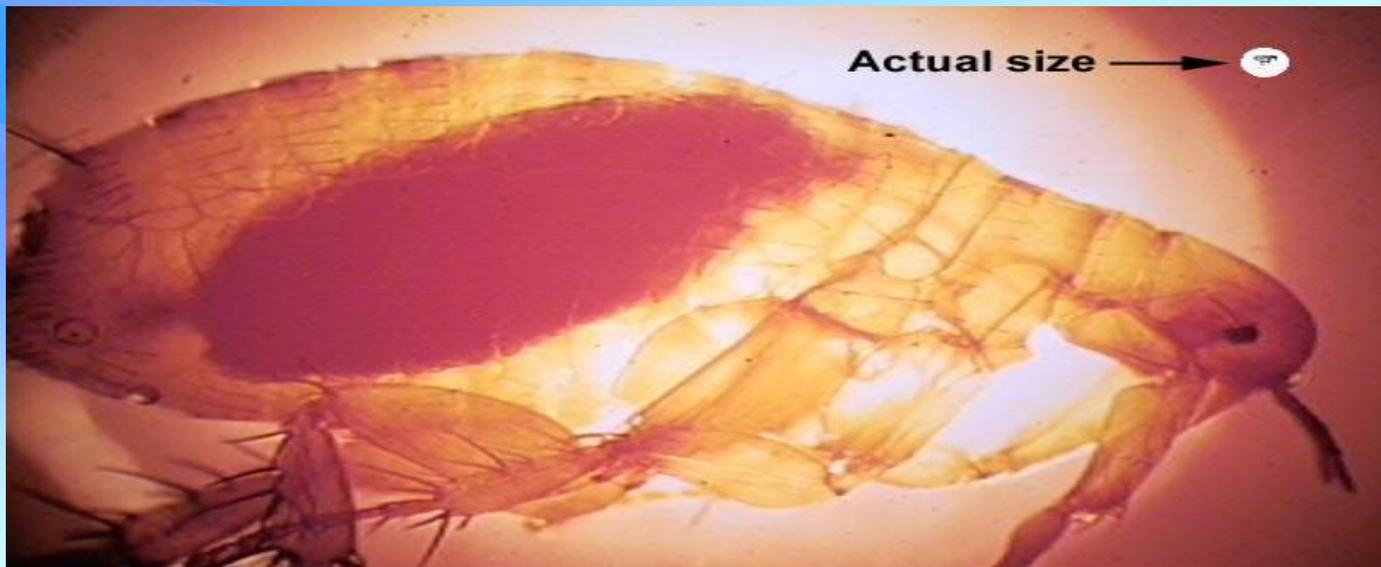


Plague – epidemiology

- **The most efficient vector for transmission is the oriental rat flea *Xenopsylla cheopis*.**
- **Man is an accidental host in the natural cycle of plague,** when he is bitten by an infected rodent flea, and **appears to play no part in the maintenance of plague in nature.**
- **Only rarely, during epidemics of pneumonic plague, is the infection passed directly from person to person.**
- Rarely, hunters can develop infection by handling contaminated animal tissues.

Plague – epidemiology (vectors)

- Main vector – Oriental Rat Flea (*Xenopsylla cheopsis*)
- Stomach becomes blocked from abundance of bacteria. When the flea bites it's next victim, the bacteria are regurgitated into the blood.



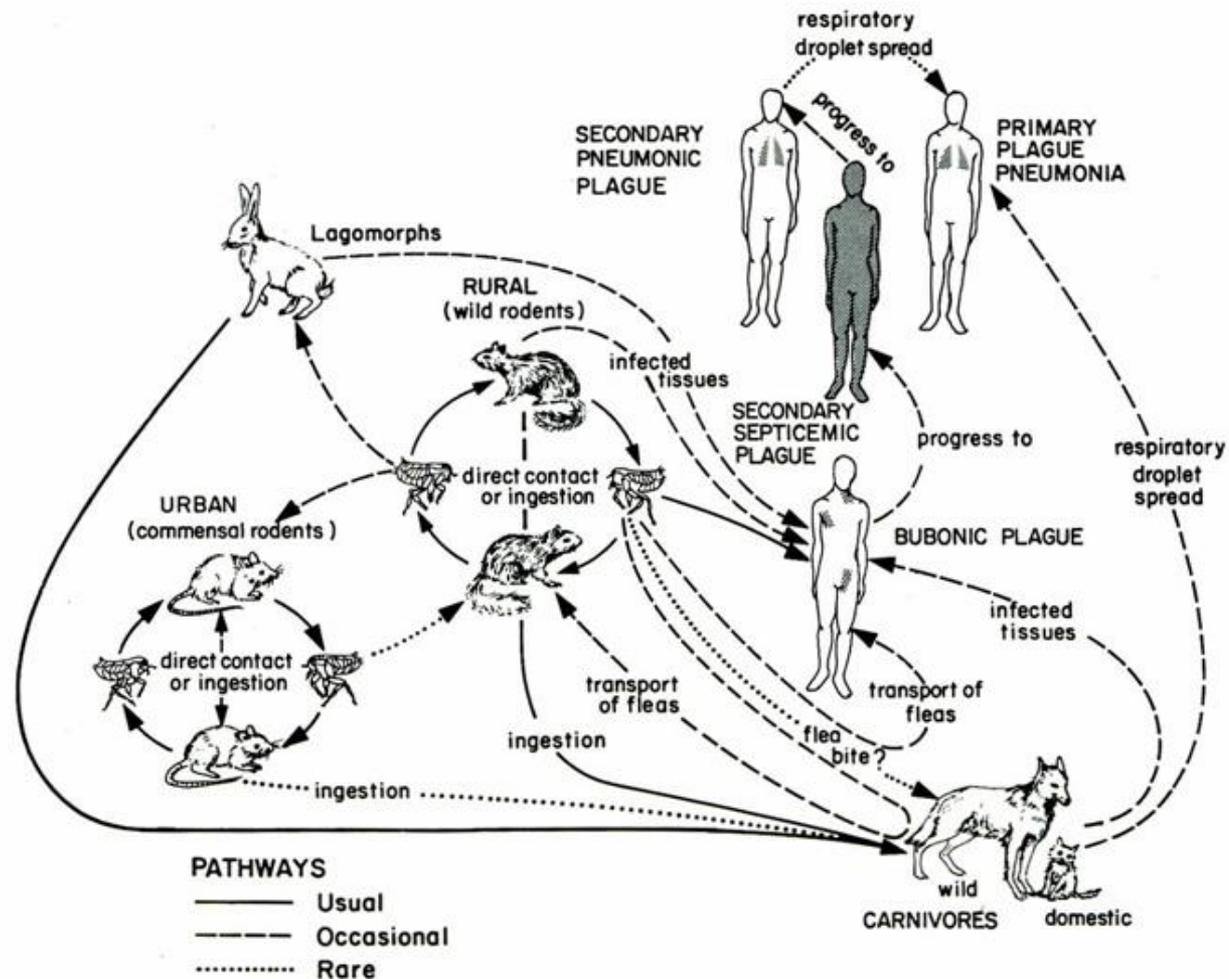


FIGURE 159-5 Epidemiology of infection caused by *Yersinia pestis* in the United States. The cyclic nature of plague and some of the mechanisms for its maintenance in nature are shown. (Adapted by Don Beard from Dr. Jack Poland, with permission)

Robert B. Crave. Plague. Infectious Diseases, 5th ed. J.B. Lippincott Co. 1994.

Plague – pathogenesis

- When a flea ingests a blood meal from a bacteraemic animal infected with *Y. pestis*, the coagulase of the organism causes the blood to clot in the foregut leading to blockage of the flea's swallowing.
- ***Y. pestis* multiplies in the clotted blood. During attempts to ingest a blood meal, a blocked flea may regurgitate thousands of organisms into a patient's skin.**
- The inoculated bacteria migrate by cutaneous lymphatics to the regional lymph nodes. **The flea-borne bacilli possess a small amount of envelope antigen (fraction I) and are readily phagocytosed by the host's polymorphonuclear leucocytes and mononuclear phagocytes.**
- ***Y. pestis* resists destruction within mononuclear phagocytes and may multiply intracellularly with elaboration of envelope antigen.**

Plague – pathogenesis

- If lysis of the mononuclear cell occurs, the bacilli released are relatively resistant to further phagocytosis.
- The involved lymph nodes show polymorphonuclear leucocytes, destruction of normal architecture, haemorrhagic necrosis, and dense concentrations of extracellular plague bacilli.
- Transient bacteraemia is common in bubonic plague, and, in the absence of specific therapy, purulent, necrotic, and haemorrhagic lesions may develop in many organs.
- Hypotension, oliguria, altered mental status, and subclinical disseminated intravascular coagulation may be noted and are attributable to endotoxaemia.

Clinical forms – bubonic plague

- Although plague infection of man can assume many and protean clinical forms, the **most common presentation is bubonic plague, which has a distinctive clinical picture** (Table 1).
- During an incubation period of 2 to 8 days following the bite of an infected flea, bacterial proliferate in the regional lymph nodes.
- Patients are typically affected by the **sudden onset of fever, chills, weakness, and headache. Usually, at the same time, after a few hours, or on the next day, they notice the bubo, which is signaled by intense pain in one anatomical region of lymph nodes, usually the groin, axils, or neck.**

Clinical forms – bubonic plague

- A swelling evolves in this area, which is so tender that the patients typically avoid any motion that might provoke discomfort. For example, if the bubo is in the femoral area, the patient will characteristically flex, abduct, and externally rotate the hip to relieve pressure on the area and will walk with a limp. When the bubo is in an axils, the patient will abduct the shoulder or hold the arm in a splint. When a bubo is in the neck, patients will tilt their heads to the opposite side.



Table 1 – Plague syndromes

Syndrome	Features
Bubonic	Fever, painful lymphadenopathy (bubo)
Septicaemic	Fever, hypotension without bubo
Pneumonic	Cough, haemoptysis with or without bubo
Cutaneous	Pustule, eschar, carbuncle, or ecthyma gangrenosum, usually with bubo
Meningitis	Fever, nuchal rigidity, usually with bubo

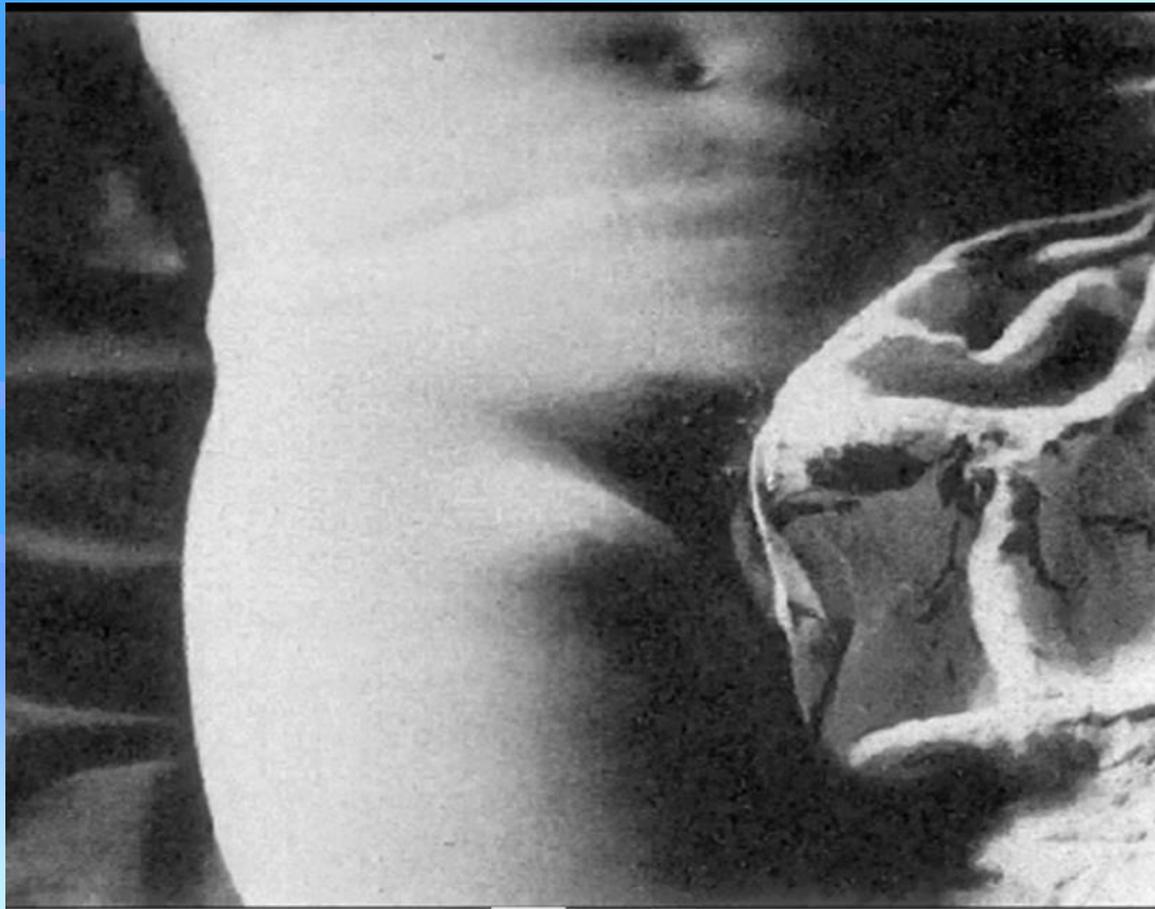
Clinical forms – bubonic plague

- The buboes are oval swellings that vary from 1 to 10 cm in length and elevate the overlying skin, which may appear stretched or erythematous. They may appear either as a smooth, uniform, ovoid mass or as an irregular cluster of several nodes with intervening and surrounding oedema. Palpation will typically elicit extreme tenderness.
- There is warmth of the overlying skin and an underlying, firm, non-fluctuant mass.
- Around the lymph nodes there is usually considerable oedema, which can be either gelatinous or pitting in nature. Occasionally, there is a large area of oedema extending from the bubo into the region drained by the affected lymph nodes.

Clinical forms – bubonic plague

- Although infections other than plague can produce acute lymphadenitis, plague is virtually unique for the suddenness of onset of the fever and bubo, the rapid development of intense inflammation in the bubo, and the fulminant clinical course that can produce death as quickly as 2 to 4 days after the onset of symptoms. The bubo of plague is also distinctive for the usual absence of a detectable skin lesion in the anatomical region where it is located as well as for the absence of an ascending lymphangitis near it.

Bubonic plague



A right femoral bubo consists of an enlarged, tender lymph node with surrounding oedema.

Clinical forms – bubonic plague

- **The groin is the most common site of the buboes in plague.** In clinical reports that have distinguished femoral from inguinal locations, the femoral site was found to be the more common.
- **Other common sites are the axillae and neck.** The reason for a given distribution of buboes is presumed to be the distribution of flea bites, which inoculate the bacteria into the skin to migrate to the regional lymph nodes.

Clinical forms – bubonic plague

- In uncomplicated bubonic plague the patients are typically prostrate and lethargic, and often exhibit restlessness or agitation.
- Occasionally, they are delirious with high fever, and seizures are common in children.
- Temperatures are usually elevated in the range 38.5 to 40⁰ C, and the pulse rates are increased to 110 to 140/min. Blood pressures are characteristically low, in the range of 100/60 mmHg, owing to extreme vasodilatation. Lower pressures that are unobtainable may occur if shock ensues.
- The liver and spleen are often palpable and tender.

Clinical forms – bubonic plague

- Most patients with bubonic plague do not have skin lesions; however, about **one-quarter** of patients in Vietnam did show **varied skin findings**.
- The most common were pustules, vesicles, eschars, or papules near the bubo or in the anatomical region of skin that is lymphatically drained by the affected lymph nodes, and they presumably represent sites of the flea bites. When these lesions are opened they usually contain white cells and plague bacilli.
- Rarely, these skin lesions progress to extensive cellulitis or abscesses. Ulceration, however, may lead to a larger plague carbuncle.

Bubonic plague



A right axillary bubo was accompanied by a purulent ulcer on the abdomen, which was the presumed site of the flea bite.

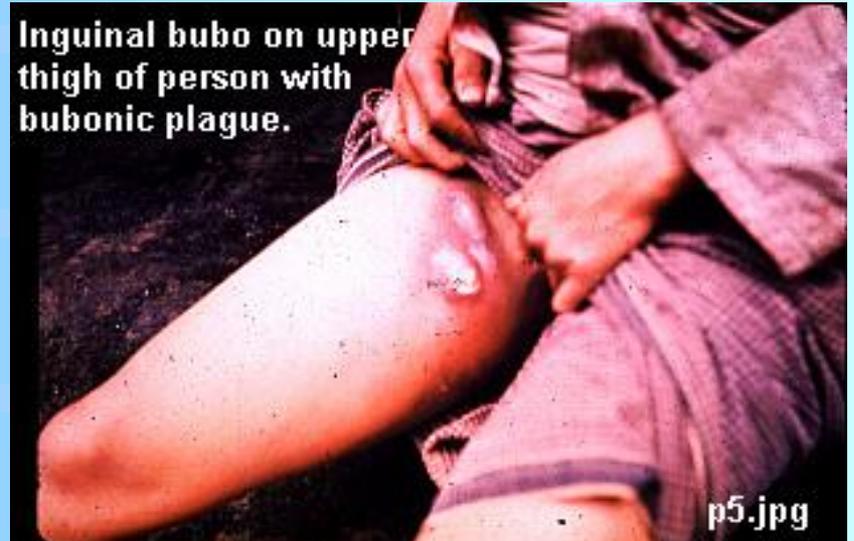
Clinical forms – bubonic plague

- Another kind of skin lesion in plague is **purpura, which is a result of the systemic disease.** The purpuric lesions may become necrotic, resulting in gangrene of distal extremities, the probable basis of the epithet "Black Death" attributed to plague through the ages. **These purpuric lesions contain blood vessels affected by vasculitis and occlusion by fibrin thrombi, resulting in haemorrhage and necrosis.**

Clinical forms – septicaemic plague

- A distinctive feature of plague, in addition to the bubo, is the propensity of the disease to overwhelm patients with a massive growth of bacteria in the blood.
- A hallmark of moribund patients with plague is high-density bacteraemia, so that a blood smear revealing characteristic bacilli has been used as a prognostic indicator in this disease.
- Occasionally in the pathogenesis of plague infection, bacteria are inoculated and proliferate in the body without producing a bubo. Patients may become ill with fever and actually die with bacteraemia but without detectable lymphadenitis.

Septicemic and bubonic plague



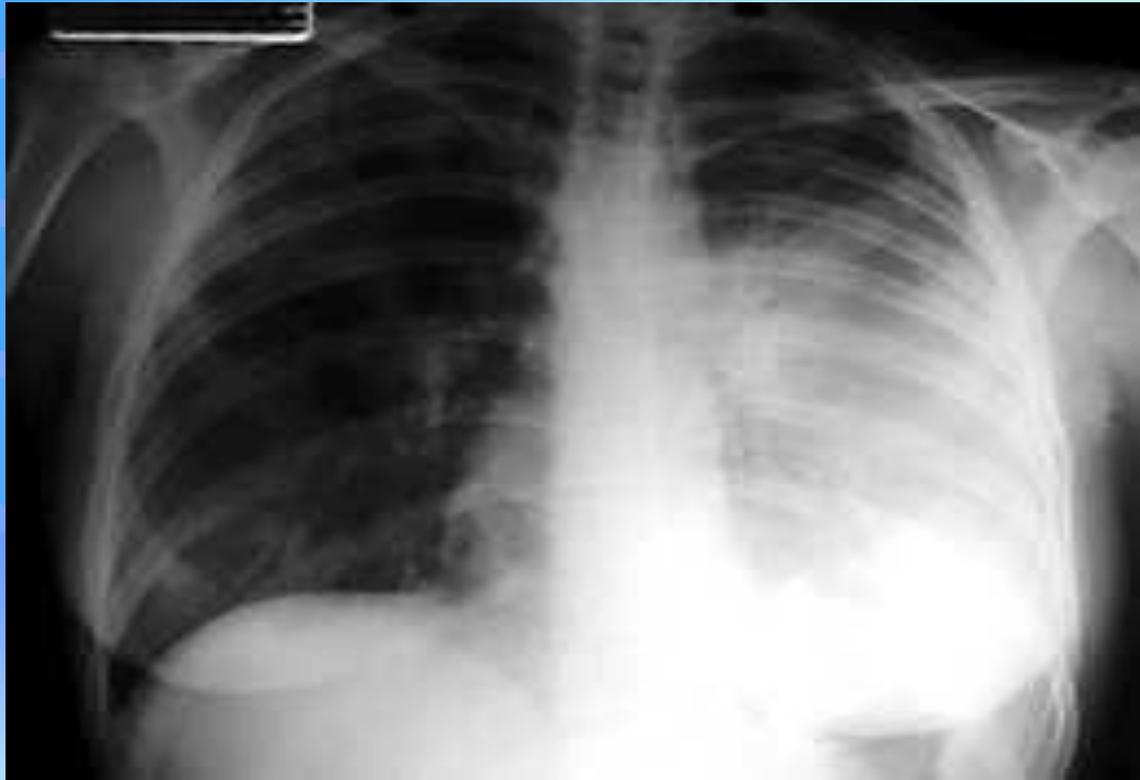
Inguinal bubo on upper thigh of person with bubonic plague.

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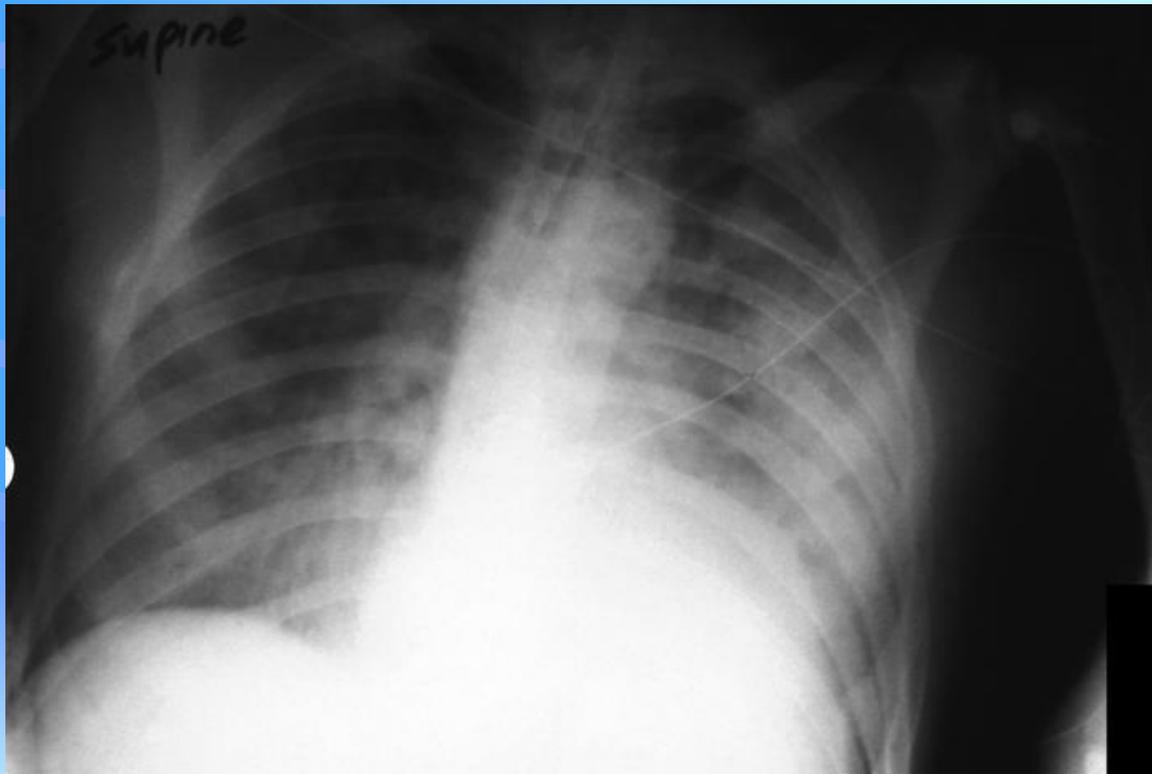
Clinical forms – pneumonic plague

- One of the feared complications of bubonic plague is secondary pneumonia. The infection reaches the lungs by haematogenous spread of bacteria from the bubo.
- In addition to the high mortality, plague pneumonia is highly contagious by airborne transmission. It presents in the setting of fever and lymphadenopathy as cough, chest pain, and often haemoptysis.
- Radiographically, there is patchy bronchopneumonia, cavities, or confluent consolidation.
- The sputum is usually purulent and contains plague bacilli.
- Primary inhalation pneumonia is rare now but is a potential threat following exposure to a patient with plague who has a cough. It can be so rapidly fatal that persons reportedly have been exposed, become ill, and died on the same day. Plague pneumonia is invariably fatal when antibiotic therapy is delayed more than a day after the onset of illness.

Pneumonic Plague



Pneumonic Plague



Plague – other syndromes

- Plague meningitis is a rarer complication and typically occurs more than a week after inadequately treated bubonic plague.
- It results from a haematogenous spread from a bubo and carries a higher mortality rate than uncomplicated bubonic plague.
- There appears to be an association between buboes located in the axilla and the development of meningitis.
- Less commonly, plague meningitis presents as a primary infection of the meninges without antecedent lymphadenitis.
- Plague meningitis is characterized by fever, headache, meningism, and pleocytosis with a predominance of polymorphonuclear leucocytes.
- Bacteria are frequently demonstrable with a Gram stain of spinal-fluid sediment, and endotoxin has been demonstrated by the limulus test in spinal fluid.

Plague – other syndromes

- Plague can produce **pharyngitis that may resemble acute tonsillitis.** The anterior cervical lymph nodes are usually inflamed, and *Y. pestis* may be recovered from a throat culture or by aspiration of a cervical bubo. **This is a rare clinical form of plague that is presumed to follow the inhalation or ingestion of plague bacilli.**
- Plague presents sometimes with **prominent gastrointestinal symptoms of nausea, vomiting, diarrhoea, and abdominal pain.** These symptoms may precede the bubo or, in septicaemic plague, occur without a bubo; they commonly result in diagnostic delay.

Plague – laboratory findings

- The white blood-cell count is typically elevated in the range of 10 000 to 20 000 cells/mm³, with a predominance of immature and mature neutrophils. Severely ill patients tend to have the higher white blood-cell counts.
- Occasionally, some patients, especially children, may develop myelocytic leukaemoid reactions with white-cell counts as high as 100 000 mm³.
- Examination of the white blood cells in the peripheral blood smear typically reveals cytoplasmic vacuolations, toxic granulations, and Dohle bodies that are characteristic of acute bacterial infections. Blood eosinophils are characteristically diminished or absent in the acute stage of infection but return to normal or elevated levels during convalescence.

Plague – laboratory findings

- Blood platelets may be normal or low in the early stages of bubonic plague.
- Although patients with plague rarely develop a generalized bleeding tendency from profound thrombocytopenia, disseminated intravascular coagulation is common in this infection.
- Fibrin(-ogen) degradation products in the sera indicative of disseminated intravascular coagulation are detected in elevated titres in most patients.
- Liver function tests, including serum aminotransferases and bilirubin, are frequently abnormally high.
- Renal function tests may be abnormal in hypotensive patients.

Plague – diagnosis

- Plague should be suspected in febrile patients who have been exposed to rodents or other mammals in the known endemic areas of the world.
- A bacteriological diagnosis is readily made in most patients by smear and culture of a bubo aspirate.
- Drops of the aspirate should be placed on to microscopic slides and air-dried for both Gram and Wayson's stains.
- The Gram stain will reveal polymorphonuclear leucocytes and Gram-negative coccobacilli and bacilli ranging from 1 to 2µg in length.

Plague – diagnosis

- Serological test, the passive haemagglutination test utilizing fraction I of Y. pestis, is available for testing acute- and convalescent-phase serum.
- **In patients with negative cultures, a fourfold or greater increase in titer or a single titer of 1:16 or higher is presumptive evidence of plague infection.**

Plague – antimicrobials

- Untreated plague has an estimated mortality rate of greater than 50 per cent and can evolve into a fulminant illness complicated by septic shock.
- **Streptomycin should be given intramuscularly in two divided doses daily, totaling 30mg/kg body weight per day for 10 days.**
- The risk of vestibular damage and hearing loss due to streptomycin is minimal.
- Renal injury as a result of streptomycin therapy is rare with this regimen; however, renal function should be monitored.

Plague – antimicrobials

- For patients allergic to streptomycin or in whom an oral drug is strongly preferred, **tetracycline is a satisfactory alternative.**
- It is given orally in a dose of 2 to 4 g day in four divided doses for 10 days.
- Tetracycline is contraindicated in children younger than 7 years of age and in pregnant women because it stains developing teeth. It is also contraindicated in renal failure.

Plague – antimicrobials

- For patients with meningitis who require a drug with good penetration into the cerebrospinal fluid and for patients with profound hypotension in whom an intramuscular injection may be poorly absorbed, chloramphenicol should be given intravenously, a loading dose of 25mg/kg of body weight followed by 60 mg/kg per day in four divided doses.
- After clinical improvement, chloramphenicol should be continued orally to complete a total course of 10 days. The dosage may be reduced to 30 mg/kg per day to lessen the magnitude of bone marrow suppression, which is reversible after completion of therapy.

Plague – antimicrobials

- Other antimicrobial drugs have been used in plague with varying success. These include sulphonamides, trimethoprim-sulphamethoxazole, kanamycin, gentamicin, and ampicillin.
- These drugs either are less effective than streptomycin or have not been subjected to adequate clinical studies and, therefore, should not be chosen.

Plague – supportive therapy

- Most patients are febrile, with constitutional symptoms including nausea and vomiting. Hypotension and dehydration are common.
- Therefore, intravenous 0.9 per cent saline solution should be given to most patients for the first few days of the illness or until improvement occurs.
- Patients in shock will require additional quantities of fluid, with haemodynamic monitoring and the judicious use of adrenaline or dopamine.
- **There is no evidence that corticosteroids are beneficial in plague.**
- Although disseminated intravascular coagulation is commonly present and purpura occasionally develops in severely ill patients, **therapy with heparin has no proven benefit in plague infections.**

Plague – local therapy

- The buboes usually recede without local therapy.
- Occasionally, however, they may enlarge or become fluctuant during the first week of treatment, requiring **incision and drainage.**
- The aspirated fluid should be cultured for evidence of superinfection with other bacteria, but this material is usually sterile.

Plague – Precautions

- Patients with uncomplicated infections who are promptly treated present no health hazards to other people.

Plague – Vaccine

- A formalin-killed vaccine, Plague Vaccine U.S.P.
- A primary series of two injections is recommended with a 1- to 3-month interval between them. Booster injections are given every 6 months for as long as exposure continues.

Plague Control

- Isolation of patients with pneumonic plague.
- Flea and rodent control.
- Start therapy if plague is suspected – can take too long to confirm.

DEPARTMENT OF PUBLIC HEALTH AND CHARITIES

KILL THE RATS

AND PREVENT THE PLAGUE

TRAP THEM POISON THEM

RAT-PROOF YOUR BUILDINGS

TRAPS—The best Trap for Houses and Stores is the large Cage Trap. Snap Traps are best in Butcher Shops, Bakeries and Restaurants.

BAIT—Should be changed daily between Cheese, Fresh Liver, Nuts, Fish-Heads and Chicken Heads and should be securely fastened to the trap. Always Soak the Traps after handling and see that they are placed close to the wall at the usual feeding place.

POISON—All druggists can furnish Good Rat Poisons. Follow Directions and **DO NOT PLACE WHERE ACCESSIBLE TO CHILDREN or DOMESTIC ANIMALS.**

DISPOSITION OF RATS | THE CITY WILL PAY A BOUNTY OF
5¢ FOR LIVE RATS
2¢ FOR DEAD RATS

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IF NOT CONVENIENT TO TAKE RATS TO STATION, PHONE TO
ELECTRICAL BUREAU 55
AND THE RAT PATROL WILL CALL FOR THEM

The RAT is the known carrier of the Bubonic Plague, Rat Sprague and other diseases. Aside from being a health menace the RAT destroys property and merchandise to the extent of \$10,000 EACH DAY IN PHILADELPHIA.

RAT-PROOFING BUILDINGS | Building the Rat out of homes and stores takes more time but in the long run is the most effective measure for destroying Rats.

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Plague as a Weapon

- Aerosolized bacteria – pneumonic plague.
- Takes 48-72 hours to confirm diagnosis.
- 50 kg of *Y. pestis* could infect 150,000 and kill 36,000 in a city of 5 million in a worst-case scenario.
- Bacteria would remain viable in an aerosol for 1 hour for a distance of 10 km.

