Summary

- Plague: infection with *Yersina pestis*, a Gram-negative bacterium
- Isolated cases or epidemic
- Transmission via fleas (importance of rat population), body lice (hygiene) or aerogenically (cough)
- Lymphadenitis (bubonic plague), pneumonia (pneumonic plague) with septicaemia and bleeding
- Isolation of cases, flea and lice eradication
- Aminoglycoside (gentamicin), fluoroquinolone or tetracycline
- Tetracycline for immediate contacts

General

Plague is an infection caused by a **Gram-negative bacterium**: ***Yersinia pestis***. This organism was isolated in 1894 by the Japanese researcher Shibasaburo Kitasato (a co-worker of Koch) and the Swiss bacteriologist Alexander Yersin (a student of Pasteur) during an epidemic in Hong Kong. The organism has a characteristic shape when stained with Giemsa or Wayson stain: a bipolar rod with a safety pin appearance. The organism is non-motile and forms no spores. The organism grows well on various tissue media. In 1897, the Japanese doctor Masaki Ogata reported that plague was transmitted by rat fleas. In 1898, Paul-Louis Simond during his work in Bombay suspected that the rat flea *Xenopsylla cheopis* might be the vector. This was confirmed experimentally in 1914 by Bacot and Martin.

Yersinia

Do not confuse *Yersina pestis* with *Yersinia enterocolitica* or *Yersinia pseudotuberculosis*. These bacteria can provoke enteritis and mesenterial adenitis (swollen lymph nodes in the mesentery, especially near the terminal ileum and the ileocolic junction). *Y. pseudotuberculosis* is maybe the cause of Izumi fever (pseudoscarlatina).

Historical perspective

There have been various well-known pandemics in history. The **Athenian "plague"** (430 BC) at the time of the Peloponnesian War (431-404 BC) was described by the Greek historian Thucydides, but the precise aetiology of this epidemic is uncertain. The profusion of different hypotheses (Ebola, *Rickettsia prowazekii*, ergotism, epidemic recurrent fever, smallpox, *Bacillus anthracis*, *Yersinia pestis*, arbovirosis, robovirosis, a variant of "Spanish" flu, etc.) shows that, in the absence of essential data, a correct diagnosis after the event is not easy.

In 542 AD, at the time of the Roman emperor Justinian, an epidemic occurred in Pelusium, in Egypt, a seaport at the mouth of the eastern branch of the Nile delta. The epidemic subsequently struck Turkey and Europe (**Justinian plague**). The consequences and terrors were described by the Byzantine historian Procopius, secretary to Belisarius, one of the most important generals under Emperor Justinian. The epidemic ended about 767.

In 1346 there were **cases of plague in Astrakhan**, situated at the mouth of the Volga (north of the Caspian Sea). Afterwards, spread occurred via the River Don to the Sea of Azov and subsequently to the shores of the Black Sea. In 1347 there were **Genoese traders in the city of Caffa** (now Feodosiya), in the south of the Crimean peninsula in the Black Sea. It was the terminus of the northern branch of the Trans-Asiatic silk route. The city was besieged by Janiberg, leader of the Kipchak Tartars, in whose camp an epidemic of plague broke out. The Tartars catapulted bodies of their own comrades who died of the disease over the walls of the city. To what extent this contributed to the spread of plague is open to question. Anyway, the plague appeared in Caffa city. Twelve Genoese ships withdrew with cases of plague on board. Their crews went ashore at various places in Constantinople, Cyprus, Messina (Sicily), Southern France and Italy, after which a major epidemic broke out in December 1347. In June 1348 the plague reached Paris. In December it arrived in England. In May 1349 a ship with a cargo of wool sailed from London to Bergen in Norway. A few days later it was found drifting with the crew dead off the Norwegian coast. The cargo was brought on land and by the end of 1349 the plague had spread throughout the whole of the country. In 1351 the plague came to Poland. The Black Death in the 14th century wiped out approximately a quarter of the population of Western Europe. Together with the other terrors of the 14th century (e.g. the Hundred Years' War between England and France, 1339-1453), this meant that the **European population declined from 73 million to 45 million**.

The term "**quarantine**" stems from 1370, when seafarers arriving in the Republic of Ragusa in Southern Italy were isolated for 40 days (quaranti giorni).

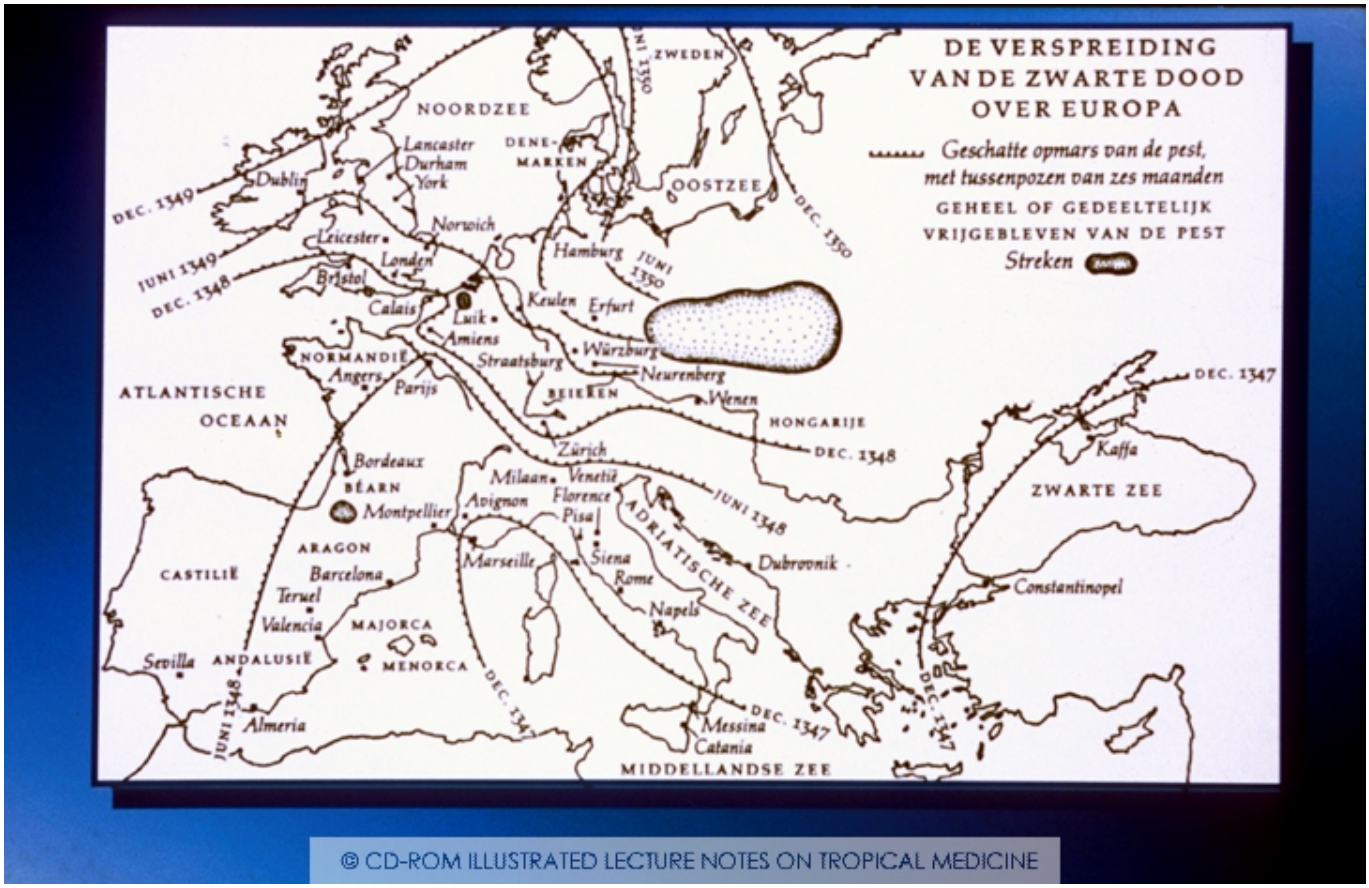
Plague also raged from the 15th to the 17th century in Europe. The Great Plague of London in 1665 totalled 70,000 deaths. The epidemic was possibly stopped by the Great Fire of London in 1666, but according to English demographic data ("Bill of Mortality") mortality had already declined before the Great Fire.

Subsequently other smaller outbreaks happened (Marseilles in 1720, Egypt in 1834). The decline of the plague has been associated with the reduction in the number of black rats and their replacement by brown rats which have less close contact with humans.

In 1860, a new epidemic arose in Yunnan, China, which later spread, first to the town of Pakhoi and then to Canton (Guangzhou), before subsequently travelling downstream and reaching Hong Kong in 1894. It was then that the organism was isolated. From this port there was further spread via ships' rats (e.g. to San Francisco 1903, Auckland, Bangkok, Manila, Rangoon, Saigon, Batavia, Tokyo, Sydney, Cape Town, Buenos Aires, Mauritius and Glasgow), which caused huge mortality, especially in India. Between 1898 and 1918, 8 to 12.5 million people died in India. The epidemic was brought to a halt in the first half of the twentieth century. In North China there was also a major epidemic. This resulted from the intensified hunting of marmots. These mammals had a valuable pelt and were also very susceptible to plague. The local Mongols knew the risk of this only too well and shot the animals instead of catching them. They also always avoided touching sick or dead animals. When the price of pelts quadrupled in 1910, there was a large influx of inexperienced amateur Chinese who hunted without precautions in search of rapid profits. The hunters also often kept warm together in underground shelters, which was ideal for transmission. Pneumonic plague broke out in Hailar and spread along the railway line to Harbin and afterwards to Vladivostok.

In the Second World War, Japanese Imperial Army's Unit 731 killed thousands of Chinese and Russians held prisoner in Japanese-occupied Manchuria, in experiments to develop chemical and **biological weapons**. Japanese doctors tested the use of plague among others. Infected *Pulex irritans* fleas were cultured and released in a few Chinese towns, resulting in small epidemics of bubonic plague.

After an absence of 50 years, plague reappeared in 2003 in **Oran and in other foci in Algeria**. New foci were discovered in 2008, including one in Libya. The rodent species *Meriones shawii* (Shaw's jird) was shown to be present in the transmission area. The animal is plague-resistant and forms an efficient reservoir for *Yersina pestis*.



Spread of plague throughout Europe during Middle-Ages

Plague = plague?

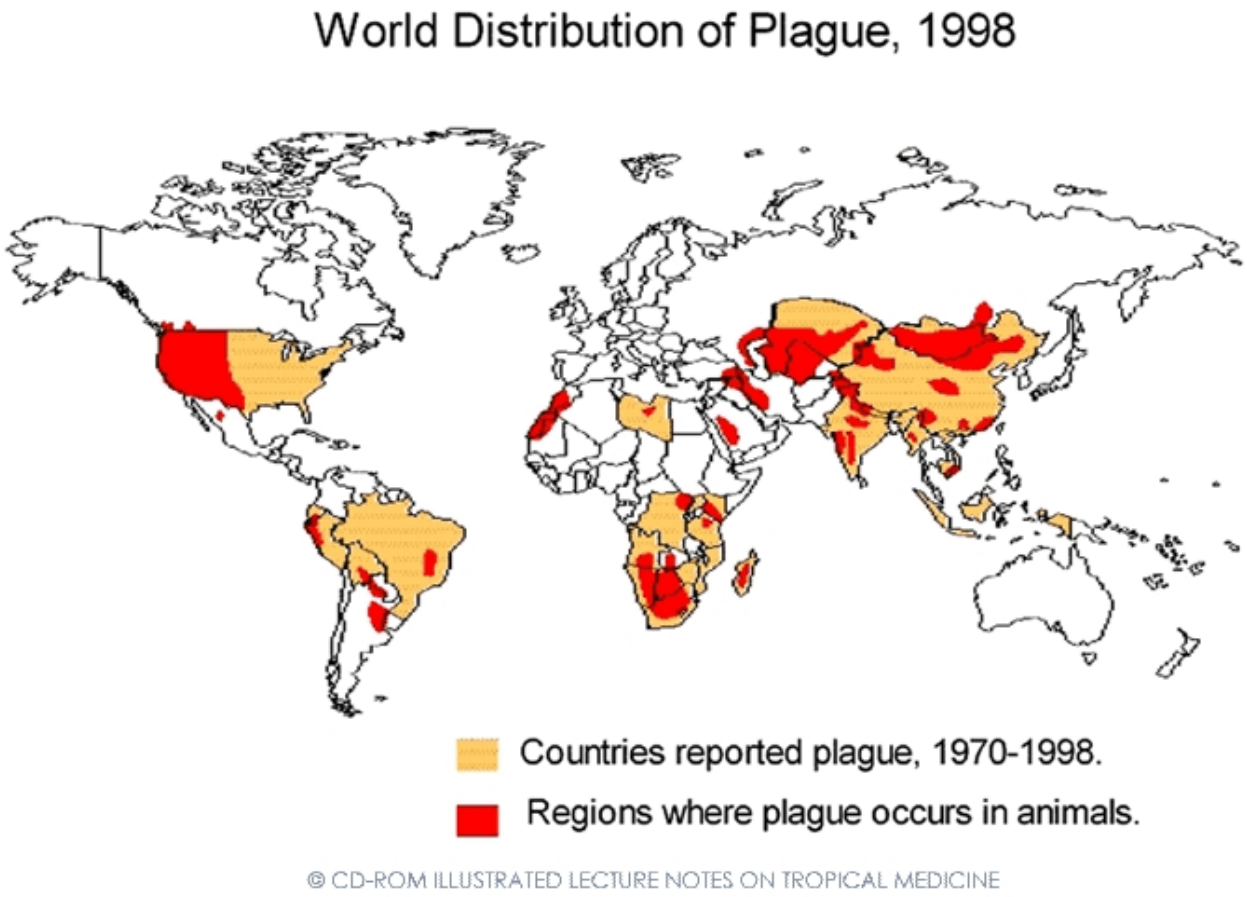
How do we know so positively that the "plague" in earlier centuries was in fact "the plague"? Naturally, there are numerous historical descriptions that are suggestive, but there still remains questions. In the case of the Athenian plague there are many question marks regarding the aetiology. There have also sometimes been epidemics of diseases with high mortality which disappeared as quickly as they had appeared and which do not

resemble any disease that we now recognise (e.g. the epidemic of lethal “sweating sickness” (1485-1551) which in the summers of 1508, 1517, 1528 and 1551, claimed many victims in England and elsewhere). The nature of the organism that caused “sweating sickness” is still unknown. In 1998, Didier Raoult (Marseilles) studied the dental pulp of non-erupted teeth from people who had died in the 16th and 18th century from plague and were buried in large graves in Lambesc and Marseilles. Using PCR technology it was possible to detect a few genes of *Yersinia pestis* in the dentition. Control teeth were negative. This technique opens new avenues for study and for obtaining a better understanding of historical epidemics.

Present situation

Plague is at present a rare, cosmopolitan disease which still persists in **various foci in several parts of the world**. From 2000 to 2009, a total of 21,725 cases of plague with 1612 deaths (7.4 percent fatality rate) were reported worldwide from 16 countries. A further 3248 cases of plague were reported to the World Health Organization (WHO) between 2010 and 2015, with 584 associated deaths. Since 2000, more than 95 percent of reported cases have been from Africa. Outbreaks of human plague, with numbers of cases ranging from 100 to more than 1000, have occurred since 1992 in DRC, Peru, India, and the Congo. Plague reappeared in Malawi, Mozambique, and India in 1994, in Algeria in 2003, and in Libya in 2009, raising concern that the disease may re-emerge as a worldwide public health hazard. Available data may be underestimates because diagnostic facilities and surveillance systems are inadequate in many areas of the world where plague is endemic or occurs in focal outbreaks.

In the Western World, the rate of plague is low, probably because the affected areas are rural and largely uninhabited. In the United States, a total of 91 cases of human plague were reported in the United States from 2000 to 2015, over 80 percent of which were the bubonic form.



Map showing areas where plague occurred in the period 1970-1998

Transmission and epidemiology

Plague is first and foremost a disease of **wild rodents** (**zoonosis**). Mammals from at least 73 genera can be infected and approximately 30 species of fleas can transmit the organism. This does not mean that they are all equally important. Many of these animals are relatively resistant to the infection. Only a few are of importance for maintaining enzootic and epizootic cycles. In a focus of infection, it is possible to obtain an idea of the local situation (plague surveillance) by serological surveys of various wild animals. Sometimes an epizootic occurs (an epidemic in animals).

Paul-Louis Simond

French researcher Paul-Louis Simond (1858-1947) helped in Bombay to combat the Indian

plague epidemic of 1897. At that time, it was thought that rats caught plague by cannibalising dead rats, and that people caught plague through tiny cuts and cracks in their feet. Simond showed it was rather difficult to infect rats by feeding them infected material. Also, mere physical contact with infectious material did not seem to infect the rats. However, pricking the feet of rats with a plague-contaminated needle infected them rather easily. Rubbing plague material on the surface of an intact rat paw produced no infection. If rats could get plague via tiny prick injuries, what might be causing them in their natural habitat? Simond considered insect bites. He knew rats were often infested with fleas. He also knew rat fleas would bite humans (fleas are less discriminatory of food sources than lice). In a critical experiment, he showed that rats did not get plague in the absence of fleas. Simond noted that not only were there large number of dead and dying rats in the streets and buildings, but that 20 laborers in a wool factory who had been cleaning the floor of dead rats had died of plague, but none of the other factory workers who had no contact with rats had become ill. He found that healthy rats groomed themselves and had few fleas, while sick rats unable to groom their fur had many. When the rats died, the fleas moved on to other hosts. Simond began to suspect fleas as intermediaries. In an experiment, he placed a sick rat at the bottom of a jar and suspended a healthy rat in a wire mesh cage above it. Although the healthy rat had no direct contact with the plague-infected one, it did become infected. Simond determined that rat fleas could jump 10 cm high without difficulties. As a control he placed a sick rat without fleas together with healthy rats in a jar. None of the healthy rats became sick (which ruled out air-borne transmission). When he introduced fleas into the jar, they developed plague and died. On 2 June 1898 he wrote Pasteur that the problem of plague transmission had been solved. It would be several years before he was believed.

The bacteria can survive for a long time in the burrows of various rodents. The infection is transmitted **from animal to animal by fleas**. When a flea sucks blood from an infected animal it ingests bacteria. These organisms then proliferate in the insect's proventriculus and stomach. The bacteria attach to the wall if they carry a specific gene, the "haemin storage locus". At the same time, they secrete an enzyme (coagulase) that coagulates the aspirated blood. This causes an **obstruction in the flea's stomach**. The flea then becomes increasingly hungry and bites more often. As a result of the obstruction, the **blood with bacteria is regurgitated**. The flea can only digest the clots at temperatures higher than 28°C ("cold fleas digest poorly"). At high environmental temperatures (>28°C) a plague

epidemic will therefore spread less rapidly and sometimes stop because the flea can digest the blood and there is much less regurgitation into the bite wound. The proventriculus of the flea in fact contains internal projections which make regurgitation difficult in “usual” circumstances. The bacteria can also be introduced into a wound by flea faeces or by crushing the insect (scratching an itchy fleabite!).



Cat flea. Ctenocephalides felis. Occasional vector of Yersinia pestis (plague) and vector of Rickettsia felis. Copyright ITM

An isolated case of plague can occur when a human is bitten by an infected flea from wild rodents such as sand rats or desert rats [gerbils] (e.g. *Meriones* sp, *Tatera* sp, *Rhombomys* sp, *Gerbillus* sp). This is then referred to as **sylvatic transmission** (“sylva” = wood). This

happens for instance to hunters, wood cutters, etc. Other animals, such as *Mastomys* sp, *Arvicanthis*, *Otomys* sp, etc., are also involved in transmission but are less important. Carnivores of the cat and dog families and species belonging to the weasel family naturally have a high probability of **being contaminated by their prey** as a result of their hunting behaviour. There are regular cases of transmission via a sick domestic cat or dog**. These animals can cough and infect humans aerogenically**. Contamination can also occur through wounds and direct contact with contaminated body fluids. Consumption of contaminated meat and liver (e.g. sick camel) can result in active infection with *Y. pestis*.

Sometimes **rodents that live close to humans are infected**. Rats, principally the brown rat (*Rattus norvegicus*, also called the Norwegian, grey or sewer rat; little contact with humans) and the black rat (*Rattus rattus*, also known as the house rat, lives close to humans) constitute the main reservoir. These rats are much more susceptible to infection than gerbils. The **plague bacterium usually kills the rat**, after which the flea *Xenopsylla cheopis* – the oriental rat flea – has to search for another source of blood, often humans. There are other fleas (e.g. *Pulex irritans* [human flea], *Nosopsyllus fasciatus* [brown rat flea], *Oropsylla montana* [rock squirrel flea], *Oropsylla silantievi* [tarabagan flea]) that can transmit plague, but these are of minor epidemiological importance. It is possible that transmission via *Pulex* was very important during the period of the Black Death in Europe.

Y. pestis may have a **reservoir in the soil**. It has been shown that *Y. pestis* can survive for at least 24 days in contaminated soil under natural condition. The upper limit is unknown at present.

The presence of *Y. pestis* in the fleas affects their behaviour, such as their preferred optimal temperature. Infected fleas appear to prefer a mean environmental temperature that is 1.6°C lower than that of non-infected fleas. Healthy rats have a body temperature of ± 38.5°C. Sick rats develop fever (i.e. >38.5°C). Thus**, infected fleas are unlikely to remain on an infected rat.** They move on to the next available host. If this is a human, then the bacterium is transferred at the same time. This has important consequences in the epidemiology of the infection with the massive release of contaminated fleas in the event of extensive rodent die-off (“ratfall”). **Humans are then accidental “hosts” to the fleas**. In this case, human-to-human transmission still does not occur.

Epidemic plague can occur e.g. via bites from the human flea (“Pulex irritans”). A patient with bubonic plague can develop **secondary pneumonic plague**. When humans develop the pulmonary form of plague, the disease **can be further transmitted from person to person by cough droplets** without further intervention by fleas or rats.

In the USA, there are several cases of plague every year following contact with sick or dead wild animals (mice, squirrels, prairie dogs, rabbits, etc). *Oropsylla montana* is an important vector in the USA. Monitoring rodent populations and their predators (e.g. coyotes) is important for predicting imminent outbreaks. It should be noted that domestic cats, dogs and other animals can also be infected with plague and develop the disease.

Historical data seem to imply that rat-die offs were not associated with human epidemics in the 1300’s. The rodent’s fleas might not have been active during the cold European winter months. Still cases of bubonic plague occurred (besides pneumonic plague) during the cold periods, very suggestive of transmission via biting arthropods. It was demonstrated that **body lice** can also transmit plague. Since they stay in human clothing, transmission during winter can be expected. Body lice can be infected when living on a septicaemic patient and stay alive for a week, producing infectious faeces. The exact role of body lice is still not well defined, but further work might clarify the epidemiology of this disease.

Yersinia pestis

Three biotypes of the bacterium are currently recognised based on the capability of glycerol fermention and nitrite to nitrate conversion. Ribotyping of the various isolates supports the recognised division of these biotypes. These are the Antiqua, Mediaevalis and Orientalis biotypes. The Antiqua biotype occurs in Africa, Southern Russia and Central Asia. The Mediaevalis biotype is found around the Caspian Sea. The Orientalis biotype is predominant in Asia and is the only one that occurs in the New World. A fourth biotype, Microtus, refers to Medievalis isolates lacking arabinose fermentation. In 1951, Devignat proposed that each of the first 3 biotypes determined each plague pandemic.

However, at present there are strong arguments to suppose that the three historic pandemics were caused by the Orientalis biotype (studies based on PCR-analysis of ancient dental pulp of victims).

Clinical aspects

Some cases are asymptomatic. After a flea bite, a local pustule or ulcer occurs, sometimes with a black crust. The bacterium spreads via the lymphatics. Some cases have clinical features of minor lymphadenitis.

Bubonic plague

The **incubation period is short (2-7 days)**. In a minority of cases (6%), there is a pustule or a carbuncle at the site of the flea bite. In most cases, no ascending lymphangitis is noted. Sudden high **fever with chills** occurs, associated with hypotension, headache and severe general malaise. The **regional lymph nodes** draining the site of the bite enlarge rapidly and are very painful. In most cases, the femoral and inguinal lymph nodes are affected, followed in terms of frequency by the axillary and cervical nodes. Plague nodes differ from other lymphadenitides through their rapid development, severe pain and accompanying toxaemia. Mild forms however also occur ("pestis minor"). The swollen lymph nodes are known as **buboes**, from which the term "bubonic plague" is derived. The buboes rapidly break open, discharging dirty, foul-smelling, necrotic tissue. There is high fever and the patient's general condition is poor, blood pressure low and the liver and spleen can be enlarged. Subcapsular splenic bleeding is not unusual. **Mortality is high (50-90%).** With rapid treatment it can be reduced to 1-2%. Blood vessels are damaged and contain clots. Subcutaneous bleeding occurs, which takes the form of petechiae, purpura and ecchymoses. Subsequently, the skin lesions become necrotic and gangrene can set in ("Black Death"). If treatment is incomplete, meningeal invasion can occur (plague meningitis). When pustules or ecthyma gangrenosum are the predominant clinical features, this is sometimes referred to as cutaneous plague.

Septicaemic plague

Sometimes **sepsis/septic shock** is clinically apparent before the lymph nodes have time to enlarge: septicaemic plague. This is an incorrect term since septicaemia also occurs in the other forms of plague. **Bacteraemia** can be very high so that sometimes bacilli can be seen in a thin or thick blood smear. Often the patient presents initially with gastro-intestinal symptoms, such as nausea, vomiting, diarrhoea and/or abdominal pain, which can lead a clinician astray. In most cases the patient dies very rapidly (1 to 2 days) in a condition of

septic shock with refractory hypotension, renal failure, stupor, ARDS and DIC (petechiae, bruising, bleeding tendency and acral gangrene).

Pneumonic plague

These days, pneumonic plague is rare. The infection can be **primary** as a result of contamination via an aerosol of plague bacteria or **secondary** through haematogenic spread to the lungs. Primary pneumonic plague has an incubation period of 2 to 4 days. The onset is acute, and the course is fulminant with fever, chest discomfort, general malaise, hypotension and severe pneumonia, with a productive cough and bloody sputum. This is usually associated with pleural effusion. Patients who cough are very contagious. At this point another person can be infected by direct person-to-person transmission. It takes the form of a **very rapidly progressive pneumonia** with almost 100% mortality within a few days. Secondary pneumonic plague initially takes the form of interstitial pneumonia with a small amount of thick, viscous sputum, subsequently progressing to the symptoms described above. It is striking how unremarkable the auscultatory findings are. It is possible but not formally proven, that *Yersinia pestis* increases its virulence after repeated passage via the lungs.

Oropharyngeal plague

Oropharyngeal plague, in which the portal of entry is the throat (ingested flea, consumption of contaminated meat, dirty hands after touching contaminated animal tissues), takes the form of a serious disease with throat pain, severely enlarged painful cervical lymph nodes and local oedema (DD diphtheria, anthrax, tularemia).

Diagnosis

Consideration should be given to the possibility of plague, particularly if there is a sudden increase in **rodent mortality in an endemic region**. The diagnosis should be considered in healthy subjects who **suddenly become very severely ill with fever, extremely enlarged painful lymph nodes, brutal pneumonia or if a rapid succession of deaths occurs within one family**.

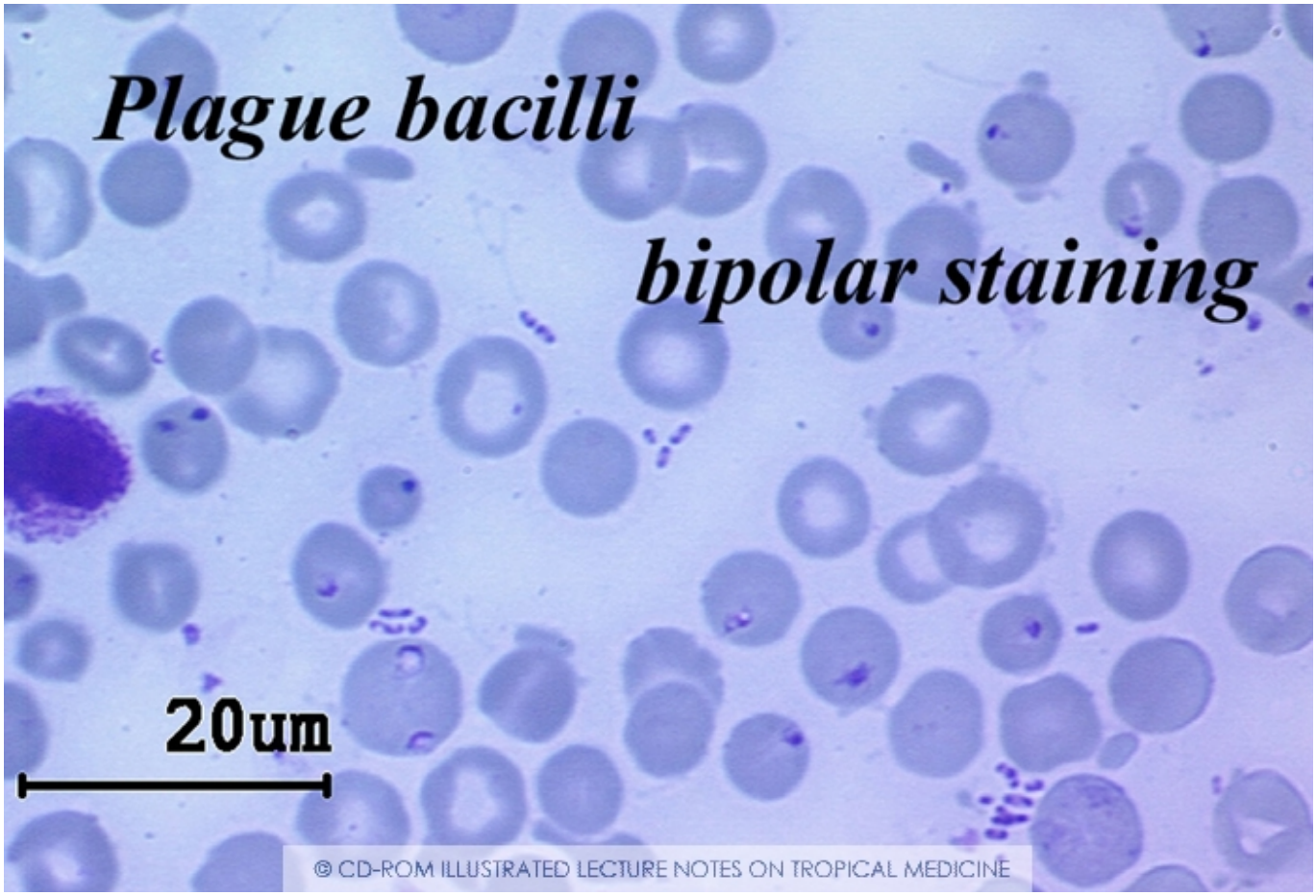
Extensive **leukocytosis** is present. **Microscopic examination** of aspirated fluid from a bubo, sputum, cerebrospinal fluid and/or peripheral blood shows bipolar Gram-negative bacilli. The buboes do not contain liquid pus. Some sterile saline (1 ml) is injected into a bubo in order to obtain an aspirate. In the words of Yersin, the fluid contains “une véritable purée de microbes”. Sometimes the bacteria can be detected in a thick or thin **blood smear**. They then have the appearance of a “safety pin” (bipolar granules). A staining method that reveals this clearly is the Wayson stain (based on basic fuchsin mixed with methylene blue in 95% ethanol and phenol). The organism is then light blue with darker terminal granules.

Culture is desirable for formal proof in view of the implications of a potentially threatening epidemic.

Serology is possible in specialised laboratories (e.g. ELISA for detecting antibodies to the F1 antigen). Approximately 5% of survivors do not seroconvert. Serology permits a retrospective diagnosis, but is not useful for the acute, individual patient.

There is also a technique available involving a dipstick coated with antibodies which can be used to detect **the F1 antigen**. This rapid test can use sputum or serum, as early as the second day of the disease. The result is known in 15 minutes and is thus clinically very useful for the individual patient and any contacts. F1-deficient mutants occur very rarely and cannot be detected with this dipstick method.

Presumptive identification of Y. pestis can also be made by polymerase chain reaction (PCR). PCR testing has been used to detect Y. pestis in skeletons which are hundreds of years old.



Blood smear with Yersina pestis bacteria. Copyright ITM

Differential diagnosis:

Bubonic plague, with its principal characteristic feature of acute buboes, need to be distinguished from:

- lymphogranuloma venereum (much slower progression)
- chancroid (slower, ulcers, fluctuating bubo)
- streptococcal/staphylococcal adenitis (general condition is good)
- filarial adenitis (progression, microfilaria, eosinophils)
- strangulated inguinal hernia.

Pneumonic plague takes the form of a rapidly progressing pneumonia. It can resemble

- a brutal bacterial pneumonia (e.g. pneumococcal)
- legionellosis, tularaemia
- anthrax, SARS (Coronaviral pneumonia)
- or hantavirus pulmonary syndrome (Sin Nombre virus).

An isolated case can be easily missed. In epidemics, there is the possibility that all pulmonary symptoms of all patients are attributed to pneumonic plague (e.g. patients with pneumococcal pneumonia may be viewed as having pneumonic plague).

Septicaemic plague develops very rapidly and resembles meningococcal septicaemia or other severe forms of Gram-negative sepsis. Confusion with acute rickettsioses (epidemic typhus) and louse-borne relapsing fever is possible.

Therapy

All patients should be **isolated**, including those with bubonic plague, because secondary pneumonic plague can develop. In 1948 it was discovered that **streptomycin** was active against the plague bacillus and this antibiotic still remains the first choice. In view of the high mortality and rapid progression, treatment must be initiated as soon as possible. The dose of streptomycin for adults is 2 x 1.5 g IM daily. If streptomycin is not available, gentamicin constitutes a good alternative. For gentamicin, a dose of 2 mg/kg tid is used. Hypotension should be treated, preferably with IV fluids. Improvement is rapid and most patients are afebrile after 3 days. It is not necessary to combine antibiotics. It is important to maintain therapy for at least 10 days.

Tetracyclines are an alternative to aminoglycosides: 2 to 4 g orally for 10 days. They are also very useful in epidemics. Quinolones are also active however not as effective and often are more expensive.

Chloramphenicol is indicated in plague meningitis and/or endophthalmitis. Initially it is given IV. After a few days, in most cases it becomes possible to switch to oral medication. Sulphonamides are also used as prophylaxis, but they are not the first choice. **Penicillins, cephalosporins and macrolides are inactive** against *Yersinia pestis*. Resistance to the common antibiotics is infrequent. Sometimes tetracycline-resistant strains are isolated. In

1995, a **multiresistant strain of *Yersinia pestis*** was isolated in Madagascar (resistance to streptomycin, kanamycin, chloramphenicol, tetracyclines, sulphonamides, ampicillin and spectinomycin). The resistance was coded by a plasmid. *Yersinia pestis* probably acquired the plasmid via horizontal transfer from another Gram-negative organism of the *Enterobacteriaceae* family.

Surveillance

Surveillance can be conducted in several ways. Carnivores can be regularly tested serologically and constitute a sensitive sentinel system of rodent plague in a specific area. *Yersinia pestis* can be detected in animals found dead in a region. The fleas can be collected from abandoned rodent nests, identified and tested. Live rodents can be captured and these animals and their fleas examined.

Prevention

Plague is a disease for which **international quarantine is mandatory** and cases must be **notified**. All patients with plague, irrespective of the presence of cough or pneumonia, should be treated in **strict isolation for at least 48 hours** (risk of secondary pneumonic plague with subsequent aerogenic transmission). The room should be decontaminated and sprayed with insecticides. Masks, goggles and protective clothing are indicated. Gloves should be worn when handling bubonic aspirates and blood.

Contacts may take tetracyclines (4 x 500 mg) or vibramycin for 1 week (ciprofloxacine or sulphonamides are an alternative). They should be closely monitored for 7-10 days.

Vaccination gives temporary protection against bubonic plague, but the vaccine is very difficult to obtain. Soldiers in the American forces during the Vietnam War were routinely vaccinated with a dead cell vaccine (3 primary injections followed by boosters, depending on the antibody titre in the blood). There was a much lower incidence in vaccinated than in the South Vietnamese forces (1/3000 cases per year of exposure).

Urban plague can usually be controlled by **quarantine** and by **rat control and flea eradication**. **Sylvatic plague cannot definitively be eradicated** in view of its animal

reservoir. In combating urban plague, **fleas should be controlled first and then the rats**. Otherwise a large number of fleas are suddenly released (since they no longer have any animal host) and then transfer to humans. It is important to have an idea of the susceptibility of the insects to various insecticides. As strains of *Xenopsylla cheopsis* and *Synosyllus fonquerniei* (flea vectors in Madagascar) have been found which were resistant to the insecticides DDT and dieldrin (organochlorine compounds), malathion or phenitrothion (organophosphates) and propoxur (carbamate). Such **resistance** data are useful if there is an outbreak.

Rat control involves the use of various methods, including rodenticides such as anticoagulants (warfarin, fumarin, bromadiolone, chlorophacinone), zinc phosphide, sodium fluoroacetate and strychnine. Rats are very social and intelligent animals and can learn to avoid poison, as well as teaching their nest mates to do so.

The concern about plague as a bioterrorism agent has led to the development of several newer vaccines, some of which are undergoing clinical testing.