8.6.17 Plague Yersinia pestis 1081

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1081 8.6.17 Plague: Yersinia pestis Michael Prentice ESSENTIALS Bubonic plague is a flea-borne zoonosis caused by the Gram-negative bacterium Yersinia pestis, which mainly affects small burrowing mam- mals including domestic rats. Human disease occurs in endemic countries—currently mainly in Africa (including Madagascar)—following bites from fleas recently hosted by a bacteraemic animal. Historical use of Y. pestis as a biological warfare agent has raised fears of its future use in bioterrorism. Clinical features—the commonest presentation is acute painful lymphadenitis (80–95% of suspected cases), with sudden onset of fever, chills, weakness, headache, and development of an intensely painful swollen lymph node (bubo). Primary septicaemia with no bubo occurs in 10% of cases. Spread to the lungs occurs in less than 10% of cases, resulting in pneumonia which can result in onward re- spiratory transmission by droplet infection. Overall mortality without treatment is 50–90%. Diagnosis and treatment—diagnosis is usually by culture from ap- propriate specimens (blood culture, bubo aspirate, sputum, cerebro- spinal fluid), but rapid confirmation can be provided by detection of Yersinia pestis F1 antigen by immunofluorescence or dipstick in clin- ical material. Aside from supportive care, early antimicrobial therapy (gentamicin, doxycycline, ciprofloxacin, levofloxacin, moxifloxacin, or streptomycin) greatly improves survival. Prevention—is by reducing the likelihood of people being bitten by infected fleas, or being exposed to infected droplets from humans or animals with plague pneumonia. Postexposure chemoprophylaxis may be advised for those who have been in unprotected close con- tact with a person with pneumonic plague. There is no current com- mercially available vaccine. Introduction Alexandre Yersin isolated the bacterium now known as Yersinia pestis in 1894 from a patient with bubonic plague in Hong Kong, during a plague pandemic when disease spread to ports all over the world from a focus in China. Most mortality in this pandemic was seen in India and China in the late 19th and early 20th cen- tury when millions died. Experimental work in India in the early years of the 20th century confirmed the flea–rat cycle of trans- mission, allowing rational control measures to be developed. This pandemic is called the third plague pandemic because of a retrospective association of bubonic plague with two historical disease pandemics. The second pandemic was the Black Death, which killed one-third of the European population between 1347 and 1352. The first plague pandemic refers to an outbreak

which began in the reign of the Roman Emperor Justinian in the 6th century AD. Ancient DNA studies have confirmed these histor- ically recorded pandemics were caused by Y. pestis strains closely resembling, but ancestral to, current pandemic strains. They have also shown Y. pestis was a common cause of septicaemic death across Europe and Asia over 5000 years ago in the Bronze Age, but was not at that time a primarily flea-transmitted pathogen. Studies combining geolocation data with phylogenetic trees of current and historical Y. pestis strains (Phylogeography) suggests plague emerged in the Qinghai-Tibet Plateau of China adjacent to intersecting ancient trade routes which later spread the disease. Aetiology Y. pestis strains form a clonal group within Y. pseudotuberculosis, an enteric pathogen of mammals spread by the faeco-oral route (this has implications for laboratory identification, see next; see also Other Yersinia, Chapter 8.6.18). These are Gram-negative bac- teria within the order Enterobacterales. Ancient DNA sequences (paleogenomics) and current pathogenicity studies have mapped a plausible stepwise evolutionary pathway for an ancestral Y. pseudotuberculosis-like organism to acquire a plague-causing phenotype. The starting point is that Y. pseudotuberculosis and Y. pestis both contain a virulence plasmid pYV which is essential to cause disease, and a very similar chromosome. Subsequent steps to respiratory and flea-bite transmission include gene acquisition in the form of two plasmids not present in Y. pseudotuberculosis, pPst (pPCP1) and pFra (pMT1), and then a handful of key inactivating mutations in Y. pseudotuberculosis genes among the many pseudo- genes identified in current Y. pestis strains. Functional predictions from Y. pestis genome sequences obtained from Bronze Age human remains suggest the earliest strains dating from 1700 to 2900 BC were capable of causing pneumonic and septicaemic plague, but could not cause bubonic plague. Strains capable of causing bubonic plague efficiently transmitted by flea vectors emerged sometime between the first and second century BC. Epidemiology Between 1 January 2010 and 31 December 2015, 3248 cases of plague in humans were reported to the World Health Organization, resulting in 584 deaths (18%), a decreasing incidence compared with previous years. The six countries reporting most of the cases over this period (accounting for over 99% of the total), were, in descending order: Madagascar, Democratic Republic of the Congo, Uganda, Peru, Tanzania, and the United States. Notably, the very large enzootic focus covering the western United States contrib- uted only 39 human cases (five fatalities) over this period. Ninety- six per cent (96%) of cases were reported from Africa (including Madagascar). In 2017 Madagascar experienced a large outbreak of 2300 cases; 76% pneumonic, 8.6% fatal. The plague is seasonal in most endemic countries, with a well-defined geographical distribution correlated with that of
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 the predominant flea vectors and rodent reservoirs, and their ecology. Most cases in the United States occur from May to October, when people are outdoors in contact with rodents and their fleas. Plague is a zoonosis with humans figuring as an incidental host. It is transmitted among animal reservoirs by flea bites and ingestion of animal tissues. The fleas of many major animal reservoirs such as burrowing rodents including ground squirrels and prairie dogs in the United States and tarbagans in Asia, can only contact humans in rural areas. Human infection is more frequent when disease occurs in small mammals in closer contact with humans, particularly urban and domestic rats. The oriental rat flea Xenopsylla cheopis is the most efficient vector. Risk factors for acquiring plague include contact with rodents or carnivores in endemic areas and presence of ref- uges or food sources for wild rodents near homes. Human to human transmission of pneumonic plague is limited to rare outbreaks in endemic areas. Fatal

plague pharyngitis has been reported following consumption of raw camel meat in endemic areas. Although there are no reports of the use of Y. pestis as a biological weapon since World War II, the possibility of bioterrorism would nowadays be in- vestigated if any case of plague, particularly pneumonic plague, was diagnosed in a nonendemic area (e.g. Europe, Eastern United States of America). Pathogenesis/Pathology In the arthropod-parasitizing portion of its life cycle, Y. pestis multiplies and forms biofilm-embedded aggregates in the flea midgut and foregut after ingestion of a blood meal containing bacteria from a mammalian host. Blocked fleas die, but make persistent efforts to feed, regurgitating oesophageal contents and inoculating Y. pestis into each bite site. Some fleas might be long- lived successful vectors without blockage. The ability to colonize and multiply in the flea midgut requires the phospholipase D activity encoded by the ymt gene on the pMT1 (pFra) plasmid. Experiments trying to achieve Y. pseudotuberculosis transmis- sion by fleas have shown that as well as adding a ymt gene, mu- tation of a small number of chromosomal genes which are intact in Y. pseudotuberculosis is required to prevent rapid flea death on infection (caused by urease activity) and promote biofilm formation. These mutations are present in all current Y. pestis strains. However, the ymt gene and most of these chromosomal mutations are absent from early Bronze Age Y. pestis sequences. This suggests plague in humans began as a disease spread by the respiratory or oral route, and efficient flea transmission, which is currently the most common mode of transmission, is a more recent development. Several key features of mammalian Y. pestis infection affecting transmissibility require a plasminogen activator protease expressed on its surface, encoded by the pla gene on the small pPst (pPCP1) plasmid. Pla is essential for Y. pestis to cause primary pneumonic plague, and the pla gene is present in the earliest Y. pestis sequences from Bronze Age human remains. It is also required after intra- dermal inoculation for multiplication in lymph nodes (bubo forma- tion) and enhances systemic spread as bacteraemia following bubo formation. There is evidence of recent evolution of Pla facilitating Y. pestis transmission by fleas. All current pandemic Y. pestis strains contain the same point mutation in pla when compared to current nonpandemic Y. pestis strains which are closer to Y. pseudotuber- culosis in phylogeny, and the early Bronze Age Y. pestis sequences. This mutation optimizes protease activity in vitro, but both sequence variants confer the ability to cause primary pneumonic plague on Y. pestis when tested in animal models. However, the current pan- demic Y. pestis strain variant of Pla increases bacteraemia following primary pneumonic plague or subcutaneous inoculation compared to the ancestral form. Maintenance of flea transmission requires extreme virulence in the mammalian host. Because of the small volume of blood in a flea meal and a large minimum infectious dose for the flea, a very high level of bacteraemia (108/ml) is required in the mammalian host to infect fleas. Few bacteria are transmitted by a flea bite and the organism has a low minimum infectious dose for mammals. In the most common current form of plague, bubonic plague, flea bites inoculate Y. pestis at approximately 26ºC. Y. pestis travels inside macrophages to the regional lymph nodes from the site of inocula- tion before switching to extracellular replication in growing necrotic foci containing large numbers of bacteria. This results in a swollen and painful lymph node termed a bubo. Extracellular survival re- quires expression of a type III secretion system (injectisome) encoded by the Yersinia virulence plasmid pCD/pYV to inject viru- lence effectors (Yop proteins) into mammalian host immune effector cells. This forestalls the usual immune response, preventing phago- cytosis. The injectisome component LcrV (V antigen) also has an extracellular anti-inflammatory activity, preventing recruitment of inflammatory cells and granuloma formation which would nor- mally terminate an infection. An antiphagocytic polypeptide cap- sule (fraction 1 or F1 antigen), specified by the caf1 gene on the pFra/pMT1 plasmid, may also be important in mammalian patho- genesis in some host species. Primary

pneumonic plague occurs following inhalation of in- fected respiratory droplets from another person or animal. In con- trast to bacteria inoculated by flea bite, bacteria inoculated in this way are already growing at 37ºC. Several important Y. pestis viru- lence factors are highly expressed at 37ºC but not 26ºC, so the pathogen is pre-armed when transmitted by this route. Animal models suggest that primary pneumonic plague is a biphasic illness with extensive manipulation of the host intrinsic immune response by Y. pestis. In a mouse model, during an initial preinflammatory phase lasting about 36 hours, extensive bacterial replication occurs in the lungs with little inflammatory response due to targeting of al- veolar macrophages by type III secretion effectors and effects of Pla on neutrophil recruitment. After 36–48 hours, a proinflammatory phase begins with upregulation of proinflammatory cytokines and influx of neutrophils to the alveolar spaces. Pla is required for this switch to inflammation to occur, but the precise mechanism is un- known.
Y. pestis can resist neutrophil-mediated killing with its type III secretion system and bacterial numbers remain high. By 72 hours after infection the continuous recruitment of neutrophils to the lungs in response to persistent replicating bacteria results in severe inflammatory damage to alveolae, with oedema and haemorrhage. The damage is thought to be caused by neutrophil-associated highly

 reactive oxygen species and proteases. The frequently fatal necrotic pneumonia of primary pneumonic plague is therefore primarily host-response-mediated.
Clinical features The most common presentation is acute painful lymphadenitis (80–95% of suspected cases). There is sudden onset of fever, chills, weakness, and headache. At the same time, or shortly afterwards, patients notice the bubo, which is signalled by intense pain in one anatomical region of lymph nodes, usually the groin, axilla, or neck (Fig. 8.6.17.1). The swelling is so tender that patients avoid any mo- tion that might provoke discomfort. If the bubo is in the femoral area, the patient will flex, abduct, and externally rotate the hip to relieve pressure on that area, and will walk with a limp. With an ax- illary bubo, the patient will abduct the shoulder or hold the arm in a splint. When the bubo is in the neck, patients will tilt their neck to the opposite side. Buboes are oval swellings varying from 1 to 10 cm in length and elevate the overlying skin, which might appear stretched or ery- thematous. They can be a single smooth uniform mass, or an ir- regular cluster of several nodes with intervening and surrounding oedema. Overlying skin is warm with an underlying tender, firm nonfluctuant mass. Patients are typically prostrate and lethargic, but can show restlessness or agitation. Occasionally, they are delirious with fever, and seizures are common in children. Fever of 38.5–40°C is usual, with pulse of 110–140/min. Blood pressure is characteristic- ally low, 100/60 mm/Hg and may be unobtainable if systemic sepsis syndrome occurs as a consequence of the host response to large amounts of circulating bacterial endotoxin. As part of this response, disseminated intravascular coagulopathy can occur involving arteri- olar thrombosis, skin and serosal haemorrhage, acral cyanosis, and tissue necrosis, as well as multiple organ failure and adult respira- tory distress syndrome. A minority of patients (10–20%) develop systemic Y. pestis sepsis with no bubo (primary septicaemic plague) and less than 10% develop secondary pneumonic plague or menin- gitis as a consequence of bacteraemia. Prevention Plague prevention measures seek to reduce the likelihood of people being bitten by infected fleas, or exposed to infected droplets from humans or animals with plague pneumonia. In plague-endemic areas, monitoring and control of the local plague hosts is important, as well as rat-proofing and insecticide treatment of houses, and wearing shoes and garments to cover the legs. Because removing the flea food supply by poisoning their normal hosts can increase human contact with starving fleas, flea control by application of insecticides prior to vector control in plague outbreak

areas is required. Infection control meas- ures for patients with suspected pneumonic plague centre on respira- tory isolation with droplet precautions (wearing of disposable masks by medical attendants to reduce the risk from large respiratory drop- lets) until they have received antibiotic treatment for 48 hours. For potential aerosol generating procedures (eliciting respiratory samples from suspected plague patients) WHO now recommends personal protective equipment (PPE) such as an N95 face mask, gown, gloves and face shield or goggles should be worn. Postexposure chemo- prophylaxis is advised for persons who have been in unprotected close contact (defined as coming within 2 m) with a person with pneu- monic plague who has not received antibiotic treatment for at least 48 h. Doxycycline, ciprofloxacin, levofloxacin, chloramphenicol, or cotrimoxazole can be used as prophylaxis. Standard isolation precau- tions are recommended for nonpneumonic plague patients. There is no currently commercially available plague vaccine in the Western world. A live attenuated vaccine based on a former French vaccine strain Yersinia pestis EV is licensed in China, Russia, and some other former Soviet Union countries to protect against bubonic and pneumonic plague when administered by par- enteral or oral routes. A large variety of candidate plague vaccines are under development. Subunit vaccines, mostly based on com- binations of mixed or fused immunogenic plasmid-specified pro- tein antigens LcrV and Fraction 1, which in some animal models protect against pneumonic challenge, administered by injection with an adjuvant, have been brought through Phase II trials in dif- ferent countries. T-cell mediated immunity is important in mouse immunity to pneumonic plague and various live vaccines likely to induce cellular immune responses to Y. pestis antigens have also been constructed. Attenuated bacterial vaccines based on heter- ologous expression of antigens including LcrV and Fraction 1 in different hosts such as the established vaccine strain Salmonella enterica Serovar typhi Ty21A, attenuated Salmonella enterica Serovar typhimurium or attenuated Yersinia pseudotuberculosis have been protective in animal trials. Viral delivery platforms de- veloped for other vaccines have been used in animals for delivery Fig. 8.6.17.1 A right femoral bubo consists of an enlarged, tender lymph node with surrounding oedema. Copyright D. A. Warrell.

section 8 Infectious diseases 1084 of FI/LcrV and other Y. pestis antigens. An oral live recombinant raccoon poxvirus vaccine expressing both Yersinia pestis F1 and truncated LcrV is under field trials in the United States for efficacy in prevention of sylvatic plague in rodents. Differential diagnosis Other infections producing acute lymphadenitis (Streptococcal lymphadenitis, cat scratch fever, and so on) do not generally share the same suddenness of onset leading to death 2 to 4 days after the onset of symptoms. The plague bubo is also distinctive in the usual absence of a detectable skin lesion or ascending lymphangitis. A mi- nority of patients show various skin lesions (pustules, eschars, or papules) presumably representing the site of flea bite in the skin area draining to the bubo (Fig. 8.6.17.2). Clinical investigation The diagnosis should be suspected in febrile patients exposed to rodents or other mammals in endemic areas. Y. pestis is on a short list of pathogens to be excluded in any unexplained outbreak of se- vere respiratory disease which could follow an aerosol release by bioterrorists. Appropriate diagnostic specimens include blood culture (usu- ally positive in bubonic plague), bubo aspirate, sputum, and cere- brospinal fluid (CSF), depending on clinical presentation, and, if necessary, post-mortem. A bubo aspirate is obtained by inserting a 10-ml syringe with a 21-gauge needle containing 1 ml of sterile saline, through the skin, into the bubo. The saline is injected and reaspirated until blood-tinged fluid appeared in the syringe. Y. pestis grows on standard laboratory media and standard trans- port media preserves viability. The organism is characterized as a slow growing, nonlactose fermenting, nonmotile Gram-negative rod, first seen at 24 hours on standard laboratory media; oxidase negative, catalase posi- tive, urease

negative, indole negative. It may be misidentified as Y. pseudotuberculosis or another Gram-negative species by routine commercial identification systems, including matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI- TOF MS). It is important to notify the laboratory if the diagnosis is clinically suspected. In the United States Yersinia pestis is a ‘Tier 1 select agent’ under bioterrorism legislation and diagnostic cultures are strictly notified and controlled. Gram stain of smears of sputum, bubo aspirate, or CSF may show small Gram-negative rods or cocco-bacilli, bipolar staining can be seen with Wayson or Giemsa stains (Figs. 8.6.17.3 and 8.6.17.4). Rapid diagnosis is provided by detection of Yersinia pestis F1 antigen by im- munofluorescence in clinical material. An F1-antibody containing dipstick has been shown to be a sensitive and specific assay in field con- ditions in Madagascar on a variety of clinical specimens (sputum, bubo Fig. 8.6.17.2 Right axillary bubo was accompanied by a purulent ulcer on the abdomen, which was the presumed site of the flea bite. Copyright Tom Butler. Fig. 8.6.17.3 Bubo aspirate shows bipolar bacilli stained with methylene blue (Wayson’s Stain). Copyright Tom Butler. Fig. 8.6.17.4 Gram stain of spinal fluid in plague meningitis shows numerous Gram-negative bacilli. Copyright Tom Butler.

1085 aspirate, CSF). Current trials of this dipstick in Africa are ongoing. Polymerase chain reaction assays for various targets and an enzyme- linked immunosorbent assay (ELISA) for Yersinia pestis LcrV antigen have also been developed, but are not in routine clinical use. Criteria for diagnosis Culture of the organism, F1 antigen detection, or seroconversion (a fourfold or greater titre change) to Y. pestis F1 antigen by passive haemagglutination testing of paired serum specimens (PHA test) are all criteria for diagnosis. Specificity of the PHA test requires confirmation with the F1 antigen haemagglutination-inhibition test. Seroconversion can occur 5 days after onset of symptoms, but is more usual between 1 and 2 weeks after onset. Treatment Streptomycin is traditionally regarded as the most effective treatment for plague at a dose of 1 g twice daily (30 mg/kg/per day) for 10 days, and was the first antimicrobial shown to be effective against pneu- monic plague. The more readily available aminoglycoside gentamicin is as effective as streptomycin in the treatment of human plague, when given at standard doses for severe sepsis. Seven-day courses of intramuscular gentamicin 2.5 mg/kg 12 hourly or oral doxycycline therapy 100 mg (adults) and 2.2 mg/kg (children) orally 12 hourly are highly effective in adults and children with bubonic, septicaemic or pneumonic plague (tetracyclines are contraindicated in preg- nancy, breastfeeding, and children younger than 7 because of tooth discolouration). In a mouse septicaemia model, third-generation cephalosporins and quinolones were as effective as streptomycin and tetracycline. In a mouse model of pneumonic plague, β-lactam anti- biotics were less effective than aminoglycosides and quinolones. Oral chloramphenicol is recommended for plague meningitis at a loading dose of 25 mg/kg followed by 60 mg/kg per day in four divided doses, reducing to 30 mg/kg per day orally on clinical improvement to complete a total course of 10 days. General therapeutic measures for systemic bacterial sepsis, including intravenous fluids, are appro- priate but no available trial data for the use of these in plague is avail- able. A consensus view of treatment for pneumonic plague resulting from biological weapon attack suggests streptomycin, gentamicin, tetracycline, or fluoroquinolones can be effective. The quinolones ciprofloxacin, moxifloxacin and levofloxacin have been approved by the Food and Drug Administration (FDA) for pneumonic and septicaemic plague treatment based on efficacy in a primate animal model, and partly because they also show efficacy against other po- tential bioterrorism organisms such as Bacillus anthracis. Although still very rare, natural antimicrobial resistance has been detected. A wild-type Y. pestis strain resistant to multiple antimicrobials was first reported from Madagascar in 1997, and subsequently a different strain resistant to the first-line antibiotic streptomycin was also identified. Worryingly, both

plasmids respon- sible for these resistance patterns were self-transferrable to other bacteria. Fortunately, no other Y. pestis strains with multiple anti- microbial resistance have subsequently been isolated in Madagascar. A nonpandemic strain of Y. pestis resistant to several antimicrobials was isolated from an animal in Mongolia. Prognosis Untreated bubonic plague has a mortality of 50–90% and un- treated meningitis, pneumonia or septicaemia is fatal in most cases. Diagnosis and appropriate therapy reduces bubonic plague and septicaemia mortality to 5–20% but delay in diagnosis and therapy can be fatal. Primary pneumonic plague mortality in the older litera- ture was reported to approach 100% untreated and be up to 50% with delayed antimicrobial therapy. However in the 2017 Madagascar pneumonic plague outbreak, the WHO reported overall case fatality rates of under 10%. Areas of uncertainty or controversy Although several FI-LcrV subunit vaccines have been developed in different countries they have not been commercialized, partly be- cause of concerns about vaccine escape with F1-negative strains and LcrV polymorphisms, and conflicting animal data on protection against aerosol challenge. Likely developments over the next 5–10 years Novel vaccines in clinical use for animals and people might affect epidemiology. More detailed paleogenomic data on the Y. pestis evo- lution timeline may be available. Manipulation of the host response in animal models might suggest a strategy to reduce primary pneu- monic Y. pestis mortality. FURTHER READING Achtman M, et al. (1999). Yersinia pestis, the cause of plague, is a re- cently emerged clone of Yersinia pseudotuberculosis. Proc Natl Acad Sci U S A, 96, 14043–8. Dennis DT, et al. (1999). Plague manual: epidemiology, distribution, surveillance and control. World Health Organization, Geneva. http:// www.who.int/csr/resources/publications/plague/WHO_CDS_ CSR_EDC_99_2_EN/en/ Hinnebusch BJ, Chouikha I, Sun YC (2016). Ecological opportunity, evolution, and the emergence of flea-borne plague. Infect Immun, 84, 1932–40. Kool JL (2005). Risk of person-to-person transmission of pneumonic plague. Clin Infect Dis, 40, 1166–72. Mead PS (2018). Plague in Madagascar—a tragic opportunity for improving public health. N Eng J Med, 378, 106–8. Mwengee W, et al. (2006). Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. Clin Infect Dis, 42, 614–21. Pechous RD, et al. (2016). Pneumonic plague: the darker side of Yersinia pestis. Trends Microbiol, 24, 190–7. Rasmussen S, et al. (2015). Early divergent strains of Yersinia pestis in Eurasia 5,000 years ago. Cell, 163, 571–82. Riddell SW, Kiska DL, Mahlen S (2016). Sentinel level clinical lab- oratory guidelines for suspected agents of bioterrorism and emerg- ing infectious diseases: Yersinia pestis. American Society for Microbiology, Washington, DC. https://www.asm.org/images/ PSAB/LRN/Ypestis316.pdf 8.6.17 Plague: Yersinia pestis

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