



Public Health
England

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Plague: interim guidance for clinicians in England managing suspected cases

November 2017

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1. Scope and summary of key actions

This guidance considers plague in returning travellers, laboratory-associated plague, and pneumonic plague acquired through human-to-human transmission in the context of a plague outbreak occurring outside the UK.

Local infectious disease specialists/microbiologists should be **consulted early**. The **Imported Fever Service** (IFS) offers additional specialist advice and clinicians are encouraged to **use this service promptly**. Direct PCR testing of clinical specimens, if indicated, is only performed at the **PHE Rare & Imported Pathogen Laboratory** after discussion with the IFS. (Refer to main text for further information)

<p>Implement appropriate Infection Control Procedures (IPC)</p>	<ul style="list-style-type: none"> • Isolation in a single side room, preferably negative-pressure • Standard airborne PPE/RPE: FFP3 mask, face protection, fluid-repellent gown, disposable gloves
<p>Send samples for diagnostic testing</p>	<p>WARN LABORATORIES OF SUSPICION OF PLAGUE All specimens should be packed securely and appropriately before transport to the laboratory (refer to local policy for high hazard pathogens)</p> <p>Obtain the following samples:</p> <ul style="list-style-type: none"> • sputum in all cases if possible; send for MC&S, and PCR* • EDTA blood for direct microscopy • blood cultures in all cases • EDTA blood for PCR if indicated • Needle aspiration of bubo if present for MC&S, and PCR* • CSF if meningitis for glucose, protein, MC&S, and PCR* <p>*Direct PCR testing requires prior discussion with IFS</p>
<p>Empirical antimicrobial therapy</p>	<ul style="list-style-type: none"> • do not wait for confirmed diagnosis – include appropriate treatment for plague in empirical regimen. • gentamicin 5mg/kg once-daily is first-line therapy for adults in most cases*; alternative is doxycycline 100mg bd. • remember to cover other common pathogens if treating empirically according to clinical syndrome. Use chloramphenicol for suspected plague meningitis. <p>* hospitals may wish to apply standard dosing practice (eg 7mg/kg once daily with monitoring of levels) if it is more convenient</p>
<p>Public Health actions</p>	<p>Plague is a notifiable disease. The local (to the patient) Health Protection Team should be informed as soon as a case is suspected.</p>

2. Background

Plague is caused by infection with *Yersinia pestis*. Rodents are the main reservoir of infection and people are most commonly infected through rodent flea bites.

Plague occurs in several countries in Africa, Asia, South America and the USA ([see map](#)). Between 2010 and 2015, there were 3,248 cases reported worldwide. Annually, most human cases occur in Africa, with Madagascar considered to be the most highly endemic country.

Infection with *Yersinia pestis* results in a variety of classical syndromes. The main clinical forms of plague infection are bubonic, pneumonic and less frequently, septicaemic plague and rarely, meningial and pharyngitic plague can occur, and atypical and non-specific presentations of infection have been reported. Bubonic plague is the most common form and is spread by bites from infected fleas from rats, while the pneumonic form is mainly spread by person-to-person transmission. Laboratory exposure may also lead to pneumonic plague.

The incubation period is generally 2-6 days (upper limit 8 days), but can be very short (even hours) after inhalation of infected droplets. The case fatality rate is high. Untreated bubonic plague has a fatality rate of 50% to 60%, which decreases to 10% to 20% with early antibiotic treatment. Untreated pneumonic plague is universally fatal. Appropriate antibiotic therapy has been shown to reduce the mortality rate to 50%. Delayed antibiotic therapy is associated with a worse prognosis.

3. When to consider plague in the context of a recognised outbreak

Plague should be considered in an individual with acute onset illness that is compatible with bubonic, pneumonic, septicaemic, meningial or pharyngeal plague (see below)

AND

the individual has travelled to an area with an active plague outbreak within the last 8 days

OR

the individual has had close contact (unprotected and within 2 meters) with a known or suspected case of plague, within the last 8 days

OR

the individual is a laboratory worker, pathologist or healthcare worker who may have been exposed to respiratory tract secretions, respiratory droplets or aerosols, microbiological cultures or body tissues from a known or suspected case of plague within the last 8 days

If an individual meets these criteria, the key responses as outlined in this guidance are:

1. Appropriate infection prevention and control measures
2. Relevant sampling for plague diagnostic testing
3. Appropriate empirical antibiotic therapy
4. Public health actions

Compatible clinical features

Bubonic plague

Bubonic plague accounts for 80-95% plague cases. Patients develop sudden onset of fever, headache, chills, and weakness and one or more swollen, tender, and painful lymph nodes (buboes). Buboes are typically non-fluctuant and may be associated with erythema and oedema of the surrounding skin. The inguinal lymph nodes are most commonly affected, but buboes may be found elsewhere e.g. axillary or cervical regions.

Pneumonic plague

Pneumonic plague results from haematogenous spread of infection from a bubo or another focus (secondary pneumonic plague), particularly if diagnosis and treatment of plague are delayed, or by direct inhalation of infected droplets (primary pneumonic plague). This latter represents the main route of human-to-human transmission, and is a feature of the current Madagascar outbreak.

Patients develop fever, headache, weakness, and a rapidly developing pneumonia with shortness of breath, chest pain, and cough. Sputum may be watery or purulent and is often blood-stained. Pulmonary haemorrhage may occur.

Bronchopneumonia, consolidation, cavities, or pleural effusions may be present on chest radiographs or CT imaging. Hilar or mediastinal lymphadenopathy may be present.

Septicaemic plague

Patients develop fever, chills, extreme weakness, gastrointestinal disturbance (abdominal pain, nausea, vomiting, diarrhoea), and shock. There may be bleeding into the skin (purpuric lesions) and other organs. Peripheral gangrene, multi-organ dysfunction and disseminated intravascular coagulation may develop later in the course of illness.

In some cases, localising signs and symptoms are absent at presentation; in others, septicaemic plague occurs secondarily to bubonic or other forms of plague, particularly if diagnosis and treatment is delayed.

Meningeal plague

Meningeal plague is uncommon. It may occur in conjunction with other forms of plague, or it may occur as a primary manifestation of infection. Symptoms and signs are similar to those seen in meningitis caused by other, more common bacteria.

Pharyngeal plague

Pharyngeal plague presents as pharyngitis and/or tonsillitis, with associated anterior cervical lymphadenitis. It is rare and may occur as a primary phenomenon or in conjunction with other forms of plague.

Atypical presentations

Atypical and non-specific presentations of plague have been described, including patients who have presented with influenza-like illness or non-specific febrile illnesses, and patients who presented with symptoms and signs suggestive of urinary tract infection, gastrointestinal infection, and upper respiratory tract infection.

4. Infection prevention and control requirements

Plague can spread from person-to-person in health care settings, primarily through contaminated droplets, direct contact with the patient or infected body fluids and by indirect contact with contaminated surfaces. It is less clear whether aerosol transmission can occur, but the greatest risk is likely related to aerosol-generating procedures in health care settings, which should be kept to a minimum. The risk of aerosol transmission from pneumonic or pharyngeal plague is probably very low; and likely negligible from bubonic plague, the commonest form, although this can evolve into pneumonic plague.

A recommended and pragmatic approach in the UK is to take appropriate measures to protect health care workers from aerosol transmission in addition to droplet transmission during the period of transmissibility. Therefore, the relevant control measures outlined below should be implemented to protect health care workers until the diagnosis has been excluded or a confirmed case has received 72 hours of appropriate antimicrobial therapy and is improving clinically.

Isolation

Patients with suspected or confirmed plague should be treated in an airborne isolation room (preferably a negative pressure isolation room, or an isolation room with a positive pressure ventilated lobby). If this is not possible, use a standard isolation room (defined as a single room with en-suite toilet and shower and a lobby where PPE can be stored, donned and doffed, and hands washed). A negative pressure room should be used if aerosol-generating procedures are undertaken. Positive pressure rooms should not be used.

Personal protective equipment, including respiratory protective equipment (PPE/RPE)

PPE/RPE should be used for the assessment of possible plague cases and treatment of confirmed cases, and should be worn at all times when in the isolation room. This comprises:

- FFP3 respirator (EN149:2001), fit tested to the wearer
- single-use fluid-repellent gown
- single-use gloves
- eye protection e.g. goggles or full face visor, preferably single-use

Only health care staff who are trained and competent in the use of this equipment should enter the patient's room. Particular care must be taken during doffing and disposal of PPE/RPE to avoid personal contamination.

Access to the patient environment

Access to the isolation room should be restricted to essential staff only.

Visits by friends and families should be restricted for cases of suspected or confirmed plague, particularly pneumonic plague. If a visit is considered essential, then visitors should use PPE under supervision of clinical staff. However, the hospital should be mindful of its responsibilities to persons who are not employees, under The Control of Substances Hazardous to Health Regulations 2002 and The Management of Health and Safety at Work Regulations 1999. Visitors should be excluded when aerosol-generating procedures are performed.

A register should be kept of all staff and visitors who enter the isolation room or who have contact (within 2 meters) with the patient.

Movement of patients

Transport of patients should be limited to providing essential medical investigations only. Portable investigations (eg portable chest radiography) should be performed where possible. If transport to other departments is unavoidable, the patient should wear a surgical facemask when being transported, to minimise the spread of infectious droplets.

Laundry

All reusable linens should be bagged and managed as "infectious laundry".

Cleaning and waste management

Contaminated environmental surfaces should be cleaned with hypochlorite solution (1000ppm available chlorine). Clinical waste should be managed according to local standard policies. Terminal cleaning should be performed at the end of care, using hypochlorite solution (1000ppm available chlorine).

For patients unable to use an *en suite* toilet, it is recommended that single-use bedpans and urine bottles are used and that these, along with excreta, are disposed of as clinical waste. If possible, liquid excreta should be solidified with high-absorbency gel. Bowel management systems and their contents should also be disposed of as clinical waste.

5. Biological sampling for laboratory diagnosis

Detection of *Y. pestis* by microscopy and culture in local laboratories, supported by reference laboratory testing, is the principal method of diagnosis. In addition, concurrent PCR testing of clinical specimens should be discussed with the [Imported Fever Service](#).

Clinicians should alert the local laboratory by telephone before sending any specimens. The local microbiologist should ensure that all specialist or reference laboratories receiving specimens are aware of the possibility of plague. Such notification enables laboratories to handle specimens at the appropriate containment level and minimise risk of transmission to laboratory staff.

Specimen tubes should be labelled prior to collection of the specimen.

All suspected cases

The following samples should be obtained from all possible cases of plague.

- sputum* for microscopy, culture and sensitivity testing (sterile screw-cap universal container or screw-top sputum container)
- sputum* for PCR[#] (sterile screw-cap universal container or screw-top sputum tube)
- blood for direct microscopy (in an EDTA tube)
- blood cultures
- blood for PCR[#] (in an EDTA tube)

* Sputum specimens should be sought in all cases, but particularly in cases of suspected pneumonic plague in which Gram-negative rods with characteristic appearance (suggestive of *Y. pestis*) may be seen on sputum microscopy. If the patient is intubated, obtain an endotracheal aspirate using a closed-suctioning system.

[#]The [Rare and Imported Pathogens Laboratory](#) (RIPL) at PHE Porton Down offers PCR testing of clinical specimens. RIPL will only accept specimens from cases that have been discussed with the [Imported Fever Service](#) in advance. PCR may provide more rapid detection, but it does not replace the requirement for local microscopy, culture and sensitivity testing. Clinicians are advised to **discuss all suspected cases** with the [Imported Fever Service](#).

Patients with buboes

Needle aspiration should be attempted, taking utmost care to avoid inoculation injuries. If no fluid or pus is obtained, a small amount of sterile saline can be injected into the

bubo and re-aspirated. The aspirate should be divided between two sterile universal containers: one for microscopy, culture and sensitivity, and one for PCR detection.

Patients with CNS involvement

CSF should be collected into sterile universal containers and analysed as for any case of bacterial meningitis, but alert all laboratories to the possibility of plague prior to analysis. In cases of meningeal plague, CSF studies typically reveal low glucose, increased protein, and a neutrophil pleocytosis. A CSF sample should also be retained for PCR detection.

Patients with pharyngeal involvement

Obtain a bacterial throat swab (Amies medium), ensuring that the palatopharyngeal arch is sampled. Throat-swab specimens are not ideal for isolation of *Y. pestis*, since they often contain many other bacteria that can mask the presence of *Y. pestis*. If available, a plain swab (without bacterial transport medium) may also be retained for PCR detection.

Diagnostic specimen handling and packaging

Remove any visible contaminating material (eg sputum or pus) on the outside of specimen containers with a paper towel. Disinfect the external surfaces of specimen tubes using wipes known to be active against *Yersinia* bacteria, or wipe down with 0.5% chlorine solution. Specimens should then be placed in an appropriate secondary container eg a screw-top Biojar. Specimens for different destinations (eg local and reference laboratories) should be packaged into separate secondary containers. Disinfect the external surfaces of the secondary container(s) before it leaves the isolation room.

Ensure that the secondary container is packed and labelled appropriately for transport to the laboratory.

Provide all relevant clinical information on the request form, including antibiotic therapy. Ensure that plague is mentioned in the request. Liaise with the laboratories so that they know to expect the specimens and that plague is being investigated or treated.

Requesting other laboratory tests

Routine haematology and biochemistry analysis of blood specimens can be performed locally, but local laboratories should be alerted about suspected or confirmed plague before the specimens are sent; this should also be made clear on request forms/electronic requests. Testing for malaria may also be performed locally. Clinical

laboratories should refer to the [separate guidance on laboratory procedures and diagnosis](#).

Public Health notifications

The [PHE Health Protection Team \(HPT\)](#) local to the patient's usual residence should be notified as soon as plague is suspected. The HPT will require a clinical summary, a detailed travel history, information about potential or known contacts, and information about the plan for diagnostic testing.

Plague is a notifiable disease under the Health Protection (Notification) Regulations 2010. *Yersinia pestis* is a notifiable organism (causative agent) under the Health Protection (Notification) Regulations 2010. [Further information on notification for clinicians and laboratories](#) is available..

6. Antibiotic therapy

All forms of plague are associated with a high mortality rate and, in addition, pneumonic plague can be associated with human-to-human transmission. Treatment with appropriate antibiotics has been shown to reduce mortality. Therefore, all patients with suspected plague should be treated empirically with antibiotics, as soon as the possibility of plague has been raised and before laboratory confirmation of infection has been received.

Streptomycin, tetracycline and chloramphenicol are the antibiotics traditionally used in the treatment of plague. Streptomycin has historically been the treatment of choice, particularly for severe infections, but is not widely available in the UK. Other aminoglycosides, such as gentamicin and kanamycin, have been successful in treatment of plague. A review of a small number of plague cases between 1985 and 1999 in New Mexico suggests that gentamicin (either alone or in combination with tetracycline) was as effective as streptomycin. A randomised clinical trial of gentamicin (2.5mg/kg IM every 12h for 7d) and doxycycline (100mg for adults and 2.2mg/kg for children orally every 12h for 7d) found that both antibiotics were effective monotherapies for adult and paediatric plague with high rates of response (94% and 97% respectively) and low rates of adverse events. Doxycycline is an acceptable alternative to gentamicin in patients (12 years and older and >45kg) who cannot tolerate aminoglycosides.

There is no clinical experience with fluoroquinolones for the treatment of human infection, although *in vitro* susceptibilities and animal experiments suggest that they would be effective for the treatment of plague.

Irrespective of the antibiotic used, the optimal duration of treatment is unknown. A duration of ten days is recommended by WHO, but some patients may require longer treatment according to clinical and microbiological response. Regimens may also require adjustment depending on a patient's age, medical history, underlying health conditions, or allergies.

Recommended antibiotics for plague

	Antimicrobial agent	Duration
Adult	<p>Gentamicin* (first choice in pregnancy) 5mg/kg intramuscularly or intravenously once a day OR Doxycycline 100mg orally twice daily OR Ciprofloxacin‡ 400mg intravenously twice daily, or for milder cases only, 500mg – 750mg orally twice daily</p> <p>OR <i>if meningeal plague is suspected:</i> Chloramphenicol given as a loading dose (25 to 30 mg/kg body weight; maximum 2 g) followed by 50 to 60 mg/kg per day (maximum 4 g per day) in four divided doses. The dose may be reduced to 25-30 mg/kg per day following clinical improvement.</p>	10 days
Child	<p>Gentamicin* 5mg/kg intramuscularly or intravenously once a day OR Doxycycline 100mg orally twice daily (NB: >12yrs and >45kg) OR Ciprofloxacin‡ 10mg/kg intravenously twice daily (maximum 400mg - not to exceed 800mg per day) or for milder cases only, 15mg/kg orally twice daily (not to exceed 1g per day)</p> <p>OR <i>if meningeal plague suspected:</i> Chloramphenicol 25mg/kg (maximum 500mg) orally or intravenously four times daily†</p>	10 days

*Renal function should be monitored and blood taken for gentamicin levels. Hospitals may wish to apply standard dosing practice, eg 7mg/kg once daily with monitoring of levels, if this is more convenient

‡Other fluoroquinolones with proven activity in animal models (eg levofloxacin) may be substituted, at equivalent doses.

†Intravenous chloramphenicol in neonates: 12.5 mg/kg twice daily for neonates up to 14 days of age; 12.5 mg/kg two to four times daily for neonates 14 – 28 days of age.

Note: penicillins, cephalosporins and macrolides have been shown to be ineffective or have variable efficacy in the treatment of plague and they should not be used for this purpose.

Antibiotic resistance

Drug-resistant isolates of *Y. pestis* appear to be rare, but have been described. Outbreaks of multidrug resistant plague have not been reported to date. Sensitivity testing is recommended for all isolates and, if required, modify antibiotic therapy according to reported susceptibility patterns.

Sensitivity testing of fourteen isolates from the 2017 Madagascar outbreak, as reported by Institut Pasteur de Madagascar in October 2017, demonstrated susceptibility to tetracycline, ciprofloxacin, streptomycin, sulphonamides, and chloramphenicol (susceptibility to gentamicin was not reported).

Supportive measures

Supportive measures that may be required include invasive monitoring in patients with shock, invasive ventilation for acute respiratory distress syndrome, renal replacement therapy and correction of clotting abnormalities. Patient placement in critical care units is the same as for other areas of a hospital (see infection prevention and control requirements, above).

Differential diagnosis

Plague is a rare disease, particularly in travellers returning to the UK. In addition to investigating possible cases, efforts should be made to investigate more common infections, including infections that can be acquired in the UK as well as travel-associated infections. Co-infections may also occur, eg concurrent malaria.

The differential diagnosis of pneumonic plague includes other acute bacterial, viral, fungal, or mycobacterial pneumonias.

The differential diagnosis of bubonic plague includes tularaemia, cat scratch disease, chancroid, lymphogranuloma venereum, bacterial lymphadenitis, tuberculosis, scrub typhus and other rickettsioses.

In addition to empirical plague-specific antibiotics, empirical treatment of other potential infections may be required. Routine laboratory tests and investigations for other infections are not prohibited, as long as the laboratory is warned of possible plague and the tests can be performed with appropriate biological containment measures in place.

7. Antibiotic prophylaxis

Post-exposure prophylaxis is only recommended for persons who have had close (<2 meters) and unprotected contact with pneumonic plague cases, or who have experienced other high-risk exposures such as bites from fleas in an epidemic area or direct and unprotected contact with bodily fluids or tissues of infected animals or humans.

The risk of adverse effects from antibiotic prophylaxis must be weighed against the risk of developing a serious disease. PHE does not recommend pre-exposure prophylaxis for healthcare or clinical laboratory staff in the UK, as the recommended PPE, IPC and biological containment precautions are considered sufficient if followed.

For adults, children and pregnant women, ciprofloxacin is the drug of choice. In general doxycycline is not recommended for use in children under 12 years unless no alternative anti-bacterial can be given. Other antibiotics such as, chloramphenicol or cotrimoxazole can be used.

Persons with significant exposure (see above) should receive antibiotic prophylaxis for seven days.

Recommended post-exposure prophylaxis

	Antimicrobial agent	Duration
Adult (including pregnant women)	Ciprofloxacin 500mg orally twice daily OR Doxycycline 100mg orally twice daily	7 days
Child	Ciprofloxacin 15mg/kg orally twice daily - not to exceed 1g per day OR Ciprofloxacin twice daily doses by age: newborn - 6 months 100mg/day 1 year - less than 3 years 200mg/day 3 years - less than 5 years 300mg/day 5 years - less than 7 years 400mg/day 7 years - less than 12 years 500mg/day 12 years and over (adult dose) 1000mg/day OR Doxycycline (only if no alternative options) >12years of age and > 45kg:100mg orally twice daily	7 days

The **PHE HPT** (local to the patient’s usual residence) should be notified of any individuals commenced on antibiotic prophylaxis because follow-up needs to be

arranged. The individuals should be monitored for the development of any illness compatible with plague while receiving prophylaxis for 8 days after exposure.

Prophylaxis should be converted to treatment-dose antibiotics if an individual develops symptoms compatible with plague, and continued for the recommended duration if a laboratory-confirmed diagnosis of plague is obtained.

8. Useful resources

PHE plague: <https://www.gov.uk/guidance/plague-epidemiology-outbreaks-and-guidance>

PHE plague risk assessment <https://www.gov.uk/guidance/plague-epidemiology-outbreaks-and-guidance#risk-assessment-for-the-uk>

PHE plague guidance for clinical laboratories (located on PHE plague page) <https://www.gov.uk/guidance/plague-epidemiology-outbreaks-and-guidance>