

Plague: Interim clinical management guidance for Ireland

Plague is a notifiable disease in Ireland under the Infectious Diseases (Amendment) Regulations 2016 (S.I. No. 276 of 2016). All medical practitioners and laboratories are required to notify it to the Medical Officer of Health.

Information on the process of notifying infectious diseases including the case definition of **Plague** is available at: <http://www.hpsc.ie/NotifiableDiseases/>

Contents

Aim of this guidance document	3
Summary of key actions	3
Background of plague	4
Differential diagnosis	5
Infection Prevention and Control Precautions	6
Transmission	6
Medical personnel and persons having close contact with infected persons	6
Laboratory workers	7
Occupational Health	7
Droplet precautions	7
Patient placement	7
PPE	7
Access to the patient environment	7
Visitors	8
Movement of patients	8
Laundry and linen	8
Environmental hygiene	8
Terminal decontamination	8
Waste management	8
Patient care equipment	8
Specimen collection	8
Laboratory investigations	9
All suspected cases	9
Patients with buboes	9
Patients with CNS involvement	10
Patients with pharyngeal involvement	10
Diagnostic specimen handling and packaging	10
Requesting other laboratory tests	10
Treatment	11
Post-exposure prophylaxis (PEP)	14
Travel advice	15
Recommended reading	15

Aim of this guidance document

The aim of this document is provide healthcare professionals with key details on clinical and laboratory management of a case of travel acquired plague.

For specific advice for the various healthcare settings please see the following algorithms:

- [Plague risk assessment for ambulance services](#)
- [Plague risk assessment and treatment options for use in a hospital setting](#)
- [Plague risk assessment for use in a primary care setting](#)

Note: This guidance was adapted for the Irish setting from three key interim guidance documents produced by US Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC) and Public Health England (PHE).

Summary of key actions

<p>Implement appropriate Infection Control Procedures (IPC)</p>	<ul style="list-style-type: none"> ➤ Isolation in an airborne isolation room, preferably negative pressure ➤ Standard + droplet precautions ➤ PPE: FFP2/3 mask or surgical mask, face protection, fluid-repellent gown, disposable gloves
<p>Send samples for diagnostic testing</p>	<p>INFORM LABORATORIES OF SUSPICION OF PLAGUE All specimens should be packed securely and appropriately before transporting to the laboratory (refer to local policy for handling & packaging hazardous pathogens) 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 Imported Fever Service, Porton Down Laboratory UK as outlined in laboratory guidance</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.
<p>Public Health actions</p>	<p>Plague is a notifiable disease. Inform local Public Health Medical Officer of Health (MoH) immediately of a suspected case.</p>

Background of plague

Plague is a bacterial zoonotic disease caused by the Gram-negative bacillus *Yersinia pestis*. Plague is predominantly a zoonosis of rodents. Plague is transmitted between animals and humans most often by the bite of infected fleas, but also by scratches from infected cats, direct contact with infected animal tissues, the inhalation of infected respiratory droplets (from either animals or humans), consumption of contaminated food or laboratory exposure.

There are three main clinical presentations of plague: bubonic, septicaemic and pneumonic. The infection can be a severe disease in humans but can be successfully treated with early antibiotic treatment. The incubation period is generally 2-6 days, but can be very short (even hours) after inhalation of infected droplets.

Bubonic plague is the most common, accounting for >80% of cases. It presents with sudden onset of fever, lethargy, headaches and pain and swelling in a lymph node area (most commonly the inguinal area). If bubonic plague is not treated, plague bacteria invade the bloodstream and spread rapidly, causing septicaemic plague, and if the lungs are seeded, secondary pneumonic plague occurs. Septicaemic and pneumonic plague may also be primary manifestations. A person with pneumonic plague may experience high fever, chills, cough, and breathing difficulty and may expel bloody sputum which is infectious for any individuals in their immediate vicinity (<2 m) who are not wearing personal protective equipment against droplet infection. If pneumonic plague patients are not given specific antibiotic therapy, the disease can progress rapidly to death.

Although the majority of patients with plague present with a swollen lymph node (bubo), some may have non-specific symptoms. For example, septicaemic plague can present with prominent gastrointestinal symptoms such as nausea, vomiting, diarrhoea, and abdominal pain (MMWR, 2006). Meningitis may occur with any of the three forms of plague.

Appropriate diagnostic samples include blood cultures, lymph node aspirates (if possible), and/or sputum, if indicated. [Special precautions are required to take respiratory samples](#). The Microbiology Laboratory should be informed that plague is suspected before samples are sent. Antimicrobial therapy should begin as soon as possible after the laboratory specimens are taken. If plague is suspected the local Medical Officer of Health should be notified immediately. If the patient has pneumonic signs, he/she should be isolated immediately and placed on droplet precautions.

Plague should be considered in any individual with an acute onset illness and the following:

Fever ($\geq 38.5^{\circ}\text{C}$)

AND

cough OR chest pain OR haemoptysis OR painful lymphadenitis OR dyspnoea

AND

has had contact with a confirmed or probable case or source of plague in the **last 7 days**

OR

has in the **last 7 days** returned from an area [currently affected by plague](#)

Differential diagnosis

Plague is a rare disease, particularly in travellers returning to Ireland. Most plague in humans since the 1990s has been reported from Africa (mainly the island of Madagascar and the Democratic Republic of the Congo). There is a current (August-November 2017) major outbreak in Madagascar with >1,000 cases of plague pneumonia. In the last decade smaller outbreaks of pneumonic plague have been recorded in the DRC, Uganda, Algeria, Madagascar, China and Peru. The western USA is a very large endemic focus for plague in animals but fewer than 10 cases per year are reported in humans. In addition to investigating possible cases, efforts should be made to investigate more common infections, including infections that can be acquired in the Ireland as well as travel-associated infections. Co-infections may also occur, e.g. 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.

Infection Prevention and Control Precautions

Transmission

Plague can be transmitted from person to person in healthcare settings by the following routes;

- Contaminated droplets
- Direct contact with a patient with plague or infected body fluids
- Indirect contact with contaminated surfaces or equipment

The risk of aerosol transmission in these settings is unclear, but is probably very low with pneumonic or pharyngeal plague and almost negligible with bubonic plague, the most common form, which occurs in 80-90% of cases, it can however develop into secondary pneumonic plague. Aerosol generating procedures (AGPs) present the greatest risk to healthcare workers (HCW) and should be kept to a minimum.

Bubonic plague is usually transmitted by;

- The bite of an infected flea
- Direct or indirect contact with infected human/animal bodily fluids or remains
- Touching or skinning infected animals.

Transmission by these routes can result in **primary bubonic plague** or in **septicaemic plague**. HCW can become infected during the management of an infected patient or during sample collection (e.g. collection of pus samples from swollen lymph nodes or buboes).

Pneumonic plague is usually transmitted by;

- Infected respiratory droplets from infected humans or animals
- Contact with infected human/animal bodily fluids
- Contact with bed linen/clothing contaminated with infected bodily fluids

HCW can become infected during the management of an infected patient or during sample collection (e.g. collection of sputum samples).

Medical personnel and persons having close contact with infected persons

Recommended precautions

In addition to standard precautions, implement **droplet precautions** while the patient is infectious. Continue these precautions until the diagnosis has been excluded or a confirmed case has received appropriate antibiotic treatment for at least 48 hours and is showing signs of clinical improvement.

Standard precautions alone are sufficient for patients in whom pneumonic plague has been excluded unless the patient is known or suspected to have an alternative infectious disease that requires additional transmission based precautions e.g. TB.

Laboratory workers

Routine bacteriologic work involving plague can be safely performed in **biosafety level 2 laboratories**. The use of a biological safety cabinet to contain aerosols that are generated unintentionally plus strict adherence to standard precautions are sufficient to prevent clinical laboratory workers from being infected with *Y. pestis*. Few laboratory-associated cases have been reported; those cases that have occurred involved unusual exposures in clinical diagnostic laboratories or in laboratories that conduct research involving live *Y. pestis*.

Occupational Health

Chemoprophylaxis (i.e. prophylactic antibiotics) should be administered to everyone who has had close exposure (i.e., within 2 meters) to persons with suspected or confirmed plague. Individuals who have not had such exposure are unlikely to become infected but should be monitored closely.

Droplet precautions

Patient placement

Patients with suspected/confirmed plague should be isolated 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 is required when undertaking aerosol-generating procedures (AGPs)☺. Positive pressure rooms are not suitable and should NOT be used.

PPE

As a precautionary measure HCWs should wear the following PPE when assessing possible plague cases and/or managing confirmed cases:

- Single use gloves
- Single use fluid repellent gown with cuffs
- Eye protection e.g. full face shield or goggles, preferably single use
- Respiratory protection
 - For primary or secondary cases of pneumonic plague and AGPs - FFP2/3 required
 - For cases of bubonic plague - surgical face mask sufficient

HCW entering the isolation room must be trained and competent in the use of PPE

Access to the patient environment

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

Visitors

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. 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 (e.g. portable chest radiography) should be performed where possible. If transport to other departments is unavoidable, the patient should be encouraged to wear a surgical facemask and follow good **respiratory hygiene and cough etiquette** when being transported.

Laundry and linen

All reusable linens should be carefully placed in an alginate stitched or water soluble bag and then placed into a laundry bag clearly identified with labels, colour-coding to indicate “infectious waste.”

Environmental hygiene

Patient isolation rooms should be cleaned at least daily using a general purpose neutral detergent in a solution of warm water followed by disinfection using chlorine based disinfectant at a dilution of 1,000 parts per million available chlorine.

Terminal decontamination

Terminal cleaning should be performed at the end of care, using a neutral detergent followed by disinfection with a chlorine based disinfectant diluted to 1,000ppm available chlorine.

Waste management

Healthcare Risk Waste should be managed in accordance with national and local guidelines.

Patient care equipment

Use patient dedicated equipment if possible or single use non-critical patient care equipment e.g. BP cuffs, sling hoists. If reusable equipment is used it should be decontaminated immediately after use and before use on another patient in accordance with the manufacturer’s instructions and local policy.

Specimen collection

WHO interim guidance on [‘How to safely collect pus samples from buboes of patients suspected to be infected with bubonic plague’](#) should be followed when collecting specimens for suspected cases of **bubonic plague** and WHO interim guidance on [‘How to safely collect sputum samples from patients suspected to be infected with pneumonic plague’](#) for the collection of specimens for

suspected cases of pneumonic plague.

Laboratory investigations

Detection of *Y. pestis* by microscopy and culture in local laboratories, supported by reference laboratory testing (Rare and Imported Pathogens Laboratory (RIPL)) at PHE Porton Down UK, is the principal method of diagnosis. In addition, concurrent PCR testing of clinical specimens should be discussed with the Imported Fever Service, PHE. Further information on laboratory sampling and testing can be found in the Interim Laboratory Guidance on Plague.

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 container)
- 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 (e.g. 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 e.g. a screw-top Biojar. Specimens for different destinations (e.g. 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.

Treatment

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 may not be widely available. Gentamicin was successful in a randomised clinical trial of plague treatment, which also found doxycycline to be effective.

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 and they are approved by the FDA in the USA for this indication.

Irrespective of the antibiotic used, the optimal duration of treatment is unknown. **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.

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.

Table 1: Antibiotic treatment choices for plague in adults

	Antibiotics	Dose	Route of admin	Notes
ADULTS	Streptomycin	1g twice daily	IM	May not be widely available
	Gentamicin	5mg/kg once daily	IV	Not FDA approved but considered an effective alternative to streptomycin. Due to poor abscess penetration, consider alternative or dual therapy for patients with bubonic disease.
	Doxycycline	100mg twice daily or 200mg once daily	IV/PO	Bacteriostatic, but effective in a randomized trial when compared to gentamicin
	Levofloxacin*	500mg once daily	IV/PO	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague. A higher dose (750mg) may be used if clinically indicated.
	Ciprofloxacin*	400mg every 8-12 hours	IV	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague.
		500-750mg twice daily	PO	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague.
	Moxifloxacin*	400mg once daily	IV/PO	
	Chloramphenicol	25mg/kg every 6 hours	IV	

*quinolones should only be used in exceptional circumstances when alternative agents are absolutely contraindicated or cannot be sourced.

Table 2: Antibiotic choices for treatment of plague in children

	Antibiotic	Dose	Route of admin	Notes
CHILDREN	Streptomycin	15mg/kg twice daily (maximum 2 g/day)	IM	May not be widely available
	Gentamicin	2.5mg/kg/dose every 8 hours	IM or IV	Not FDA approved but considered an effective alternative to streptomycin. Due to poor abscess penetration, consider alternative or dual therapy for patients with bubonic disease.
	Doxycycline	Weight <45kg: 2.2mg/kg twice daily (maximum 100mg/dose) Weight ≥ 45kg: same as adult dose	IV or PO	Bacteriostatic, but FDA approved and effective in a randomized trial when compared to gentamicin. ² No tooth staining after multiple short courses. ⁴
	Levofloxacin*	10mg/kg/dose (maximum 500 mg/dose)	IV or PO	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague.
	Ciprofloxacin*	15mg/kg/dose every 12 hours (maximum 400mg/dose)	IV	Bactericidal. FDA approved based on animal studies but limited clinical experience treating human plague.
		20mg/kg/dose every 12 hours (maximum 500mg/dose)	PO	
	Chloramphenicol (for children >2 years)	25mg/kg every 6h (maximum daily dose, 4g)	IV	Not widely available

Table 3: Antibiotic treatment for plague in pregnant women

	Antibiotic	Dose	Route of admin	
Pregnant Women	Gentamicin	Same as adult dose	IM or IV	See notes above
	Doxycycline	Same as adult dose	IV	See notes above
	Ciprofloxacin	Same as adult dose	IV	See notes above

*quinolones should only be used in exceptional circumstances when alternative agents are absolutely contraindicated or cannot be sourced.

Post-exposure prophylaxis (PEP)

Post-exposure prophylaxis is indicated in persons with known exposure to plague, such as those in close contact with a pneumonic plague patient or having direct contact with infected body fluids or tissues.

CONTACT EXPOSURE DEFINITION

1. Exposure **within 2 metres** of a confirmed or probable case of plague
2. Aircraft/ship exposure within 2 metres of a probable or confirmed plague case in the last 7 days. A risk assessment to identify contacts (including passengers or crew) of the case should be carried out.
3. Contact with the following items without appropriate personal protective equipment (PPE)
 - infected substances of human origin (SoHO*)
 - laboratory exposure to plague infected materials
 - contaminated fomites
4. Contact with a sick animal/flea bite in a plague affected area

Duration of post-exposure prophylaxis to prevent plague is 7 days. The recommended antibiotic regimens for PEP are as follows:

Prophylaxis for close contacts:

Contact type	Preferred agents	Dose	Frequency	Route
Adults	Doxycycline	100mg	Twice daily	Oral
	Ciprofloxacin	500mg		
Children	Ciprofloxacin	15mg/kg (not to exceed 1g/day)		
	OR Ciprofloxacin by age:			
	newborn - 6 months	50mg		
	1 year <3 years	100mg		
	3 years - <5 years	150mg		
5 years - <7 years	200mg			
7 years - <12 years	250mg			
12 years and over (adult dose)	500mg			
Pregnant women	OR Doxycycline <i>(only if no alternative options)</i>			
	>12 years of age and >45kg	100mg		
Pregnant women	Doxycycline ¹	100 mg		
	Ciprofloxacin ¹	500 mg		

*Including but not limited to body fluids, body tissues, organs etc.

¹ Doxycycline and ciprofloxacin are pregnancy categories D and C, respectively. PEP should be given only when the benefits outweigh the risks.

Travel advice

WHO does not advise any travel or trade restrictions on Madagascar based on current information available on this outbreak.

Travellers to Madagascar and other countries where plague occurs are advised to take these preventive measures:

- Use of personal protection against fleabites. As Madagascar is a malaria endemic area, the use of mosquito repellents for malaria can protect against flea bites;
- Avoidance of direct contact with sick or dead animals;
- Avoidance of close contact with sick persons in particular with patients diagnosed with pneumonic plague or patients with symptoms consistent with pneumonic plague;
- Avoidance of crowded areas where cases of pneumonic plague have been recently reported;
- Contacting travel clinics before departure to get information about the current plague outbreak in Madagascar including preventive measures and symptoms of pneumonic plague;
- Seeking immediate medical care if compatible symptoms are developed.

Recommended reading

[CDC Guidance on Plague for Healthcare Professionals](#)

[European Centre for Disease Prevention and Control Interim Guidance on Plague Management on Aircraft and Ships.](#)

[Public Health England Interim Guidance for Clinical Management of Plague](#)

[Public Health England Interim Laboratory Guidance Plague](#)

Federal Register. Draft guideline for isolation precautions in hospitals. 1994;59:55552-70.

White ME, Gordon D, Poland JD, Barnes AM. Recommendations for the control of Yersinia pestis infections. Infection Control 1980;1:326-9.

Dennis DT. Plague, method of. In: Rakel RE, ed. Conn's current therapy. Philadelphia: WB Saunders Co., 1996:124-6.

Burmeister RW, Tigertt WD, Overholt EL. Laboratory-acquired pneumonic plague: report of a case and review of previous cases. Ann Intern Med 1962;58:789-800

Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management Working Group on Civilian Biodefense. JAMA. 2000 May 3;283(17):2281-90.