GUIDELINES FOR ACTION IN THE EVENT OF A DELIBERATE RELEASE

Contents: page:
1 Background and Clinical Information 2
  1.1 Introduction 2
  1.2 Epidemiology 2
  1.3 Clinical features 3
  1.4 Mortality 4
  1.5 Organism survival 4
  1.6 Antimicrobial susceptibilities 4
2 Clinical procedures 5
  2.1 Diagnosis and collection of samples 5
  2.2 Treatment 6
  2.3 Infection control practice 7
  2.4 Prophylaxis and follow-up 8
  2.5 Environmental decontamination 10
  2.6 Protection of frontline workers 10
  2.7 Patient, visitor and public information 11
3 Laboratory procedures 12
  3.1 Risk assessment 12
  3.2 Isolation and identification 12
  3.3 Confirmation 13
  3.4 Waste disposal 13
  3.5 Reference laboratories 13
  3.6 Transport of samples 13
  3.7 Protection of laboratory staff 15
4 Public Health procedures 16
  4.1 Surveillance and detection 16
  4.2 Case definition 16
  4.3 Public health action 17
  4.4 Epidemiological investigations 18
5 List of national specialists 19
6 References 20

Note: Comments are welcome from healthcare, laboratory and public health professionals, and should be sent to DRcomments@hpa.org.uk. These guidelines may be subject to change as comments are received, so please ensure that you have the latest version, available on the HPA website.
http://www.hpa.org.uk/infections/topics_az/deliberate_release/default.htm

For this version of the guidelines changes were made to the following sections of the previous version:
1.2.1 Table 1
2.4
3.6
6
1. **BACKGROUND**
These guidelines are intended for healthcare, laboratory and public health professionals to guide clinical, laboratory and public health action in the event of a deliberate release of plague.

1.1 **Introduction**
Plague is an acute infection caused by *Yersinia pestis*. It is a zoonosis (human infection of animal origin), but human-to-human transmission can occur, principally through infectious respiratory droplets.

1.1.1 **Deliberate release of plague**
Although the creation of an infectious plague aerosol is not easy, threat of a deliberate release of plague may result from the release of large quantities of *Y. pestis* in an aerosol. Aerosolised *Y. pestis* results in primary pneumonic plague. This threat is considered serious because:
- The organism can cause severe, rapidly fatal infection.
- Secondary cases may arise from contact with cases of pneumonic plague.
- The disease has a reputation that would cause panic.

1.2 **Epidemiology**
Natural infection occurs in a range of animal species, predominantly rodents. Isolated cases and outbreaks of human plague are still reported regularly from several countries in Africa, Asia and South America, and the USA. Humans usually acquire the infection through the bite of a flea that has previously fed on an infected animal. During the 1980s approximately 1000 cases/year were reported to the World Health Organisation. This increased during the 1990s to a peak of over 5,000 in 1997. In the UK, the last outbreak of plague was between 1908 and 1919, and the last notified case was in 1930.

1.2.1 **Transmission**
Although naturally occurring infection is usually transmitted by the bites of infected fleas, there have been several reported cases from the USA of infection acquired, presumably by inhalation, from infected cats. Human-to-human transmission can occur through infectious respiratory droplets from cases of plague pneumonia. This usually requires close contact with symptomatic cases. Pneumonic plague is probably not as contagious as it is commonly believed to be (Kool, 2005), with an estimated $R_0$ of only 1.3 from an analysis of past outbreaks, even before control measures are implemented (Gani & Leach, 2004). A recent study estimated a secondary infection rate of 8% (Begier et al. 2006). Bubonic and other forms of plague in humans, without secondary pneumonia, are not considered to be contagious.

1.2.2 **Infectious dose**
The infectious dose by inhalation is approximately 100-500 organisms.

1.2.3 **Incubation period**
With primary pneumonia the incubation period is short, usually only 1-4 days (maximum 6 days). The incubation period for bubonic and septicaemic plague is longer, generally 2-8 days.

1.2.4 **Period of communicability**
Pneumonic plague is transmissible to other people as long as there are viable organisms in the sputum. In practice this would be for no longer than 72 hours after starting effective antibiotic treatment.
1.3 Clinical features

It can be expected that any malicious or deliberate release of plague bacteria will involve aerosol exposure. Clinicians should be aware of the possibility of plague pneumonia, and the occurrence of a single strongly suspected case should be immediately reported to the Consultant in Communicable Disease Control (CCDC), or relevant out-of-hours cover, at the local Health Protection Unit (HPU) and to the duty doctor at the HPA Centre for Infections (020 8200 6868 - 24 hour service).

The diagnosis of plague should be considered if cases of the following clinical presentations occur in previously healthy patients, especially if two or more cases arise that are linked in time and place:

- Sudden onset of severe, unexplained febrile respiratory illness
- Unexplained death following a short febrile illness
- Sepsis with Gram-negative coccobacilli identified from clinical specimens

1.3.1 Pneumonic plague

This may occur due to primary respiratory infection, or as a complication of the bubonic or septicaemic forms of disease. Although uncommon in naturally occurring plague, it is the expected presentation following the deliberate release of aerosolised *Y. pestis*. Previously healthy patients, with no history of travel to a plague-endemic area and with no known risk factors for plague exposure, presenting with a severe and rapidly progressive pneumonia, including symptoms of haemoptysis and gastroenteritis should raise the possibility of pneumonic plague.

The illness usually begins with intense headache and malaise, fever, vomiting, and commonly abdominal pain, diarrhoea and marked prostration. Chest pains, cough and dyspnoea develop with the production of watery, bloodstained sputum. Physical signs in the lungs are often minimal but chest X-rays show evidence of multilobar consolidation, cavities or bronchopneumonia. Respiratory failure develops quickly and mortality is high. Appropriate antibiotic treatment must be given within 24 hours of onset if mortality is to be reduced.

Pneumonic plague may result in human-to-human transmission via infectious droplets from patients with a productive cough. Patients are still contagious up to 72 hours after starting appropriate antibiotic treatment. It is also a potential risk in laboratory workers handling cultures of *Y. pestis*.

1.3.2 Bubonic plague

This is the most common clinical form of naturally occurring plague, and occurs following a bite from an infected flea. The illness begins with a sudden onset of fever, chills, headache, nausea, vomiting and prostration; 6-8 hours after onset of symptoms a bubo (swollen lymph node or group of nodes) develops. Buboes are characterised by severe pain, swelling and marked tenderness. Lymph nodes draining the area of an infected bite are affected; groin, axillary and cervical nodes are most commonly affected. There is surrounding oedema and the overlying skin is warm, reddened and adherent. Complications include septicaemia, secondary pneumonia and meningitis. This form is unlikely to occur in a deliberate release.

1.3.3 Other presentations

- Septicaemic plague may occur as a complication of untreated bubonic plague or pneumonic plague, and may develop in the absence of obvious signs of primary disease. It is characterised by a high density of organisms in the blood, without
clinically apparent buboes or other focus. Symptoms and signs are indistinguishable from other Gram-negative septicaemias, and include septic shock and disseminated intravascular coagulation.

- **Plague meningitis** is rare but may occur as a complication of inadequately treated infection elsewhere. It presents with symptoms and signs common to all types of pyogenic meningitis.

- **Pharyngeal plague** is very rare and possibly results from ingestion or inhalation of the organism. The tonsils are swollen and inflamed with anterior cervical lymphadenopathy and swelling of the parotid area.

Clinical pictures illustrating the different forms of plague are available via the Deliberate Release homepage of the HPA website http://www.hpa.org.uk/infections/topics_az/deliberate_release/default.htm

1.4 **Mortality**
The high mortality, approaching 100% for pneumonic and septicaemic forms and around 60% for bubonic plague, has fallen dramatically with the advent of effective antibiotic therapy. In cases reported to the WHO during the 1990s, the overall fatality rate was 7%. In uncomplicated bubonic plague this may be as low as 5%, but in septicaemic plague the case fatality rate may be 33% or higher. The prognosis is worse in patients with pulmonary involvement and primary pneumonia remains invariably fatal if treatment is delayed more than 24 hours. With prompt treatment the fatality rate decreases below 10%.

1.5 **Organism survival**
*Y. pestis* is a small Gram-negative coccobacillus, which does not form spores. It remains viable for about an hour after an aerosol release. Organisms are killed by heating at 56°C for 15 minutes, and by exposure to sunlight for 4 hours. Survival is prolonged in dried blood and secretions.

1.6 **Antimicrobial susceptibilities**
*Y. pestis* is generally susceptible to a large number of antibiotics including aminoglycosides, β-lactams, trimethoprim, fluoroquinolones, cephalosporins, tetracyclines, chloramphenicol and sulphonamides. Most of the therapeutic guidelines suggest using gentamicin or streptomycin as first line therapy with ciprofloxacin as an alternative. Chloramphenicol should be used for treatment of meningitis because good concentrations are achieved in the cerebrospinal fluid.

Isolates resistant to tetracyclines have been found in Madagascar. Two streptomycin-resistant strains, also found in Madagascar, have been reported. One of these was multidrug resistant to ampicillin, tetracycline, chloramphenicol, sulphonamides, kanamycin, spectinomycin and minocycline, but remained susceptible to trimethoprim, fluoroquinolones and cephalosporins. Antibiotic resistances were plasmid-mediated and could be transferred to other strains of *Y. pestis*.

In experimental infections in mice, including plague pneumonia, the aminoglycosides and fluoroquinolones are the most active agents against *Y. pestis*. Cephalosporins are much less effective. In other mouse experiments ciprofloxacin was superior to doxycycline for prophylaxis against *Y. pestis* infection.
2 CLINICAL PROCEDURES

2.1 Diagnosis and collection of samples
Clinical features depend on the route of exposure. A deliberate release is most likely to be by aerosol and result in pneumonic plague which may be transmitted person-to-person via infectious droplets from patients with a productive cough. Patients are still contagious up to 72 hours after starting appropriate antibiotic treatment.

2.1.1 Precautions for sampling
Samples should be taken while wearing the best available (highest efficiency) face and eye protection in addition to Standard Universal Precautions. A disposable surgical face mask will reduce the risk from large respiratory droplets, however, where available at least a medium efficiency FFP2 mask should be used. The utmost care must be taken to avoid inoculation injuries.

2.1.2 Samples to be taken from acutely ill humans
- Blood for culture
- Sputum
  - If a bubo is present, aspiration should be attempted - if no fluid or pus is obtained a small amount of sterile saline can be injected and re-aspirated.
- CSF should be taken, if clinically relevant.
- Acute and convalescent sera should be sent to the reference laboratory - serological diagnosis is possible and useful in culture-negative cases. However antibodies may not be detectable when the patient first presents.

Samples should be identified as 'High Risk' according to local protocols. A request form giving full clinical details and information on antibiotic treatment should accompany all samples. Chain of evidence documentation should also accompany all specimens; however in larger incidents this would only be required for several of the initial cases.

2.1.3 Post-mortem specimens
Post-mortem samples may be taken to assist diagnosis, including:
- Blood
- Bubo aspirate
- CSF (if clinically relevant)

However, full post-mortems are strongly discouraged if plague is suspected (see 2.3.4). If a post-mortem is carried out, samples of lung, spleen or lymph node should be sent (transport medium is not necessary, but it will not damage specimens).

2.1.4 Samples to be taken from the environment
Environmental sampling is unlikely to provide useful information because the organism dies rapidly outside the body. Expert advice will be provided if indicated.

2.1.5 Transport of samples
Strict procedures should be followed for the transport of samples of suspected *Y. pestis* to the laboratory, both from the clinical environment to the laboratory, and from local laboratories on to the reference laboratory. These are outlined in section 3.6. *Y. pestis* cultures fall into category A for the purposes of transport. All samples should be transported as per UN 602 as described in "Appendix 1.2 Transport of infectious substances" in “Biological agents: Managing the risks in laboratories and healthcare premises.” Advisory Committee on Dangerous Pathogens (ACDP), Health and Safety Executive (HSE) May 2005 accessed at http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf
2.2 Treatment
Streptomycin, tetracycline and chloramphenicol are the antibiotics traditionally used in the treatment of plague. Streptomycin has been the treatment of choice, particularly for severe infections. Other reports have found that aminoglycosides, such as gentamicin and kanamycin are 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 (Boulanger et al., 2004). A recent 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 (Mwengee et al. 2006).

There is no clinical experience with fluoroquinolones for the treatment of human infection, although in vitro susceptibilities and animal experiments suggest that fluoroquinolones would be effective for the treatment of plague (Steward et al. 2004).

Table 1: Recommended treatment for plague

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Gentamicin</strong> † (first choice in pregnancy) 5mg/kg intramuscularly or intravenously once a day or 2mg/kg loading dose followed by 1.7mg/kg intramuscularly or intravenously three times daily</td>
<td>14 days</td>
</tr>
<tr>
<td>or if aminoglycosides are unsuitable</td>
<td></td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong> † 400mg intravenously twice daily</td>
<td></td>
</tr>
<tr>
<td>For milder cases only 500mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>or <strong>Doxycycline</strong> 100mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>or if plague meningitis suspected</td>
<td></td>
</tr>
<tr>
<td><strong>Chloramphenicol</strong> 25mg/kg intravenously four times daily</td>
<td></td>
</tr>
<tr>
<td><strong>Child</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong> † 10mg/kg intravenously twice daily (maximum 400mg) - not to exceed 800mg per day</td>
<td>14 days</td>
</tr>
<tr>
<td>For milder cases only 15mg/kg orally twice daily – not to exceed 1g per day</td>
<td></td>
</tr>
<tr>
<td>or <strong>Doxycycline</strong> 100mg oral twice daily (NB: only for children &gt; 8yrs and &gt;45kg)</td>
<td></td>
</tr>
<tr>
<td>or if plague meningitis suspected</td>
<td></td>
</tr>
<tr>
<td><strong>Chloramphenicol</strong> 25mg/kg (maximum 500mg) orally or intravenously four times daily</td>
<td></td>
</tr>
</tbody>
</table>

* Renal function should be monitored and blood taken for gentamicin or streptomycin levels.
† Other fluoroquinolones with proven activity (e.g. ofloxacin, levofloxacin) may be substituted, at equivalent doses.
2.2.1 **Antibiotic supplies**

In a major incident information on how to access stocks of antibiotics for the initial three day treatment or prophylaxis can be found on the DH website at: http://www.dh.gov.uk/assetRoot/04/13/53/71/04135371.pdf

2.3 **Infection control practice**

2.3.1 **Decontamination of exposed persons**

The risk of acquiring infection from the contaminated clothing of persons exposed to *Y. pestis* is low. In the event of a known exposure, the risk for re-aerosolisation is uncertain and is likely to depend on a number of variables, including the quantity of organisms on the surface; the type of surface and host factors. An incident specific risk assessment will be required.

In situations where the threat of exposure to *Y. pestis* exists, cleansing of skin and potentially contaminated fomites such as clothing, personal possessions or environmental surfaces should take place. Decontamination of persons exposed to plague includes:

- Removal of contaminated clothing and possessions – it should be stored in labelled double plastic bags until exposure has been ruled out.
- If exposure is confirmed, all contaminated material must be incinerated or autoclaved.
- Minimal handling of clothing and fomites to avoid agitation.
- Instructing exposed persons to shower thoroughly with soap and water- appropriate facilities will be provided at the scene as necessary.
- Instructing attending personnel to wear full PPE when handling contaminated clothing and other fomites.

2.3.2 **Isolation of patients**

Person-to-person spread can occur from inhalation of infectious droplets of sputum (see 1.2.1). Cases of suspected and confirmed pneumonic plague should be nursed in standard isolation in a single room, with the door closed wherever possible, for the first 72 hours of treatment. Culture proven cases should remain in isolation until there is also clinical improvement. In the event of a large-scale event, patients may be cohort isolated in a designated ward.

All persons entering or leaving the room should wear the best available (highest efficiency) face and eye protection in addition to Standard Universal Precautions – gloves, gowns and hand washing. Patients with pneumonic plague should, in addition, be asked to wear surgical masks in order to minimise the generation of infectious respiratory droplets. Transport of patients should be limited to essential medical investigations only. Patients should wear surgical masks during transport to minimise the spread of infectious droplets.

Transmission of plague via respiratory droplets requires close contact, and standard isolation is regarded as sufficient for infection control. However in the event of small numbers of cases, the use of negative pressure ventilation isolation rooms may be considered if they are available.

2.3.3 **Cleaning, disinfection & waste disposal**

Normal procedures for standard isolation are appropriate. Contaminated environmental surfaces should be cleaned with hypochlorite solution (5,000ppm available chlorine).
2.3.4 Post-mortem procedures

Autopsy

The risk of acquiring plague following contact with the body of a person who has died from the disease is low; person-to-person transmission can occur from pulmonary cases and there is evidence of autopsy transmission.

Autopsy examinations are strongly discouraged if plague is suspected, as the body fluids and tissues in a patient who has died of the disease are likely to have large numbers of the \textit{Y. pestis} present and there is a risk of aerosolising these organisms. If an autopsy is necessary expert advice must be sought from the HPA. The Pathologist must be informed of the known or suspected diagnosis. Standard precautions for post-mortem examinations on patients infected with Containment Level 3 organisms are appropriate. Instruments should be autoclaved. Antibiotic prophylaxis (see section 2.4) should be offered to mortuary staff if the deceased had not completed a 72 hour course of appropriate antibiotics.

Similarly, body preparation should be carried out with normal control of infection procedures. Standard precautions for the disposal of bodies infected with Containment Level 3 pathogens should be observed, and the undertaker should be informed. Cremation is the preferred method for disposal of the deceased. Embalming of bodies should not be undertaken because the body fluids are likely to contain large numbers of the causative bacteria and therefore the process of embalming exposes the embalmer to an unacceptable risk.

Pacemaker removal

Pacemaker removal is permitted. Pacemaker should be treated with hypochlorite solution (10,000 ppm available chlorine), bagged and disposed of appropriately (not by incineration).

2.4 Prophylaxis and follow-up of persons at risk of plague infection

In the event of exposure to a deliberate release of \textit{Y. pestis}, or after contact with a case of pneumonic disease, antibiotic prophylaxis should be initiated as soon as possible. Contacts of cases of bubonic plague should be assessed for the need for prophylaxis. The regimens outlined in Table 2 are recommended. For adults, children and pregnant women, ciprofloxacin is the drug of choice. Pharmacokinetic studies have shown that ciprofloxacin achieves far higher concentrations in lung macrophages than penicillins, and is therefore a more effective prophylactic antibiotic. Ciprofloxacin has the added advantage that it is also an effective prophylactic treatment for other potential agents that may be used in deliberate release scenarios such as anthrax and tularemia.

The risk of adverse effects from antibiotic prophylaxis must be weighed against the risk of developing a serious disease. Paediatric use of fluoroquinolones and tetracyclines can be associated with adverse effects that must be weighed against the risk of developing a lethal disease. 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 could be used.

After initial treatment with ciprofloxacin, doxycycline may be substituted to complete the seven day prophylaxis. Persons who come into contact (<2m) with patients with pneumonic plague should receive antibiotic prophylaxis for seven days. In healthcare and laboratory staff with continuing exposure, prophylaxis should be extended to seven days.
after the last contact with a patient or sample considered to be infectious. Prophylaxis should continue until exposure has been excluded.

The duration of initial course of antibiotic treatment is under review but is currently three days. Only the initial course of antibiotics for prophylaxis is held in pods as part of the antibiotic stockpile. Arrangements for the supply of the remainder of the prophylactic course are being developed and individuals should be advised to report to their own GP. See DH Patient Group Directions for the initial and further supply of ciprofloxacin and the further supply of doxycycline in the event of exposure to a suspect biological agent www.dh.gov.uk/PolicyAndGuidance/EmergencyPlanning/EmergencyPreparednessArticle/fs/en?CONTENT_ID=4069610&chk=in7ZEF

In a major incident information on how to access stocks of antibiotics for the initial treatment or prophylaxis can be found on the DH website at: http://www.dh.gov.uk/assetRoot/04/13/53/71/04135371.pdf

### Table 2: Recommended prophylaxis after exposure to *Y. pestis*

<table>
<thead>
<tr>
<th>Adult (including pregnant women)</th>
<th>Antimicrobial agent</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial (3 day) treatment</td>
<td><strong>Ciprofloxacin</strong> 500mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>Further (4 day) treatment</td>
<td><strong>Ciprofloxacin</strong> 500mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td><strong>Doxycycline</strong> 100mg orally twice daily</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child</th>
<th>Antimicrobial agent</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial (3 day) treatment</td>
<td><strong>Ciprofloxacin</strong> 15mg/kg orally twice daily - not to exceed 1g per day</td>
<td></td>
</tr>
<tr>
<td>Further (4 day) treatment</td>
<td><strong>Ciprofloxacin</strong> 15mg/kg orally twice daily (maximum 500mg) - not to exceed 1g per day</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin dose depends on age and weight, as a guide:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>newborn – 6 months</td>
<td>100mg/day</td>
<td></td>
</tr>
<tr>
<td>1 year – &lt;3 years</td>
<td>200mg/day</td>
<td></td>
</tr>
<tr>
<td>3 years – &lt;5 years</td>
<td>300mg/day</td>
<td></td>
</tr>
<tr>
<td>5 years – &lt;7 years</td>
<td>400mg/day</td>
<td></td>
</tr>
<tr>
<td>7 years – &lt;12 years</td>
<td>500mg/day</td>
<td></td>
</tr>
<tr>
<td>12 years+(adult dose)</td>
<td>1000mg/day</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td><strong>Doxycycline</strong> &gt;45kg adult dose (see above)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>\leq 45kg: 2.2mg/kg orally twice daily (not to exceed 200mg per day)</td>
<td></td>
</tr>
</tbody>
</table>
2.4.1 Immunisation
The inactivated vaccine, consisting of formalin-killed bacteria, is no longer available. This vaccine had uncertain efficacy in protecting humans, particularly from plague pneumonia, and the long time interval to produce antibodies means that it would be ineffective in the event of a deliberate release of the organism. New sub-unit vaccines are being developed and have much greater efficacy in mice even against plague pneumonia, but have not yet been evaluated for immunogenicity in humans.

2.4.2 Contacts of cases
All unprotected contacts of cases of symptomatic pneumonic plague should receive antibiotic prophylaxis as described in section 2.4. The infection is not contagious until symptoms develop and patients have a productive cough. Other forms of plague are not generally contagious. Contacts are defined further in section 4.3.5.

2.5 Environmental decontamination
The initial risk to human health following a release of plague occurs during the period in which the bacteria remain airborne, called primary aerosolisation. The duration and scale of the infectious risk depends on the duration for which bacteria remain airborne, the distance they travel before they fall to the ground, and the survival of the organism in aerosol. This depends on meteorological conditions and the aerobiological properties of the dispersed aerosol. The organisms are killed rapidly by drying and exposure to sunlight.

In the event of a known release, an **exposed zone** will be defined according to the time and place of release in order to identify all persons exposed to primary aerosolisation. The area surrounding the site of release will remain designated as an exposed zone until sufficient time has elapsed and the risk of infection has subsided – see section 4.

Expert advice will be provided to determine the time after release for which bacteria are likely to remain an infectious risk. Once this has elapsed, the organisms can be considered dead and non-infectious, therefore environmental decontamination is not required.

2.6 Protection of frontline workers
This includes all emergency staff involved in management at the scene of a release, and healthcare staff involved in the care of patients.

2.6.1 Protective clothing
The release of *Y. pestis* will create an **exposed zone** that presents a high risk of inhaling the agent. Any personnel entering this zone should wear a biologically-resistant suit with outer gloves and boots (for example a CR1, PRPS or gas-tight suit), and a correctly fitting high-efficacy particulate respirator of FFP3 standard **AT ALL TIMES**.

Healthcare workers will not normally be asked to enter this zone, but may be called into it to treat casualties, for example if an explosive device has accompanied the release of biological agent. In this case the appropriate protective clothing should be worn.

Exposed persons will normally be moved from the exposed zone, through decontamination if necessary, and into a place of safety (see section 4.3.1) for medical assessment. Frontline workers involved in decontamination, and others who have had any contact with contaminated clothing and fomites should observe Standard Universal Precautions (gloves, gowns and hand washing) and in addition should wear high efficiency (FFP3) masks and...
Guidelines for Action in the Event of a Deliberate Release: Plague

eye protection. Healthcare workers who attend exposed persons after decontamination has been completed need observe Universal Precautions only.

Healthcare workers involved in the management of hospitalised patients with all forms of plague, should use the best available (highest efficiency) face protection, this would be at least a surgical mask but preferably a medium efficiency FFP2 face mask and eye protection in addition to Standard Universal Precautions. Mortuary staff should use similar barrier protection. More sophisticated countermeasures for airborne protection are not required.

2.6.2 Antibiotic prophylaxis
Post exposure prophylaxis should be given to all frontline workers who are called into the exposed zone, and those who are subsequently involved in the decontamination of exposed persons.

In addition healthcare workers attending patients with suspected or confirmed pneumonic plague (who are within 72 hours of starting treatment), and mortuary staff who handle the deceased (who have not received a full 72 hour course of treatment) should also receive prophylactic antibiotics - as described in section 2.4.

In addition to antibiotic prophylaxis, frontline workers involved at the scene of a release, and healthcare workers and mortuary staff involved in the management of plague cases should be advised to seek urgent medical attention should they develop a febrile illness within 7 days.

2.7 Other Considerations – patient, visitor and public information
Fact sheets have been prepared by Department of Health for distribution in the event of an incident. http://www.dh.gov.uk/assetRoot/04/01/88/54/04018854.pdf
3 LABORATORY PROCEDURES

3.1 Risk assessment

*Y. pestis* is a Hazard Group 3 pathogen and should thus be covered by existing risk assessments for handling such organisms in diagnostic laboratories. All laboratory procedures should be performed by experienced scientists in a Containment Level 3 facility using a Class 1 protective cabinet.

3.1.1 Receipt of samples

Samples should have been labelled as “High Risk” by the submitting staff, and should be handled according to local protocols for such samples. Chain-of-evidence documentation should accompany specimens. In larger incidents, this would only be required for several of the initial cases.

3.2 Isolation and identification

Direct smears from clinical samples as well as from cultures may be stained with Gram, Giemsa or Wayson’s (if available) stains to demonstrate bipolar staining coccobacilli. Rapid presumptive identification can be made by immunofluorescence staining of smears using specific F1 antibodies labelled with fluorescein – smears should be heat fixed and sent to the Reference Laboratory.

3.2.2 Culture

*Y. pestis* is a small Gram negative coccobacillus, which commonly exhibits bipolar staining and pleomorphism, particularly in clinical specimens. The diagnosis of plague must be confirmed by culture. Specimens for culture should be inoculated onto blood agar and MacConkey agar, and incubated aerobically at 28°C for optimal growth. Aspirates and CSF should also be placed into an enrichment broth with subculture after 24-48 hours. The addition of *Yersinia* CIN agar may be useful for culture of “contaminated” specimens, i.e. sputum.

On blood agar the organism forms tiny, translucent colonies after 24 hours. After 48 hrs incubation colonies range between 1-2mm in diameter and grey-white to slightly yellow in colour; there is no haemolysis. On MacConkey agar it appears as pinpoint non-lactose fermenting colonies, which disappear after 2-3 days, presumably due to autolysis. *Y. pestis* is catalase positive and oxidase negative. Biochemical identification can sometimes be made using API 20E or other commercial test strips, although these may not be reliable, so suspected isolates should always be referred to the Reference Laboratory for further testing.

3.2.3 Antibiotic sensitivity

Antimicrobial susceptibility tests must be set up as early as possible. Use standard laboratory methods at Containment Level 3, but ensure that isolates are referred to the Reference Laboratory for confirmatory testing.

3.2.4 Serology

Serological diagnosis is possible but antibodies may not be detectable when the patient first presents. However it is useful in culture-negative cases. Acute and convalescent sera should be sent to the Reference Laboratory for testing. The laboratory should be warned in advance that sera are being submitted.
3.3 **Confirmation and Additional Tests**
All suspect isolates must be sent to the Reference Laboratory (see section 3.5) which must be notified prior to the dispatch of samples. Tests available include direct immunofluorescence for F1 antigen, specific phage lysis, and PCR for the F1 capsular antigen, the pesticin gene and the plasminogen activator gene.

3.4 **Waste disposal**
Waste should be disposed of according to local procedures for Hazard Group 3 pathogens.

3.5 **Reference laboratory**
All suspect isolates and clinical samples should be sent to the Reference Laboratory for confirmation taking care to observe the procedures for transportation outlined in section 3.6. The sender’s name and address should be clearly marked. The reference laboratory must be telephoned prior to sending to expect the sample. Samples should be forwarded urgently to:

**Mr Tom Cheasty**  
HPA Centre for Infections  
Laboratory of Enteric Pathogens  
61 Colindale Avenue  
London  
NW9 5HT  
Tel: (+44) 020 8327 6173  
Fax: (+44) 020 8905 9929

3.6 **Transportation of samples with suspicion of *Y. pestis***
Strict procedures apply for transport of samples to the laboratory. Biological agents, or materials that contain or may contain them, are allocated to UN Division 6.2 – infectious substances. Infectious substances are divided into Category A or Category B. Full details are given in Appendix 1.2 Transport of infectious substances in *Biological agents: Managing the risks in laboratories and healthcare premises*. ACDP HSE May 2005, available at [http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf](http://www.advisorybodies.doh.gov.uk/acdp/managingtherisks.pdf) and in the Department of Health’s guidance, available at [http://www.dh.gov.uk/assetRoot/04/11/48/13/04114813.pdf](http://www.dh.gov.uk/assetRoot/04/11/48/13/04114813.pdf)

Cultures of *Y. pestis* are Category A infectious substances capable of causing disease in humans or animals and are therefore assigned to UN2814 and must be packaged in accordance with UN Packaging Instructions PI620 (road/rail) /PI602 (air). P620 and P602 are identical specifications but given different codes in ADR and ICAO regulations respectively (for a full description of PI see [http://www.unece.org/](http://www.unece.org/)). Category A transfers should be individually requested through an approved courier. The service will be a next day, tracked door-to-door delivery, which must be signed for at collection and receipt.

Clinical samples are generally classified as Category B and are assigned to UN3373 ("Biological Substance, Category B") and should be packaged in accordance with UN PI650. Clinical samples may be posted.

Packaging must meet with UN performance requirements i.e. UN-type approved packaging for Division 6.2 substances. The packaging should consist of an inner package (watertight receptacle, watertight secondary packaging, an absorbent material in sufficient quantity to...
absorb the entire contents placed between the receptacle and the secondary packaging) and a rigid outer package of adequate strength for capacity, mass and intended use. Packages should be marked with the proper shipping name (e.g. UN 2814), and the appropriate warning label (i.e. the danger sign for infectious substances).

The following procedures should be adopted for the transport of all specimens, and also all cultures for confirmation. These apply within hospitals and laboratories as well as for specimens sent to the reference laboratory:

- The primary container (bijoux or similar) should be screwed tight, labelled and placed in an intact plastic bag.
- A ‘High Risk’ label should be affixed to both specimen and request form. The latter should include any other relevant information and include adequate clinical details to indicate level of suspicion.
- Under no circumstances should the request form be placed in the same bag as the specimen.
- The bag should be sealed, using tape or heat sealer. Separate bag should be used for each specimen.
- Each specimen must then be placed in a leak-proof secondary container with sufficient absorbent material to absorb all the contents should leakage occur.
- Each specimen must be packaged individually - i.e. three specimens, three separate packages.
- The secondary container should be externally disinfected – e.g. by wiping with hypochlorite (1,000ppm).

3.6.1 Samples sent within hospitals and laboratories
Samples should be transported according to local arrangements for High Risk specimens. Precautions should include:

- Secondary containers should be placed within a final outer tertiary packaging.
- This packaging must comply with UN-type approved packaging for the transport of infectious substances.
- The package should be certified to this standard and carry the appropriate UN certification numbers on the tertiary packaging along with the following information:
  1. BIOHAZARD – danger of infection symbol Class UN 6.2.
  2. Instructions not to open if found.
  3. Telephone number of a responsible person - e.g. Consultant Microbiologist, Laboratory Manager.
- The container should be transported either by an approved courier for cultures (UN 2814) or by post for clinical samples (UN 3373), without delay, directly to the reference laboratory.

3.6.2 Samples sent within hospitals and laboratories

- Secondary containers should be placed in a good quality box, which is well taped up and clearly labelled "Pathological Specimen – Open only in Laboratory”.
- Specimens should be transported by hand by a responsible person using the above packaging.
- Vacuum-tube systems should not be used for transportation of specimens within hospitals or laboratories.
- Extra care should be taken to ensure that laboratory records are kept to a high standard.
3.7 Protection of laboratory staff

All laboratory procedures must be performed in a Containment Level 3 facility using a Class 1 biological safety cabinet. Under these circumstances antibiotic prophylaxis is not recommended unless there is an inoculation injury or a spillage causing aerosols (i.e. blood, sputum, liquid culture or bacterial suspension). Prophylaxis may be required for staff who handled samples, in the open laboratory, from patients subsequently shown to have plague.

Any member of laboratory staff, working with specimens or cultures from plague patients, who develops a febrile/respiratory illness, should seek urgent medical attention.
4 PUBLIC HEALTH PROCEDURES

4.1 Surveillance and detection of deliberate releases of plague
A deliberate release may be overt with an announcement and/or confirmation by environmental sampling. However, it is also possible that a deliberate release may be covert and will not be identified until the first cases of disease arise.

Even a single confirmed case of plague must be regarded with a high index of suspicion of deliberate release. Cases that occur in people who have returned from endemic areas should be investigated to ascertain that the illness did not occur due to deliberate release of Y. pestis.

In addition, a deliberate release should be considered in the event of two or more suspected cases of plague that are linked in time and place, especially geographical related groups of illness following a wind direction pattern (analogous to legionnaire’s disease). Expert advice will be provided in order to confirm the occurrence of a covert release and assist with epidemiological investigations to define an exposed zone in time and space.

Rodents and cats are susceptible to plague, so close coordination with veterinary colleagues is essential. Infected animals could also act as an ongoing source of potential human infection.

4.2 Case Definition

4.2.1 Suspected cases
The diagnosis of plague should be considered if cases of the following clinical presentations occur in previously healthy patients, especially if two or more cases arise that are linked in time and place:

- Sudden onset of severe, unexplained febrile respiratory illness
- Unexplained death following a short febrile illness
- Sepsis with Gram-negative coccobacilli identified from clinical specimens

The level of suspicion of plague depends on local circumstances at the time – in the event of a known or suspected deliberate release, or among contacts of plague cases, the threshold for making a diagnosis of plague should be lower. If plague is suspected, microbiological specimens should be sent, and consideration should be given to initiating empirical treatment pending results.

4.2.2 Probable case
A case that clinically fits the criteria for suspected plague, and in addition, positive results for antigen or PCR are obtained on one or more specimens by the Reference Laboratory. A presumptive diagnosis, by positive PCR or detection of F1 antigen on suspect isolates, will be available within one working day.

4.2.3 Confirmed case
A case that clinically fits the criteria for suspected plague and in addition is culture positive and has a 4-fold rise in titres obtained by the Reference Laboratory. The definitive tests for Y. pestis are:

- Culture of Y. pestis from a clinical specimen and confirmation of identification by phage lysis. Result available within 48 hours of receipt of culture.
- A significant (≥ 4-fold) change in antibody titre to F1 antigen in paired serum samples.
4.3  Public Health Action

4.3.1  Procedure for handling persons exposed to the initial release

Depending on the site and method of release, plague bacteria may be dispersed over a wide area but do not remain infectious in aerosol form for more than a few hours. Expert advice will be required to define an exposed zone in time and space.

All individuals who have been present in the exposed zone need to be identified. In the event of an overt release, some of them will still be at the scene when emergency services respond to the incident. This group will be decontaminated and then referred to health workers at a nearby place of safety for assessment and prophylaxis (this will be a clinical area just outside the exposed zone and within the cordon that will be established at the scene of the incident). Others will have left the scene before emergency services arrive and will be identified later after details of the incident have been made public.

Because of the potential for person-to-person transmission, those exposed should go to designated centres. Procedures need to ensure that these individuals are appropriately decontaminated, receive prophylaxis at the designated centres, and have their details collected for follow up. Should symptoms develop, those exposed should be assessed rapidly at an A&E department, taking appropriate infection control precautions.

In the event of a covert release it will not be possible to define an exposed zone until two or more suspected or confirmed cases have arisen. Epidemiological investigations may allow an exposed zone to be defined or recognise other exposures. Procedures will be required for offering prophylaxis to exposed persons, and possibly for collection and decontamination of exposed clothing and other fomites.

4.3.2  Post-exposure prophylaxis for persons at risk of plague

There are three groups of individuals for which prophylaxis may be indicated:

I  Individuals who were present in the exposed zone should be offered post-exposure prophylaxis as outlined in Table 2

II  Frontline workers may require prophylaxis as described in section 2.6.2

III  Contacts of cases of plague – see sections 2.4.2 and 4.3.5

If suspected or confirmed cases of plague arise outside among people who were not at risk of exposure but have been in close contact in time or space, the defined parameters of the exposure should be reconsidered with a view to extending post-exposure prophylaxis.

Prophylaxis for other groups may be considered in the event of an incident. However, it is not advisable to give antibiotics to people who do not have a clear history of having been present at the time and site of release or subsequently exposed to cases of plague. It is inappropriate to provide antibiotics to large numbers of people who have not been exposed, but who are generally concerned or have non-specific mild illness. Rather than prophylaxis, increased surveillance, prompt investigation and treatment are encouraged.

4.3.3  Follow-up for persons at risk of plague infection

This includes all those exposed or identified as at risk for possible infection or transmission, as well as contacts of plague cases, as defined in section 4.3.5. After an overt release, a basic set of personal details needs to be collected from all persons present in the exposed zone. Similar details also need to be collected from all contacts of plague cases.

Those at risk of infection should receive post-exposure prophylaxis, and in addition all exposed persons should monitor themselves for the development of fever and/or respiratory symptoms for a period of seven days and report to the appropriate medical
4.3.4 Case finding
Links between cases of suspected plague may not be immediately apparent to clinicians, and if a covert release is suspected, it is important that there should be enhanced surveillance for other cases with advice to health care workers and other individuals.

4.3.5 Preventing secondary spread
Person-to-person spread of pneumonic plague may occur through infected respiratory droplets. Therefore, all contacts of cases of pneumonic plague should receive antibiotic prophylaxis as described in section 2.4, and should be followed up as described in section 4.3.3.

For the purposes of defining contacts, this should include all people who have had close contact with symptomatic cases of pneumonic plague. Presymptomatic cases and other forms of the disease are not contagious.

Expert advice on the definition of close contacts will be provided as indicated, but it is likely to include short periods of intimate contact (at a distance less than 2 meters), and longer periods of household or office contact with those with symptoms; but exclude transient contact such as in shops or in the street.

4.4 Epidemiological investigation
If a case is strongly suspected or confirmed, immediately notify the CCDC at the local HPU (or relevant out-of-hours cover) and the HPA Centre for Infections (020 8200 6868, 24 hours). If cases arise due to a covert release, or following an overt release but in people who have not been present in the exposed zone, it is important to collect some epidemiological details in addition to a basic set of personal details. This is in order to define or redefine the exposed zone and aid identification of others at risk of infection. Details should be as thorough as possible, whilst recognising that in the event of a large release with multiple exposed persons or cases, it may not be possible to collect comprehensive information from everyone.

The aim of epidemiological investigations may be:
- Following a covert release, to assist definition and ongoing review of the temporal and spatial parameters of the exposed zone so that post exposure prophylaxis can be distributed appropriately.
- Following an overt release, to guide review of the exposed zone if cases arise in persons who were not present within it.

4.4.1 Epidemiological sampling
Y. pestis would not persist in the environment for prolonged periods. In the event of suspected deliberate release of a biological agent, microbiological samples will be taken from the environment by the police. Samples will be tested in designated laboratories.

There is no rapid test that can be offered to inform asymptomatic people, who suspect they have been exposed, whether or not they have been infected. Collection of acute and convalescent sera from asymptomatic people, who have been exposed to a release, or who fit the definition of contacts of plague cases may provide useful epidemiological data and information about the efficacy of prophylaxis. Obviously the practicalities of this depend on the scale of the incident.
5. LIST OF NATIONAL SPECIALISTS

**Clinical expert advice**
Dr Michael D Smith  
Consultant Microbiologist  
Taunton and Somerset Hospital  
Musgrove Park  
Taunton TA1 5DB  
Tel: (+44) 01823 342424  
Fax: (+44) 01823 259453  
E-mail: mike.smith@tst.nhs.uk

Dr David AB Dance  
Regional Microbiologist  
Health Protection Agency SW  
Tamar Science Park  
Plymouth PL6 8BX  
Tel: (+44) 01752 437143  
Mobile: 0777 333 1065  
E-mail: david.dance@phnt.swest.nhs.uk

**Laboratory diagnosis**
Mr Tom Cheasty  
Laboratory of Enteric Pathogens  
HPA Centre for Infections  
61 Colindale Avenue  
London NW9 5HT  
Tel: (+44) 020 8327 6173  
Fax: (+44) 020 8905 9929  
E-mail: tom.cheasty@hpa.org.uk

**Public Health**
Dr Dilys Morgan  
HPA Centre for Infections  
Emerging Infections and Zoonoses Department  
61 Colindale Avenue  
London, NW9 5HT  
Tel 0208 327 7474  
E-mail: dilys.morgan@hpa.org.uk

Dr John M Watson  
HPA Centre for Infections  
61 Colindale Avenue  
London NW9 5EQ  
Tel: (+44) 020 8327 7481  
Fax: (+44) 020 8200 7868  
E-mail: john.watson@hpa.org.uk

Out of hours contact details are held at HPA Centre for Infections by the 24 hr on call duty doctor, Tel: (+44) 020 8200 6868
6. BIBLIOGRAPHY

6.1 General Reviews
1. Centre for infectious disease research and policy (CIDRAP) University of Minnesota. Plague: Current, comprehensive information on pathogenesis, microbiology, epidemiology, diagnosis, treatment, and prophylaxis. (Last updated 5 March 2007) http://www.cidrap.umn.edu/cidrap/content/bt/plague/biofacts/plaguefactsheet.html


6.2 References


