T U L A R E M I A

INTERIM PHLS GUIDELINES FOR ACTION
IN THE EVENT OF A (SUSPECTED) DELIBERATE RELEASE

Note: these are interim guidelines. Comments are welcome from healthcare, laboratory and public health professionals, and should be sent to dkrepski@phls.org.uk. Since these are interim guidelines, they may be subject to changes as comments are received, so please ensure that you have the latest issue and version: the most up to date is version 1, available through the PHLS website at www.phls.org.uk/facts/deliberate_releases.htm

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PHLS-CDSC                                                                    1
INTERIM GUIDELINES FOR ACTION IN THE EVENT OF A DELIBERATE RELEASE
TULARAEMIA [VERSION1]
ISSUED BY CDSC; ISSUE DATE: 29/11/01
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1 BACKGROUND

1.1 Introduction

The discovery of tularaemia is attributed to McCoy who reported a plague-like illness in ground squirrels from Tulare county, California, in 1911. The disease is caused by the Gram-negative pleomorphic bacterium, *Francisella tularensis.* Two subspecies, type A, *(F. tularensis* subsp *tularensis/nearctica*) and type B (*F. tularensis* subsp *holarctica/palearctica*) cause disease in man and have been considered as potential biological agents. The SCHU S-4 strain of type A is one of the most infectious pathogenic agents known, requiring inoculation or inhalation of fewer than ten organisms to cause disease.

Humans become naturally infected through diverse environmental and animal exposures but there has been no documented person to person transmission.

Six forms of tularaemia are recognised:

- Ulceroglandular)
- Oropharyngeal) 45%-85% of naturally occurring cases
- Oculoglandular)
- Pneumonic: <5% of cases
- Septicaemic:<5% of cases
- Typhoidal: up to 25% of cases

1.1.1 Deliberate release of *F. tularensis*

Francisella tularensis does not occur naturally in the United Kingdom and the very few numbers of cases seen have all been acquired abroad.

The World Health Organisation (WHO) and Centres for Disease Control and Prevention (CDC) in the United States anticipate that the greatest impact in terms or mortality and morbidity following intentional release of *F. tularensis* would be achieved through aerosolisation of a virulent strain, making inhalation into the lungs the most likely route of infection.

Monkeys that inhaled the SCHU S-4 strain developed acute bronchiolitis within 24 hours of exposure to 1-μm particles and within 48 hours of exposure to 8-μm particles. Bronchopneumonia was most pronounced in animals exposed to the smaller particles.

1.2 Epidemiology

1.2.1 Transmission

Francisella tularensis infects more than 100 species of wild mammals, birds, and insects worldwide. A variety of small mammals, including voles, mice, water rats, squirrels, rabbits, and hares, are natural reservoirs of infection. They acquire infection through bites by ticks, flies, and mosquitoes, and by contact with contaminated environments. Although enzootic cycles of *F. tularensis* typically occur without notice, epizootics with extensive 'die-offs' of animal hosts may herald outbreaks of tularaemia in humans. The ecosystems depend on the subspecies and locality.

Infection with type B strains occurs across northern Europe (including Scandanavia), Russia and Japan and large outbreaks have occurred. Disease due to type B *F. tularensis,* by comparison with type A infection,is relatively mild, with negligible mortality. Naturally occurring infection with type A is more sporadic and often severe. It is restricted to defined geographical foci in North America, where it accounts for 90% of reported tularaemia.

Naturally acquired human infection occurs through a variety of mechanisms:
- Bites of infected arthropods including Dermacentor and Ixodes ticks (summer months).
- Handling infectious animal tissues or fluids.
- Direct contact or ingestion of contaminated water, food, or soil.
- Inhalation of infective aerosols eg from handling damp hay.

People of all ages and both sexes appear to be equally susceptible to tularaemia.

Human to human transmission has not been documented.

1.2.2 Infectious dose

The infectious dose is very low and depends upon the portal of entry and type of *F. tularensis*. Approximately 10-50 type A organisms can initiate infection by the inhalational route. If SHU S4 strain is used <10 organisms would be required.

1.2.3 Incubation period

Symptoms usually appear between 2-5 days (range: 1-21 days) post exposure.

1.2.4 Period of communicability

Human to human spread has not been reported following casual contact. Handling of infectious secretions or tissues may pose a risk to health care workers due to the low infectious dose.

1.3 Clinical features

Tularaemia classically presents as one of six clinical syndromes, depending on the route of infection and biotype of the infecting organism. Size of the inoculum and host immune status influence the severity and extent of disease. Onset of infection is usually acute and is heralded by fever, chills, headache and myalgias. Following a deliberate airborne release the most likely presentation would be pneumonic or septicaemic tularaemia.

1.3.1 Pneumonic tularaemia

This usually results from the direct inhalation of contaminated aerosols but can also follow haematogenous spread from another site. In primary inhalation the disease commonly presents as <u>an acute flu-like illness with or without clinical pneumonia/pneumonitis</u>. Features include fever, non-productive cough, pharyngitis, pleuritic chest pain and hilar lymphadenopathy. This can progress to a severe pleuropneumonitis with moderate sized pleural effusions. When consolidation occurs this is usually nonlobar, with patchy infiltrates. Chest signs may, however, be minimal or absent. Volunteers challenged with aerosols of virulent *F. tularensis* type A regularly developed systemic symptoms of acute illness 3-5 days following exposure and 25-50% showed radiological evidence of pneumonitis early in the infection. In the largest airborne outbreak involving type B organisms, which occurred in Sweden in 1966/7, only 10% of serologically confirmed cases had symptoms suggestive of pneumonia. In most cases of established pulmonary disease, progression tends to be less dramatic than that seen with anthrax or plague, although mortality rates in excess of 30% may occur.

1.3.2 Septicaemic tularaemia

The patient presents as an acute 'Gram-negative' sepsis with fever, abdominal pain, diarrhoea, and vomiting which may be prominent early in the course of illness. The patient typically appears toxic and may progress to septic shock, disseminated intravascular coagulation, haemorrhage, acute respiratory distress, confusion and coma.

1.3.3 Ulceroglandular tularaemia

Naturally occurring ulceroglandular tularaemia usually arises from handling a contaminated carcass or following an arthropod bite. Typically a local papule arises at the site of inoculation accompanied by generalised symptoms including fever and aches. The lesion may be pruritic and enlarges to form a pustule, which ruptures and develops into a painful, indolent ulcer. This may or may not be accompanied by eschar formation. Differential diagnosis includes cutaneous anthrax (surrounding oedema is usually not as prominent as in cutaneous anthrax), plague, lymphogranuloma venerium, granuloma inguinale, and cat-scratch fever. A localised vesiculopapular eruption may also occur. As the lesion progresses it is accompanied by tender enlargement of one or more regional lymph nodes, which may become fluctuant and rupture releasing caseous material. Local disease often continues to progress despite appropriate antibiotic therapy.

1.3.4 Oculoglandular tularaemia

This follows airborne exposure, autoinoculation or after cleaning infected animal carcasses. Ulceration of the cornea produces chemosis and pain and is accompanied by tender preauricular lymphadenopathy.

1.3.5 Oropharyngeal tularaemia

Acquired by drinking contaminated water or food, direct inoculation from the hands to the mouth and sometimes by inhaling contaminated droplets or aerosols. Affected persons may develop a stomatitis, but more commonly an exudative pharyngitis or tonsillitis ensues with or without painful mucosal ulceration.

1.3.6 Typhoidal tularaemia

An acute flu-like illness, often with diarrhoea and vomiting. This may follow ingestion or inhalation of *F. tularensis*. Pneumonic changes, mucocutaneous lesions and regional lymphadenopathy are usually absent.

Glandular tularaemia may occur in the absence of an obvious site of inoculation.

1.4 Mortality

Untreated, the overall mortality for all types of tularaemia is 8%, 4% for ulceroglandular and 30-50% for typhoidal, septicaemic and pneumonic types. With appropriate treatment, mortality is reduced to 1%.

1.5   Organism Survival

The survival of *F. tularensis* in aerosols is short and infective doses are not likely to persist in air for more than a few hours. Survival in non-chlorinated water can occur for up to 90 days.

1.6   Antimicrobial Susceptibilities and Animal Studies

Aminoglycoside antibiotics (eg gentamicin), are bactericidal against *F. tularensis* and are currently the treatment of choice for pneumonic or typhoidal tularaemia (and severe forms of glandular disease). Fluoroquinolones have shown promise because of their low toxicity and potential for oral therapy. Chloramphenicol and tetracyclines are associated with high relapse rates. The beta-lactams, except for carbapenems, are considered ineffective. Macrolide antibiotics are not recommended. If doxycycline or ciprofloxacin are given 48 hours before challenge and continued for 5 days after challenge in a murine model, these antibiotics protected against intraperitoneal infection. However all mice succumbed once the antibiotics were stopped. If treatment was continued for 10 days after challenge, then fewer relapses occurred.

2 Clinical procedures

2.1 Diagnosis and collection of samples

The first indication of a deliberate release via aerosol will be a cluster of acute, severe, flu-like illness with respiratory symptoms and unusual epidemiological features eg occurring in previously healthy young adults.

Type B strains released into water or food would probably present as a typhoidal illness or stomatitis/pharyngitis/tonsillitis with mucosal ulceration and tender cervical lymphadenopathy. In the highly unlikely event of release through direct contact eg via contaminated mail package, an ulceroglandular presentation would probably predominate.

Identification of *F. tularensis* in clinical specimens (detailed in 2.1.2) may be delayed for some time or missed altogether when procedures for routine microbiological screening of bacterial pathogens are followed, and it is unlikely that laboratory identification would be the initial event that alerted authorities to a deliberate release of this organism unless cysteine enriched media such as BCYE are used.

2.1.1 Precautions for sampling

The organism is most infectious by the inhalation route as fewer than 10 organisms of certain strains of type A *F. tularensis* may result in pulmonary tularaemia. Infection may occur through the skin, mucous membranes, gastrointestinal tract, and lungs via infectious animal tissues or fluids, direct contact with or ingestion of contaminated water, food, or soil, and inhalation of infective aerosols. During the taking of clinical samples healthcare workers should observe universal contact precautions ie wearing and plastic aprons followed by thorough handwashing. Healthcare workers should protect skin lesions with a water-proof dressing. Although person to person transmission has not been documented following casual contact, the use of goggles and face-masks, of the type used to manage MDR-TB cases, is recommended if infected secretions are likely to be aerosolised during sampling. All laboratory work must be performed in a Class I safety cabinet in a containment level 3 facility. Exposure during examination of an open culture plate can cause infection and in several outbreaks the identity of the pathogen first became apparent after laboratory staff became infected after handling cultures on the open bench.

2.1.2 Samples to be taken from acutely ill humans

In suspected inhalational tularaemia specimens of sputum, pharyngeal washings, fasting gastric aspirates, pleural fluid and blood may be culture positive for *F. tularensis*. Both radiometric and nonradiometric blood culture systems can detect *F. tularensis,* but subculture to cysteine rich medium such as BCYE is necessary for isolation. Other samples include exudates from lesions and biopsies of lymph nodes or cutaneous lesions. The procedure for transport of specimens to the laboratory is outlined in section 3.6. The laboratory must be informed in advance.

2.1.3 Samples to be taken from the environment

Francisella tularensis does not produce spores. Type A strains survive for only a few hours following deliberate release due to desiccation, UV radiation and oxidation. Type B strains may survive for months in surface water and soil. If samples of exposed water, soil, dust and clothing are taken they should be processed as described in section 3.2

2.1.4 Samples to be taken from others who have or may have been exposed

The decision to issue antibiotic prophylaxis following deliberate or accidental release should be taken following a risk assessment of likelihood and extent of exposure. Appropriate antibiotics should be started, if possible, within 24 hours of such an exposure (see section 2.4). Serological screening of exposed individuals may be useful in establishing the extent of exposure (2-4 weeks) following covert or overt release.

2.2 Treatment
Table 1: recommended treatment for tularaemia

	Initial Therapy	Optional therapy if strain is proven susceptible	Duration
Adults	Gentamicin 7mg/kg per day IV recommended post dose level (6 to 14 hours later) At 6 hours it should be =< 6.5 mg/liter. At 14 hours =<2 mg/litre. (For all stages in between use Hartford nomogram). If available, streptomycin can be used, 1g twice daily IM	Ciprofloxacin 400mg iv every 12hr (change to oral 500mg bd when appropriate)	10 days for aminogly-cosides. 14 days for cipro

Children*	Gentamicin 2.5 mg/kg IM or IV three times daily or, if available, streptomycin 15/mg/kg twice daily (should not excede 2g/d).	Ciprofloxacin 20-30mg/kg per day iv divided into 2 daily doses, not to exceed 1g per day (change to oral therapy when appropriate)	10 days for aminogly-cosides. 14 days for cipro
Pregnancy*	Same as for non pregnant adult		

*Ciprofloxacin is not licensed for use in children or pregnant women.

Gentamicin, for 10 days, is effective in the treatment of tularaemia. It is given intravenously up to 7mg/kg per day. Antibiotic levels should be taken 6 to 14 hours later. At 6 hours the gentamicin level should be =< 6.5 mg/litre. At 14 hours =<2 mg/litre. For all stages in between the Hartford nomogram can be used. Streptomycin up to 15mg/kg twice daily by intramuscular injection was regarded as the drug of choice for the treatment of non-meningeal tularaemia in both adults and children but it is no longer widely available in the UK. A minimum of 10 days should be given and subsequent dosing adjusted in accordance with renal function and serum levels. It is recognised that these agents are not routinely used as monotherapy in the treatment of acute febrile illnesses including pneumonia. When Tularaemia is suspected but not confirmed microbiologically or serologically, an aminoglycoside should be added to an appropriate antibiotic regimen and **not used** as a single agent. Other antibiotics can be stopped when the identity of *F. tularensis* is confirmed and antibiotic susceptibility data available. Ciprofloxacin is active in vitro and in animal studies and has been used successfully to treat a number of cases in both children and adults, including a large non-randomised study in Spain where 21 of 22 patients,with predominantly ulceroglandular disease,were cured. Tetracycline and chloramphenicol are bacteriostatic against *F. tularensis* and if they are used in treatment at least 21 days therapy is required to reduce the chance of relapse. Due to the poor penetration of aminoglycosides into CSF chloramphenicol may be added to streptomycin in the treatment of patients with clinical features of meningitis.

2.2.1 Treatment of mass casualties

Treatment of large numbers of casualties following a deliberate release may warrant the use of oral ciprofloxacin and doxycycline. The risk of side effects from medication would not preclude their use in children, in such a situation.

2.3 Infection control practice

2.3.1 Decontamination of exposed persons
The number of viable organisms that are re-aerosolised following the handling of contaminated clothing of exposed individuals is probably low. Clothing from exposed individuals should be placed, with minimum agitation, in sealed plastic bags prior to laundering using a hot cycle (ie >70°C). In view of the fact that the identity of any biological agent is unlikely to be known at the time of release, exposed individuals should be instructed to shower thoroughly using soap and water.

2.3.2 Isolation of patients
- Standard universal precautions including gloves, gowns and hand washing are recommended for patients with tularaemia.
- Although person to person spread of *F. tularensis* has not been reported following casual contact, isolation of patients in a side room or as a cohort on a ward, is recommended for pulmonary disease or where there is a danger of aerosolisation from lesions during sampling.
- Facemasks of the type used for nursing MDR-TB cases, eg Tecnol or 3M (all tested and approved to European standard EN 149) and goggles should be worn when attending to isolated patients. Lesions should be covered with a waterproof dressing.

2.3.3 Cleaning, disinfection and waste disposal
Contaminated environmental surfaces should be cleaned with 1.0% hypochlorite solution (10,000 ppm). NB. This should not be applied to body surfaces. Laundry and garments should be placed in plastic bags and laundered through a hot cycle (>70°C) when *F. tularensis* is confirmed.

2.3.4 Post-mortem
Post-mortem examinations are not recommended if tularaemia is suspected. However if they are undertaken, standard universal precautions should be observed with the use of gloves, aprons, masks (see section 2.3.2) and eye protection.
Cremation is the preferred method of disposal for the deceased. Embalming of bodies is strongly discouraged.

2.4　Prophylactic treatment for persons exposed to *F. tularensis*

Table 2:　　　Recommended prophylaxis after exposure to *F. tularensis*

Antimicrobial agent	Adults	Children*	Duration
Oral Fluoroquinolones Ciprofloxacin	500mg bd	20-30mg per kg of body mass daily, divided into two doses – as a guide 10kg: 125mg bd 20kg: 250mg bd 30kg: 375mg bd 40kg: as for adult	14 days
If fluoroquinolones are not available or are contraindicated Doxycycline	100mg bd	5mg per kg body mass per day divided into two doses	14 days

*Ciprofloxacin is not licensed for use in children or pregnant women. There have been no formal studies of the use of ciprofloxacin during pregnancy, but is unlikely to be associated with a high risk of abnormalities of foetal development. There is some evidence that the use of fluoroquinolones in children (including by breast feeding mothers) may be associated with tendinopathy and arthropathy.

Ciprofloxacin is the prophylactic agent of choice when there is a credible threat of exposure to a biological agent. The regimen may be modified when information regarding the identity and/or antibiotic susceptibility of an organism becomes available. One small study, in which volunteers were exposed to an aerosol of a virulent strain of *F. tularensis,* showed that oral tetracycline 1g/day for 24 days or 2g/day for 14 days were effective in preventing clinical infection if given within 24 hours of exposure. A shorter course was associated with symptomatic tularaemia in two of ten exposed individuals.

In the case of significant exposure of a laboratory worker, via aerosol or autoinoculation of infected material from a patient with tularaemia, ciprofloxacin or doxycycline should be started immediately and given for 14-21 days.

Fluoroquinolones and tetracyclines may be associated with adverse effects in children and their use must be weighed against the risk of developing an infectious disease with significant morbidity and mortality.

2.4.1 Immunisation

A live attenuated vaccine was developed and has been used to immunise laboratory staff who work with *F. tularensis.* The vaccine is unlicensed and provides incomplete protection, particularly against inhalational tularaemia. It is not currently recommended for use as postexposure prophylaxis.

2.4.2 Contacts of cases

There is no need to provide antibiotic prophylaxis to contacts of patients unless there is concern that they were also exposed to the initial release.

2.5 Environmental decontamination

The greatest risk of acquiring tularaemia from deliberate airborne release follows exposure to the primary aerosol in the exposure zone. The duration and scale of the infectious risk depends on the duration for which organisms remain airborne and the distance they travel before falling to the ground. This depends on meteorological conditions and the aerobiological properties of the aerosol. The aerosol is likely to have completely dispersed before the first cases appear. The more pathogenic type A strains are unlikely to survive for long on environmental surfaces due to desiccation, solar radiation and oxidation and the risk of developing infection following secondary dispersal is likely to be low. If there is visible contamination, such as in the case of laboratory spillage, surfaces should be cleaned with 1.0% hypochlorite solution (10,000 ppm; equivalent to one part household bleach added to nine parts water). The current level of chlorination used in UK mains water supplies, ie 0.5-1 ppm available chlorine, kills 99-100% of *F. tularensis* organisms within five minutes at 10°C. Boiling rapidly kills *F. tularensis*.

2.6 Protection of healthcare workers

This involves all emergency staff involved in management at the scene of a release as well as those involved in treating patients with tularaemia.

2.6.1 Protective clothing

Following an overt release of *F. tularensis* the area affected by primary aerosolisation will depend on the time and place of release. This **exposed zone** presents a high risk of infection, and anyone entering it should wear full protective equipment including gas permeable suits and breathing apparatus (respirator is not needed). Health care workers will not normally be asked to enter this zone, however it is possible that they may be called to treat casualties, for example if an explosive device has accompanied the release of a biological agent. In this case the appropriate protective clothing should be worn.

Exposed persons will normally be moved from the exposed zone, through decontamination and into a holding area for clinical assessment and the administration of prophylaxis.

Professionals involved in the decontamination of exposed individuals and handling of contaminated clothing and fomites should observe standard universal precautions–gloves, plastic aprons along with face masks (as described in section 2.3.2) and eye protection if splashing is likely. Hands should always be washed after the removal of gloves. Those handling individuals who have been decontaminated do not need to take special precautions.

2.6.2 Antibiotic prophylaxis and immunization
Healthcare workers entering the exposed zone should be offered antibiotic prophylaxis as outlined in section 2.4.
Prophylactic antibiotics may also be considered for frontline workers involved in other activities including:
- Decontamination of exposed persons
- Handling of exposed persons
- Management of patients or disposal of bodies of patients dying of tularaemia

Decisions about to whom prophylaxis should be offered, should be taken on an individual basis according to duration and degree of exposure and taking into account the availability and side effects of prophylactic treatments available. The live attenuated vaccine currently used for the protection of laboratory staff who work with live *F. tularensis* provides incomplete protection against inhalational tularaemia and is not currently recommended for use as postexposure prophylaxis.

2.7 Patient visitor and public information
Fact sheets have been prepared for distribution in the event of an incident.

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3 Laboratory procedures

3.1 Risk assessment

Francisella tularensis, particularly type A is an extremely hazardous pathogen and has been associated with severe infection in exposed laboratory personnel. Although currently regarded as an ACDP category 3 pathogen and covered by existing risk assessments extreme caution should be exercised when handling such organisms in diagnostic laboratories. Any exposure through leakage or breakage of clinical specimens, from patients known or thought to have tularaemia, should be reported immediately to the laboratory safety officer, infection control team and occupation health physician so that a risk assessment can be performed and appropriate action taken.

3.11 Receipt of samples

All clinical specimens from patients known or thought to have tularaemia should be labelled 'High risk' by the submitting staff and further work, including unpacking, conducted in a properly maintained Class I protective safety cabinet within a containment level 3 facility.

3.2 Isolation and identification

In the event of there being a credible risk of tularaemia arising from a deliberate release it is recommended that a senior member of the clinical or laboratory staff contact one of the national specialists listed at the end of this document to discuss processing of specimens, along with appropriate Consultants in Communicable Disease Control (CCDCs) and the duty doctor at CDSC. The handling of material that is likely to contain viable *F. tularensis,* by inexperienced personnel, is strongly discouraged.

3.2.1 Culture

Francisella tularensis type A is a small (0.2x0.2-0.7µm) encapsulated, pleomorphic Gram-negative bacterium. It can be readily distinguished from the Gram-positive rod *Bacillus anthracis* and does not show the characteristic bipolar staining of *Yersinia pestis.* It is a fastidious organism requiring cysteine-enriched media such as cysteine-glucose blood agar, or BCYE *Legionella* medium, for growth. Positive blood cultures showing small Gram-negative bacilli that fail to grow on conventional media should be subcultured to such media. Small, 1-2mm grey-white colonies, appear after 24-72 hours in CO_2 enriched air at 37°C although growth may be delayed and cultures should be held for at least 10 days before discarding.

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The organism is non-motile, is a slow catalase producer, oxidase negative, H_2S positive and produces acid but not gas from glucose, maltose and mannose. It can be differentiated from other Gram-negative organisms except *Legionella* spp due to cysteine dependence. *Legionella* spp are motile and do not produce H_2S. Attempts to isolate *F. tularensis* strains should be avoided in the absence of adequate containment facilities.

Francisella tularensis type B grows poorly on primary culture and is best isolated by subcutaneous injection into white mice.

3.2.2 Antibiotic sensitivity

This should be performed by a laboratory experienced in handling *F. tularensis.* (See list of national specialists at the end of this document).

3.2.3 Serology

Serodiagnosis of tularaemia can be performed using ELISA. A significant rise in antibody titre demonstrated on samples of acute and convalescent sera (2-4 weeks later) offer a confirmatory diagnosis of tularaemia. This would be unlikely to provide useful information for initial management of an outbreak although a single high titre offers a presumptive diagnosis in a patient who has not been previously vaccinated (CDC criteria).

3.2.4 Molecular methods

Primers specific for *F. tularensis* have been developed and PCR may offer the best means of rapid diagnosis in samples from patients with suspected tularaemia. Specimen collection and transport should be discussed with Dr G Lloyd (details at the end of this document).

3.3 Confirmation

This should be performed by a laboratory experienced in handling *F. tularensis.* (See list of national specialists at the end of this document).

3.4 Waste disposal

In the laboratory, surfaces that have been contaminated with *F. tularensis* should be disinfected with 1.0% hypochlorite solution (10,000 ppm). Hands should be washed after removing gloves. All waste containers should be autoclaved.

3.5 Reference laboratory

See list of national specialists at the end of this document.

3.6   Transportation of samples with suspicion of *F. tularensis*

The following procedures should be adopted for the transport of all specimens and cultures that are suspected or known to contain *F. tularensis*. These apply within hospitals and laboratories as well as for specimens sent to the reference laboratory:

- Every effort should be made to avoid external contamination of specimen containers during specimen collection.
- The primary container should be screwed tight, labelled and placed in an intact plastic bag.
- A 'high risk' label indicating the level of suspicion should be placed on both the specimen and the request form and relevant details included.
- The request form must not be placed in the same bag or compartment as the specimen.

3.6.1 Samples sent to the reference laboratory

- The outer bag should be sealed using tape or a heat sealer. Pins, staples and metal clips should not be used. A separate bag should be used for each specimen.
- Each specimen should then be placed in a leak-proof secondary container with sufficient absorbant material to absorb the contents should leakage occur.
- Only one specimen should be placed in each secondary container.
- The secondary container should be wiped down with 1% hypochlorite solution (10,000 ppm).
- Secondary containers should be placed within a final outer tertiary packaging that complies with the UN 602 standard packaging of infectious substances by air, road or rail.
- 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- eg. Consultant Microbiologist, laboratory manager.
- The container should be transported by an approved courier, without delay, directly to the reference laboratory.

All enquiries regarding the sending of specimens from a patient with suspected tularaemia should be discussed with one of the national specialists listed at the end of this document.

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.

4   PUBLIC HEALTH PROCEDURES

4.1   Surveillance and detection of deliberate releases of tularaemia

A deliberate release may be overt with an announcement and/or confirmation by environmental sampling. However, a deliberate release may be covert and will not be identified until the first cases of disease arise. Indigenous tularaemia has never been recorded in the UK, but cases are occasionally imported. Person to person spread of tularaemia has not been documented.

Surveillance is based on identification of 'suspected' and/or 'confirmed' cases by clinicians and/or medical microbiologists, who should notify the local CCDC immediately.

In case of 'suspected deliberate release' the duty doctor of PHLS-CDSC should be notified immediately (tel. 0208-200 6868). Case definitions, including those for 'suspected deliberate release' are listed in the next paragraph (4.2).

4.2   Case Definitions

4.2.1 Suspected case

- A severe, unexplained febrile illness or febrile death in a previously healthy person.
- Severe unexplained respiratory illness in otherwise healthy people.
- Severe unexplained sepsis or respiratory failure not due to a predisposing illness.
- Severe sepsis with unknown Gram-negative coccobacillary species, that fails to grow on standard blood agar, identified in the blood or cerebrospinal fluid.

If tularaemia is suspected, microbiological specimens should be sent to the reference laboratory, and consideration should be given to initiating empirical treatment pending results. Obviously the level of suspicion of tularaemia depends on local circumstances at the time – in the event of a known or suspected deliberate release the threshold for suspecting tularaemia should be lower.

As discussed in section 3.3, clinical microbiology laboratories should also be alert to the possibility of tularaemia. If the clinical syndrome is suggestive of tularaemia the sending of samples should be discussed with one of the national specialists listed at the end of this document.

4.2.2 Confirmed case
A case that clinically fits the criteria for suspected tularaemia, and in addition, definitive positive results are obtained on one or more pathological specimens by the reference laboratory (see paragraph 2.1).

4.2.3 Suspected deliberate release.
Two or more **suspected** cases of tularaemia that are linked in time and place, especially geographical related groups of illness following a wind direction pattern (analogous to legionnaire's disease).

4.2.4 Deliberate release.
Single confirmed case of indigenously acquired tularaemia not explained by occupational exposure.

4.3 Public Health Action following <u>confirmed</u> deliberate release

4.3.1 Handling of exposed persons
Depending on the site and method of release, tularaemia bacteria may be dispersed over a wide area. In contrast to anthrax, inhalation of fewer than 10 organisms can cause disease. If an incident is regarded as having 'credible risk' for release of any biological agent, including *F. tularensis*, expert advice will be provided by the responding authority ie police, to define the **exposed zone** in time and space. Definition of the exposed zone may need reviewing if cases arise in persons who were not present within it. All individuals who have been present in the exposed zone need to be identified. 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 when they approach GPs and A+E departments after details of the incident have been made public. Procedures need to ensure that these individuals are appropriately decontaminated, receive prophylaxis, and have their details collected for follow up.

4.3.2 Post-exposure prophylaxis
There are two groups of individuals for which prophylaxis is indicated:

I   **Individuals who have been present in the exposed zone** should be offered post-exposure prophylaxis as outlined in Table 2.
II **Healthcare workers** may require prophylaxis as described in section 2.6.2.

If suspected or confirmed cases of tularaemia arise among persons who have been outside but in close proximity to the exposed zone in time or space, the defined parameters of the exposed zone should be reviewed 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. 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 illnesses.

4.3.3 Environmental sampling

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.

4.4 Public Health action following <u>suspected</u> deliberate release

If deliberate release of tularaemia is suspected (see paragraph 4.2.4), the PHLS-CDSC should be notified immediately. Following a suspected release, expert advice should be sought from the responding police unit to define (in time and space) the **zone** of likely exposure.

4.4.1 Epidemiological investigation

All individuals who have been present in the suspected exposed zone need to be identified. From all (suspected) cases and all individuals likely to be exposed the following information should be collected:

- Demographics, including address and telephone number
- Clinical symptoms
- Epidemiological information regarding exposure: time, place, other people present

4.4.2. Post exposure prophylaxis

All individuals present during the time and place of likely exposure need to receive prophylaxis as advised for those with confirmed exposure (paragraph 4.3.2).

4.5 Immunisation of general public.

This is not currently recommended

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