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Anthrax after September 11th 2001- *What to look for and how to treat it*

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Abstract
Anthrax is a serious bacterial infection with a particularly high mortality in its gastrointestinal, pulmonary, and meningitic forms with a worldwide distribution, although it is most common in the developing world. Gastrointestinal and pulmonary anthrax results in death within hours or a few days of the onset of serious symptoms and the diagnosis is usually made post-mortem. Treatment of wild type anthrax is usually with penicillin in high dose. The production of anthrax for large scale bioterrorism is difficult and requires sophisticated facilities. There is a greater risk that anthrax used as a bioterrorist weapon will be antibiotic resistant and ciprofloxacin is a more appropriate antibiotic choice until the antibiotic sensitivity of the anthrax strain being deployed becomes known. Post exposure prophylaxis should be continued for two months due to the long delay that sometimes occurs before spores germinate once within the human host. A live vaccine is available but requires a large number of injections and its use is largely limited to military personnel.

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Anthrax after September 11th 2001

What to look for and how to treat it

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Summary
Anthrax is a serious bacterial infection with a particularly high mortality in its gastrointestinal, pulmonary, and meningitic forms with a worldwide distribution, although it is most common in the developing world. Gastrointestinal and pulmonary anthrax results in death within hours or a few days of the onset of serious symptoms and the diagnosis is usually made post-mortem. Treatment of wild type anthrax is usually with penicillin in high dose. The production of anthrax for large scale bioterrorism is difficult and requires sophisticated facilities. There is a greater risk that anthrax used as a bioterrorist weapon will be antibiotic resistant and ciprofloxacin is a more appropriate antibiotic choice until the antibiotic sensitivity of the anthrax strain being deployed becomes known. Post exposure prophylaxis should be continued for two months due to the long delay that sometimes occurs before spores germinate once within the human host. A live vaccine is available but requires a large number of injections and its use is largely limited to military personnel.

Introduction
In early October last year I was on my way back to Edinburgh from a meeting in London. A signalling failure just outside Paddington station meant that a journey on the Heathrow Express extended from 15 to 75 minutes, during which time I watched the BBC News summary more times than I would have wished, particularly since the delay threatened my return that night to Edinburgh. BBC News majored on the bioterrorist outbreak of anthrax which was then in its early phases in the USA. The index case became ill on October 2nd in Florida and died a few days later[1]. To my surprise a disease which I had treated several times at a teaching hospital in Tanzania 20 years previously was now apparently of global interest. On my return to Edinburgh I offered to give a short presentation at the Grand Round at the Western General Hospital, since if Al Qaeda was responsible it was at least remotely possible that the UK, as the closest ally of the USA, might also be a target. This paper is a direct result of that presentation and seeks to summarise what we know about anthrax, its clinical presentations and treatment, both in endemic and bioterrorist forms.

The causative organism and pathogenesis
Anthrax derives its name from the Greek word *anthrakos* meaning coal due to the appearance of a coal black centre in the lesion in the cutaneous form. Anthrax is caused by a gram positive, spore forming, toxin producing aerobic rod, *Bacillus anthracis*. Although in vitro it grows as long chains, in the human host it appears as single organisms or chains of 2 or 3 bacilli [1]. The vegetative bacillus does not survive long in a putrefying carcass, only 3-4 days at 25° C [2]. Escaping bacilli at temperatures above 20°C form spores which may survive decades, but these are destroyed by dry heat of 150°C, boiling for 10 minutes, and autoclaving. The toxin has three parts, of which two are important, an oedema factor and a lethal factor [2]. Lethal factor stimulates the release of tumour necrosis factor and interleukin-1â contributing to sudden death [2].

The lethal factor is a protease with a particular amino acid substrate which could be a target for

the development of an inhibitor[1]. Infection is initiated after introduction of a spore through a break in the skin or mucosa and the vegetative form is germinated after ingestion by macrophages and may then pass to regional lymph nodes and the spleen. Extracellular multiplication then occurs with toxin production [2]. Lethal factor is produced and released in a burst, causing fever, disorientation, coma, and death. In rhesus monkeys, inhaled spores are deposited in alveolar spaces and then transported to mediastinal lymph nodes where germination occurs up to 60 days later. It was this observation that has led to the recommendation that antibiotic prophylaxis should be continued for 60 days after inhalational exposure[2].

Epidemiology of wild type anthrax

Anthrax has a worldwide distribution but is now most common in developing countries, principally in Africa and Asia. Historically, some outbreaks have been massive. In 1945 an outbreak in Iran caused one million sheep deaths[1], and between 1979 and 1985 an outbreak in Zimbabwe caused 10,000 human cases[2]. Even in developed nations anthrax has continued to cause problems. Between 1944 and 1994, the USA reported 224 cases, of which 18 were inhalational[3]. Occasional cases have surfaced elsewehere in the developed West, for instance in 1976 fatal pulmonary anthrax was contracted from bone meal fertiliser in the UK [4]. Cutaneous anthrax occurred in a casual labourer in London in 1996[5], and a Norwegian who skin-popped heroin in 2000 [6]. The annual total for cases worldwide is estimated at 20,000-100,000 [2].

The anthrax bacillus as a bioterrorist weapon

The use of anthrax as a bioterrorist weapon was extensively reviewed only 2 years before the 2001 outbreak by Inglesby in the Journal of the American Medical Association [1]. There has been interest in anthrax as a weapon of war for many years. During WWII British scientists conducted experiments on Gruinard Island off the West coast of Scotland and several decades elapsed before it was successfully decontaminated. Aum Shinrikyo terrorists in Japan made at least eight unsuccessful attempts to release aerosols of anthrax spores before their more tragically effective release of sarin nerve gas in a Tokyo subway in 1995. After the Gulf War, Iraq admitted producing and deploying weaponized anthrax in missiles, lending weight to the view that a clear threat remained, a threat which has now become all too obvious[1].

A few litres of standard broth culture prepared in a kitchen can produce sufficient spores to infect a few people if sent through the post. Lyophilising cultures into powder requires simple equipment, but ultra refining spores is necessary if more extensive bioterrorism is planned. Particles need to be between 1-5μm [1] and electrostatically neutral in order to avoid clumping [11]. This is probably beyond the ability of small groups and it has been estimated that for an attack on an urban population of 5 million, the aerial discharge of 50 kg of highly refined spore-containing powder would be needed to cause 250,000 cases [2].

The major experience with anthrax in bioterrorist form comes from Russia. In 1979 accidental discharge into the atmosphere occurred at a biological warfare research establishment at Sverdlovsk. Precise figures are not available but it is thought that 100 inhalational cases may have occurred of which 66 were fatal, all aged over 24 years [1]. Cases in humans occurred up to 4 km and in animals up to 50 km from the factory site [1]. On the basis of experiments in primates the dose in humans causing 50% lethality is between 2500 and 55,000 spores [1] and this amount is not visible to the naked eye.

The strain of anthrax used in bioterrorism in late 2001 in the USA was a derivative of Ames strain used worldwide by researchers, and first isolated from a dead animal in Ames, Iowa in the 1950s. Preliminary analysis suggested the presence of constitutive and inducible beta lactamases and for this reason treatment with penicillin, ampicillin or amoxicillin was not recommended [2]. The CDC website does not give a clear total for the number of human cases associated with this outbreak at the point of writing this paper in May 2002 but by 28th November 2001 23 cases had been identified of which 11 were inhalational and 12 cutaneous [1].

Principal clinical manifestations

Cutaneous anthrax (Figures 1-4)

This occurs as the result of direct contact with viable organisms invading through a skin break. Person to person spread does occur but very rarely and has been documented as a result of sharing scrubbing brushes used during bathing[3]. The cutaneous form is referred to as a malignant pustule, but this is a misnomer since there is no pus unless secondary bacterial infection occurs. The incubation period is 1-7 days, following which a pimple grows rapidly over 2-4 days. The initial itchy painless vesicle is 1-2cm in diameter and filled with clear or serosanguinous fluid. As the vesicle enlarges satellite vesicles develop with impressive surrounding oedema. When the vesicle ruptures it forms an ulcer covered by a black eschar by day 4-5. Without the use of antibiotics resolution occurs after 10 days and in 80-90% of cases healing occurs without scarring. Ulceration may still occur after antibiotic use and total resolution may take 2-6 weeks.

Figure 2. Facial 'malignant pustule' with erythema and oedema spreading down onto the anterior chest wall. The patient was hypotensive and febrile.

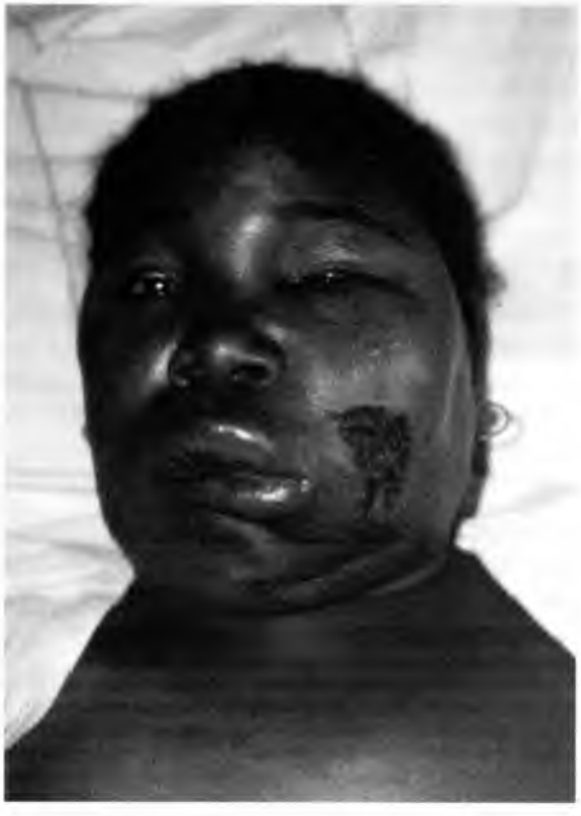
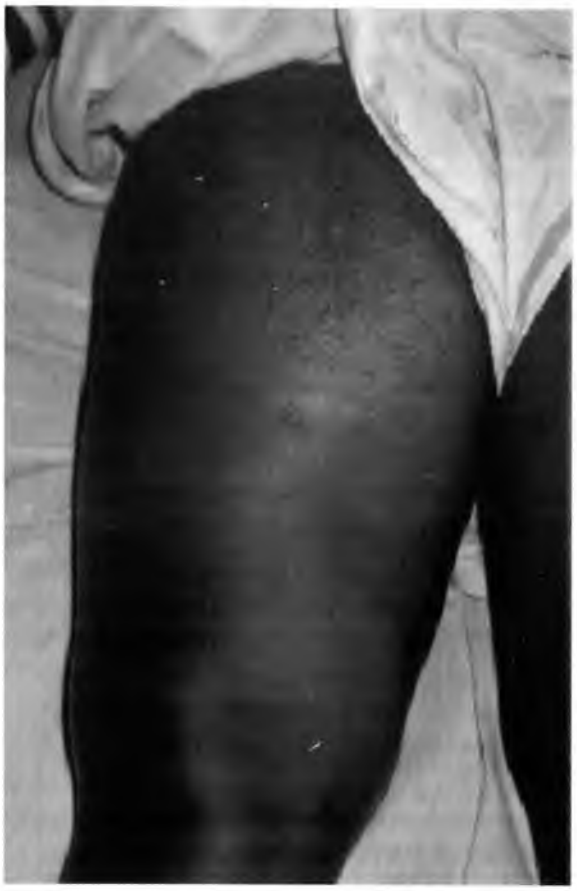


Figure 1. Facial cutaneous anthrax with marked oedema.

The differential diagnosis (see over) is wide and the list is based in part on the paper by Dixon et al published in 1999 [1].

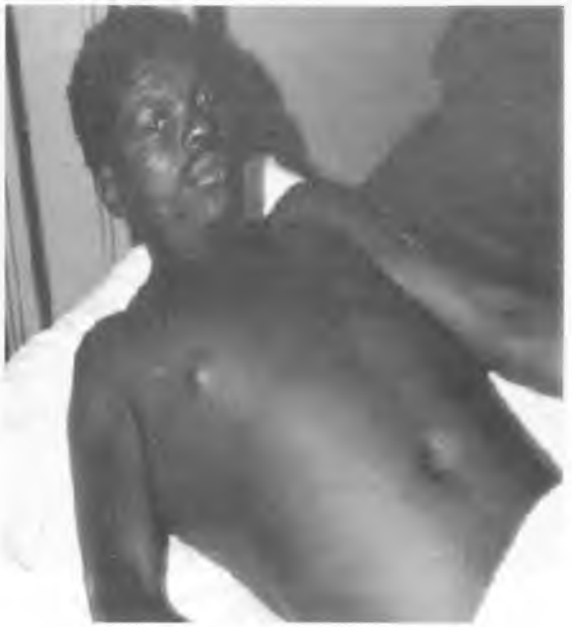
Gastro-intestinal anthrax

This occurs as a result of eating infected meat and comprises 95% of cases with a mortality of only 1%. The incubation period is 1-7 days after ingestion, during which an eschar develops on the intestinal mucosa, usually in the terminal ileum or caecum but it may occur anywhere from the oropharynx downwards [3]. Gross mesenteric lymphadenitis follows and perforation of the intestine may occur at the site of the eschar. Gastrointestinal anthrax is usually undiagnosed until too late. The clinical features are sudden onset of severe diffuse abdominal pain, nausea and vomiting and variably, watery or bloody diarrhoea may be present. On physical examination there will usually be fever, rebound tenderness, shock, and collapse, and ascites may be present after 2-4 days. Death occurs in a few hours or recovery may occur after 10-14 days.



Above: Figure 3a. Marked oedema in cutaneous anthrax affecting the thigh. No clear malignant pustule is seen. A BCG scar is present in the centre of the photograph.

Below: Figure 3b. Ulceration in the same patient during convalescence.



Above: Figure 4
One of four patients admitted to Kilimanjaro Christian Medical Centre, Tanzania in 1977. They had found a dead zebra, carried it to their village and cooked it over an open fire. The three patients who had eaten zebra meat developed severe abdominal symptoms suggestive of an intra-abdominal catastrophe and died in the surgical department. This patient had marked cutaneous invasion of spores as a result of having carried the zebra on his right shoulder. He has oedema of the anterior chest wall, visible as nipple oedema, and was severely hypotensive. He died four hours later.

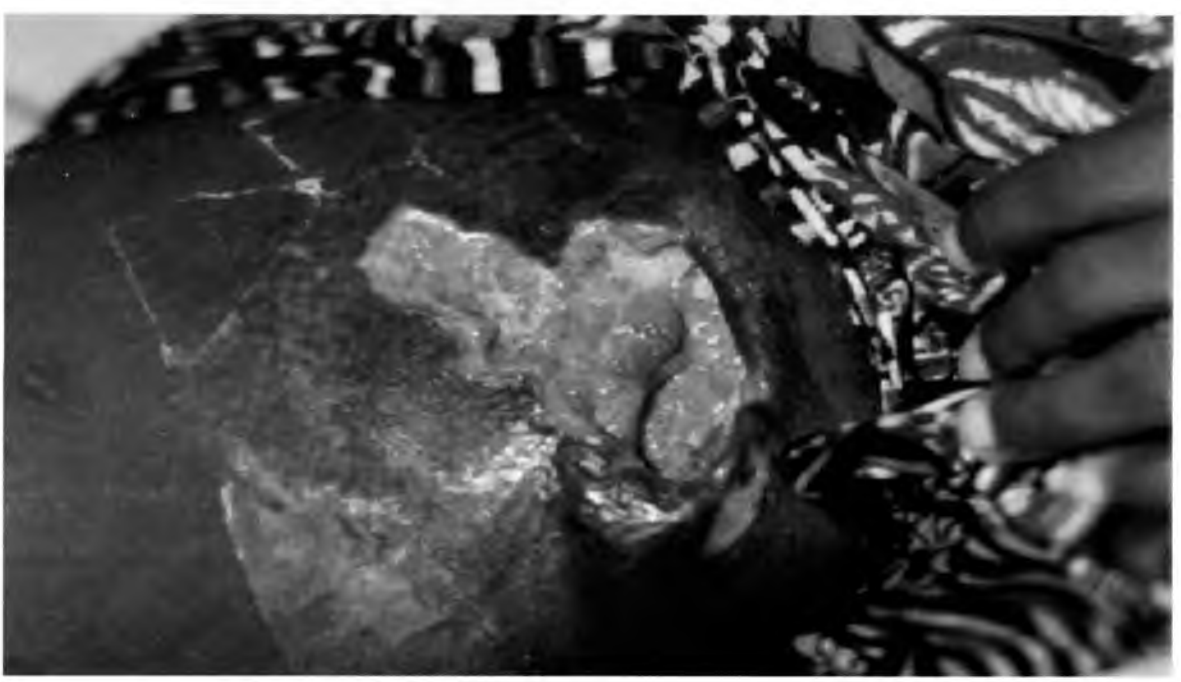


Table 1: Differential Diagnosis of Cutaneous Anthrax

Disease	**Causative organism**
Ecthyma gangrenosum	*Pseudomonas aeroginosa*
Rat bite fever	*Streptobacillus moniliformis*
Ulceroglandular tularaemia	*Francisella tularensis*
Plague	*Yersinia pestis*
Rickettsial pox	*Rickettsia akari*
Scrub typhus	*Rickettsia tsutsugamushi*
Tick bite fever	*Rickettsia conorri and africae (Figures 5&6)*
Orf	*Parapoxvirus (Figure 7)*
Staphylococcal infection	*Staphylococcus aureus*
Cutaneous TB	*Mycobacterium tuberculosis*
Leprosy	*Mycobacterium leprae*
Buruli ulcer	*Mycobacterium ulcerans*
Spider bite	*Loxosceles reclusa*[19]

Pulmonary anthrax

Pulmonary anthrax occurs as a result of the inhalation of spore-laden dust. The incubation period is 1-6 days. Prior to the 1960s in the USA, workers in goat hair mills were exposed to high concentrations of viable spores but there were few cases of inhalational anthrax. However when dispersed in the air as an aerosol anthrax spores can present a real hazard even long distances downwind, as demonstrated by the Sverdlovsk outbreak in 1979. Modal incubation is 10 days, but in the Sverdlovsk outbreak some cases occurred up to 6 weeks after accidental discharge. Longer incubation times probably occur with smaller inocula. During the first few days patients have no symptoms or 'flu' for a few days and then there is abrupt onset of chills, a strident cough, blood stained vomit due to haematogenous spread to the gut, dyspnoea and cyanosis, and on examination moist chest sounds and signs of systemic collapse. The spleen and axillary lymph nodes may be enlarged. A chest X-ray may show widened mediastinum, and

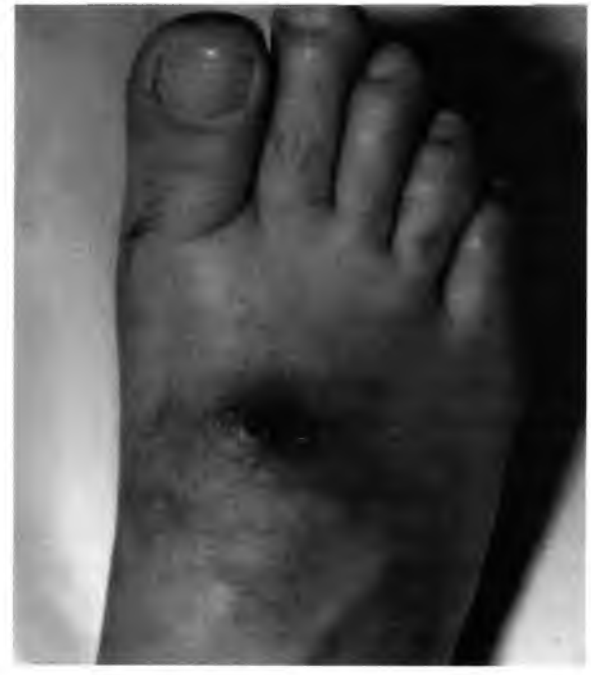


Figure 5. Tick typhus lesion in visitor to Tenerife (Rickettsia conorii)

blood culture becomes positive within 2-3 days of the onset of symptoms (sample chest X-rays can be down loaded from the CDC website). Death usually occurs in 2-3 days but milder cases occur with bronchitic symptoms.

Anthrax meningitis

This is rare, but may arise from any form of the disease. It is characterised by blood stained CSF and the prognosis is poor. A few cases of recovery have been recorded if antibiotics are combined with anti-toxin and prednisolone.

Laboratory diagnosis

This is usually by microscopy and culture. In cutaneous lesions gentle sampling is recommended with a moist sterile applicator. Blood cultures become positive in 6-24 hours[12], but may be negative if antibiotics have been given. The earliest that confirmation could be expected would be 48 hours but if a laboratory has not been notified about the possibility of anthrax the diagnosis may be missed [12]. In gastrointestinal or pulmonary anthrax death often precedes accurate diagnosis. Dry nasal swabs allow detection of anthrax spores. Serological tests are not usually helpful. Anthrax ELISAs only rise in 70-90% of convalescent patients [1]. PCR is available in only a few centres.

Figure 6. Tick typhus lesion in visitor to Kruger Game reserve (Rickettsia africae)

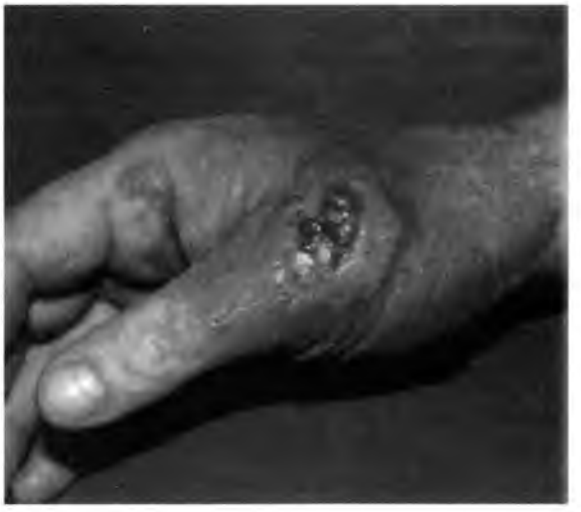


Figure 7. Orf virus infection (Dr Clifford Leen's patient)

Treatment for wild type anthrax

Anthrax is sensitive to penicillins, fluoroquinolones, tetracyclines, chloramphenicol, gentamycin, erythromycin, clindamycin, vancomycin and first generation cephalosporins. Isolates of natural strains are rarely resistant to penicillin, although resistance has been reported in India [1]. There is some natural resistance to cotrimoxazole, second generation cephalosporins and aztreonam.

Varying advice is given for acutely ill cases in current textbooks, but initially benzyl penicillin should be given in a dose of 2.4 G 4-6 hourly, initially iv for three to five days. Cutaneous sores become sterile in one to two days. Plasmaphoresed serum from a vaccinated person *'may be lifesaving'* [3].

Treatment of anthrax bio-terrorism

The Russians are reported to have bio-engineered an anthrax strain resistant to tetracyclines and penicillin[1], but there is, as yet, no evidence of engineered quinolone resistance. The concerns already mentioned of delayed germination of spores carried after exposure to the primary aerosol means that short courses of antibiotic

may be insufficient. Initial treatment is ciprofloxacin 400mg iv 12 hourly, although in sensitive strains optimal treatment is with benzyl penicillin as above iv. The antibiotic may be administered orally when the patient's clinical condition improves. The total duration of therapy should be 60 days.

Supportive therapy if oedema is extensive may include corticosteroids. Other general measures include the prevention of septic shock and maintenance of fluid and electrolyte balance.

Anthrax post-exposure prophylaxis

The agent of choice is ciprofloxacin 500mg twice daily for 60 days. Alternatives are doxycycline 100mg twice daily for 60 days or amoxycillin 500mg three times daily for 60 days. Hart and Beeching have cautioned that such prophylactic treatment should be given only to those who really need it, since ciprofloxacin in prolonged courses may induce resistance in commensal organisms, and these in turn may transmit resistance to pathogenic organisms[1].

Vaccination

An anthrax vaccine consisting of an attenuated strain has been given to members of the US armed forces since 1998. Six injections are given over 18 months, the first three in the first month and aerosol challenge studies in monkeys suggest complete protection at 8 weeks and 88% protection at 100 weeks[Swartz]. No serious adverse events have been reported but vaccine supplies are extremely limited. In the UK advice on the use of the vaccine must be obtained from the Public Health Laboratory Service[14].

Web-site sources of information

www.phls.co.uk/advice/anthrax_guidelines

www.bt.cdc.gov/DocumentsApp/anthrax

www.travax.scot.nhs.uk

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