Cutaneous anthrax: acute and resolving stages
Pictures from the late Professor Margaretha Isaacson's personal collection

CONTENTS

EPIDEMIC PRONE DISEASE SURVEILLANCE : JANUARY-APRIL

Disease		CUMULATIVE	ECP	FSP	GAP	KZP	LPP	MPP	NCP	NWP	WCP	RSA
AFP, cases from whom specimens have been received	<= 15 years	2004 / 2005	4 / 6	3 / 7	10 / 9	9 / 21	27 / 6	4 / 2	3 / 1	4 / 7	7 / 6	71 / 65
Measles, IgM positive results	All ages	2004 / 2005	0 / 383	0 / 0	81 / 31	U / 56	0 / 1	1 / 2	0 / 0	0 / 1	0 / 10	82 / 484
Rubella, IgM positive results from measles IgM negative patients	All ages	2004 / 2005	29 / 67	0 / 0	19 / 15	U / 19	6 / 4	9 / 12	2 / 0	8 / 8	1 / 5	74 / 130
CCHF	All ages	2004 / 2005	0 / 0	1 / 0	0 / 0	0 / 0	0 / 0	0 / 0	1 / 0	2 / 0	0 / 0	4 / 0
Rabies, human	All ages	2004 / 2005	0 / 1	0 / 1	0 / 0	6 / 0	0 / 0	1 / 0	0 / 0	0 / 0	0 / 0	7 / 2
Haemophilus influenzae, invasive — All serotypes	All ages	2004 / 2005	0 / 3	4 / 2	36 / 30	9 / 5	0 / 1	2 / 5	0 / 0	0 / 1	19 / 10	70 / 57
Serotype b	All ages	2004 / 2005	0 / 1	1 / 0	6 / 3	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	7 / 4
Non-serotype b	Age < 5 years	2004 / 2005	0 / 0	0 / 0	1 / 4	1 / 1	0 / 0	0 / 1	0 / 0	0 / 0	3 / 1	5 / 7
Non-typable		2004 / 2005	0 / 1	1 / 0	10 / 6	1 / 0	0 / 0	0 / 1	0 / 0	0 / 0	5 / 0	17 / 8
Unknown serotype		2004 / 2005	0 / 0	2 / 0	1 / 6	3 / 2	0 / 0	1 / 0	0 / 0	0 / 0	4 / 3	11 / 11
Meningococcal disease	All ages	2004 / 2005	7 / 3	4 / 4	19 / 42	7 / 1	0 / 3	1 / 3	1 / 0	8 / 1	18 / 11	65 / 68
Streptococcus pneumoniae, invasive — All ages		2004 / 2005	24 / 61	41 / 48	434 / 466	94 / 88	19 / 11	46 / 54	5 / 8	24 / 30	145 / 119	832 / 885
Age < 5 years		2004 / 2005	11 / 25	15 / 19	170 / 140	34 / 31	7 / 3	11 / 15	2 / 2	9 / 10	58 / 59	317 / 304
Penicillin, non-susceptible, all ages		2004 / 2005	3 / 16	8 / 17	129 / 138	24 / 39	2 / 3	10 / 12	0 / 2	5 / 10	36 / 28	217 / 265
Susceptibility unknown, all ages		2004 / 2005	1 / 5	6 / 3	39 / 70	12 / 9	2 / 2	5 / 10	0 / 1	0 / 4	17 / 16	82 / 120
Salmonella species - invasive isolates	All serotypes excl. S. typhi	2004 / 2005	7 / 22	6 / 6	231 / 172	29 / 18	5 / 3	8 / 14	0 / 0	4 / 1	23 / 23	313 / 259
Salmonella species - enteric isolates	All serotypes excl. S typhi	2004 / 2005	51 / 49	17 / 5	83 / 90	20 / 44	14 / 1	1 / 19	0 / 1	17 / 10	65 / 32	268 / 251
Salmonella typhi	All ages	2004 / 2005	4 / 7	0 / 0	7 / 5	3 / 3	2 / 0	4 / 11	0 / 0	0 / 0	5 / 6	25 / 32
Shigella species	All serotypes	2004 / 2005	51 / 75	16 / 21	84 / 114	42 / 64	13 / 7	4 / 11	0 / 1	2 / 3	120 / 85	332 / 381
Vibrio cholerae 01	All serotypes	2004 / 2005	23 / 0	0 / 0	3 / 0	0 / 0	0 / 0	213 / 0	0 / 0	28 / 0	0 / 0	267 / 0

U = unavailable, 0 = no isolates received

Note: The above are NICD laboratory data and do not nececessarily reflect a quantitative measure of disease in the country.

2

PERTUSSIS – NEW CHALLENGES FROM AN "OLD" DISEASE

Gillian de Jong, Epidemiology Unit, NICD

INTRODUCTION

The availability of an effective vaccine against *Bordetella pertussis* since the 1950's has substantially reduced the morbidity and mortality from this disease, preventing an estimated 760 000 deaths annually.[1] In many countries the original whole cell vaccine (wP) has since been replaced by various formulations of the acellular vaccine (aP), which has been shown to be equally effective with an improved side effect profile.[2]

However, despite adequate vaccine coverage in many parts of the world, pertussis continues to contribute a substantial burden of disease in un-immunised infants and increasingly recognised infection and/or disease in adolescents and adults. In the last decade there appears to have been a substantial increase in pertussis cases amongst immunised populations.[3] The reasons for this are not fully elucidated but are in part due to improved case detection and laboratory diagnostic procedures. Effective surveillance for pertussis is an essential part of planning for control of this disease and there are many challenges around both of these goals.

GLOBAL EPIDEMIOLOGY

The true burden of disease globally is difficult to define. There are an estimated 50 million cases of pertussis and 300 000 pertussis-related deaths annually.[1] The greatest morbidity and mortality is seen amongst un-immunised or incompletely immunised infants who have more severe disease and are more likely to have complications. Ninety percent of pertussis–related deaths occur in this group.[2]

Increasingly, pertussis is also recognised as an important cause of disease in adolescents and adults with waning immunity.[4] Older individuals would be expected to have less severe disease and fewer complications but substantial economic costs have been shown to be associated with unrecognised infection in this group and, more importantly, they serve as an important source of infection for non-immune infants.[5]

The Global Pertussis Initiative (GPI) was formed in 2001 under an educational grant from Sanofi Pasteur. This is a group of experts from 17 countries that aim to better define the epidemiology of disease and formulate solutions to the global burden of pertussis. Unfortunately Africa and most of the developing world are not represented on the GPI and data from such countries are limited.[6]

SURVEILLANCE CHALLENGES

Gathering reliable global data on pertussis is limited by several potential obstacles. There are no standardised clinical case definitions, making inter-country comparisons difficult. Furthermore, accurate diagnostic facilities for confirmation of *Bordetella pertussis* are limited in many countries, particularly in the developing world. Recognition and reporting of cases by health care workers is inadequate particularly in adults and adolescents. Many clinicians recognise pertussis as an important disease entity in infants but fail to include it in the differential diagnosis of adults and adolescents where symptoms and signs may be atypical and morbidity less obvious. In addition, passive notification systems have been shown to significantly underestimate disease burden.[7]

DIAGNOSTIC CHALLENGES

Most clinicians will recognise the classic signs of paediatric pertussis – the presence of a paroxysmal cough, post-tussive vomiting, inspiratory whoop and prolonged cough.[2] However, disease presentation may be modified by many factors including age, previous immunisation or infection, antibiotic exposure and concurrent infection with other pathogens.[8] Clinical presentations in adults and adolescents are most easily misdiagnosed. This previously immunised or exposed group frequently present atypically with the absence of a classic whoop and less prolonged cough.[2] Several studies in Australia, Denmark, France and the USA estimate that 12-32% of adolescents with cough of 1-2 weeks duration have pertussis infection.[8] However in countries with a high prevalence of pulmonary TB, such as SA, a history of chronic cough alone would not usually prompt consideration of a diagnosis of pertussis.

Even where the diagnosis is considered clinically, laboratory confirmation is difficult. Culture for *B.pertussis* remains the gold standard for laboratory diagnosis due to its specificity. However it has a poor sensitivity, particularly later in disease when patients are most likely to present. Sensitivity is influenced by quality and timing of specimen collection and laboratory expertise.[2] Specimens should include a properly performed nasopharyngeal aspirate or nasopharyngeal swab ideally inoculated directly onto a suitable culture medium (e.g.: Regan Lowe medium) at the bedside. The organism is fastidious and grows slowly. Culture plates must be incubated for at least 7 days before reported negative.[9]

The available direct fluorescent antibody tests for direct antigen detection have been shown to have poor sensitivity and specificity and should not be relied on for diagnostic confirmation.[9]

More recently, polymerase chain reaction (PCR) has been increasingly used for diagnosis on clinical specimens, which has many advantages. Results

are rapid and less dependent on delays in transport as even non-viable organisms may be detected. Several PCR targets have been used with varying success. Some of these targets such as the IS481 are found in other *Bordetella* spp. such as *B.holmesii* and are therefore not specific. Many experts suggest the use of 2 targets for consensus in diagnosis by this method. The sensitivity and specificity if this test is dependent on the targets used and the quality control of the test in specific laboratories.[9]

Serological diagnosis using an ELISA is also available in some countries and is used routinely for surveillance in the state of Massachusetts in the USA.[10] Acute and convalescent sera can be taken or a single serum sample. Appropriate cut-offs have not yet been determined in many instances, making interpretation difficult.[9,11]

At present, it is likely that a combination of laboratory tests will provide the most accurate diagnosis.[11] Culture of the organism has an advantage in that it also allows for surveillance of antibiotic resistance and molecular epidemiological typing in outbreak situations.

PERTUSSIS IN SOUTH AFRICA
Pertussis is a notifiable disease in South Africa. The disease should be reported based on clinical suspicion alone and does not require laboratory confirmation for notification. However laboratory tests should be performed where available. At present there is no active surveillance for pertussis and given our national health priorities such surveillance has justifiably not been a priority. Only 60 cases of pertussis were notified to the Department of Health from January 2000 to September 2004. This is likely to represent a substantial underestimate of the true prevalence of disease in South Africa.

South African infants are routinely immunised with the whole cell vaccine at 6, 10 and 14 weeks of age as part of the National EPI (Expanded Program on Immunization). Laboratory diagnosis in the public sector has generally relied on culture until more recently when the Division of Infection Control (NHLS) at Johannesburg Hospital introduced a qualitative PCR using the IS*481* gene target (personal communication Dr Else Marais). This can be performed on a nasopharyngeal swab (dacron <u>not</u> calcium alginate swabs) and/or aspirate specimens. Despite it's limitations, culture continues to be regarded as the gold standard and should be performed in parallel with PCR.

THE FUTURE
Having recognised the substantial ongoing burden of disease due to pertussis and the large potential source of infection from adolescents and adults, several strategies for control have been proposed. Australia,

Canada, the USA and most European countries have already licensed acellular pertussis vaccines for use in adults and adolescents. Many of these countries have introduced or have recommended universal immunisation of adolescents. Ultimately both adults and adolescents would require a booster dose if the aim is not only to protect this group from disease but also to decrease the large pool of individuals infectious for non-immune infants.[1] Several additional strategies have been proposed including immunisation of pregnant women in the 3rd trimester, immunisation of families of neonates during the first 4 weeks of life and immunisation of those in contact with high risk groups such as health care workers. More information on safety and efficacy of these strategies is required.[2] Essential to our success in control of this disease would also be a better understanding of the correlates of protection and duration of immunity following vaccine and/or natural infection and further research in this area is being conducted.

In South Africa, we must continue to strengthen EPI services and increase awareness and reporting of this disease amongst clinicians. Although there are many competing health priorities, it would be of value to better define the true burden of disease through use of an active surveillance system and this is currently under discussion.

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ANTHRAX

John Frean, Special Bacterial Pathogens Unit, NICD

Three laboratory-confirmed cases of cutaneous anthrax in humans have occurred in Schmidtsdrift and Delportshoop in the Northern Cape Province of whom one case had fatal systemic involvement with Bacillus anthracis*, identified on a blood culture. A further 9 suspected human cases of cutaneous anthrax have been identified on epidemiological investigation. It appears that members of the community handled and ate the meat of a dead cow from a farm in Schmidtsdrift. Environmental health officials have since confiscated any remains of the carcass. The health authorities are actively looking for more clinical cases and investigating the farm from which the cattle allegedly originated. Extensive health promotion has* been undertaken in the area.

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INTRODUCTION

Anthrax is a zoonosis caused by the aerobic Gram-positive spore-forming *Bacillus anthracis.* Anthrax is enzootic in most of Africa and Asia, some European countries, some areas of the Americas and Australia, with sporadic occurrences elsewhere. The incidence of notified human disease in South Africa is presently very low (see Figure 1; Source: *Epidemiological Comments*, SA Department of Health, 1990).

conditions and can survive for many decades. Figure 2 shows the basic transmission processes in anthrax.

Anthrax spores only develop when viable bacilli are exposed to air. This occurs when dying animals bleed terminally from mouth, nose and anus. Opening or butchering of carcasses of suspected animal victims should not be done, to minimise spore formation.. Spores remain viable in the soil for many years and, by contaminating grazing and cattle feed, may infect livestock or wild game. Herbivores are much more susceptible to anthrax than carnivores and humans. Tabanid flies (horseflies) have been implicated in mechanical transmission of cutaneous anthrax, and blood-feeding flies are also responsible for the contamination of leaves of trees around dead game animals, which provides a source of infection for highly susceptible browsers such as kudu.

Human anthrax occurs in 3 forms: cutaneous, intestinal, and pulmonary. Humans are moderately resistant; in industrially-exposed workforces, annual case rates were 0.6 to 1.4%. Workers suffered no ill effect from inhaling 600 - 1300 spores per 8-hour shift, and cases in wildlife workers are very rare despite extensive exposure. Estimates of infectious doses are as follows:

Figure 1: The annual number of Human Anthrax cases in South Africa, 1921 to 1989
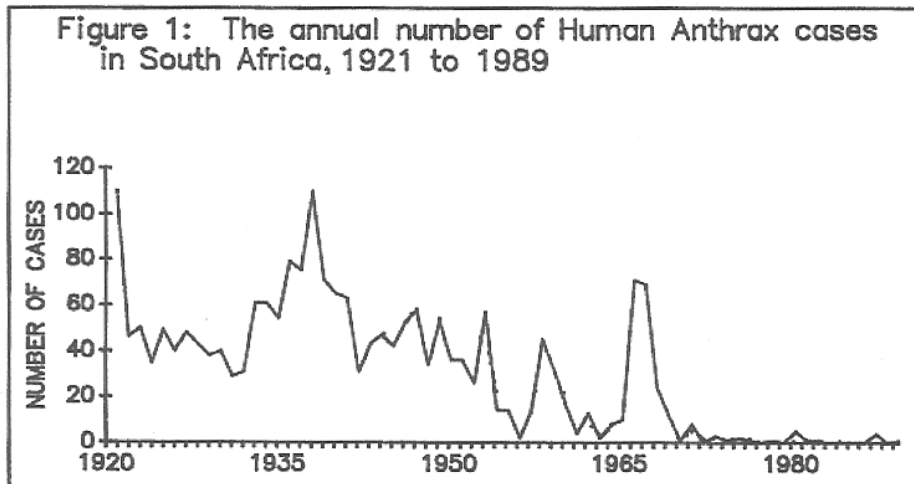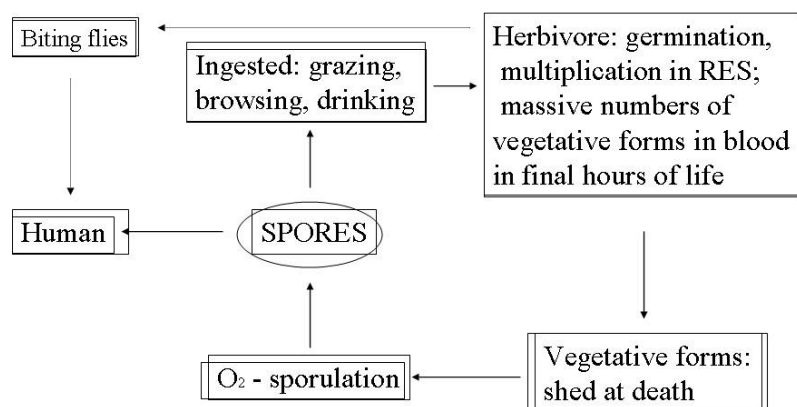
B. anthracis is extremely monomorphic and biochemical, serological, and phage typing methods are of no use for characterizing it. Genomic differences are also hard to detect, but tandem repeats on the *vrrA* gene show that there are 5 distinct groups. Unlike other *Bacillus* species, *B. anthracis* is an obligate pathogen because environmental germination of spores and multiplication of vegetative forms is unlikely to occur significantly frequently. The ecology of anthrax is complex and no single model explains the relationship between season, rainfall, temperature, soil, vegetation, and incidence of anthrax in a location. Spores are extremely resistant to environmental

- Cutaneous: required spore number low, but cut or abrasion needed

- Pulmonary: LD_{50} in primates ranges from 2 500 to 760 000 spores

- US Defence Department consensus for pulmonary infection: 8 000 - 10 000 spores

- Inhaled particle size important; <5mm most infectious

- Intestinal: not known, but mucosal injury is probably a prerequisite

Figure 2. Infection Cycle of Anthrax

Biting flies → Ingested: grazing, browsing, drinking → Herbivore: germination, multiplication in RES; massive numbers of vegetative forms in blood in final hours of life

Human ← SPORES

O₂ - sporulation ← Vegetative forms: shed at death

PATHOGENESIS

The basic sequence of events in all forms of the disease is:

- spore entry via lungs or epithelial lesion (skin or gut)
- germination starts, organisms are carried to lymphatic system
- vegetative forms multiply, infect blood stream
- RES filters bacilli out, but may be eventually overwhelmed
- fulminant septicaemia and toxaemia (usual in gastrointestinal and pulmonary anthrax, uncommon in cutaneous anthrax).

B. anthracis posesses 2 main virulence factors, each encoded on a plasmid: a capsule of poly-D-glutamic acid (anti-phagocytic) and a toxin complex comprising 3 synergistically acting proteins, protective antigen (PA), lethal factor (LF), and oedema factor (EF). PA binds to host cell receptors, host protease cleaves off 20 kDa portion, exposing receptor site; LF and EF then compete to bind to PA; (PA+LF) and (PA+EF) are internalised, LF and EF then released into cytosol. EF is an adenylate cyclase, which leads to cAMP production and altered water and ion movements, causing the characteristic oedema. EF also impairs neutrophil function and inhibits cytokine release from monocytes. LF is a metalloenzyme endopeptidase that cleaves 2 protein kinases and disrupts signalling pathway in host cells, particularly macrophages. Cell growth and maturation are affected. The macrophage response includes release of TNF and IL-1. Endothelial cells also damaged, contributing to the typical terminal bleeding seen in animals.

Cutaneous anthrax: This form of disease is usually acquired by handling contaminated meat or animal products (bonemeal, hides, brushes etc.) when spores may enter through skin abrasions resulting in cutaneous anthrax, also known as malignant pustule. Common sites are the face, hands and forearms. After an incubation period of a few hours to several days, a small papular lesion appears around which develop vesicles. The lesion breaks down, becomes an ulcer which eventually shows the characteristic black central eschar. Satellite vesicles may be seen at the periphery of the ulcer and extensive oedema surrounds the lesion (Figs 3, 4). Typically there is no pain or pus. Regional lymphadenitis may occur. If untreated, systemic spread may follow, with fulminant septicaemia and/or meningitis. The mortality of untreated cutaneous anthrax is up to 20% because of these complications. The skin lesions resolve with minimal scarring. The differential diagnosis of uncomplicated cutaneous anthrax includes furuncle, orf, vaccinia, glanders, syphilitic chancre, erysipelas, ecthyma, and spider bite; of the more severe forms: orbital cellulitis, dacrocystitis, deep tissue infection, necrotising group A streptococcal infections, staphylococcal cellulitis.

Pulmonary or inhalation anthrax: This results from inhalation of spores. The condition ('woolsorters' disease') initially presents with a non-specific 'flu-like illness, followed after some days by severe haemorrhagic mediastinitis associated with fever, dyspnoea, cyanosis, tachypnoea and tachycardia. In addition there may be lung consolidation, pleural effusions, massive oedema of chest and neck, and shock is not uncommon. This is usually associated with systemic infection and *B. anthracis* may be cultured from blood and various body fluids. Chest x-ray typically shows marked mediastinal widening; sometimes necrotising pneumonic changes and/or pleural effusion occur.

Gastrointestinal anthrax: There are 2 forms of anthrax that follow ingestion of *B. anthracis* spores.

Intestinal anthrax comprises nausea, vomiting, fever, abdominal pain, haematemesis, bloody diarrhoea, massive ascites, toxaemia, shock and death. Differential diagnosis includes food poisoning, acute abdomen, haemorrhagic gastroenteritis, and necrotising enteritis due to *C. perfringens.*

Figure 3 : Cutaneous anthrax: acute and resolving stages

Figure 4 : Cutaneous anthrax: note extensive oedema
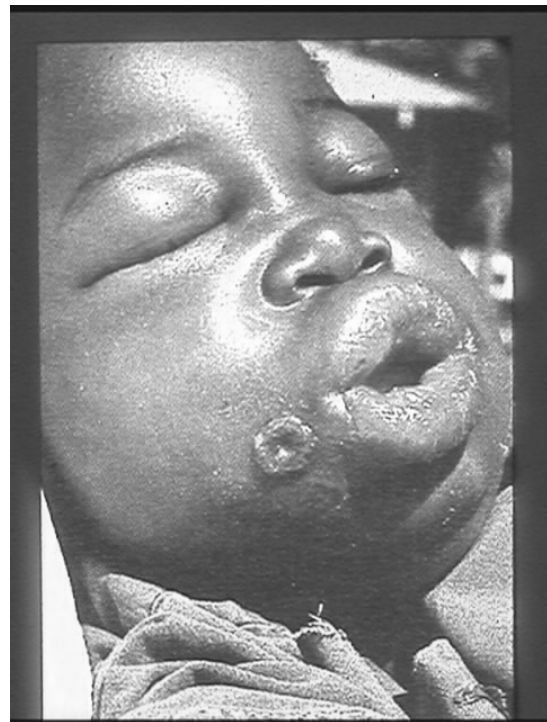
Oropharyngeal anthrax comprises sore throat, dysphagia, fever, neck lymphadenopathy, and toxaemia, and carries 50% mortality even if treated. Differential diagnosis includes streptococcal pharyngitis, Vincent's or Ludwig's angina, parapharyngeal abscess, and deep tissue infection of neck.

Meningeal anthrax is characteristically a haemorrhagic meningitis with bloody CSF, and is usually a complication of other forms of systemic anthrax. It is a fulminant condition with almost 100% mortality unless recognised early and treated aggressively.

DIAGNOSIS

The geographic/occupational history and the history of the patient's associates and animals is of utmost importance and, together with the clinical features, is usually virtually conclusive. Laboratory confirmation is obtained by blood culture, microscopy and culture of cutaneous lesion material and of vesicle contents (Fig. 5) and by ELISA testing of acute and convalescent blood specimens. Nasal swabs are taken for culture where there is a risk of airborne spore inhalation eg 'white powder' incidents. Great care must be taken with the disposal of all anthrax-contaminated materials because of the danger of disseminating the highly-resistant spores. Full post-mortem examination of animals or humans suspected of having died of anthrax is prohibited because of the inevitable

dissemination of spores. Tissue (e.g. spleen or liver) for post-mortem diagnosis may be obtained by means of a trochar and canula, or a viscerotome, or blood may be taken by cardiac puncture with a large-bore needle.

TREATMENT

Patients with anthrax need not be isolated (person-to-person spread is not normally a risk), but cutaneous lesions should be protected, and precautions taken with blood, secretions and other body fluids. The antibiotic of choice remains penicillin G or amoxycillin. In penicillin-allergic persons, erythromycin, doxycycline or chloramphenicol may be used as alternatives. Recently, because of concerns about bioterrorism and the possibility of antibiotic

Figure 5 : Gram stain of blood culture showing large Gram-positive bacilli

resistance-engineered organisms, quinolones or doxycycline are recommended when persons are exposed in credible bioterrorism incidents. Intravenous hydrocortisone may be lifesaving in cases with massive oedema threatening airways obstruction. In cutaneous anthrax, corticosteroids may help to control excessive oedema. Intravenous penicillin G, 18-24 million units/day, or IV amoxycillin is used in inhalation anthrax. This may be combined with other effective agents such as doxycycline and quinolones. Despite this and supportive treatment, inhalation anthrax is usually fatal, unless diagnosed and treated early and aggressively.

PREVENTION AND CONTROL

Notification of animal and human cases is obligatory. There has been an upsurge in interest in human immunisation and post-exposure prophylaxis following concerns about bioterrorism, and possible biowarfare against US forces in Iraq. The current vaccine for humans is a cell-free culture filtrate of attenuated *B. anthracis* strain, and PA is the protective immunogen. Its efficacy was demonstrated in monkey challenge tests, but there is limited experience of efficacy in humans and supplies are limited at present. In theory, postexposure use would reduce duration of antibiotic use. In China, and the former USSR, live spore vaccines were used in humans, but none such vaccines are licensed in the West for this pupose. Post-exposure antibiotic prophylaxis following inhalational exposure with ciprofloxacin, amoxicillin or doxycycline should be continued for 60 days, because of the variable time to germination of inhaled spores. Such extended periods are not necessary for cutaneous or gastrointestinal exposure.

In animals, a live spore vaccine (Sterne strain 34F2: toxin+, capsule-) gives a protective effect for one 1 year. In principle, compliance with vaccination regulations will eliminate the problem of domestic stock anthrax but this tends to break down where veterinary services have deteriorated due to economic factors or persistent conditions of war. The latter

situation was responsible for the massive outbreak (>6000 cases) of human anthrax in Zimbabwe (then Rhodesia) just prior to its independence. In the domestic stock outbreak situation, isolation and quarantine of affected herds, with efficient animal vaccination and proper disposal of carcasses, will quickly terminate the outbreak. In poor communities, however, the absence of veterinary services and unwillingness to discard valuable meat often perpetuates the risk to animals and humans. In some African cultures, proof of death of a cow in the form of skin and horns, is needed to show the owner. Community education and involvement in control measures in such circumstances is a prerequisite for success.

Domestic stock that has died of anthrax should be deeply buried or burnt. Most human cases (usually cutaneous) in southern Africa follow informal butchering of livestock that has died of unrecognised anthrax. In South Africa such cases mostly occur in North West Province, most recently in the Schmidsdrif-Danielskuil area. Although adequate cooking will kill the anthrax organisms, butchery leads to risk of cutaneous infection and the risk of consumption of undercooked meat. With game animals in a natural habitat, such carcass disposal is clearly impractical (and unnecessary). The carcass is fed on by scavengers (hyena, jackals, vultures, even lion) which widely disseminate the spores. Waterholes tend to accumulate spores which reach high concentrations in the water in dry seasons, when the sediment is disturbed by animals wading in to drink. Transmission is then more likely to occur. Anthrax is part of the natural ecology in places like the Kruger Park, Botswana, Namibia, Zambia and Zimbabawe, where large epizootics in game animals occur periodically. Roan antelope are particularly susceptible and in the past efforts were made to selectively vaccinate and protect this already rare species.

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