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Review

# *Streptococcus zooepidemicus*: An emerging canine pathogen

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ABSTRACT

*Streptococcus equi* subsp. *zooepidemicus* (*S. zooepidemicus*) has caused several outbreaks of haemorrhagic pneumonia in dogs in recent years. This highly contagious and often fatal disease is characterised by sudden onset of clinical signs including pyrexia, dyspnoea and haemorrhagic nasal discharge. Post mortem examination typically reveals pulmonary haemorrhage and pleural effusion. Histopathology demonstrates fibrino-suppurative, necrotising and haemorrhagic pneumonia in most cases. The pathogenesis of *S. zooepidemicus* infection in dogs is incompletely understood. Bacterial virulence factors as well as host factors may contribute to the severe outcome. *S. zooepidemicus* occasionally causes zoonotic infections with potentially serious consequences. Canine vaccines for *S. zooepidemicus* are currently not available and prevention of the disease therefore relies on limiting bacterial spread by implementing stringent control measures in kennels. Further research, particularly sequence analysis of canine strains, is required to gain insights into epidemiology and pathogenesis of this emerging disease.



## Introduction

In recent years several outbreaks of haemorrhagic pneumonia in large dog populations have been described (Chalker et al., 2003; Kim et al., 2007; Pesavento et al., 2008; Byun et al., 2009). These were characterised by a high mortality rate despite intensive treatment. Affected dogs showed severe respiratory distress and a rapidly deteriorating clinical condition. Haemorrhagic pneumonia and severe pleural effusion were diagnosed post mortem. Whilst the disease most commonly occurred in dogs housed in groups, a fatal case in a pet dog has also been reported (Gibson and Richardson, 2008). The causative agent isolated in all cases was *Streptococcus equi* subsp. *zooepidemicus* (*S. zooepidemicus*).

*S. zooepidemicus* is a commensal organism of horses, frequently present in the upper respiratory and the lower genital tracts. It may act as an opportunistic pathogen leading to the formation of abscesses, neonatal septicaemia and endometritis with reproductive failure (Timoney, 2004). Severe respiratory disease has been reported in horses following transport stress and the clinical signs are similar to those observed in dogs, with sudden onset dyspnoea and haemorrhagic nasal discharge (Oikawa et al., 1994). The bacterium is also an important pathogen of pigs in Asia, causing widespread disease outbreaks in China in 1975 and Indonesia in 1994 (Soedarmanto et al., 1996; Fan et al., 2008). The infection in pigs was characterised by polyarthritis, bronchopneumonia and diarrhoea, and the disease spread rapidly through pig populations leading to a high mortality. During the outbreak in Indonesia the infection also spread to a monkey population (Soedarmanto et al., 1996).

*S. zooepidemicus* has been isolated from seals in Europe during outbreaks of phocine distemper virus, although it has not been determined whether the bacterium contributed to the disease in these animals (Akineden et al., 2007). In ruminants, *S. zooepidemicus* causes sporadic mastitis (Las Heras et al., 2002; Pisoni et al., 2009).

Systemic streptococcal disease in racing greyhounds was first observed in the late 1970s (Wyand and Sherman, 1978). Within the last 3 years, however, the disease has been reported more frequently and from several geographical locations (Kim et al., 2007; Pesavento et al., 2008). This review summarises our current knowledge of this disease in dogs.

## Epidemiology

Many questions remain unanswered regarding the epidemiology of *S. zooepidemicus* infections in dogs. The bacterium does not appear to be a common commensal organism in dogs. Studies of the microflora of the nose and tonsils have identified a high prevalence of beta-haemolytic streptococci in the healthy dog population, but typing of these isolates according to the bacterial group specific antigens (Lancefield typing) (Quinn et al., 1994) showed that only few isolates belonged to Lancefield group C, of which *S. zooepidemicus* is a member. The majority of isolates were from Lancefield group G, which contains *Streptococcus canis* (Smith, 1961).

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A study by Biberstein et al. (1980) characterised canine beta-haemolytic streptococci from various sites and found predominantly those of group G. Only 4/254 isolates analysed showed results consistent with *S. zooepidemicus* based on Lancefield group and fermentation pattern. Three of these were isolated from the respiratory tract and one from the skin.

The introduction of *S. zooepidemicus* into canine populations may occur via asymptomatic carriers. More recent prevalence data for healthy dogs are required to determine if carriage has become more common. The bacterium is certainly able to spread between dogs as outbreaks at kennels often affect large numbers of animals within a short time. Analysis of *S. zooepidemicus* isolates using multilocus sequence typing showed that some canine isolates from geographically distinct locations were genetically related (Webb et al., 2008). This may indicate that certain strains are more able to cause infection and disease in dogs. Other canine isolates are closely related to equine strains, and as horses are frequently infected with *S. zooepidemicus,* they may act as a reservoir for other species such that the bacterium may be introduced into canine populations by direct contact with horses. This appears unlikely for dogs housed in research facilities and urban kennels although indirect contact via staff members that have been in contact with horses may be important; however this has not been conclusively proven. Molecular typing of isolates may not only help to identify the source of outbreaks but also reveal transmission patterns within populations.

## Pathogenesis

Currently there are insufficient data to determine the basis of the apparent high virulence of *S. zooepidemicus* in dogs. This section will therefore discuss possible factors that may contribute to pathogenesis.

### *Susceptibility of the host population*

Severe illness and rapid spread of disease often occurs if a new pathogen is introduced to a naïve population. With increasing prevalence of antibodies to the infectious agent within the population, the rate of mortality would be expected to decrease over time. *S. zooepidemicus* was rarely isolated from healthy dogs in previous studies (Smith, 1961) and if this still applies it may indicate that few dogs become infected and therefore only a minority of dogs may have acquired a specific immune response to *S. zooepidemicus.* Alternatively, infection in dogs may be transient and might be missed during prevalence studies. Serological surveys may give a more accurate picture of the current prevalence of *S. zooepidemicus* infection in the canine population.

### *Predisposing factors*

Co-factors such as transport stress have been shown to be important for the development of respiratory disease caused by *S. zooepidemicus* in horses (Oikawa et al., 1994) and transfer to an unfamiliar environment is likely to be a stressful event for dogs. In addition, mixing of animals from various origins leads to the introduction of a wide variety of other respiratory pathogens, which may, at least in part, explain why most outbreaks of *S. zooepidemicus* in dogs have occurred in rehoming or research kennels.

Viruses have been shown to facilitate bacterial adherence to respiratory cells (Avadhanula et al., 2006) and both viruses and bacteria can affect the defences of the respiratory tract by disturbing ciliary movement (Chilvers et al., 2001; Anderton et al., 2004). In horses, equine influenza has been considered a predisposing factor for *S. zooepidemicus* infection of the respiratory tract (Timoney, 2004). Viral and bacterial co-infections have also been reported in dogs infected with *S. zooepidemicus*. In a US study, 3/6 dogs were found to be co-infected with canine adenovirus type 2, canine herpesvirus or canine distemper virus (Pesavento et al., 2008). Furthermore, canine distemper was identified as a co-infection in two dogs in an earlier US study (Garnett et al., 1982). *S. zooepidemicus* has also been isolated during outbreaks of canine influenza virus in greyhounds (Yoon et al., 2005).

Analysis of a group of 14 dogs housed at a UK kennel and affected with severe respiratory disease, revealed a mixed infection of *S. zooepidemicus* and other agents in six dogs. The co-infecting agents were *Bordetella bronchiseptica* ($n = 1$), *Mycoplasma cynos* ($n = 2$), canine herpesvirus ($n = 1$) or a combination of these ($n = 2$). From the remaining eight dogs however, only *S. zooepidemicus* was isolated. All 14 dogs were negative for canine adenovirus, canine distemper virus, canine respiratory coronavirus and influenza virus (V. Chalker and K. Erles, unpublished data).

Experimental inoculation with *S. zooepidemicus* has been reported only in one dog. The dog developed clinical signs of severe dyspnoea and characteristic findings of haemorrhagic pneumonia at post mortem examination. It was however, also shown to be positive for canine distemper virus by immunofluorescence (Garnett et al., 1982). Infections with multiple agents are likely to occur in most kennelled populations. Further studies are required to determine if viral and bacterial co-infections play a role in the pathogenesis of *S. zooepidemicus* in dogs.

### *Bacterial virulence factors*

The rapid onset of disease and fast deterioration of clinical condition in many dogs infected with *S. zooepidemicus* is similar to streptococcal toxic shock syndrome in man caused by *Streptococcus pyogenes.* In this syndrome the main site of inflammation is often the subcutaneous tissue, usually following skin trauma, but there are common clinical features of an acute illness including fever, hypovolaemia and coagulopathy (Lappin and Ferguson, 2009). Toxic shock is characterised by an over exuberant inflammatory response, which leads to increased vascular permeability, vasodilation, increased coagulation and recruitment of inflammatory cells to the site of infection (Lappin and Ferguson, 2009).

Components of the bacterial wall as well as bacterial toxins, such as the *S. pyogenes* toxin streptolysin O, have been shown to induce production of inflammatory cytokines such as interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)-α (Hackett and Stevens, 1992; Muller-Alouf et al., 1994). In addition, *S. pyogenes* produces pyrogenic exotoxins, which act as superantigens (Proft and Fraser, 2003). The presence of superantigen genes in strains of *S. pyogenes* has been linked to increased virulence in invasive disease (Musser et al., 1991; Luca-Harari et al., 2008). Superantigens activate a large proportion of T-lymphocytes, leading to the production of cytokines, which activate neutrophils and trigger the release of vasoactive factors. These act on the endothelium to increase permeability and cause vasodilation. Cytokines also activate factors which promote coagulation (Lappin and Ferguson, 2009).

Some pathological findings in dogs, such as severe pleural effusion, extensive pulmonary haemorrhage and systemic hypovolaemia, suggest that vascular damage is present. Superantigen genes have been detected in some isolates of *S. zooepidemicus* (Korman et al., 2004; Alber et al., 2005; Holden et al., 2009). The presence of two superantigen genes from *Streptococcus equi* subsp. *equi*, *seeH* and *seeI*, was investigated by PCR in two of the outbreaks of haemorrhagic pneumonia in dogs but the isolates were found to be negative (Kim et al., 2007; Byun et al., 2009).

Currently there are insufficient data to determine whether superantigens or other bacterial toxins are involved in the patho-

genesis of *S. zooepidemicus* in dogs. Recent advances in technology however have enabled rapid analysis of whole bacterial genomes including *S. zooepidemicus* (Holden et al., 2009). These developments will allow investigation of canine strains to identify virulence factors that may be novel or may have deleterious effects on the immune system of dogs.

## Clinical signs

Dogs infected with *S. zooepidemicus* may initially display clinical signs similar to 'kennel cough' including a moist cough and nasal discharge. Pyrexia is often observed with body temperatures ranging from 39.2 to 41.7 °C. In most cases the disease progresses rapidly, leading to depression, anorexia and tachypnoea. Haemorrhagic nasal discharge or haematemesis have frequently been reported (Sundberg et al., 1981; Byun et al., 2009). Dogs often develop severe dyspnoea and die within 24–48 h of first showing clinical signs of respiratory disease (Kim et al., 2007). The disease may lead to a sudden deterioration in the animals' condition and dogs may be found dead in kennels without any preceding clinical signs (Garnett et al., 1982). Haemorrhagic oral or nasal discharge may be seen in such cases or may be noticed when the carcass is moved.

Dogs that are in contact with affected dogs or their secretions, frequently develop pneumonia but sometimes show a milder disease and present with purulent nasal discharge and tonsillitis (Garnett et al., 1982).

## Pathology

The macroscopic findings in the lower respiratory tract of dogs affected by *S. zooepidemicus* are remarkably consistent and invariably severe. Pulmonary oedema and haemorrhage are prominent features of infection and might be due to direct vascular damage by bacterial toxins or the effect of inflammatory mediators on the endothelium. The volume of haemorrhagic pleural effusion is often marked (Fig. 1), ranging from 50 to 900 mL (Pesavento et al., 2008; Byun et al., 2009) and often a large amount of red-tinged froth is present within the nasal cavity, trachea and bronchi (Kim et al., 2007; Byun et al., 2009). The fluid might contain free clotted blood.

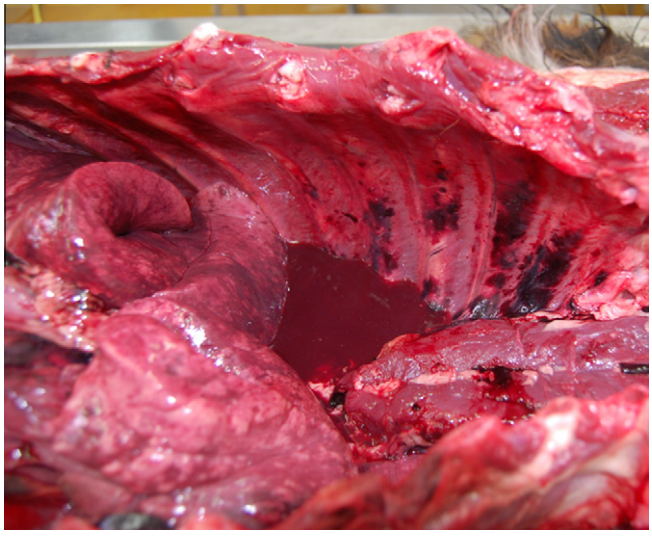

**Fig. 1.** Opened thoracic cavity of a dog, which died acutely from *S. zooepidemicus* pneumonia. The cavity contains a large volume of haemorrhagic fluid and multiple petechial haemorrhages in the parietal pleura.

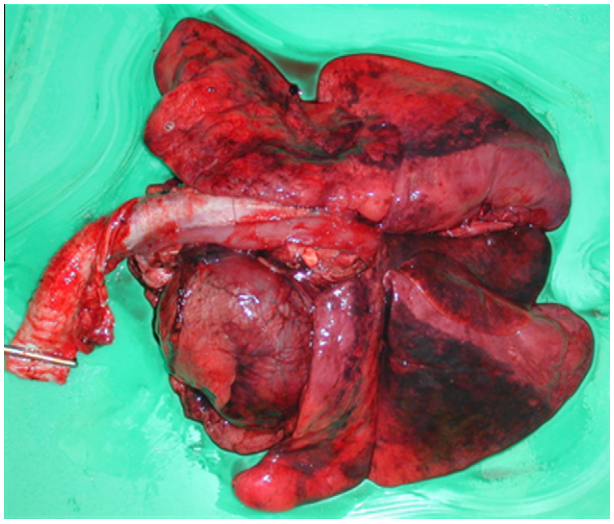

**Fig. 2.** Lung and heart from a dog with a history of severe dyspnoea and haemorrhagic nasal discharge. The lung lobes show extensive areas of haemorrhage and consolidation.

Grossly, the lungs are multifocally or diffusely dark red, firm (consolidated) and frequently fail to collapse upon opening the thorax (Fig. 2). No consistent difference in lesion distribution has been observed between cranial or caudal lung lobes. Petechial and ecchymotic haemorrhages on the surface of the visceral and parietal pleura (Fig. 1), mediastinum, pericardium, diaphragm and within mediastinal and bronchial lymph nodes and thymus have been frequently observed. In some cases concurrent acute necrotising rhinitis and sinusitis have been reported (Pesavento et al., 2008).

In the vast majority of reported cases, *S. zooepidemicus* causes a severe acute to peracute fibrino-suppurative, necrotising and haemorrhagic pneumonia or bronchopneumonia with frequent pleural involvement. There is extensive to lobular flooding and obliteration of alveolar spaces with numerous neutrophils and exudation of large quantities of fibrin admixed with proteinaceous fluid (Figs. 3 and 4) (Sundberg et al., 1981; Pesavento et al., 2008).

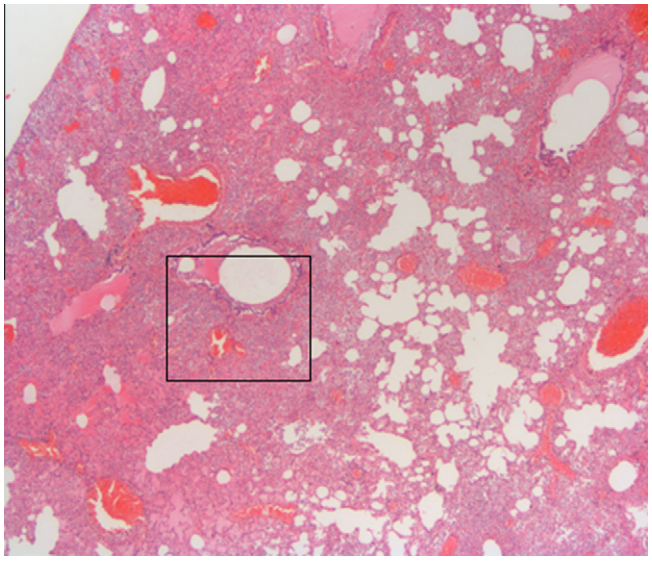

**Fig. 3.** Multifocally extensive fibrino-suppurative necrotising and haemorrhagic pneumonia. H&E. Magnification ×20. The boxed area is shown at higher magnification in Fig. 4.

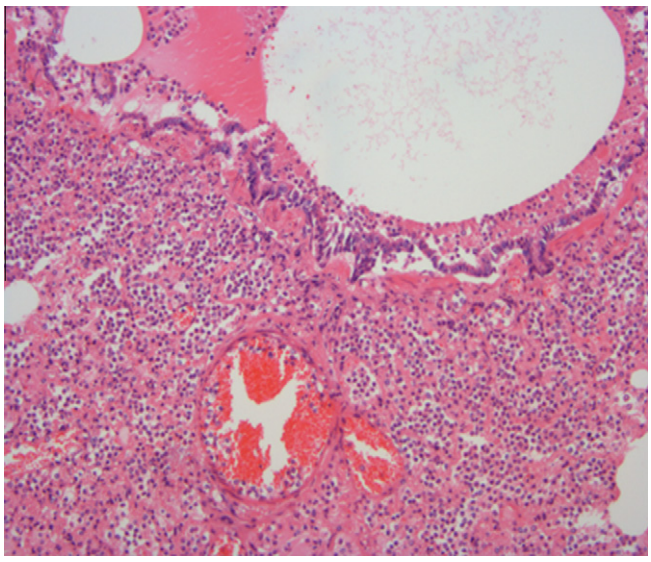

**Fig. 4.** Diffuse infiltration of alveolar spaces with numerous neutrophils admixed with fibrin and extravasated erythrocytes. H&E. Magnification ×100.

Widespread necrosis of pneumocytes and alveolar endothelial cells results in destruction of alveolar architecture. Small blood vessels often contain fibrin thrombi with entrapped erythrocytes and leukocytes.

Variable numbers of Gram-positive cocci might be observed within alveolar spaces or occasionally within alveolar macrophages. These bacteria are present either as short chains or more often, large clusters filling the alveolar lumen (Fig. 5). Inflammation of the terminal bronchioles has been reported in the majority of cases, however involvement of the larger, more proximal conducting bronchioles and bronchi is more variable (Garnett et al., 1982). In some cases the bronchi contain abundant mucus, admixed with necrotic cell debris, degenerate neutrophils, erythrocytes and fewer mononuclear inflammatory cells (Kim et al., 2007), most likely coughed up from lower in the respiratory tract. A mild suppurative tracheitis has also been reported (Byun et al., 2009).

Whilst severe fibrino-suppurative, necrotising and haemorrhagic pneumonia is by far the most frequent histological presentation, a minority of dogs have a fibrinous and/or haemorrhagic pneumonia (Priestnall et al., 2009), which may reflect earlier infection or less intense host inflammatory response.

Involvement of other organs is less consistent; however lesions within bronchial lymph nodes, tonsils and the spleen are frequently reported. Lymph node lesions range from marked depletion (Byun et al., 2009) to lymphoid hyperplasia (Garnett et al., 1982). Sinus histiocytosis in lymph nodes and the spleen, haemorrhagic lymphadenitis and myeloid hyperplasia within the bone marrow have also been reported. Septic thromboemboli, composed of large colonies of coccoid bacteria, have sometimes been observed in splenic sinusoids, renal glomeruli, lymph nodes, adrenal glands and brain (Garnett et al., 1982; Pesavento et al., 2008). Petechial and ecchymotic haemorrhages within other organs, most often the intercostal muscles and myocardium have also been observed (Garnett et al., 1982).

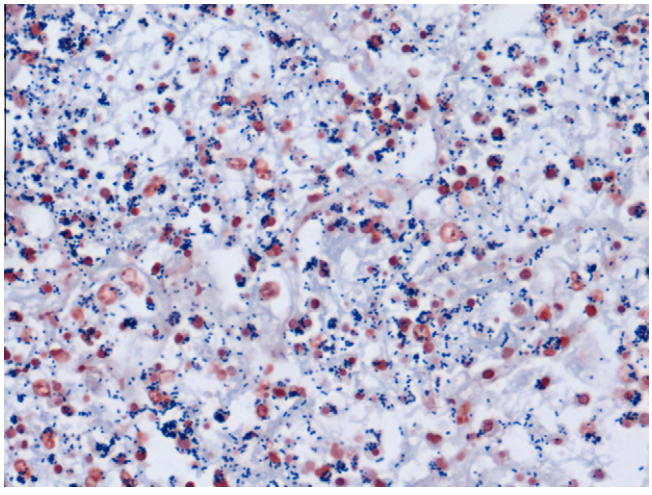

**Fig. 5.** Alveolar spaces contain numerous Gram-positive coccoid bacteria, sometimes forming short chains, and often present within the cytoplasm of neutrophils. Gram stain. Magnification ×400.

## Diagnosis

### *Bacteriology*

Investigation of fatal cases should include the collection of lung samples from which *S. zooepidemicus* is reliably cultured (Pesavento et al., 2008). *S. zooepidemicus* has also been successfully isolated from nasal swabs and a transtracheal lavage from a dog with chronic lower respiratory tract disease and from throat swabs of dogs with coughing and purulent nasal discharge (Garnett et al., 1982; Abbott et al., 2010). Analyses comparing isolation rates from respiratory lavages to those from nasal or oropharyngeal swabs have not been carried out. It is likely that tracheal or broncho-alveolar lavages are most informative, but the clinical condition of the patient may preclude these procedures.

Isolation of *S. zooepidemicus* from clinical samples is carried out using media selective for Gram-positive bacteria, such as Columbia agar with 5% sheep or horse blood containing colistin and nalidixic acid. On blood agar the bacteria show a clear zone of haemolysis around colonies (β-haemolysis). Preliminary typing is carried out to determine the group specific antigens by methods such as latex bead agglutination (Lancefield grouping). *S. zooepidemicus* belongs to Lancefield group C while *S. canis*, which is commonly found in dogs, belongs to Lancefield group G (Quinn et al., 1994). Several group C streptococcal species other than *S. zooepidemicus* have been isolated from dogs including *Streptococcus dysgalactiae* subsp. *equisimilis* (Ramos-Vara et al., 1994) and *S. equi* (Ladlow et al., 2006). Further typing is therefore required to confirm the presence of *S. zooepidemicus*.

Biochemical methods such as the API20 Strep kit (BioMérieux) are widely used. PCR and real-time PCR methods have been developed for rapid detection and identification of *S. zooepidemicus* and *S. equi* in horses (Alber et al., 2004; Baverud et al., 2007). Direct PCR on clinical samples without prior culture was not performed in those studies. However, PCR on nasopharyngeal swabs and guttural pouch lavages was found to be more sensitive for the detection of *S. equi* than bacterial culture (Newton et al., 2000). Similar studies for the detection of *S. zooepidemicus* in dogs will be required to ensure that the most sensitive detection method is applied.

### *Haematology*

Dogs showing clinical signs of respiratory disease due to *S. zooepidemicus* have been found to exhibit neutrophilia and monocytosis (Garnett et al., 1982; Abbott et al., 2010). Analysis of blood samples from 11 dogs with *S. zooepidemicus* infection during an outbreak in the UK showed neutrophilia (14.58–43.44 × $10^9$ cells/

L) and monocytosis (1.34–5.45 $\times 10^9$ cells/L) in seven cases. Three of these also showed lymphopenia (0.4–0.87 $\times 10^9$ cells/L). In two dogs lymphopenia was the only finding (0.2–0.81 $\times 10^9$ cells/L), while one dog showed leukopenia (3.85 $\times 10^9$ cells/L) and one dog did not exhibit any abnormal findings (K. Erles, unpublished data). Overall, these results are consistent with inflammation due to bacterial infection.

Two dogs, which showed normal levels of neutrophils or mild neutrophilia, were euthanased within hours of blood sampling due to severe respiratory distress and histopathological analysis revealed marked pneumonia (K. Erles, unpublished data). During bacterial inflammation levels of circulating neutrophils may decrease due to margination within blood vessels and recruitment to the site of inflammation (Blackwood, 2005). It is possible that in dogs with systemic streptococcal disease, overwhelming demand on the bone marrow pool would eventually lead to neutropenia.

### *Differential diagnoses*

Clinical signs similar to streptococcal toxic shock syndrome in humans have been reported in dogs following infection with *S. canis*. In one study, four dogs developed necrotising fasciitis, necrotising and suppurative bronchopneumonia and septic emboli in several organs. Two dogs showed mainly respiratory distress and post mortem analysis revealed suppurative pneumonia and oedema and congestion in other organs (Miller et al., 1996). All dogs that developed necrotising fasciitis had a history of minor trauma, which probably served as the route of entry for *S. canis*. The two dogs, which developed respiratory distress, had suffered from chronic respiratory disease for weeks to months before developing severe clinical signs.

*S. canis*, unlike *S. zooepidemicus*, is a commensal organism commonly isolated from throat swabs of healthy dogs. It is possible that *S. canis* was able to cause severe disease in these two dogs due to previous tissue damage in the respiratory tract. There was no report of spread of *S. canis* to other dogs, however this may have been due to these dogs being kept as pets rather than in large groups (Miller et al., 1996).

Bronchopneumonia in dogs is most commonly caused by secondary bacterial infections following impairment of the host defences (Brady, 2004). Infection with respiratory viruses such as canine distemper virus or canine adenovirus type 2 may predispose the lung to invasion by *Bordetella bronchiseptica* or opportunistic pathogens such as *Pasteurella* spp. Outbreaks of canine distemper virus or canine adenovirus type 2 in housed dogs may therefore lead to multiple cases of bronchopneumonia (Benetka et al., 2006; Norris et al., 2006). Both viruses typically lead to interstitial pneumonia and necrotising bronchiolitis, however secondary bacterial infections will cause suppurative bronchopneumonia (Mellema, 2004).

Canine influenza virus also has to be considered as a differential diagnosis. It was originally isolated from greyhounds with haemorrhagic pneumonia in Florida. The virus was subsequently detected in dogs in other parts of the USA but was mainly associated with milder respiratory disease (Dubovi and Njaa, 2008). One outbreak of severe pneumonia in greyhounds in Iowa involved both canine influenza virus and *S. zooepidemicus* (Yoon et al., 2005).

In individual dogs a number of additional possible causes of bronchopneumonia, such as aspiration of stomach contents or diseases, which lead to immune suppression, have to be investigated (Brady, 2004). Sporadic cases of haemorrhagic pneumonia in dogs have also been reported following infection with extraintestinal pathogenic *Escherichia coli* strains (Handt et al., 2003).

It is important to bear in mind that both bacteria and/or viruses might be involved when collecting samples from dogs with respiratory disease. Viral transport media contain antibiotics and are unsuitable for bacterial isolation. Similarly bacterial transport media are unsuitable for virus isolation and may contain components which inhibit PCR diagnosis (Gibb and Wong, 1998; Cloud et al., 2002). The diagnostic laboratory will be able to offer advice on appropriate sampling media for the test to be carried out and should therefore be contacted prior to sampling.

## Treatment

In dogs with respiratory disease that show additional clinical signs such as pyrexia, anorexia and depression, treatment with broad-spectrum antibiotics should be initiated without delay. It is nevertheless important to submit samples for bacterial isolation and antibiotic sensitivity profile to ensure the most appropriate antimicrobial treatment.

Isolates of *S. zooepidemicus* from dogs in several studies were found to be susceptible to penicillin, ampicillin, amoxicillin and enrofloxacin (Byun et al., 2009) whilst some isolates were resistant to tetracycline and doxycycline (Garnett et al., 1982; Pesavento et al., 2008). Treatment with penicillin (40,000 iu) and streptomycin (20 mg/kg) IM every 12 h in combination with IV lactated Ringer's solution was found effective in one study (Kim et al., 2007). During other outbreaks, fatalities were common despite treatment (Byun et al., 2009). In some cases, this may be due to the use of ineffective drugs; however fatalities are also likely to be a consequence of the rapid progression of the disease.

Even early antimicrobial therapy may not be able to stop initiation of the inflammatory cascade which leads to hypotension and multiple organ dysfunction. If the clinical condition worsens, supportive measures for shock such as fluid therapy should be initiated. For further information on the diagnosis and treatment of severe sepsis the readers are referred to a comprehensive review by Brady and Otto (2001).

## Prevention

*S. zooepidemicus* is shed in respiratory secretions and has been detected in environmental samples from a kennel in which infected dogs were housed (Pesavento et al., 2008). Affected dogs should be housed separately to limit the spread of bacteria among dogs. In addition, staff should wear dedicated protective clothing when caring for diseased dogs and thoroughly clean and disinfect hands after handing them. Items such as leads or bowls that were used for dogs suspected of shedding *S. zooepidemicus* should be cleaned and disinfected before further use. Premises in which diseased dogs were kept should also be thoroughly cleaned and disinfected before introducing new dogs. *S. zooepidemicus* is inactivated by commonly used disinfectants containing quaternary ammonium compounds, phenol-based agents or oxidising agents (Slater, 2007). Such husbandry measures have been found to be fundamental for the control of *S. zooepidemicus* outbreaks (Pesavento et al., 2008; Byun et al., 2009). Good hygiene standards will also minimise the risk of transmission of *S. zooepidemicus* to dog handlers.

There are no vaccines for the prevention of *S. zooepidemicus* infection in dogs. Experience gained from vaccination of other species against streptococcal diseases may however prove valuable for their future development. The immunogenic surface protein SzP of *S. zooepidemicus* has been expressed in a *Salmonella* vector for protection of horses against uterine infection. Intranasal vaccination of horses with this construct was shown to induce mucosal immunity by increasing specific IgA levels in nasal and uterine secretions (Causey et al., 2010). SzP has also been shown to be protective in mouse studies (Timoney et al., 1995), however due to a hypervari-

able region within the protein, cross-protection of vaccines based on SzP against challenge with other strains needs to be determined. Deletion of the gene for SzP has been shown to result in a strain with markedly reduced virulence which conferred protection against challenge to mice (Hong-jie et al., 2009). Targeted mutation to create attenuated strains has also been employed for the development of live vaccines against *S. equi* in horses. Subunit vaccines, incorporating several *S. equi* proteins have shown promising results in mice (Waller and Jolley, 2007).

## Zoonotic disease due to *S. zooepidemicus*

Human infection with *S. zooepidemicus* generally occurs sporadically and is often associated with underlying diseases (Barnham et al., 1989). Nevertheless, the outcome may be severe and a case of fatal toxic-shock like syndrome has been reported (Korman et al., 2004). Respiratory disease including pharyngitis, bronchitis and pneumonia in humans has also been described (Dolinski et al., 1990). Outbreaks in humans, such as epidemic glomerulonephritis (Balter et al., 2000) or septicaemia (Kuusi et al., 2006) following consumption of contaminated dairy products are rare. Although carriage of *S. zooepidemicus* in horses is widespread, only a few cases of transmission to humans have been reported (Low et al., 1980; Downar et al., 2001). Animal to human transmission was often not proven due to a lack of isolation or characterisation of the corresponding isolate from the suspected animal host.

So far, one case of transmission from a dog to a handler has been described (Abbott et al., 2010). The isolates from dog and handler were compared using molecular analysis and found to be identical (Abbott et al., 2010). It is not known if dogs pose a high risk of zoonotic infection. *S. zooepidemicus* strains that infect dogs may be more virulent than those infecting horses. Moreover it is possible that dogs shed larger quantities of *S. zooepidemicus* than horses. In many cases of *S. zooepidemicus* infection, dogs produced copious amounts of nasal discharge, which poses a risk of infection for humans via the skin or the respiratory route.

The risk of transmission via the skin should be minimised by wearing protective clothing and gloves when treating dogs with respiratory disease. Due to the transmission of *S. zooepidemicus* via the respiratory route in one case, it has been suggested that additional measures should include wearing of safety glasses and respiratory protection (Abbott et al., 2010). Early signs of systemic streptococcal infection in humans often include fever, malaise, nausea and, in case of entry via a skin lesion, pain, swelling and a skin rash around the affected area. It may be advisable to educate staff on these clinical signs to ensure that medical attention is sought without delay.

## Conclusions

*S. zooepidemicus* can seriously affect the health of dogs. Treatment is often unsuccessful and vaccines are currently not available. In order to improve the control of this disease, it is crucial to raise awareness amongst veterinary clinicians and nurses to ensure that cases are recognised early. This will allow the implementation of suitable protocols to minimise the spread of infection within a population. Measures to protect staff and owners from zoonotic infection during treatment and patient care are also imperative.

Many questions remain unanswered with regards to the high pathogenicity of this organism in dogs. Analysis of whole bacterial genomes can now be performed with relative ease. This might allow identification of potential virulence factors which may lead to the development of new strategies for the diagnosis, prevention and treatment of this bacterial disease.

## Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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