Epidemiology and Pathogenicity of Zoonotic Streptococci

Marcus Fulde and Peter Valentin-Weigand

Abstract Zoonotic infections caused by *Streptococcus* spp. have been neglected in spite of the fact that frequency and severity of outbreaks increased dramatically in recent years. This may be due to non-identification since respective species are often not considered in human medical diagnostic procedures. On the other hand, an expanding human population concomitant with an increasing demand for food and the increased number of companion animals favour conditions for host species adaptation of animal streptococci. This review aims to give an overview on streptococcal zoonoses with focus on epidemiology and pathogenicity of four major zoonotic species, *Streptococcus canis*, *Streptococcus equi* sub. *zooepidemicus*, *Streptococcus iniae* and *Streptococcus suis*.

Contents

M. Fulde
Medizinische Hochschule Honnover, Institut für Medizinische Mikrobiologie und Krankenhaushygiene, Carl-Neuberg-Str. 1 30625 Hannover, Germany
e-mail: fulde.marcus@mh-hannover.de

P. Valentin-Weigand (✉)
Institut für Mikrobiologie, Zentrum für Infektionsmedizin,
Stiftung Tierärztliche Hochschule Hannover,
Bischofsholer Damm 15, 30173 Hannover, Germany
e-mail: peter.valentin@tiho-hannover.de

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1 Introduction

Infections caused by *Streptococcus* spp. have received little attention in zoonosis research. Some zoonotic species, e.g. *S. suis*, are considered to be neglected due to non-identification during routine diagnostic procedures in human medicine. On the other hand, since streptococci *per se* are classified as facultative pathogens, almost all endothermic and many poikilothermic animal species as well as humans harbour at least one streptococcal species as commensal on skin and/or mucosal surfaces (Facklam 2002). Poor hygiene, secondary infections or underlying immunodeficiency, often results in streptococcosis of the natural host, whereas true host–species jumps seem to be rather rare events. Usually, zoonotic infections caused by streptococci do not result in notified epidemics or pandemics, but they can lead to severe and life-threatening diseases of individuals (Abbott et al. 2010; Baiano and Barnes 2009; Galperine et al. 2007; Lam et al. 2007; Lun et al. 2007; Wertheim et al. 2009). On the other hand, outbreaks have been reported which were related to highly virulent zoonotic strains, as exemplified by the *S. suis* outbreak in China 2005 or the *S. zooepidemicus* outbreak in Brazil 1997/98 (see below). Fortunately, such outbreaks have not been caused by human-to-human transmission, but are limited to infections from contaminated food or close contact with infected animals (Balter et al. 2000; Chen et al. 2007; Tang et al. 2006). This suggests that these zoonotic streptococci are not well adapted to the human host.

The wide distribution of streptococcal species and the incomplete characterisation of clinical isolates to species-level render a predication about the zoonotic potential of certain species difficult (Facklam 2002). Furthermore, Lancefield typing is not sufficient to discriminate zoonotic streptococci. For example, *S. agalactiae* (GBS) isolates leading to neonatal sepsis and meningitis harbour a different geno- and phenotype than GBS strains causing mastitis in cattle or infections in fish (Dogan et al. 2005; Martinez et al. 2000; Oliveira et al. 2006; Pereira et al. 2010; Sukhnanand et al. 2005). Similarly, a different genotype is discussed for *S. pneumoniae* serotype 3 strains causing pneumonia in race horses

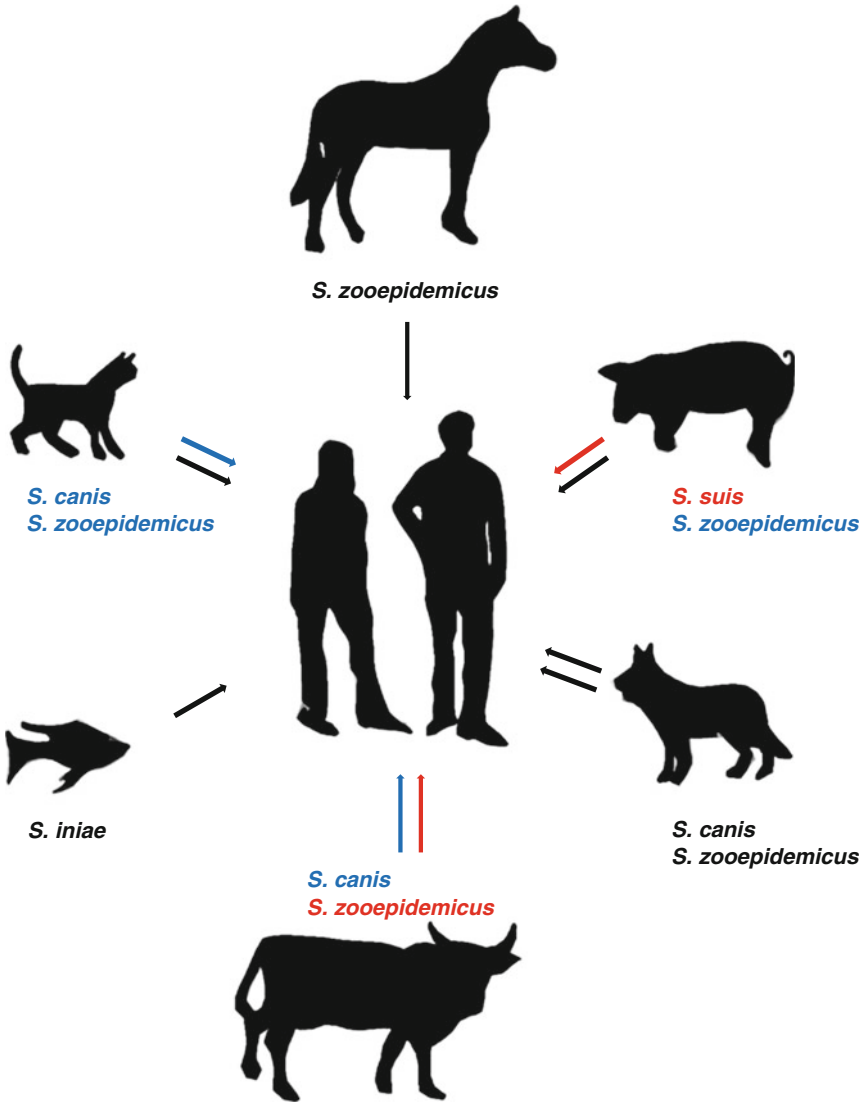

Fig. 1 Schematic figure representing host–pathogen relations of zoonotic streptococci. *Black arrows* indicate the transmission to one individual, whereas red arrows illustrate the origin of outbreaks. An identification of zoonotic species in animals without a proven transmission to humans is coloured *blue*

as compared to those from humans and strains isolated from a variety of rodents (Blunden et al. 1994; Van der Linden 2009).

Considering the complexity of zoonotic and potentially zoonotic streptococcal infections, we will focus in this review on the proven zoonotic species *S. canis*, *S. equi* sub. *zooepidemicus* (*S. zooepidemicus*), *S. iniae* and *S. suis* with emphasis on

epidemiology and pathogenicity. A scheme illustrating the natural hosts of these species and their transmission to humans is depicted in Fig. 1.

2 *Streptococcus canis*

2.1 General Features

S. canis was first described taxonomically by Devriese and co-workers in 1986, but was known as a causative agent of mastitis in cows and a variety of different clinical pictures in dogs and cats much earlier (Devriese et al. 1986). Phenotypically, *S. canis* is characterised as large-colony-forming, ß-haemolytic group G streptococcus (GGS) of animal origin distinguishable from other GGS, such as *S. dysgalactiae* subsp. *equisimilis* (*S. equisimilis*, large-colony-forming, ß-haemolytic GGS derived from human) and members of the *S. anginosus* group (minute ß-haemolytic colonies derived from humans) (Efstratiou et al. 1994; Devriese et al. 1986). Biochemical identification of human GGS is based on positive α- and *β*- galactosidase activity, negative hyaluronidase- and *β*- glucoronidase activity as well as on negative acid production from trehalose catabolism (Efstratiou et al. 1994; Devriese et al. 1986). The composition of the cell wall peptidoglycan represents a remarkable rare phenotype with its main constituents being lysine, threonine and glycine (Devriese et al. 1986). Interestingly, the inability of *S. canis* to lyse human fibrin represents another factor for distinguishing human and animal GGS, as already shown by Butaye (1956). However, this feature might be also important for pathogenesis of *S. canis* infections (as described in Sect. 2.3).

In addition to the phenotypic properties, early genetic studies based on DNA hybridisation and 16S rRNA sequencing revealed that *S. canis* is a member of the large group of pyogenic streptococci (Kawamura et al. 1995; Devriese et al. 1986). This was confirmed in detailed phylogenetic studies by Jensen and Kilian (2012) and Lefebure et al. (2012). Both groups found that human specific *S. pyogenes* (GAS) and *S. dysgalactiae*, comprising GGS from human origin (*S. equisimilis*) and bovine group C streptococcus (GCS, *S. dysgalactiae* sub. *dysgalactiae*), represent the closest relatives of *S. canis*.

Several groups identified genetic markers for species-specific detection of *S. canis*, such as specific sequences of genes coding for the superoxide dismutase *sod*A (Poyart et al. 1998; Whatmore et al. 2001), the DNA mismatch repair protein *mut*S (Whatmore et al. 2001), the CAMP factor (*cfg*) (Hassan et al. 2003) and the RNase P (*rnp*B) (Tapp et al. 2003). Hassan et al. (2003) developed a PCR based on species-specific sequences of the 16S rRNA gene and the 16S-23S rRNA gene intergenic spacer region. Nevertheless, routine diagnostic of streptococci is usually limited to determination of the Lancefield group which might result in an underrepresentation of *S. canis* in data banks (Lam et al. 2007).

2.2 Epidemiology and Zoonotic Relevance

S. canis represents a constituent of the resident microflora of domestic carnivores colonising skin and mucosae of urinary, gastrointestinal and reproductive tract mainly in dogs and cats (Devriese et al. 1986). Lyskova et al. (2007) reported a carrier rate of 18 % for dogs and 12.7 % for cats, respectively, in an epidemiological study of 926 samples from 324 animals. The importance of *S. canis* as an infectious agent in dogs was clearly demonstrated by Lamm et al. (2010) who showed in a retrospective study of 393 samples from streptococcal infections in dogs that 22.4 % were caused by *S. canis*. In addition to domestic carnivores as primary host species, Hamilton and Stark (1970) reported cases of bovine mastitis with animal GGS as the causative agent, suggesting that the bovine udder might be a further niche of this facultative pathogen. In a few cases, *S. canis* was isolated from rats, minks, mice, rabbit, foxes and horses (Corning et al. 1991; Iglauer et al. 1991).

Severe and life-threatening diseases in dogs with β-haemolytic streptococci as the causative agent were reported since the 1930s of the last century (Hare and Frye 1938). Today, it is known that the spectrum of clinical symptoms resulting from *S. canis* infections in dogs is highly divers. It ranges from mild and superficial pyogenic infections of the skin and mucosae of the respiratory and urogenital tract to more severe clinical pictures such as pneumonia, mastitis, abortion, cellulitis and septicaemia of newborns (Biberstein et al. 1980; DeWinter and Prescott 1999; Kruger et al. 2010). In addition, in the mid-1990s, several reports were published describing identification of *S. canis* as the causative agent of streptococcal toxic shock-like syndrome (STSS) and Necrotising Fasciitis (NF) in dogs in Southern Canada and USA (Miller et al. 1996, Prescott et al. 1995). In addition to the clinical pictures described in dogs, there are some reports on sporadic cases of *S. canis* associated contagious lymphadenitis, arthritis and myositis in cats (Iglauer et al. 1991; Swindle et al. 1980; Tillman et al. 1982). Nevertheless, *S. canis* infections in cats seem to be more often associated with severe outbreaks presenting as STSS, NF, sepsis and meningitis reaching mortality rates of up to 30 %. It is very likely that this phenomenon is due to the limited space in catteries and shelters resulting in close contact of the animals and easier transmission. Interestingly, a recent study by Kruger et al. (2010) proposed a clonal origin of *S. canis* strains causing STSS and NF in cats, which seems to be contradictory to the scenario described in dogs (DeWinter et al. 1999).

In contrast to the broad spectrum of clinical pictures and tissue sites involved in *S. canis* infections of domestic carnivores, in cattle infection may lead to subclinical mastitis characterised by elevated somatic cell counts (SCCs) (Chaffer et al. 2005; Hassan et al. 2005). Although the carrier rate of *S. canis* in the udder of cows is low ($\sim$1 %, Hamilton and Stark 1970; McDonald and McDonald 1976), and outbreaks of mastitis are rare events, morbidity might reach >30 %. Tikofsky and Zadoks (2005) described a scenario for an outbreak of *S. canis* mastitis in a dairy herd. A cat suffering from chronic sinusitis caused by *S. canis* was the most likely source as evaluated by bacterial culture and ribotyping. The authors stated

that dissemination of the bacterium from cow to cow was a result of an insufficient hygiene management including contaminated udder and insufficient post-milking teat disinfection. Nevertheless, this example shows the ability of *S. canis* to spread across species barriers.

Cases of human infections caused by *S. canis* are rare, but may be underestimated due to insufficient diagnostic practice limited to Lancefield typing (Lam et al. 2007). It is believed that transmission to humans occurs mainly via direct contact or as a result of animal bites. However, in most cases, aetiology of *S. canis* infection is unknown (Galperine et al. 2007). Two cases of septicaemia due to dog bite and close vicinity to pet dogs were reported by Takeda et al. (2001) and Bert and Lambert-Zechovsky (1997), respectively. Interestingly, detection of *S. canis* as the causative agent of ulcers in dog owners increased during the last years (Lam et al. 2007), suggesting a possible emerging role of this zoonosis in the near future.

2.3 Virulence and Pathogenesis

Despite its role as an emerging infective agent in animals and humans, knowledge on pathogenesis and virulence factors of *S. canis* remains elusive. However, similarities in disease establishment and progression, clinical pictures, pathology and outcome of infections with *S. pyogenes* infections suggest the existence of comparable virulence mechanisms, although data from animal infections are lacking. An initial attempt to prove this hypothesis was reported by DeWinter et al. (1999). Using Southern Blot analyses, the genomes of 15 *S. canis* isolates from cases of STSS and NF in dogs were screened for GAS-associated virulence factor genes, such as *emm*, *ska*, *spe*A, *spe*B, *spe*C, *mf, ssa*, *scp*, *has*A and *slo*. Interestingly, only two respective genes were detected, *slo* and *emm* (DeWinter et al. 1999). In another study, Igwe et al. (2003) identified a new allele of the GAS superantigen (SAg) smeZ. SAgs are phage-encoded virulence factors extensively studied in GAS. Their toxoid nature is based on high affinities for major histocompatibility complex II (MHC class II) molecules and T cell receptors on professional antigen presenting cells. Upon activation, a cytokine "storm" comprising pro-inflammatory cytokines (TNF-α and IL-1β) as well as T cell mediators (IL-2) are induced leading to severe clinical and pathological changes, such as fever, hypotension, shock and multi-organ failure (Igwe et al. 2003; Proft and Fraser 2007) which resembles the clinical symptoms of STSS in *S. canis* infected dogs. The identification of putative *emm* genes in *S. canis* genomes was surprising, since *S. canis*, like other animal specific and zoonotic pathogens, is characterised as *emm* negative according to the established PCR test for *emm* typing described by the Center for Disease Control (CDC, Atlanta, USA). Probably, due to poor genome information, it took 12 years until a second publication verified the existence of an M-like protein in *S. canis* SCM (Fulde et al. 2011a). Detailed biochemical studies characterised SCM as an alpha-helical protein with a high probability to form dimers on the bacterial surface. SCM specifically binds to plasminogen (PLG) with

high specificity and affinity. Accordingly, numerous other M proteins identified in human-specific GAS and *S. equisimilis*, as well as M-like proteins of animal specific (e.g. *S. equi* sub *equi*) and zoonotic species, e.g. *S. zooepidemicus* and *S. iniae* (Baiano et al. 2008, 2009; Bergmann et al. 2011; Meehan et al. 2001; Nitsche-Schmitz et al. 2007; Nitsche et al. 2006; Smeesters et al. 2008; Timoney et al. 1997, 2010), bind extracellular matrix (ECM) and serum proteins. However, in contrast the well-known PLG-binding M Protein PAM on the surface of GAS (Wistedt et al. 1995), SCM interacts with the C-terminal part of PLG, named mini-PLG (mPLG). Only few studies have been published on the interaction of pathogens with mPLG (Ljungh 2000; Rojas et al. 2008; Ullberg et al. 1992) and SCM displays the first receptor proven so far. The role of mPLG in pathogenesis is unclear but an involvement in endothelial cell migration during wound repair is discussed (Hayashi et al. 2009). Since wounds display the main entry site for S. canis, it may be speculated that interaction with mPLG in wound fluids represents a yet unknown pathogenicity mechanism.

The immobilisation of the zymogen plasminogen on the surface of different streptococcal species and its subsequent activation to the broad spectrum serine protease plasmin by the main streptococcal PLG-activator (PA) streptokinase (SKA) is a common and well-known mechanism for tissue destruction and dissemination of invasive isolates within the host (Sun et al. 2004). However, as already described by Butaye (1956), *S. canis* does not possess any fibrinolytic activity in human serum. This inability is not restricted to a certain host as described for *S. zooepidemicus* (Fulde et al. 2011a; Schroeder et al. 1999) and supports results by DeWinter et al. (1999) who postulated that the genomes of 15 different *S. canis* strains lack a gene coding for streptokinase. Nevertheless, surface-bound plasminogen could be activated by host-derived PA, such as urokinase (uPA) which enables *S. canis* to degrade fibrin matrices and disseminate through semi-synthetic thrombi. An illustration of fibrin degradation by S. canis is shown in Fig. 2.

In addition to the interaction of *S. canis* with plasminogen, an association with albumin, IgG and fibrinogen was reported by Laemmler and co-workers (Lammler et al. 1988). Although the authors did not comment on the responsible bacterial binding proteins or possible virulence mechanisms, it is conceivable that in analogy to pyogenic streptococci, binding to ECM and serum proteins is a prerequisite for establishing *S. canis* infections. For example, since M protein-mediated binding to fibrinogen confers anti-phagocytic properties, immobilisation of albumin leads to an inactivation of the antibacterial peptide MIG/CXCL9 (Egesten et al. 2011). Furthermore, the interaction of streptococci with IgG occurs mainly in a "non-immunogenic" way by binding to the conserved F_c-fragment (Lewis et al. 2008) which seems to be similar in zoonotic *S. canis* (own unpublished data).

Surface exposed metabolic enzymes with a secondary function (moonlighting enzymes) are well-known players in streptococcal disease progression (Pancholi and Chhatwal 2003). Hitzmann et al. (2012) recently reported the existence of the Arginine Deiminase System (ADS), an energy providing pathway catabolising arginine, on the surface of zoonotic *S. canis*. Its possible role in pathogenesis was

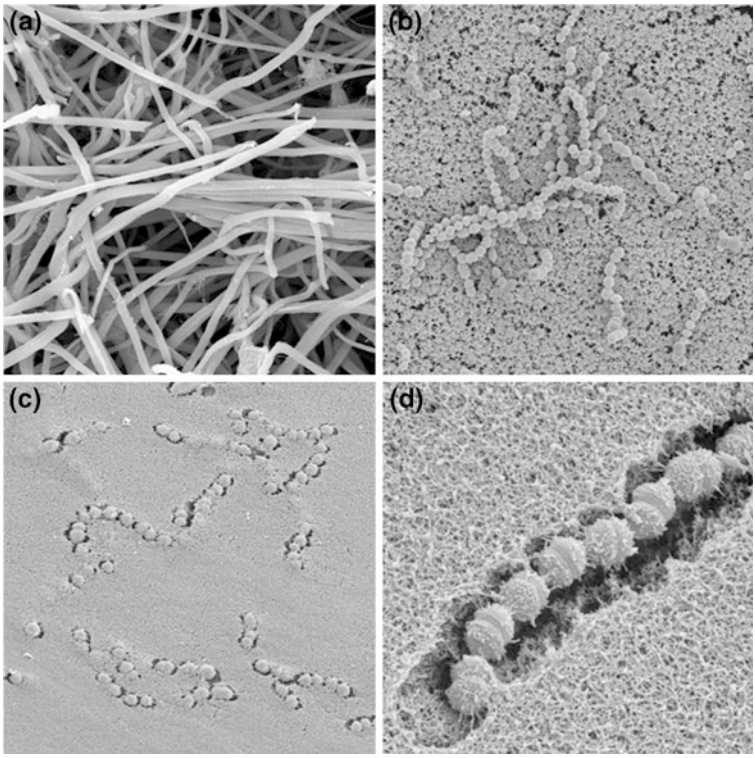

Fig. 2 Fibrin degradation by zoonotic *S. canis* **a** Fibrin bundles form a dense network in semi-synthetic thrombi. **b** PLG-coated *S. canis* strains strongly attach to fibrin bundles. **c, d** Immobilisation of proteolytic plasmin activity on the bacterial surface leads to fibrinolytic phenotype of *S. canis*. (EM pictures provided by Manfred Rohde, HZI Braunschweig, Germany).

described earlier for the zoonotic pathogen *S. suis* by Gruening et al. (2006), and therefore is described in Sect. 5.3.

3 *Streptococcus equi* sub. *zooepidemicus* (*Streptococcus zooepidemicus*)

3.1 General Features

S. zooepidemicus belongs to the large group of pyogenic streptococci with a ß-haemolytic, large-colony-forming phenotype comparable to other members such as GAS, S. *equisimilis* and *S. canis*, respectively (Facklam 2002; Efstratiou et al. 1994; Barnham et al. 1987a). *S. zooepidemicus* harbours the Lancefield group C antigen, and is, therefore, serologically closely related to *S. equi* and *S. equisimilis*,

respectively. Differentiation of these species is done biochemically based on species-specific fermentation patterns of carbon sources. For example, *S. equisimilis* is able to utilize trehalose, whereas *S. equi* and *S. zooepidemicus* lack this ability. Instead, *S. zooepidemicus* ferments lactose and sorbitol in contrast to *S. equisimilis* and *S. equi*, respectively (Bannister et al. 1985).

Recent phylogenetic studies shed more light on the inter-species relationships in the pyogenic group of streptococci. These studies revealed that *S. equisimilis* is closely related to human pathogenic GAS forming a common clade together with the zoonotic GGS *S. canis* (Jensen and Kilian 2012), whereas *S. equi* and *S. zooepidemicus* share a genome identity of more than 98 % (Timoney 2004). Moreover, it is widely accepted that *S. equi* has evolved from an ancestral strain of *S. zooepidemicus* (Webb et al. 2008). Holden et al. (2009) compared the genomes of a highly virulent *S. equi* isolate with a *S. zooepidemicus* strain from a healthy thoroughbred racehorse. As expected, both genomes were highly identical comprising approximately 2,000 open reading frames (ORFs). However, the authors conclude from their studies that gain and loss of genes or their functions, respectively, might have forced *S. equi* to evolve from a mucosal colonizer of different animals (*S. zooepidemicus*) to a highly specialised pathogen of horses as sole host (Holden et al. 2009).

The close relationship between *S. equi* and *S. zooepidemicus* complicates the development of a discrimination scheme other than time-consuming biochemical analysis (Webb et al. 2012). However, discrimination of both species is important since strangles, the main disease caused by *S. equi*, is a highly contagious infection of the upper respiratory tract constituting a major infectious disease threat in horses (Waller and Jolley 2007). The availability of the genome sequences will hopefully allow to identify new genetic markers for differentiation of both subspecies. Very recently, Webb et al. (2012) presented a quantitative triplex PCR with improved discrimination, a promising step towards eradication of strangles.

3.2 Epidemiology and Zoonotic Relevance

Although *S. zooepidemicus* is considered as an opportunistic pathogen in a large variety of mammalian species including cats, rodents, minks, monkeys and seals (Ryu et al. 2011; Akineden et al. 2005, 2007; Matz-Rensing et al. 2009; Blum et al. 2010; Britton and Davies 2010; Literak and Mraz 1991), the majority of cases were reported from domestic animals such as horses, dogs, pigs and ruminants, respectively. In horses, *S. zooepidemicus* represents a commensal of mucosae of the upper respiratory and the lower genital tract (Barquero et al. 2010; Priestnall and Erles 2011). As an opportunistic pathogen it can cause secondary infections after primary virus infection, as well as after predisposition by stress or tissue injuries (Timoney 2004; Ryu et al. 2011). Nevertheless, in several epidemiological studies *S. zooepidemicus* was found to constitute a major causative agent of purulent infections in horses and foals (Ryu et al. 2011; Panchaud et al. 2010; Erol

et al. 2012; Gaede et al. 2010; Clark et al. 2008). Typically, such infections lead to severe respiratory diseases with sudden onset dyspnoea and haemorrhagic nasal discharge accompanied by pyrexia, coughing, leucocytosis and neutrophilia (Priestnall and Erles 2011; Oikawa et al. 1994, 1995). Furthermore, dissemination of *S. zooepidemicus* in inner organs, such as liver, lung, brain and kidney as well were joints (Timoney 2004) often results in clinical pictures constituting as neonatal septicaemia, pyogenic abscesses, ulcerative keratitis and endometritis concomitant with reproductive failures (Timoney 2004; Priestnall and Erles 2011; Wada 2012).

Notably, *S. zooepidemicus* is emerging as cause of severe and life-threatening diseases in dogs (Priestnall and Erles 2011; Pesavento et al. 2008; Byun et al. 2009). In contrast to infections in horses, emerging dog infections frequently occur as outbreaks (Priestnall and Erles 2011). Clinical pictures are similar to those obtained in horses. Several studies reported that fatal outbreaks exhibit as haemorrhagic pneumonia and septicaemia, respectively, with a rapid disease progression (Priestnall and Erles 2011; Pesavento et al. 2008; Byun et al. 2009; Kim et al. 2007a; Sundberg et al. 1981; Garnett et al. 1982) often ending fatal within 24–48 h. In milder cases, typical symptoms are pyrexia, coughing, anorexia and tachypnoea (see also an excellent review by Priestnall and Erles (2011)).

In addition to *S. suis*, *S. zooepidemicus* is a major pathogen in swine in Asia. Outbreaks were reported from Sichuan, China (1975) and Indonesia (1994) with fatal cases of more than 300,000 pigs in 2 weeks. Typical clinical symptoms include arthritis, diarrhoea, bronchopneumonia, endocarditis and meningitis (Fan et al. 2008; Feng et al. 2010; Soedarmanto et al. 1996). Interestingly, during the large outbreak in Indonesia, a single, highly virulent *S. zooepidemicus* clone spread to a monkey population and led to severe disease similar as described for pigs (Soedarmanto et al. 1996).

S. zooepidemicus-induced severe and deep tissue infections have been observed in ruminants, such as goat, sheep, cattle, lama, camels and alpaca (Aubry et al. 2000; Barnham et al. 1987a; Hewson and Cebra 2001; Jones et al. 2009; Las et al. 2002; Younan et al. 2005; Pisoni et al. 2009). However, the majority of reports focussed on its role as a causative agent of mastitis.

Human outbreaks have been associated with unpasteurised milk and its products. For example, two outbreaks occurred in 2003 in Gran Canaria and Finland, respectively (Kuusi et al. 2006; Bordes-Benitez et al. 2006). In both cases, cheese produced from raw milk was the source of infection. People suffered septicaemia, aortic aneurism, pneumonia, meningitis and septic arthritis with partially fatal outcome. A special complication with regard to *S. zooepidemicus* infections is the development of post-streptococcal glomerulonephritis (PSGN) (Francis et al. 1993; Barnham et al. 1983, 1987b). One unusual large outbreak occurred from 1997 to 1998 in Nova Serrana, a rural province in Brazil (Balter et al. 2000). Again cheese from contaminated milk was the source of infection. In total, 253 cases of acute nephritis were reported of which three had a fatal progression and seven required dialysis. Extensive epidemiological studies including whole genome sequencing of the respective outbreak strain were applied. However, bacterial

factors promoting the establishment of PSGN remains unknown (Beres et al. 2008; Sesso and Pinto 2005; Nicholson et al. 2000). The transmission of *S. zooepidemicus* from livestock products other than milk or cheese, respectively, is discussed but not yet clearly proven. For example, Yuen et al. (1990) characterised *S. zooepidemicus* strains from Hong Kong isolated from infected human and pig individuals and found major genotypical and phenotypical similarities. The fact that *S. zooepidemicus* represents one of the major pathogens in swine in Asia and that Asian people frequently consume undercooked pork strongly suggests that transmission from pigs to human occurs (Yuen et al. 1990).

Transmission of *S. zooepidemicus* from companion animals to humans is frequently described in the literature. Most of the cases originated in horses, probably due to the wide distribution of *S. zooepidemicus* as a commensal in this species (Minces et al. 2011). Nevertheless, one case of transmission from dog to human was described (Abbott et al. 2010). In this case, the likely mode of transmission was via wound infection or aerosols rather than ingestion. Typical clinical symptoms in humans range from purulent abscesses of skin and mucosae to severe illnesses, such as endocarditis, endophthalmitis, septic arthritis, pneumonia and meningitis. Clinical outcome depends on the mode of transmission, the immunecompetence of the patient and the repertoire of virulence factors of the pathogen.

3.3 Virulence and Pathogenesis

S. zooepidemicus is believed to be the evolutionary ancestor of *S. equi* and both species share an overall genome identity of more than 98 %. But there is much less known about virulence factors in *S. zooepidemicus* as compared to *S. equi*. Comparative genome analysis by Holden et al. (2009) identified phage-associated genes, such as sAGs, a phospholipase A_2 toxin and an integrative conjugative element harbouring an iron acquisition system with similarities to a pathogenicity island of *Yersinia pestis* (Holden et al. 2009). Furthermore, the identification of genes possibly encoding pili in the genome of *S. zooepidemicus*, which could facilitate adherence and colonisation in horses, might reflect the evolution from a generalist to a specialist.

S. zooepidemicus possesses a hyaluronic capsule synthesised by genome products of the *has* operon (Blank et al. 2008; Paillot et al. 2010). Hyaluronic capsule is one of the most important virulence factors of streptococci facilitating anti-phagocytic properties. Furthermore, Wibawan et al. (1999) demonstrated that capsule positively correlates with the ability to adhere to HeLa cells. Whether or not this mechanism resembles the interaction between GAS and CD44 remains to be proven (Schrager et al. 1998). Similar to *S. canis*, *S. zooepidemicus* is also characterised as *emm*-negative according to the guidelines of the CDC. Nevertheless, Timoney et al. (1995) were able to identify a M-like protein (SZP) which protects mice against a lethal infectious dose of *S. zooepidemicus* but not against *S. equi* (Timoney et al. 1995). Similar to SCM, SZP is assumed to form an alpha–

helical structure but it does not possess A, B and C repeats characteristic for M proteins of human pathogenic GAS and *S. equisimilis* (Smeesters et al. 2008). SZP harbours variable- and hyper-variable regions in the N-terminal part of the mature protein (Walker and Timoney 1998). In accordance to other M and M-like proteins, SZP binds to fibrinogen (Timoney et al. 1997). Thus, an anti-phagocytic activity is plausible. However, to the best of our knowledge, a direct correlation was not yet reported. Recently, Hong-Jie et al. (2009) found that *szp*-deficient *S. zooepidemicus* mutant strains were >1,000-fold less virulent in an intramuscular mouse model (Hong-Jie et al. 2009). An interesting explanation was given by Ma et al. (2012). They found that *S. zooepidemicus* recruits thioredoxin (TRX) via SZP to the bacterial surface which, in turn, inhibits *inter alia* the deposition of complement factor 3, and thereby protects against phagocytic killing.

Binding to ECM- and plasma proteins is a crucial step in streptococcal pathogenesis. For example, as extensively studied for GAS, the interaction with fibronectin (FN) leads to a significant increase in adherence and invasion in epithelial and endothelial cells (Schwarz-Linek et al. 2006), and thus might represent a prerequisite for colonisation of and dissemination in the host. FN binding and subsequent attachment to host cells is well-known for *S. zooepidemicus* isolates (Valentin-Weigand et al. 1988). During the years, two proteins (FNZ and SFS) were identified with affinities to FN (Lindmark and Guss 1999; Lindmark et al. 1996). Although at least FNZ seems to induce a protective immunity in a mouse infection model, its role in pathogenesis remains elusive (Flock et al. 2006). ZAG is a surface-associated proteinous receptor for IgG, albumin and the plasma proteinase inhibitor α_2-macroglobulin (α_2M) (Jonsson et al. 1995). Potential benefits resulting from a recruitment of IgG and albumin, respectively, are already discussed in the *S. canis* section. Interestingly, Valentin-Weigand et al. (1990) showed an anti-phagocytic effect of surface bound α_2M on equine group C streptococci in vitro. The in vivo relevance, however, has not yet been demonstrated. In addition to the ability to bind (and inactivate) immunoglobulins, *S. zooepidemicus* possess two endopeptidases (IdeZ and IdeZ2) in its proteome which specifically cleave IgG from a variety of different species (Hulting et al. 2009; Lannergard and Guss 2006). Homologues in GAS constitute important virulence factors essential for circumventing antimicrobial properties (Pawel-Rammingen 2012; Akesson et al. 2006; Pawel-Rammingen et al. 2002). Furthermore, factors known to be important for establishing streptococcal infections were also reported in *S. zooepidemicus*. For example, the cytolysin streptolysin S (SLS), responsible for the β-haemolytic phenotype of pyogenic streptococci, was identified in the genome of *S. zooepidemicus* (Flanagan et al. 1998). SLS has been extensively studied and characterised as a virulence factor in GAS and human GGS. Thus, it may also be important for disseminating infections of other streptococci. Very recently, Paillot et al. (2010) identified the genetic determinants of three novel sAG- encoding genes in the genome of a *S. zooepidemicus* strain (Paillot et al. 2010). This was an interesting finding since *S. zooepidemicus*, in contrast to its closest relative *S. equi*, was classified as sAG negative, a likely prerequisite for its commensal lifestyle (Paillot et al. 2010).

4 *Streptococcus iniae*

4.1 General Features

S. iniae is a major fish pathogen first isolated in 1976 from a freshwater dolphin. It is widely spread geographically, mainly in North America, Middle East and the Asia–Pacific region. *S. iniae* infections lead to meningoencephalitis and other pathologies which result in high economic losses in aquaculture due to high rates of morbidity and mortality (Locke et al. 2007a). Death might occur without accompanying signs or specific clinical symptoms related to central nervous system (CNS) dysfunction, including loss of orientation and erratic swimming (Agnew and Barnes 2007).

S. iniae is also considered as an emerging agent of zoonotic infections, most of which are associated with processing of fresh fish (Baiano and Barnes 2009). In humans, infection often leads to bacteraemic cellulitis which may be followed by other invasive forms of diseases, such as endocarditis, meningitis, arthritis or sepsis.

S. iniae is genetically closely related to group B streptococci as revealed from 16S rRNA sequencing. It is not assigned to any Lancefield group and shows ß-haemolysis on blood agar (noteably, highest expression was observed with blood from freshwater dolphin (Pier et al. 1978)). Isolates show some variation in colony morphology, e. g. isolates from Asian patients are more mucoid (Lau et al. 2006). Virulent strains express an exopolysaccharide capsule. The capsule operon genes show homology to those of other streptococci, including *S. agalactiae*, *S. suis* and *S. thermophilus* (Lowe et al. 2007). *S. iniae* isolates from diseased fish and humans showed less genetic diversity than isolates from healthy fish in Canada (Facklam et al. 2005; Fuller et al. 2001). Two distinct serotypes of *S. iniae* have been identified based on their reaction with rainbow trout antisera. Serotypes also differ in their biochemical properties. Serotype 1 strains are positive for reaction with arginine dihydrolase and ribose, whereas serotype 2 strains are negative for both (as reviewed by Agnew and Barnes (2007)). Serotype 2 emerged after a vaccination program in Israel and includes strains producing and releasing large amounts of extracellular polysaccharide (Eyngor et al. 2008). Importantly, serotype 2, but not serotype I strains have been reported to survive in piscine phagocytes and induce their apoptosis (Zlotkin et al. 2003), probably due to the differences in the extent of capsule coverage of the bacterial surface.

4.2 Epidemiology and Zoonotic Relevance

S. iniae is an emerging invasive fish pathogen responsible for major economic losses in warm water finfish aquaculture worldwide (Agnew and Barnes 2007; Shoemaker et al. 2001). Diseases caused by *S. iniae* infection have been described

in at least 27 fish species, including trout (Eldar and Ghittino 1999), tilapia (Shoemaker et al. 2001), barramundi (Bromage et al. 1999) and hybrind striped bass (Shoemaker et al. 2001) (see also an excellent recent review by Agnew and Barnes (2007)). Carrier fish are considered to play an important role in fish-to-fish transmission. Currently, it is not known whether *S. iniae* has its origin in wild fish and has been distributed by ocean current and movement of fish, or whether its amplification in aquaculture has led to distribution into neighbouring fish populations (Agnew and Barnes 2007).

S. iniae is considered as an emerging zoonotic agent as noted at the International Conference on Emerging Infectious Diseases in 2000. In humans, it mainly causes bacterial cellulitis as a consequence of soft tissue injuries during preparation of fresh fish. However, severe complications have been described, including arthritis, meningitis, endocarditis and osteomyelitis (Sun et al. 2007; Weinstein et al. 1997). Notably, human infections by ingestion of contaminated fish have not been reported. Human cases are rare and sporadic, but continue to be reported and are likely to increase in the future due to enhanced surveillance. Epidemiological data showed that mainly elderly people with Asian origin are affected. The racial predominance may be related to a cultural preference for fresh whole fish in cooking, as suggested by Finkelstein and Oren (2011).

Importantly, it has to be mentioned that *S. iniae* is not included in commercial and clinical databases and diagnostic kits. Thus, it is very likely that *S. iniae* infections in humans are underreported due to non-identification.

4.3 Virulence and Pathogenesis

S. iniae harbours a number of virulence factors with high homology to respective factors of *S. pyogenes*. Important examples include the M-like protein SiM (Locke et al. 2008), the β-haemolysin S (Locke et al. 2007b) and an α-enolase (Kim et al. 2007b). For some of these factors, the interaction with the host has been described. As expected from the homology, these functions are reminiscent of the pathogenesis of *S. pyogenes*. Nevertheless, the mechanisms underlying the adaptation of *S. iniae* to fish as preferred host are not known. This preference is very prominent, as *S. iniae* is, for example, able to multiply in naive trout blood but hardly survives in naive human blood (Zlotkin et al. 2003). Furthermore, *S. iniae* rapidly translocates through trout skin epithelial cell monolayers covered with mucus (Eyngor et al. 2008).

A number of virulence factors of *S. iniae* have been confirmed in experimental infections of white striped bass (recently reviewed by Baiano and Barnes (2009)). The capsule and the M-like protein SiM (genes: *sim*A and *sim*B) protect *S. iniae* against opsonophagocytosis (Locke et al. 2007a, 2008). The phosphoglucomutase (gene: *pgm*) is also crucial for virulence since it is involved in cell wall morphology, surface capsule expression and resistance to cationic antimicrobial peptides (Buchanan et al. 2005). Furthermore, *S. iniae* expresses a cytolysin

homologous to SLS from *S. pyogenes*. The *sag* operon is involved in SLS formation and a *sag*A mutant is highly attenuated in virulence (Locke et al. 2007b).

In general, *S. iniae* resembles a typical blood pathogen that disseminates to different organs similar to some other invasive streptococcal species, such as group A and B streptococci. However, the pathogenesis of diseases caused by *S. iniae* is only partially understood. Most likely, the first step is adherence and colonisation of tissues followed by translocation into the blood circulation, similar to other invasive streptococci. The mechanism(s) of invasion into deeper tissue are not known. However, studies using epithelial cells of rainbow trout epithelial cells showed that *S. iniae* invaded the cells and persisted intracellular for short time periods. Invasion was followed by rapid translocation and dissemination in the fish (Eyngor et al. 2007). Evasion of defense mechanisms in the blood then allows a generalised bacteraemia, which is required to establish disease. A hallmark of *S. iniae* pathogenicity is its ability to survive phagocytic killing, as reflected by its rapid dissemination to systemic sites in the blood circulation system. Therefore, the interaction between *S. iniae* and phagocytes is considered to be crucial for the pathogenesis. A virulent *S. iniae* strain survived within pronephros macrophages in vitro (Zlotkin et al. 2003). Furthermore, monocytes carried approximately 70 % of the bacteria present in the blood of diseased fish. Based on these results, Zlotkin et al. (2003) postulated in a Trojan horse theory that *S. iniae* might enter the CNS by "hijacking" migrating monocytes/macrophages. Induction of apoptosis in macrophages was also suggested as an effective mechanism of *S. iniae* to prevent priming of the immune system (Zlotkin et al. 2003).

The virulence properties of *S. iniae* and its invasive nature as a pathogen make it an excellent model pathogen to study pathogenicity mechanisms of human streptococci, such as group A and B streptococci and pneumococci. Experimental infections have been reported in a number of different species, e. g. zebrafish (Miller and Neely 2004). Recently, we described an intraperitoneal *S. iniae* infection model for tilapia. This infection model includes for the first time pathohistological screening of brains and eyes as read out parameter and a novel multiplex PCR for confirmation of the virulence genotype of the challenge strain (Baums et al. 2012). In the future such models shall allow comparative analyses of different streptococci with respect to host–pathogen-interactions at different infection stages.

5 *Streptococcus suis*

5.1 General Features

S. suis is a major porcine and zoonotic pathogen occurring worldwide. It can cause severe diseases in pigs, e.g., sepsis, meningitis, arthritis and pneumonia resulting in enormous economical losses in the swine industry (Staats et al. 1997). In

humans, meningitis is the most common presentation, though *S. suis* can also be associated with other systemic complications such as sepsis, pneumonia and, as observed for the first time in two outbreaks in China, STSS (Gottschalk et al. 2007; Tang et al. 2006).

S. suis shares antigenic features with group D streptococci, but it is genetically distinct and serogrouping is not used for its identification. It produces α- or β-haemolysis on sheep and horse blood agar, respectively. Based on its capsular polysaccharides, 35 serotypes have been described to date. However, strains of serotypes 32 and 34 have been suggested to be more closely related to *S. orisratti* (Hill et al. 2005). Distribution of serotypes differs between geographical regions. Most European strains associated with disease belong to serotypes 1, 2, 7, 9 and 14 (Allgaier et al. 2001; Silva et al. 2006; Wisselink et al. 2000). Worldwide, serotype 2 is most prevalent. In recent years, serotype 9 has emerged as common pig isolate in Germany and The Netherlands, serotype 7 is highly prevalent in Scandinavia and serotypes 1 and 14 in the United Kingdom (Baums and Valentin-Weigand 2009; Perch et al. 1983; Tian et al. 2004; Wisselink et al. 2000). In contrast, in Canada and the USA serotypes 2, 1/2, and 3 are most frequently associated with disease (Messier et al. 2008). A specific sequence type (ST), ST7, which appeared to have evolved from the highly pathogenic ST1 type of a serotype 2 strain, was found to be responsible for human outbreaks in China and directly associated with the STSS (Feng et al. 2010; Ye et al. 2006, 2009). The ST7 carries a putative pathogenicity island (designated 89 K), possibly involved in development of STSS (Chen et al. 2007; Zhao et al. 2011).

5.2 Epidemiology and Zoonotic Relevance

Pigs and wild boars are considered as natural reservoirs of *S. suis* (Baums et al. 2007; Clifton-Hadley and Alexander 1980). Different mucosal surfaces might be colonised by *S. suis*. In weaning piglets, *S. suis* is an abundant coloniser of the upper respiratory and alimentary tract (Baele et al. 2001; Lowe et al. 2011; O'Sullivan et al. 2011; Su et al. 2008a, b). Tonsillar carrier rates up to 100 % have been reported (Arends et al. 1984; Clifton-Hadley 1983; Mwaniki et al. 1994a, b), persisting even after treatment with penicillin (Staats et al. 1997). The sow may harbour *S. suis* also in the genital tract. Healthy carriers of virulent *S. suis* strains are the main source of infection, and thus play an important role in the epidemiology of *S. suis* diseases in pigs and humans (Arends et al. 1984; Ngo et al. 2011). Faeces, dust, water and feed may be secondary sources of infection (Staats et al. 1997). Vectors such as flies (Enright et al. 1987) and mice (Williams et al. 1988) can play a role in disease transmission.

Pigs of any age can be infected with *S. suis*, but susceptibility generally decreases with age following weaning. Outbreaks are usually due to the introduction of a carrier into the herd. Within a carrier herd, outbreaks occur especially in young animals disposed to stress conditions. As *S. suis* is a facultative pathogen,

different biotic and abiotic factors such as virus infections, corrosive gases and crowding are thought to promote *S. suis* diseases in modern swine production.

Several modes of transmission between animals in a herd have been suggested. Piglets born to sows with genital infection may acquire the infection vertically (Amass et al. 1997). Transmission can also occur by nose-to-nose contact (Berthelot-Herault et al. 2001), or by infection through the navel, genital or alimentary tract (Staats et al. 1997). After infection, colonised pigs will usually harbour the bacteria in their tonsils. Some animals will remain healthy carriers, whilst other will sooner or later develop clinical signs (Gottschalk and Segura 2000). Morbidity rarely exceeds 5 %, although it can reach more than 50 % in cases of poor hygiene and concurrent disease (Staats et al. 1997). With appropriate treatment mortality is usually low (ca. 5 %), but can be up to 20 % in untreated herds.

The infection is recognised as a zoonosis associated with meningitis, septicemia and endocarditis in humans for a long time (Arends and Zanen 1988). Occupational exposure to pigs and pork is worldwide the most important risk factor for *S. suis* infections (Fittipaldi et al. 2012). Mostly, human infections appear as sporadic cases in persons exposed to pigs or pig products, with an incidence of 3/100,000 (almost 1,500 times higher than among persons not involved in pig industry) (Arends and Zanen 1988). It seems that contamination is through direct contact with infected pigs or meat products and infection via conjunctiva or skin lesions (Arends and Zanen 1988). In addition, human infections have been associated with contact with wild pigs (Rosenkranz et al 2003).

Zoonotic infections have been reported mainly in countries with intensive swine production. In a study by Smith et al. (2008), 73 swine-exposed and 67 non-swine-exposed US adults were tested for antibodies to *S. suis* serotype 2. Results suggested that human infection with *S. suis* occurs more frequently than currently documented. Furthermore, *S. suis* pathotypes isolated from human infections were frequently detected in pigs, and recent outbreaks of porcine infections paralleled those in humans. Even though reported numbers of human infections are relatively low, there is a potential risk that *S. suis* may constitute a more important public health problem than currently recognised. This is underlined by the outbreak in China (in 2005), in which totally unexpected severe clinical presentations of streptococcal toxic shock-like syndrome due to *S. suis* infection was observed in infected individuals (Yu et al. 2006). The *S. suis*-induced toxic shock was associated with high mortality rates. This new outcome of *S. suis* infection in humans might reflect the evolutionary emergence of more virulent strains. Accordingly, the outbreak in China was due to the emergence of a serotype 2 strain that contained a pathogenicity island designated 98 K. Thus, the potential that *S. suis* may suddenly emerge as disease threat by acquiring new capacities for establishing infection, e.g. by altering the human immune response, should not be underestimated (Yu et al. 2006; Gottschalk et al. 2010; Holden et al. 2009).

Outbreaks of human infections such as described mainly occur in low-income countries with intensive pig production, which is largely due to very close contact of humans to pigs and little awareness of the disease within the population at risk. In countries with increasingly intensive pig farming, like China, Thailand or

Vietnam, the risk for humans of acquiring *S. suis* infection is unknown, since it is not a notifiable disease and has been largely neglected by routine laboratory diagnostics. On the other hand, the two largest published case series of human *S. suis* infections are from these regions and account for more than 50 % of all reported cases (Takeuchi et al. 2012; Wertheim et al. 2009). Notably, in Vietnam, *S. suis* is the most important cause of bacterial meningitis in adults (Mai et al. 2008). This is related to eating "high risk" dishes, such as undercooked blood and intestine (Nghia et al. 2008) suggesting that oral infection is an additional infection route to be considered. Therefore, zoonotic infections by *S. suis* are considered a significant, yet unrecognised burden in large parts of Southeast Asia. The urgent need for research on this neglected zoonotic pathogen is underlined by the emergence of strains which are highly virulent for humans and by the spread of antibiotic resistance within the *S. suis* population (Palmieri et al. 2011).

5.3 Virulence and Pathogenesis

Various virulence or virulence-associated factors of *S. suis* serotype 2 have been identified in the last years, among which the capsule is the only proven essential virulence factor protecting the pathogen against phagocytosis (Smith et al. 1999). Some other factors have been shown to contribute to survival in the host and virulence in experimental infections of mice and piglets, respectively. Recently, several reviews have been published on this topic, e.g. by Baums and Valentin-Weigand (2009) and Fittipaldi et al. (2012).

A number of surface associated and secreted proteins of *S. suis* serotype 2 exhibit the same or very similar functions as homologous factors of other pathogenic streptococci. Important examples are peptidoglycan polysaccharide deacetylase, opacity factor of *S. suis*, fibronectin- and fibrinogen-binding protein of *S. suis*, enolase and suilysin (Baums et al. 2006; de Greeff et al. 2002; Esgleas et al. 2008; Fittipaldi et al. 2008a; Jacobs et al. 1994). On the other hand, surface associated or secreted factor with unique functions for *S. suis* have not yet been described. Furthermore, though many functional assays were carried out with cells of porcine origin, clear evidence for functional adaptation to pigs as the main host is lacking for *S. suis*. Most recently, we have identified a porcine IGM specific protease of *S. suis* which might well represent such a functional adaptation mechanism (Seele et al., manuscript in revision).

The molecular mechanisms of pathogenesis of *S. suis* infections are only partially understood. Most studies have addressed *S. suis* meningitis in mouse and pig models. Major steps in pathogenesis resemble those of other invasive streptococcal infections, such as adherence to and colonisation of mucosal surface(s), invasion into deeper tissue and translocation in the bloodstream. A hallmark of *S. suis* pathogenicity is its ability to disseminate in the blood circulation and to maintain a bacteraemia for certain time. This is considered to be crucial to cause meningitis. Thus, major mechanisms in pathogenesis of *S. suis* infections are those involved in

(i) invasion of *S. suis* through the epithelial cell barriers, (ii) evasion of killing by complement and phagocytosis and (iii) invasion into the cerebrospinal fluid (CSF) or other target sites.

Bacterial factors, such as the FN and fibrinogen binding protein (FBPS) (de Greeff et al. 2002) or the cell wall component lipoteichonic acid (LTA) mediate adherence of bacteria to target cells for initial colonisation (Fittipaldi et al. 2008b; Vanier et al. 2007). Another bacterial mechanism involved in colonisation might be the formation of a biofilm which probably enhances bacterial resistance to innate and adaptive host defence mechanisms and treatment with antibiotics (Bonifait et al. 2008). To get access into deeper tissues bacteria might invade the respiratory epithelium either intra- or intercellularly. Suilysin, the haemolysin of *S. suis*, is discussed to play a role in interaction of *S. suis* with epithelial cells and disruption of these cells due to its cytolytic function (reviewed by Fittipaldi et al. (2012). Furthermore, the capsule is assumed to be involved in host-epithelial cell interaction. Since its main function is protection against phagocytosis after entering the bloodstream (Benga et al. 2008; Fittipaldi et al. 2012; Chabot-Roy et al. 2006; Charland et al. 1998; Segura and Gottschalk 2002), it has been proposed that the capsule is downregulated during colonisation of the mucosal epithelium to allow adherence and invasion of the bacterium to overcome this first barrier (Gottschalk and Segura 2000; Okamoto et al. 2004; Willenborg et al. 2011). Accordingly, unencapsulated *S. suis* strains showed higher adhesion and invasion rates, indicating a negative correlation between encapsulation and interaction with host cells (Benga et al. 2004; Gottschalk et al. 1991). A possible explanation for this phenotype is the masking effect of the capsule (Vanier et al. 2007; Lalonde et al. 2000; Tenenbaum et al. 2009).

A topic which has not yet received much attention in research on *S. suis* pathogenicity is the metabolic adaptation of the pathogen and its relation to virulence gene regulation in different host niches. During infection, *S. suis* encounters various (stress) conditions, e. g. low pH or low availability of nutrients and oxygen. At present very little is known about the mechanisms of streptococcal survival in the host under such conditions. A recently identified catabolic enzyme system, the Arginine Deiminase System (ADS), may play an important role in adaptation to low pH, such as in host cell phagolysosomes (Benga et al. 2004; Fulde et al. 2011; Gruening et al. 2006; Winterhoff et al. 2002). The ADS per se is a secondary enzymatic system catabolising arginine, and concomitantly produces citrulline, ATP, CO_2 and ammonia. The system is strictly regulated by a variety of different environmental stimuli, e.g. carbon starvation, oxygen content and substrate availability. It is plausible to assume that *S. suis* is able to alkalize its environment by synthesis of ammonia during arginine catabolism, and thereby protects itself against acidic damage. This mechanism may allow *S. suis* to reside in acidified phagolysosomes, thus representing an advantage in establishing invasive infections as proposed recently (Benga et al. 2004; Fulde et al. 2011; Gruening et al. 2006). Further hints towards a link between metabolic adaptation and regulation of virulence traits have been found in a recent paper on the role of

glucose and the regulator catabolite control protein A (CcpA) in capsule expression and virulence of *S. suis* (Willenborg et al. 2011).

A major first line of host defense against *S. suis* is phagocytic killing by neutrophils. Accordingly, infiltrations with large number of neutrophils are typically found in respective lesions, such as in meningitis. In the absence of opsonising antibodies virulent *S. suis* serotype 2 strains are not efficiently killed by porcine neutrophils, suggesting that the pathogen has evolved strategies to evade intra- and extracellular antimicrobial activity of neutrophils. Several virulence-associated factors have been identified, among which the most intensively studies is the bacterial capsule (see above). Other factors possibly involved include D-alanylation of lipoteichoic acid and suilysin, as reviewed recently by Baums and Valentin-Weigand (2009) and Fittipaldi et al. (2012). Future studies will have to dissect the yet unknown molecular steps involved in *S. suis* interactions with neutrophils.

For induction of meningitis *S. suis* has to reach the CSF. It has been shown that *S. suis* adheres to and invades into brain microvascular endothelial cells (BMEC) and porcine choroid plexus epithelial cells (PCPEC), the main components of the blood–brain barrier (BBB) (Tenenbaum et al. 2005, 2009; Benga et al. 2005; Charland et al. 2000; Vanier et al. 2004). An increased tight junction permeability and loss of barrier function was proposed to be associated with cytotoxic effects of suilysin (Charland et al. 2000; Vanier et al. 2004). Furthermore, *S. suis* can stimulate the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-8 and monocyte chemotactic protein-1 (MCP-1) by BMEC, which in turn may alter the BBB permeability (Vadeboncoeur et al. 2003). However, Tenenbaum et al. (2009) described the entry of *S. suis* into the CNS as a transcellular translocation without destruction of CPEC lining of the BBB (Tenenbaum et al. 2009).

A hallmark of pathogenicity (and immune control) of *S. suis* is its ability to induce inflammation, which is characterised by massive infiltrations of neutrophils into lesions (see above). A number of *S. suis* components, both cell-wall associated and secreted factors, have been shown to induce release of pro-inflammatory cytokines which in turn may either help to control acute infection or contribute to immunopathology (Segura et al. 1999, 2002, 2006). The interaction of *S. suis* with innate and adaptive immune mechanisms of the host is crucial for both pathogenesis and immune control of *S. suis* infections. Nevertheless, this topic is out of the scope of this article, and thus will not be addressed in further detail here.

Taken together, at present, we still have only a very scattered picture of the molecular host–pathogen interactions that contribute to pathogenesis of *S. suis* infections. Furthermore, it is unclear which of the virulence-associated factors and mechanisms identified in mouse and pig play similar roles in zoonotic infections. The experience during the Chinese outbreak 2005 (see above) has shown that highly virulent strains/clones can evolve that are equally pathogenic for pigs and humans. This emphasizes the urgent need for future studies on the evolution, epidemiology and pathogenicity of such highly virulent strains.

6 Conclusions

For a long time, streptococcal species other than GAS and *S. pneumoniae* were considered solely as animal specific pathogens. Zoonotic infections were neglected, since they were assumed to occur only very rarely and accidentally in human individuals. The emergence of two large severe outbreaks in human population caused by *S. suis* and *S. zooepidemicus*, respectively, increased awareness of public health authorities. A rapidly growing human population concomitant with an increased demand for food as well as the increase in companion animals with very close daily contact within families will most likely foster evolution of zoonotic streptococci. Thus, the future task will be to develop strategies against zoonotic streptococcosis by improving diagnosis and control of infections in pets, livestock and humans. The poor current knowledge of the evolution of human pathogenic strains and of the mechanisms of host-specific adaptation urgently demands in-depth information about the possible modes of transmission, emergence of antibiotic resistance and prevalence of zoonotic streptococci. This requires that experts from different geographical regions and scientific backgrounds combine their efforts in a synergistic matter to follow the one medicine concept also in research on zoonotic streptococci.

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