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Streptococcus canis, the underdog of the genus

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ABSTRACT

Streptococcus canis is a multi-host pathogen that causes disease of varying severity in a wide range of mammals, including humans. Dogs and cats appear to be the primary hosts and may play a role in transmitting infection to humans. The broader epidemiology of *S. canis*, however, is still poorly understood, as are its virulence mechanisms, antimicrobial resistance (AMR) and population structure. In this review we gather existing knowledge on *S. canis*, describing its epidemiology in animals and humans and present information on virulence factors, classification schemes and AMR prevalence. We describe the main ecological niches of *S. canis* in companion animals, discuss potential risk factors for infection in humans and propose a multi-host transmission cycle. We show that current knowledge on *S. canis* virulence determinants is limited and sometimes contradictory. We illustrate the different typing systems proposed to classify *S. canis*. We also report the range of known AMR phenotypes and the emergence of new mechanisms of resistance. Finally, we discuss the zoonotic potential of *S. canis*, highlighting the need for further evidence in this area. *Streptococcus canis* may be regarded as a neglected pathogen of one health concern. Further research is needed for its better understanding and effective control.

1. Introduction

The name *Streptococcus canis* was first used in 1937 to identify streptococci implicated in infection in dogs (Stafseth et al., 1937). Only in the late 1980s was the name formally ascribed to a bacterial species with defined phenotypic characteristics (Devriese et al., 1986), when it was described as Gram positive, β-haemolytic, Lancefield group G pyogenic coccus that could infect dogs and cattle (Devriese et al., 1986). Numerous biochemical and physiological traits of the newly identified species were reported (Devriese et al., 1986).

Streptococcus canis was initially thought to be solely a canine and bovine pathogen (Devriese et al., 1986) but has since been isolated from a range of mammals including cats, rats, rabbits, minks, foxes, Japanese racoon dogs, kinkajous, seals, sea lions, otters, badgers and humans (Richards et al., 2012; Numberger et al., 2021). It might be possible that *S. canis* is able to cause disease in all the above mentioned species, making it one of the streptococcal pathogens with the widest host range (Fulde and Valentin-Weigand, 2012). Despite its broad host tropism, *S. canis* has not been given the same attention as other streptococci (Fulde and Valentin-Weigand, 2012) and this is probably due to the limited number of confirmed cases of infection in humans (Lam et al., 2007). Since most streptococcal isolates from human samples are not identified to the species level, however, the true disease burden of *S. canis* disease in humans is difficult to estimate (Lam et al., 2007).

Knowledge around *S. canis* epidemiology in human and veterinary medicine is based on a restricted number of studies, summarised in Table 1. It remains unclear how and to what extent inter-species transmission occurs, as well as which risk factors predispose humans to disease. While the zoonotic potential of *S. canis* is now widely accepted, the scientific evidence remains limited. Virulence mechanisms, population structure and antimicrobial resistance (AMR) determinants are also poorly characterised in *S. canis*. This review aims to gather all available knowledge on *S. canis* to contextualise some of the unanswered questions surrounding this multi-host pathogen. As the tiles of a mosaic form a bigger picture only when put together in an ordered pattern, we trust this review will offer a partial yet clearer picture of *S. canis*, presenting the topic in a critical and accessible way.

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2. Epidemiology and clinical presentations of *S. canis* infection

2.1. Companion animals

In dogs and cats, *S. canis* is regarded as an opportunistic pathogen that can colonise the skin and mucosae of asymptomatic individuals (Lysková et al., 2007a; Timoney et al., 2017). When implicated in disease, *S. canis* is mainly associated with skin infections (Devriese et al., 1986), with the most common isolation sites being the oral and nasal cavities, the external ear canal, rectum and the genital mucosae (Fig. 1) (Devriese et al., 1992; Lysková et al., 2007a). However, infection in dogs and cats may sometimes result in severe clinical syndromes such as arthritis (Iglauer et al., 1991), myocarditis (Matsuu et al., 2007), necrotising fasciitis, pneumonia, meningitis, sepsis and streptococcal toxic shock syndrome (STSS) (Prescott et al., 1995; Pesavento et al., 2007).

In a 2007 study, 6.5% of healthy dogs (n = 35/539) and 5.9% of healthy cats (n = 10/169) tested positive for carriage of *S. canis*, which was isolated principally from the rectum of both species, the praeputium of dogs and the oral cavity of cats (Lysková et al., 2007a). In the same study, it was isolated from various body sites in 22.2% of dogs.

(n = 39/176) and 4.8% of cats (n = 2/42) with ongoing infections. Among clinically ill dogs, it was frequently isolated from those with signs of gastrointestinal disease, urogenital infection, otitis externa and rhinitis. In clinically ill cats, *S. canis* was isolated from just two of 42 specimens. However, since co-infection with other pathogens was not considered, it is impossible to determine whether *S. canis* was responsible for the clinical signs reported. As sampling was skewed towards canine samples and external ear canal specimens (Lysková et al., 2007a), this may have contributed to biases in the results reported.

Two other studies report a high prevalence of *S. canis*-associated otitis externa in pets. In one, *S. canis* was shown to be the third most common microorganism isolated from dogs with otitis externa (29.9% of the cases) (Lysková et al., 2007b), being found significantly more frequently in the ear canals of dogs with otitis externa than from healthy dogs ($P < 0.001$) (Lysková et al., 2007b). Another study revealed a prevalence of 20.83% from the ears of cats with otitis externa, although the sample size was very small (n = 24) (Dégi and Cristina, 2011).

In a work by Lamm et al., the prevalence of streptococcal isolation from all canine specimens submitted to a diagnostic laboratory was 20.5% (n = 499/2432), of which 22.4% (n = 106/499) were confirmed as *S. canis* (Lamm et al., 2010). A high proportion of the sampled dogs that tested positive for *Streptococcus* spp. (n = 267) showed co-infection with other pathogens, meaning that causative role of streptococci in those disease cases could not be established. The authors found that *S. canis* was the most common streptococcal species isolated from infection sites in dogs and that *S. canis* infection can be associated with dermatitis, septicaemia, placentitis and pneumonia (Lamm et al., 2010).

A more recent work by Guerrero et al. suggested an association between vaginal carriage of β-haemolytic streptococci and neonatal death in dogs (Guerrero et al., 2018). No significant difference in the frequency of vaginal isolation of *S. canis*, however, was found between dogs with healthy litters and dogs experiencing neonatal losses (Guerrero et al., 2018). The role of *S. canis* vaginal colonisation in canine fertility is still unclear and further studies are required.

Streptococcus canis outbreaks have also been reported in feline colonies and shelters. An outbreak of contagious arthritis due to *S. canis* in a cat breeding colony over a six-month period has been described (Iglauer et al., 1991). A high level of inbreeding among colony cats was suggested to have contributed to susceptibility to infection (Iglauer et al., 1991), although outbreaks have also been detected among shelter cats. Three outbreaks of *S. canis* infection in cat shelters were reported (Pesavento et al., 2007), two of which were characterised by skin ulceration, sinusitis and meningitis while a third outbreak was associated with necrotising fasciitis and sudden death (Pesavento et al., 2007).

Table 2 provides a summary of all case reports referenced in this subsection.

2.2. Production animals

In cattle, *S. canis* is a recognised cause of mastitis (Chaffer et al., 2005; Hassan et al., 2005; Tikofsky and Zadoks, 2005). Although the prevalence of Group G *Streptococcus* mastitis is thought to be low (Wilson et al., 1997), *S. canis* mastitis outbreaks have been reported, with herd prevalence as high as 38% (Chaffer et al., 2005). In a case of *S. canis* sub-clinical mastitis outbreak that affected 22% (n = 11/49) of a dairy herd, pulse field gel electrophoresis (PGFE) genotyping revealed the isolates were either identical or very closely related, suggesting a clonal spread of *S. canis* that may be explained by cow-to-cow transmission (Hassan et al., 2005). A study by Tikofsky and Zadoks described another mastitis outbreak that affected 13% (n = 12/90) of lactating cows in a dairy herd (Tikofsky and Zadoks, 2005). The origin of the outbreak was thought to be a cat with chronic sinusitis due to *S. canis* infection. The cat, whose infection predated the outbreak, lived in close contact with the herd. All bovine and feline *S. canis* isolates showed the same ribotype pattern, supporting the hypothesis that the cat was the outbreak source and that infection subsequently spread from cow to cow (Tikofsky and Zadoks, 2005). A similar case of an outbreak of bovine sub-clinical *S. canis* mastitis associated with a cat was reported by Eibl et al. (Eibl et al., 2021). In this instance, strains of the same multilocus sequence type (MLST) were isolated from nine cows and one cat living in contact with the herd, but no directionality of transmission could be determined

Table 1
Summary of published epidemiological studies on the burden of *S. canis* infection in different host species.

Reference	Population sampled	Site of isolation	Prevalence of isolation	Clinical manifestations	Biases
Lysková et al. (2007a)	Dogs and cats with ongoing infection	Various body sites	22.2 % in dogs (39/176) and 4.8 % in cats (2/42)	Otitis externa, skin infections, GIT infections, urogenital infections, rhinitis	Sampling bias in favour of canine and external ear canal specimens. Potentially undetected coinfections.
Lysková et al. (2007b)	Dogs with otitis externa	External ear canal	29.9 % (29/97)	Otitis externa	Frequent coinfections with other pathogens
Galpérine et al. (2007)	People, patients of the University Hospital of Bordeaux, France	Various body sites	1.3 % (80/6404) of all streptococcal isolations	Skin and soft tissue infections, bacteraemia, urinary infections, osteoarticular infections, pneumonia	Frequent coinfections with other pathogens
Lamm et al. (2010)	Dogs with ongoing infection	Various body sites	4.4 % (106/2432)	Dermatitis, septicaemia, pneumonia, placentitis	Frequent coinfections with other pathogens
Dégi et al., 2011	Cats with otitis externa	External ear canal	20.8 % (5/24)	Otitis externa	Small sample size
Timoney et al. (2017)	Young healthy cats	Upper respiratory tract and reproductive tract	14.1 % (25/177)	Asymptomatic carriage	Sampled cats all attended a small animal clinic for elective procedures
Guerrero et al. (2018)	Dogs who had delivered litters in which neonatal death occurred	Vagina	91 % (21/23)	Neonatal death	Small sample size

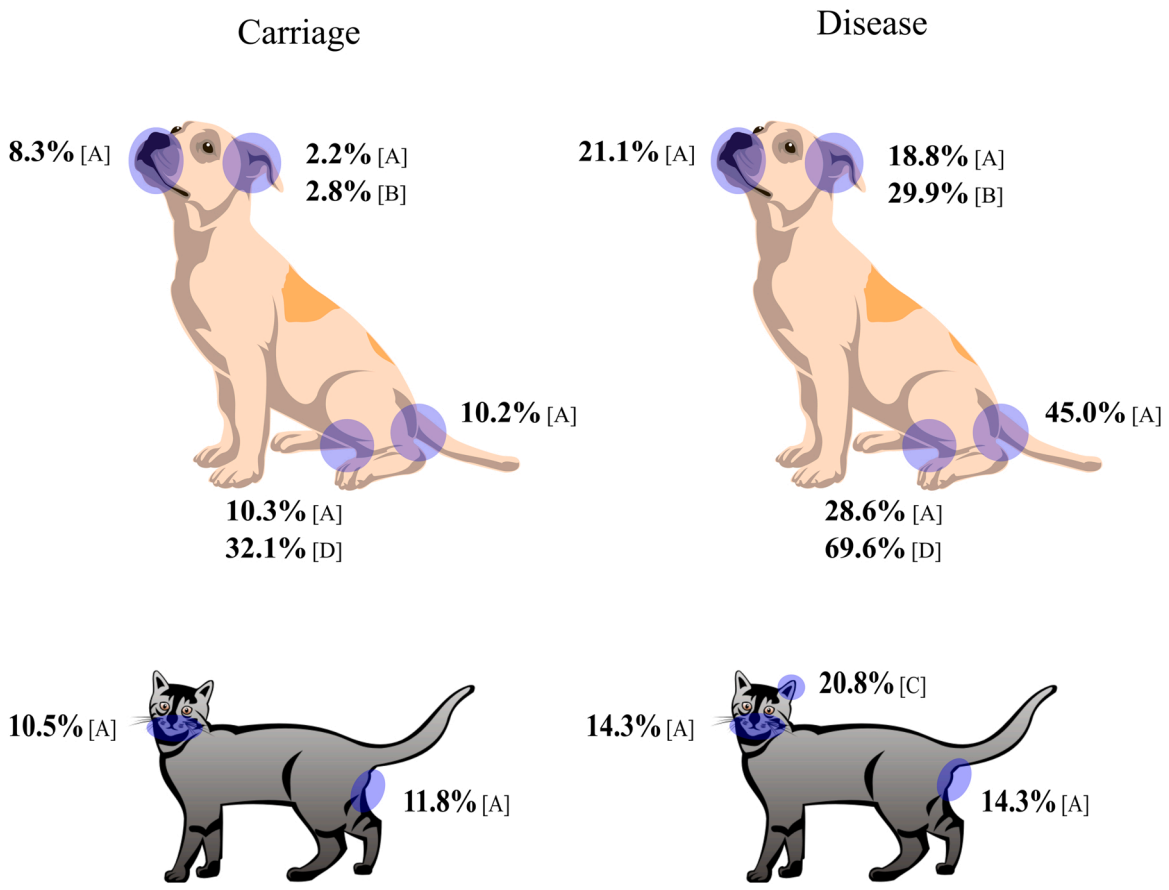

Fig. 1. Main isolation sites of *S. canis* in healthy and diseased dogs and cats. Prevalence of isolation in relevant body sites is reported, together with bibliographic references (A: Lysková et al., 2007a; B: Lysková et al., 2007b; C: Guerrero et al., 2018; D: Dégi et al., 2011). In dogs, *S. canis* is more frequently isolated from the oral and nasal cavities, the ear canal, the rectum and the genital mucosa. In cats, it is more commonly isolated from the oral and nasal cavities, the ear canal and the rectum.

Table 2
Case reports of *S. canis* infection in companion animals reviewed for this study.

Reference	Host species	Number of cases	Clinical manifestations	Suggested predisposing factors
Iglauer et al. (1991)	Cat	6	Arthritis	Possible genetic predisposition due to high inbreeding
Prescott et al. (1995)	Dog	3	Necrotising fasciitis	Trauma
Matsuu et al. (2007)	Cat	1	Myocarditis	Acquired mitral stenosis associated with congenital malformation of the mitral valve complex
Pesavento et al. (2007)	Cat	> 150 (3 outbreaks)	Skin ulceration, sinusitis, meningitis, necrotising fasciitis	Indirect contact with dogs and concomitant upper respiratory tract infections

(Eibl et al., 2021). These reports highlight the potential spread of infectious agents from pets to cattle, which should be considered when assessing biosecurity measures in dairy farms. Both reports, however, rely on low discrimination methods to assess the genetic relatedness of bovine and feline isolates (Salipante et al., 2015; Tsang et al., 2017), so should not be considered as conclusive evidence of cats being the source of infection in outbreak scenarios. Importantly, *S. canis* mastitis outbreaks have been documented in dairy herds that were not in contact with dogs and cats, suggesting alternative routes of herd infection may occur (Chaffer et al., 2005).

Król et al. demonstrated the contagious potential of *S. canis* among cows (Król et al., 2015). Relatedness of the outbreak isolates was confirmed by random amplified polymorphic DNA (RAPD) analysis and PFGE. The authors also showed that *S. canis* was capable of causing long-term sub-clinical mastitis that persisted for up to 14 months (Król et al., 2015). A summary of *S. canis* mastitis case reports in dairy cattle is shown in Table 3.

Table 3
Case reports of *S. canis* infection in dairy cattle with subclinical mastitis.

Reference	Number of cases	Herd size	Proportion of herd affected	Suggested risk factors
Chaffer et al. (2005)	26	69	38%	Not mentioned
Hassan et al. (2005)	11	49	22%	Not mentioned
Tikofsky and Zadoks (2005)	46 Group G *Streptococcus* cases. 12 confirmed *S. canis* cases	90	51% Group G *Streptococcus*. 13% confirmed *S. canis*	Direct contact with an infected cat
Król et al. (2015)	17	76	22%	Not mentioned
Eibl et al. (2021)	9	59	15%	Direct contact with an infected cat

2.3. Role in human health

Streptococcus canis appears to be rarely isolated from humans, although the actual infection burden is hard to estimate (Lam et al., 2007). It shares the same Lancefield classification (group G) with other β-haemolytic streptococci, such as *S. dysgalactiae* and *S. anginosus*, recognised to infect humans. The determination of Lancefield antigenic group is often sufficient for diagnostic and public health purposes and for this reason the prevalence of *S. canis* infection is likely to be underestimated (Lam et al., 2007).

In a retrospective study carried out at the University Hospital of Bordeaux from 1997 to 2002, *S. canis* was confirmed in 1% (n = 80/6404) of all *Streptococcus*-positive samples submitted for culture (Galpérine et al., 2007). Clinical and microbiological data available for a subset of cases (n = 54) revealed that *S. canis* was mainly involved in skin and soft tissue infection (n = 35), and occasionally implicated in bacteraemia (n = 5), urinary tract infection (n = 3), osteoarticular infection (n = 2), pneumonia (n = 1) and asymptomatic carriage (n = 8). Toxic shock was noted in two patients. The majority of the cases for which clinical data was available were confirmed as community acquired (n = 39) and mortality attributable to *S. canis* infection was 3.7% (n = 2/54). Most patients had comorbidities that predated infection and the majority of *S. canis*-positive samples for which data were available (n = 42/54) contained additional bacterial pathogens (Galpérine et al., 2007). It is, therefore, impossible to determine to what extent the presence of *S. canis* contributed to pathology. Fig. 2 illustrates the common sites of *S. canis* isolation in humans (Galpérine et al., 2007).

Sporadic cases of human infection were described in the literature as case reports, with clinical manifestations such as purulent skin infection (Bert and Lambert-Zechovsky, 1997; Whatmore et al., 2001; Lam et al., 2007), cellulitis (Takeda et al., 2001; Lam et al., 2007), septicaemia (Bert and Lambert-Zechovsky, 1997; Takeda et al., 2001; Whatmore et al., 2001; Ohtaki et al., 2013; Taniyama et al., 2017), endocarditis (Amsallem et al., 2014; Lacave et al., 2016; Mališová et al., 2019), arthritis and bone infection (Tarabichi et al., 2018; McGuire et al., 2021). The majority of case reports of *S. canis* infection involve patients above 60 years of age, with various comorbidities or previous trauma.

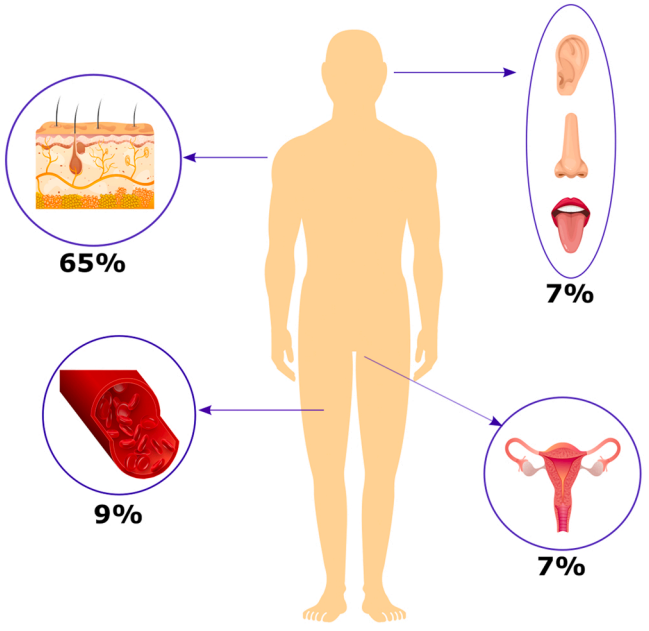

Fig. 2. Sites of *S. canis* isolation in humans (Galpérine et al., 2007). This bacterium was isolated principally from the cutaneous tissue, bloodstream, ear-nose-throat (ENT) sphere and vaginal swabs. Percentages refer to the frequency of isolation from the total number of *S. canis*-positive samples.

Notably, a proportion of cases describe prior interactions with dogs (Takeda et al., 2001; Lam et al., 2007; Ohtaki et al., 2013; Amsallem et al., 2014; Lacave et al., 2016; Taniyama et al., 2017; Tarabichi et al., 2018; Mališová et al., 2019; McGuire et al., 2021), in particular dog bites or scratches (Takeda et al., 2001; Taniyama et al., 2017; Tarabichi et al., 2018). However, more direct evidence to support the hypothesis that dogs may be a source of *S. canis* zoonotic infection was presented in only one report, which described a woman developing *S. canis* septicaemia two weeks after a dog bite (Takeda et al., 2001). *Streptococcus canis* was also isolated from the dog's oral cavity and both human and canine strains shared the same PFGE pattern, suggesting a canine-to-human transmission event (Takeda et al., 2001). Although generally reliable, PFGE results are occasionally discordant with higher resolution methods such as whole genome sequencing (Salipante et al., 2015). Further evidence is required to clarify the role dogs play in the transmission of *S. canis* to humans.

The reviewed case reports of human *S. canis*-associated disease are summarised in Table 4.

Based on the epidemiological studies and clinical reports available, a transmission cycle for *S. canis* including the environment, human, canine, feline and bovine hosts is hypothesised and is visually represented in Fig. 3.

2.4. Genotyping of S. canis

The MLST scheme developed for *S. canis* is based on allelic variation of seven housekeeping genes, namely *gki*, *gtr*, *murI*, *mutS*, *recP*, *xpt* and *yqiZ* (Pinho et al., 2013). As alluded to in the previous section, there is no evidence that links STs to specific clinical disease manifestation. Only a single study suggested an association between ST-4, 8, 11, 12, 13, 14, 17, 27 and 38, all belonging to clonal complex 13 (CC-13), and canine ulcerative keratitis (Enache et al., 2020) but this is based on a small number of cases and is not statistically supported. With regards to STs and species-specificity, it was shown that isolates sharing the same ST may be isolated from multiple species, including humans, companion animals and wildlife (Pinho et al., 2013).

A genotyping system based on allelic diversity of the *scm* gene has been proposed (Pinho et al., 2019). According to this scheme, 41 allelic variants are grouped into 12 SCM types, forming two major groups. Group I SCM variants (SCM types 1–7) have an IgG binding domain and are most commonly isolated from diseased patients. Group II SCM proteins (SCM type 8–12) lack this domain, which is thought to have anti-phagocytic activity, and the role of group II SCM in pathogenesis is not yet fully understood. MLST has been shown to be a good predictor of SCM type, although the converse is not true (Pinho et al., 2019).

Fukushima et al. suggested an alternative SCM-based typing scheme, which currently encompasses 15 types (Fukushima et al., 2018, 2020a). Based on this scheme, SCM types 1–9 are classified as group I (corresponding to group I in the scheme by Pinho et al.) and types 10–15 are classified as group II (group II also for Pinho et al.). The author of this scheme suggests that SCM group I strains are more commonly isolated in Japan (Fukushima et al., 2020a). As with the scheme of Pinho et al., MLST was shown to be a good predictor of SCM type, although, again, the opposite was not the case. Notably, a significantly higher prevalence of macrolide/lincosamide genetic resistance determinants and fluoroquinolone-resistant phenotype was detected among group I compared to group II strains (Fukushima et al., 2020a).

Recently, an association was found between high-frequency CIA and Fukushima SCM types 10 and 11, as well as high-frequency CIA and STs 21 and 41 (Yoshida et al., 2021). It should be noted, however, that a limited number of isolates were tested (n = 40) and therefore the resulting low frequency or absence of some SCM types and STs might have been a source of bias. Moreover, the threshold value used to separate low-frequency from high-frequency CIA isolates was arbitrarily chosen with the CIA value for almost one fifth of the isolates tested was just above or just below the threshold value (Yoshida et al., 2021). It

Table 4
Reports of *S. canis* infection in humans.

Reference	Host species	Number of cases	Clinical manifestations	Suggested predisposing factors
Bert and Lambert-Zechovsky (1997)	Human	1	Septicemia	Comorbidities, direct contact with a dog, > 60 years of age
Takeda et al. (2001)	Human	1	Cellulitis and septicemia	Comorbidities, dog bite, > 60 years of age
Whatmore et al. (2001)	Human	2	Wound infection (first case) and bacteremia (second case)	Not mentioned for the first case, comorbidities and > 60 years of age for the second case
Ohtaki et al. (2013);	Human	1	Septicemia	Trauma, direct contact with a dog, > 60 years of age
Amsallem et al. (2014)	Human	1	Endocarditis	Comorbidities, direct contact with a dog, > 60 years of age
Lacave et al. (2016)	Human	1	Endocarditis	Comorbidities, direct contact with a dog, > 60 years of age
Taniyama et al. (2017)	Human	1	Cellulitis and bacteremia	Comorbidities, dog bite, > 60 years of age
Tarabichi et al. (2018)	Human	1	Periprostetic joint infection and septicemia	Knee prostesis, dog scratch, > 60 years of age
Mališová et al. (2019)	Human	1	Endocarditis	Comorbidities, direct contact with a dog, > 60 years of age
McGuire etal (2021)	Human	1	Periprostetic joint infection	Hip surgery, direct contact with a dog, > 60 years of age

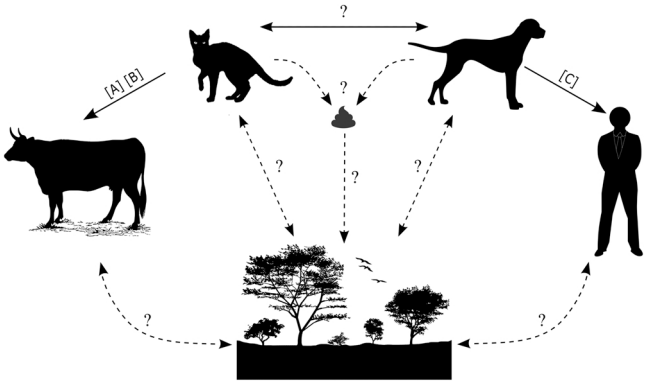

Fig. 3. Schematic representation of a possible transmission cycle of S. canis. The main host species of S. canis appear to be dogs and cats. Dogs and cats have been reported as a potential source of infection for humans and cattle, respectively (A: Tikofsky & Zadoks 2005; B: Eibl et al., 2021; C: Takeda et al., 2001). Streptococcus canis can be frequently isolated from the rectum of dogs and cats, implying that faecal contamination of the environment, although never demonstrated to our knowledge, may occur. Environmental contamination may be a source of infection not only for dogs and cats but also for other susceptible species, namely wildlife and humans. In the diagram, S. canis transmission is represented through solid arrows (direct route) and dashed arrows (indirect route). Question marks are added next to transmission routes that have not been proven yet.

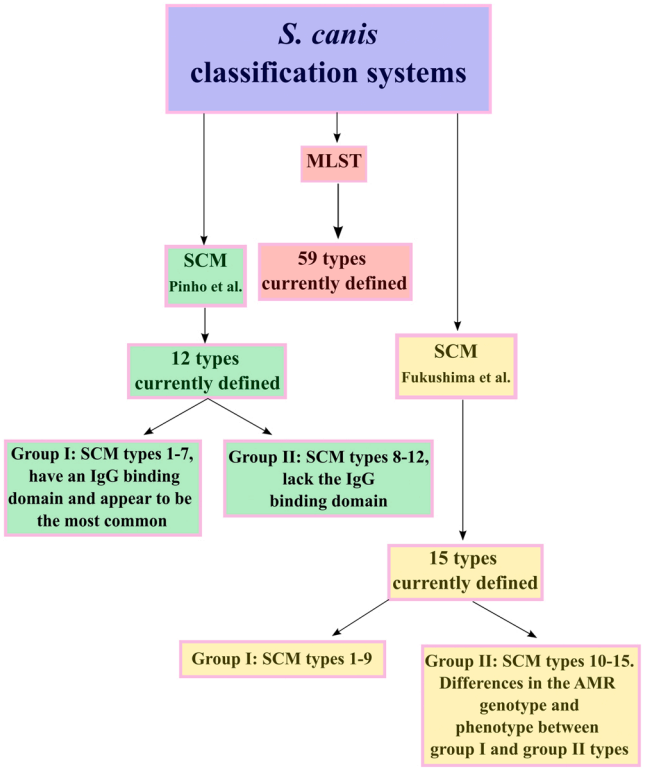

Fig. 4. Virulence factors of *S. canis* and their role in pathogenicity. Although the expression and function of SCM, surface fibrillae and FBP is supported by experimental evidence, the expression and activity of neuroaminidase B, SLO, SLS and CAMP factor is inferred from knowledge of other pathogenic streptococci. Tissue adhesion is understood to be facilitated by SCM, surface fibrillae and, potentially, neuroaminidase B. SCM also prevents phagocytosis, a process which may also be impeded by SLO, SLS and CAMP factor. The third main virulence activity of SCM appears to be tissue invasion mediated by plasminogen binding and activation. Tissue invasion may also be facilitated by SLO, SLS and CAMP factor, which are known to possess lytic activity towards leucocytes in other pathogenic streptococci. Finally, experimental evidence shows that FBP can trigger intracellular invasion of *S. canis*, facilitating bacterial survival.

remains uncertain, therefore, whether an association exists between CIA and specific strains of *S. canis*.

A third SCM-based classification scheme has been described by Timoney et al. 2017. Four SCM types were detected among *S. canis* isolates (n = 25) from healthy and diseased cats. SCM type 1 strains were most commonly derived from diseased cats, while SCM type 4 strains were almost exclusively isolated from healthy individuals. The authors concluded that type 1 strains were strongly associated with disease and that type 4 strains were avirulent in cats. However, type 1 strains were also isolated from healthy cats and one type 4 strain was implicated in a case of bacteraemia, suggesting both types can be associated with either clinical disease or asymptomatic carriage (Timoney et al., 2017).

Fig. 4 summarises the three main genotyping schemes proposed for *S. canis*.

2.5. Virulence mechanisms

The knowledge on pathogenesis and virulence mechanisms of *S. canis* is currently limited. This may be explained by the low prevalence of infection in humans and production animals together with the fact that it is broadly sensitive to commonly used antibiotics, which may contribute to it being given a low priority (Galpérine et al., 2007; Pinho et al., 2013). However, the health threat represented by *S. canis* should not be underestimated, particularly in light of the severe disease cases reported in humans and the documented acquisition of AMR (Takeda et al., 2001; Galpérine et al., 2007; Lam et al., 2007; Lacave et al., 2016; Tan et al., 2016; Fukushima et al., 2020b; McGuire et al., 2021). Potential virulence determinants of *S. canis* are summarized in Table 5.

The presence of sequences homologous to well-characterised *S. pyogenes* virulence genes was assessed in the genome of *S. canis*,

Table 5
Virulence traits investigated in *S. canis* in the literature.

Virulence traits	Evidence provided	Reference
Arginine deaminidase system (ADS)	Experimental evidence and bioinformatic analysis	Hitzmann et al. (2013)
Christine, Atkins and Munch-Peterson (CAMP) factor	Detection of homologous gene based on WGS bioinformatic analysis	Richards et al. (2012)
Intracellular invasion	Experimental evidence	Yoshida et al. (2021)
Neuroaminidase B	Detection of homologous gene based on WGS bioinformatic analysis	Richards et al. (2012)
Resistance to phagocytosis	Experimental evidence – hypothesised role of M protein	DeWinter et al. (1999)
Streptococcus canis M-like (SCM) protein	Detection of homologous gene based on Southern hybridisation	DeWinter et al. (1999)
	Detection of homologous gene based on WGS bioinformatic analysis	Richards et al. (2012)
	Experimental evidence - adherence and tissue invasion, plasminogen-mediated	Fulde at al., 2011a
	Experimental evidence - resistance to phagocytosis	Fulde et al. (2013)
	Experimental evidence - overall virulence activity questioned. SCM might facilitate adhesion and persistence in the vaginal environment and biofilm formation	Cornax et al. (2021)
Streptolysin O (SLO)	Detection of homologous gene based on Southern hybridisation	DeWinter et al. (1999)
	Detection of homologous gene based on WGS bioinformatic analysis	Richards et al. (2012)
Streptolysin S (SLS)	Detection of homologous gene based on WGS bioinformatic analysis	Richards et al. (2012)
Surface fibrillae	Direct observation through electron microscopy	DeWinter et al. (1999)

including 15 isolates from dogs diagnosed with STSS and/or necrotising fasciitis, by Southern hybridisation (DeWinter et al., 1999). Genes homologous to the *S. pyogenes slo* and *emm*, encoding streptolysin O and the M protein, respectively, were detected in the genome of the majority of isolates analysed. However, no matches were found to eight other *S. pyogenes* virulence genes (*speA*, *speB*, *speC*, *speF*, *scpA*, *hasA*, *ska* and *ssa*). Resistance to phagocytosis and presence of surface fibrillae were also observed as *S. canis* virulence characteristics (DeWinter et al., 1999).

More recently, genomics has been used to characterise virulence of *S. canis* with 34 candidate virulence genes detected (Richards et al., 2012). Most of these virulence genes constitute part of the *S. pyogenes* pangenome and have been implicated in tissue invasion. The carriage of *slo* and *emm* homologous genes, already described by De Winter et al. (DeWinter et al., 1999), was confirmed in *S. canis*. While an orthologue for *S. pyogenes* exotoxin streptolysin S (SLS) was identified, no genes encoding pyrogenic exotoxins (i.e. those responsible for *S. pyogenes*-associated toxic shock syndrome) were found, suggesting alternative mechanisms in the pathogenesis of *S. canis*. Some similarity with *S. agalactiae* and *S. pneumoniae* virulence genes, such as those encoding CAMP factor and neuroaminidase B, was also found in the *S. canis* genome analysed (Richards et al., 2012).

Components of the arginine deiminase system (ADS) have been characterised in *S. canis* genome, giving insights into a metabolic pathway that could have a role in colonisation and disease (Hitzmann et al., 2013). ADS, which is responsible for the catabolism of arginine and production of ATP, citrulline, ornithine, ammonia and carbon dioxide, has been shown to be involved in virulence of *Streptococcus suis* by increasing its tolerance to adverse environments (Fulde et al., 2011b). Three enzymes of the *S. canis* ADS are localised on the cell surface, with possible implications for its virulence, so further investigation is warranted (Hitzmann et al., 2013).

The ability of *S. canis* to invade host cells was recently demonstrated (Yoshida et al., 2021). In *S. pyogenes*, cell invasion ability (CIA) is mediated by surface proteins such as fibronectin-binding proteins (FBPs) (Walker et al., 2014). The presence of genes with homology to *S. pyogenes* FBPs in the genome of *S. canis* has been shown together with experimental evidence of CIA in human and animal *S. canis* isolates (Yoshida et al., 2021). All 43 isolates tested showed intracellular invasion, but CIA was highly variable. Due to the lack of required clinical data no link could be made between levels of CIA and disease severity (Yoshida et al., 2021) and the role of CIA in *S. canis* pathogenesis, thus, remains unknown.

The most extensively studied virulence factor of *S. canis* is the M-like protein SCM (Fulde et al., 2011a). Experimental evidence showed that the *S. canis* SCM protein binds to plasminogen of humans, pigs, goats, cats and dogs. Interaction with plasminogen facilitates bacterial adherence and tissue invasion, the latter occurring through fibrinogen and fibrin degradation (Fulde et al., 2011a). SCM was also shown to cooperate in plasminogen recruitment with another surface-expressed virulence factor, enolase, and to have anti-phagocytic activity (Fulde et al., 2013). The *scm* gene has been confirmed as universally present in the *S. canis* population, although with substantial allelic variation (Pinho et al., 2019). In particular, some *scm* variants lack the putative IgG binding domain which is thought to contribute to the anti-phagocytic activity of SCM (Bergmann et al., 2017; Pinho et al., 2019). Moreover, some *scm* alleles are associated with lower binding affinity to plasminogen than others (Fulde et al., 2013; Pinho et al., 2019).

Although according to some studies SCM appears to be linked to *S. canis* virulence (Fulde et al., 2011a, 2013), recent findings, based on comparisons between a wildtype strain and an SCM-deficient mutant, questioned the role of SCM in clinical infection (Cornax et al., 2021). The SCM-deficient mutant showed reduced ability to form biofilms compared to the wildtype, but haemolytic activity and survivability in the presence of aminising and oxidising agents were not impacted by the lack of *scm*. There was no effect on survival after exposure to canine macrophages, human neutrophils and human whole blood or the ability to induce an immune response through cytokine production from human monocytes. When tested in vivo, the wildtype strain and the mutant were equally virulent in mouse models of dermal and systemic infection. The SCM-deficient strain, however, showed reduced adhesion and persistence in a murine model of vaginal colonisation when compared to the wildtype, suggesting that SCM might confer fitness advantages in particular anatomical sites (Cornax et al., 2021). Overall, the role of SCM as a virulence factor in *S. canis* is unclear with recent evidence suggesting a marginal involvement in disease progression.

A correlation between molecular characteristics of bacterial strains and clinical outcome of infection has not yet been shown for *S. canis*. Evidence based on limited numbers of isolates from dogs with toxic shock syndrome and/or necrotising fasciitis suggested that there was no specific genotype associated with severe disease in dogs (DeWinter and Prescott, 1999). Another study, which included more isolates from dogs and cats also failed to demonstrate a connection (Kruger et al., 2010). Further studies, using larger sample sizes and high-resolution genotyping are required to clarify the association between molecular characteristics of *S. canis* strains and clinical disease.

A visual summary of *S. canis* virulence factors is provided in Fig. 5.

2.6. Antimicrobial susceptibility

Streptococcus canis infections are successfully treated with ampicillin, amoxicillin and clavulanic acid or vancomycin in human medicine and amoxicillin and clavulanic acid or penicillin in veterinary medicine (Takeda et al., 2001; Tikofsky and Zadoks, 2005; Lam et al., 2007;

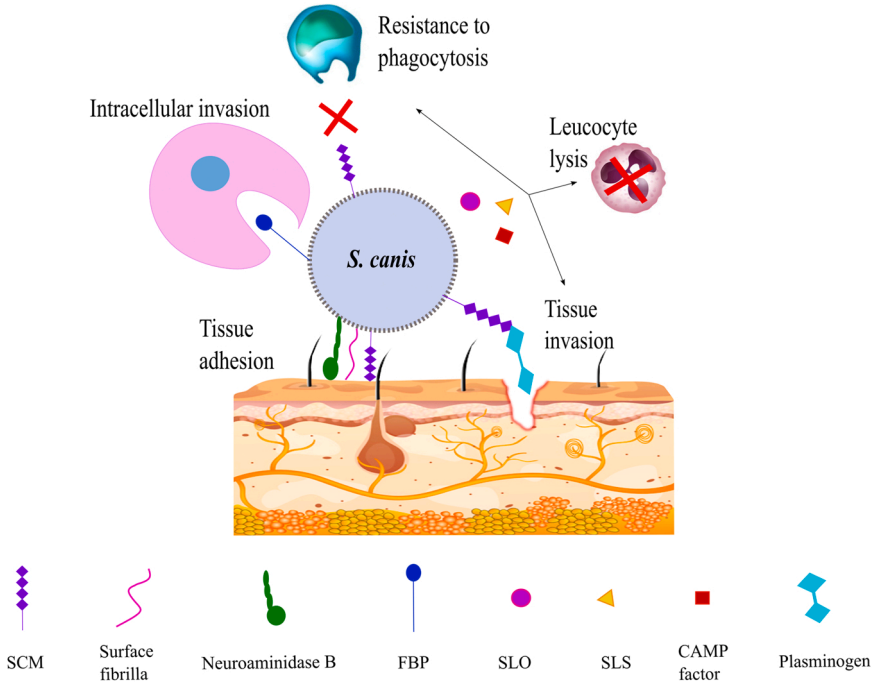

Fig. 5. Schematic representation of the three main classification systems proposed for *S. canis* (Pinho et al., 2013, 2019; Fukushima et al., 2020a).

Lysková et al., 2007a; Pinho et al., 2013; Lacave et al., 2016; Tarabichi et al., 2018). The most commonly encountered AMR phenotype among *S. canis* strains is tetracycline resistance, which is expressed by 30–40% of all the isolates and associated with the carriage of *tet*(M), *tet*(O), *tet*(S), *tet*(K) and *tet*(L) genes (Galpérine et al., 2007; Lysková et al., 2007b; Pinho et al., 2013; Fukushima et al., 2020b; Yoshida et al., 2021). Although less frequent, macrolide, lincosamide and streptogramin (MLS) resistance phenotypes have been detected in *S. canis* strains, particularly in association with the presence of the *erm*(A), *erm*(B), *mef*(A) and *aadA* genes (Galpérine et al., 2007; Lysková et al., 2007b; Pinho et al., 2013; Fukushima et al., 2020b; Yoshida et al., 2021). Occasional resistance to gentamicin and rifampicin has also been reported in *S. canis* (Galpérine et al., 2007).

The occurrence of fluoroquinolone resistance associated with specific amino acid substitutions in the quinolone resistance-determining region (QRDR) of the *gyrA*, *gyrB*, *parC* and *parE* genes has recently been documented in a small number of resistant strains (Fig. 6) (Fukushima et al., 2020b). Table 6 shows the proportion of Fukushima SCM group I and SCM group II strains sharing a macrolide/lincosamide resistance genotype and expressing a fluoroquinolone-resistant phenotype (Fukushima et al., 2018).

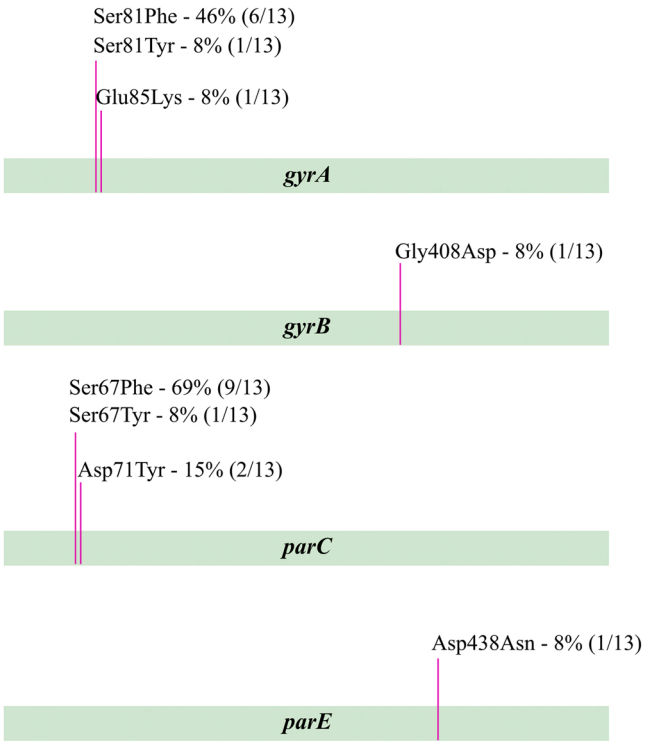

Fig. 6. Amino acid substitutions observed in the QRDR regions of *gyrA*, *gyrB*, *parC* and *parE* in thirteen fluoroquinolone-resistant isolates of *S. canis*. Percentages and fractions represent the proportion of fluoroquinolone-resistant isolates carrying that mutation. Fluoroquinolone resistance was confirmed when the MIC for Levofloxacin by Etest was > 1 μg/mL (Fukushima et al., 2020b).

2.7. Zoonotic potential

The ability of *S. canis* to colonise and cause disease in a variety of mammals is well documented (Richards et al., 2012). Human infections are understood to be rare, although there has recently been an increase in reported cases (Takeda et al., 2001; Galpérine et al., 2007; Lam et al., 2007; Lacave et al., 2016; Tan et al., 2016; McGuire et al., 2021), and little is known about epidemiology in humans. Since dogs and cats are recognised as the main host species of *S. canis*, it is likely that human infection can result from direct 'pet-to-people' transmission, making *S. canis* a potentially zoonotic pathogen (Richards et al., 2012). This hypothesis has been supported by reports of human infections following dog bites and other forms of interaction with companion animals (Bert and Lambert-Zechovsky, 1997; Takeda et al., 2001; Lam et al., 2007). It remains unclear, however, whether all *S. canis* strains possess the same multi-species tropism profile or whether adaptation has occurred. Preliminary evidence based on MLST classification suggests that *S. canis* strains of the same ST can be found in both animals and humans (Pinho et al., 2013, 2019), inferring lack of host adaptation and zoonotic potential. However, it may be argued that MLST fails to represent

Table 6
Proportion of *S. canis* group I and group II SCM strains sharing a specific AMR genotype or phenotype in a study by Fukushima et al. Only AMR profiles with a statistically significant difference in prevalence between SCM groups are reported. Statistical significance is displayed as p value < 0.05 calculated through the Fisher's exact probability test (two-sided) (Fukushima et al., 2018).

AMR profile	Group I SCM	Group II SCM	Statistical significance
Macrolide/lincosamide resistance genotype	25% (15/55)	7.5% (3/40)	p = 0.0313
Fluoroquinolone resistance phenotype	12.5% (7/55)	0% (0/40)	p = 0.0389

accurately the diversity of bacterial populations when compared to more discriminatory genomic methods (Tsang et al., 2017). Better evidence is required to aid our understanding of the epidemiology of *S. canis* and provide insight into public health risks.

3. Conclusion

Historically considered a canine pathogen, *S. canis* is now known to cause disease in a variety of mammals, including humans. Dogs, however, appear to be the primary host and it is considered that this bacterium is part of the skin and mucosal microbiota of healthy individuals. Clinical manifestations of *S. canis* infection range from mild superficial inflammation to severe invasive disease in dogs, cats and humans. In cattle, *S. canis* is responsible for sub-clinical mastitis, which may have an important impact on productivity and animal welfare. Risk factors for *S. canis* infection are currently unknown, although in humans most cases involve elderly individuals with comorbidities. Direct interaction with dogs, particularly via bites and scratches, is thought to be an important driver of infection in humans, but evidence to support this hypothesis is currently limited. Mechanisms underlying *S. canis* pathogenesis remain unclear although putative virulence genes have been detected in its genome. The most well-characterised candidate is the SCM protein, which showed virulence potential in vitro but proved to have only a minor involvement in disease development in a murine model. Nevertheless, *scm* plays an important role in *S. canis* strain classification, being used by three typing schemes, supplementing the established MLST scheme. The most common AMR in *S. canis* are towards tetracyclines and MLS, although they are not first line antibiotics for the treatment of streptococcal infections. The recent acquisition of fluoroquinolone resistance conferring mutations should be the subject of future monitoring. Direct transmission of *S. canis* strains from one host species to another appears likely, although it has only been partially demonstrated and requires confirmation through high-discriminatory genotyping methods. This is important given the relatively high prevalence of asymptomatic *S. canis* colonisation in dogs. In conclusion, *S. canis* infections are rare in humans compared to those caused by other bacteria but their real incidence might be underestimated by limitations in diagnostic laboratories, where streptococcal infections are rarely identified to the species level. Regardless of its true disease burden, *S. canis* infections can be life-threatening in humans and companion animals alike and with important questions on transmission, zoonotic importance and AMR potential still unanswered, this pathogen is a worthy focus of continued research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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