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QUORUM SENSING IN VETERINARY PATHOGENS: MECHANISMS, CLINICAL IMPORTANCE AND FUTURE PERSPECTIVES

F. Boyen, V. Eeckhaut, F. Van Immerseel, F. Pasmans, R. Ducatelle and F. Haesebrouck

Department of Pathology, Bacteriology and Avian Diseases, Faculty of Veterinary Medicine,
Ghent University, Salisburylaan 133, 9820 Merelbeke, Belgium

filip.boyen@UGent.be

ABSTRACT

Under certain circumstances the individuals of a bacterial population may find advantages in acting together and making “collective decisions”. This phenomenon is better known as quorum sensing. When the concentration of signal molecules produced by the surrounding bacteria exceeds a certain threshold, the bacterial population acts as a single organism, collectively expressing virulence genes, biofilm forming genes, etc. Several mechanisms of quorum sensing are discussed, each with its distinct signal molecules and respective receptors. Some of these mechanisms are restricted to sensing intraspecies signalling, but interspecies and even interkingdom signalling have also been described. Several veterinary pathogens such as *Staphylococcus aureus*, *Staphylococcus pseudintermedius*, *Pseudomonas aeruginosa* and *Salmonella* Typhimurium use quorum sensing as a means to optimize virulence gene expression and host colonization. Therefore, targeting of the QS mechanisms may provide a novel strategy for combating bacterial infections, also in veterinary medicine.

Key words: quorum sensing, signal molecules, veterinary pathogens

INTRODUCTION

The communication mechanism that enables bacteria to make ‘collective decisions’ is called ‘quorum sensing’. For this purpose, small chemical signal molecules are synthesized and secreted into the environment. By using specific detection systems to sense the concentration of these signal molecules, the surrounding bacteria are aware of the bacterial cell density. When the signal molecule concentration reaches a critical threshold, the gene expression and, as a result, the behaviour of the total population is changed (Figure 1).

Quorum sensing (QS) was first described in the 1970s, when Nealson and colleagues (1970) investigated the bioluminescence of *Vibrio fischeri* and *Vibrio harveyi*. Ever since, QS has been assigned a role in various mechanisms of gene regulation: biofilm formation (Haesebrouck et al., 2007; Irie and Parsek, 2008), virulence adaptation (Salmond et al., 1995; Vendeville et al., 2005), the production of antimicrobial substances (Salmond et al., 1995; Kleerebezem, 2004), motility (Bearson and Bearson, 2007; Atkinson et al., 2008), sporulation (Lazazzera, 2000), etc. Although these mechanisms have mostly been studied in non-pathogenic bacteria or in human pathogens, the last few years, more studies have been conducted focusing on bacterial species of veterinary importance.

In this manuscript, the different mechanisms of QS, some examples of the exploitation of QS by bacterial pathogens of veterinary importance, and possible applications in future veterinary medicine are reviewed.

MECHANISMS OF QUORUM SENSING

Quorum sensing in Gram positive bacteria: autoinducing polypeptides

Gram positive bacteria mainly use post-translational modified oligopeptides as QS signal molecules (Lyon and Novick, 2004). These autoinducing polypeptides (AIPs) are made up of 5 to 17 amino acids with side chain modifications consisting, for example, of isoprenyl groups (*Bacillus* spp.) or thiolactone rings (*Staphylococcus* spp.) (Ji et al., 1997; Lyon and Novick, 2004). The AIPs are synthesized in the cytoplasm as precursor peptides, and then cleaved, modified and transported to the extracellular environment (Lyon and Novick, 2004). In the surroundings of the producing bacterial cell, the AIPs can be detected by membrane-bound two-component detection systems. Detection of the AIPs by the sensorial part of the two-component systems leads to phosphorylation and therefore activation of the response regulator protein (Lyon and Novick, 2004; Waters and Bassler, 2005). This response protein interacts with the target promoter DNA and the expression of the QS regulated genes is switched on (Figure 2).

The structure of the signal peptide varies between different Gram positive species. Since the binding efficiency on the receptors is highly dependent on the chemical structure of the AIPs, it is generally accepted that mainly Gram positive, but also some Gram negative bacteria use this system for intraspecies communication (Goerke et al., 2003; Dirix et al., 2004; Novick and Geisinger, 2008).

Quorum sensing in Gram negative bacteria: N-acylhomoserine lactones

In Gram negative bacteria, the signal molecules are N-acylhomoserine lactones (AHLs), which are also called autoinducer 1 (AI-1). They consist of a conserved homoserine lactone ring which is connected to an acyl side chain of variable length (4 to 18 carbon atoms) and variable extra modification. AHLs with a short acyl side chain can diffuse passively in and out the bacterial cell (Moré et al., 1996; Fuqua et al., 2001). This is in contrast with AHLs with a long acyl side chain and the AIPs, which need active transport mechanisms to cross the bacterial cell membrane (Fuqua et al., 2001; Novick and Geisinger, 2008).

LuxI homologous proteins play a major role in the synthesis of the AHLs, which increase in concentration as the cell density increases. At a critical concentration, LuxR homologues bind the signal molecules and subsequently regulate gene transcription (Fuqua et al., 2001; Waters and Bassler, 2005) (Figure 2). It is becoming more and more obvious, however, that there is a considerable diversity in the way in which the LuxI and LuxR homologues from different bacterial species operate (Smith et al., 2006). Since the LuxR type proteins only detect specific AHLs, this QS system is also mainly used for intraspecies communication. Nevertheless, LuxR type proteins that are able to detect several AHLs have been described. For example, SdiA of *Salmonella* is believed to be mainly involved in interspecies bacterial communication (Walters and Sperandio, 2006).

Quorum sensing in both Gram positive and Gram negative bacteria: autoinducer 2

In the late 1990s, a second QS system was discovered in various Gram negative bacteria (Surette et al., 1999). In this system, the autoinducer (AI-2) is a furanosyl borate ester that is formed by the LuxS protein (Waters and Bassler, 2005). To date, AI-2 has been described in more than 50 different bacterial species, comprising both Gram positive and Gram negative bacteria (Surette et al., 1999; Schauder et al., 2001; Hardie and Heurlier, 2008). In *Vibrio harveyi*, the receptor for the AI-2 molecules is the periplasmatic LuxP

protein. The LuxP-AI-2 complex binds to a second protein, LuxQ, which is a two-component protein that contains both a sensor kinase domain and a response regulator domain (Neiditch et al., 2005). In low bacterial concentrations, and therefore in the absence of the AI-2, LuxQ phosphorylates LuxO with the aid of the LuxU intermediary protein, which in turn activates the transcription of a repressor protein blocking the transcription of the luciferase operon. At high bacterial densities, the AI-2 presence induces the phosphatase activity of LuxQ, which inactivates LuxO, resulting in the LuxR mediated transcription of the luciferase operon (Neiditch et al., 2005) (Figure 2). The LuxR component of this system should not be confused with the LuxR protein of *Vibrio fischeri* (see above). The autoinducer AI-2 could serve as a ‘universal signal’ for interspecies communication (Xavier and Bassler, 2003), though in most enteric bacteria the genes that are directly regulated by AI-2 code for an ABC transporter system and it has been suggested that the role of AI-2 is mainly metabolic (Vendeville et al., 2005; Walters and Sperandio, 2006; Rezzonico and Duffy, 2008).

Quorum sensing beyond bacterial borders: autoinducer 3

Enterohaemorrhagic *Eschericia coli* (EHEC) is the cause of various food-borne outbreaks of severe intestinal disease and the causative agent of the hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) in humans (Moxley et al., 2004; Karch et al., 2005). EHEC motility and attaching and effacing virulence genes are regulated by a QS mechanism (Moxley et al., 2004) that involves the poorly characterized auto inducer 3 (AI-3), which is produced by several enteric bacterial species (Kendall and Sperandio, 2007). Since epinephrine/norepinephrine induce the same virulence gene expression in EHEC and since the effects of AI-3 can be inhibited by adrenergic receptor antagonists, AI-3 probably is structurally similar to epinephrine/norepinephrine (Sperandio et al., 2003). In addition, the presence of epinephrine/norepinephrine itself may serve as a QS

signal. Apart from the EHEC QseE/F two-component system, QseB/C has been identified as the receptor/response regulator of both AI-3 and epinephrine/norepinephrine in a number of bacterial species (Clarke et al., 2006; Walters and Sperandio, 2006) (Figure 2). Therefore, this adrenergic receptor is thought to play a role in interkingdom signaling (Kendall and Sperandio, 2007).

CLINICAL SIGNIFICANCE OF QUORUM SENSING IN VETERINARY PATHOGENS

Staphylococcus aureus

The *agr* (accessory gene regulator) QS system in *Staphylococcus aureus* (*S. aureus*) is one of the most studied QS mechanisms in Gram positive bacteria. Using sequence analysis, *S. aureus* can be divided into 4 different *agr* specific groups. The AIPs of one *agr* group inhibit the expression of the *agr* expression of the other groups (Novick, 2003). Several haemolysins, enterotoxins, exfoliating toxins, enzymes and surface proteins are regulated by *agr*. Therefore *agr* has been assigned various functions in the pathogenesis of *S. aureus* infections in several animal species.

In rabbits, *S. aureus* infections lead to skin infections, mastitis and internal abscessation. Low virulent strains may occasionally infect an individual animal, while highly virulent strains are the cause of chronic problems and they spread rapidly throughout the rabbitry (Vancraeynest et al., 2006). It has been shown that highly virulent strains are clonal and grouped into *agr* type IV (Vancraeynest et al., 2006). In addition, it has been shown that *agr* deletion mutants are attenuated in their capacity to induce endocarditis, osteomyelitis and endophthalmitis in rabbits (Cheung et al., 1994; Gillaspay et al., 1995; Booth et al., 1995).

S. aureus is worldwide the most frequently isolated bacterium from bovine intramammary infections. In contrast to highly virulent rabbit associated *S. aureus* isolates,

strains from bovine mastitis cases are predominantly classified in *agr* group I and to a lesser extent in *agr* groups II and III (Buzzola et al., 2007; Vautor et al., 2008). Bovine *S. aureus* strains belonging to *agr* group I show significantly increased capacities to be internalized in bovine mammary epithelial cells and persist in higher numbers in murine mammary glands (Buzzola et al., 2007), while *agr* group II strains might prefer the extracellular niche and therefore might be more dependent on biofilm formation (Melchior et al., 2009). In addition, it has been suggested that penicillin resistance in bovine *S. aureus* strains is correlated to the presence of *agr* group I genes (Melchior et al., 2009).

In contrast, for example, to *Pseudomonas aeruginosa*, biofilm formation in *S. aureus* is negatively regulated by the main QS system. *Agr* dependent expression contributes to the detachment of biofilms and subsequent colonization of new sites (Boles and Horswill, 2008). Therefore, although still speculative, the QS dependent detachment from biofilms may render some *S. aureus* strains more capable of spreading through a herd and causing chronic problems at the herd level (e.g. highly virulent rabbit strains). This may also explain why *agr*⁺ and *agr*⁻ variants of *S. aureus* might have a cooperative interaction in certain types of infections (Traber et al., 2008).

Staphylococcus pseudintermedius

Staphylococcal strains formerly designated as *Staphylococcus intermedius* (*S. intermedius*) are currently assembled in the so-called *S. intermedius* group (SIG), consisting of *S. intermedius*, *Staphylococcus pseudintermedius* (*S. pseudintermedius*) and *Staphylococcus delphini* (*S. delphini*) (Hajek, 1976; Varaldo et al., 1988; Devriese et al., 2005; Devriese et al., 2009). From a clinical point of view, *S. pseudintermedius* is probably the most significant species of the SIG, being an important canine opportunistic pathogen, often isolated from dermatitis, otitis and other secondary infections in dogs (Bannoehr et al.,

2007). Since *S. pseudintermedius* produces toxins analogous to the *agr* dependant toxins of *S. aureus*, it has been hypothesized that the *S. pseudintermedius* toxins are regulated by a comparable QS mechanism (Sung et al., 2006). However, the *Staphylococcus* spp. of the SIG differ from all other *Staphylococcus* spp., including *S. aureus*, in the fact that their AIP contains a lactone instead of a thiolactone ring (Dufour et al., 2002; Ji et al., 2005; Novick and Geisinger, 2008). This nonapeptide shows both auto-inducing and cross-inhibiting activities (Ji et al., 2005). DNA sequencing revealed the presence of four predicted AIP variants within the SIG (Bannoehr et al., 2007). Novick and Geisinger (2008) suggest that the divergence of the lactone containing AIP of the SIG from the thiolactone containing AIP of *S. aureus*, may be correlated to the divergence of *S. pseudintermedius* towards the canine host. However, the fact that no association could be made between the AIP variants of the SIG and the different host species, disease status of the host, clinical or geographic origin of the strains might nuance this hypothesis (Bannoehr et al., 2007).

Pseudomonas aeruginosa

Pseudomonas aeruginosa (*P. aeruginosa*) is an important opportunistic pathogen in human and veterinary medicine. *Pseudomonas* infections are difficult to treat since this bacterium is resistant to several antimicrobial agents (Rubin et al., 2008; Weese, 2008) and its antimicrobial susceptibility is even lower when it is present in biofilms (Haesebrouck et al., 2007; Girard and Bloemberg, 2008). *P. aeruginosa* may cause various tissue infections in different animal species, which illustrates the adaptability of this bacterium. A multitude of virulence factors are regulated by at least one of the 2 different QS systems present in *P. aeruginosa*: Las and Rhl (Whiteley et al., 1999; Girard and Bloemberg, 2008).

Pseudomonas is notorious for its capability to form biofilms. Through the formation of a biofilm, the bacteria are able to colonize all kinds of animal tissues, plants and inert

surfaces, thereby increasing environmental persistence (Haesebrouck et al., 2007). In addition, bacteria inside a biofilm are difficult to kill either by antimicrobial substances or by host defense mechanisms, and therefore often result in chronic infections that do not respond to antimicrobial therapy. Since *P. aeruginosa* is found ubiquitously in water, wet surfaces are predisposed to be colonized with a *P. aeruginosa* biofilm. In veterinary medicine, the biofilm producing capability of *P. aeruginosa* is most feared in cases of infections involving invasive devices or implants (Weese et al., 2008). *P. aeruginosa* is also a severe complicating factor in cases of equine ulcerative keratitis (Keller and Hendrix, 2005), in dermatitis, otitis externa and urinary tract infections in small animals (Rubin et al., 2008), in fleece rot in sheep (Kingsford and Raadsma, 1997), in bovine mastitis, which is often associated with contaminated udder washing water or contaminated intramammary dry-cow preparations (McLennan et al., 1997), and in hemorrhagic pneumonia in mink (Hammer et al., 2003).

Even though QS often favors the expression of virulence genes, Tron et al. (2004) showed that *P. aeruginosa* canine otitis externa isolates share a deficiency of one or more components of the Rhl QS system, leading to the loss of the elastase virulence factor. The virulence factor that favors colonization of canine ears may be under the negative control of the QS system, or a factor that facilitates removal of the bacterium from the canine ears may be under the positive control of Rhl. The authors postulate that either this phenotype might be present before infection or else it might be acquired after infection in an effort to adapt to the novel environment. Recent research suggests an alternative explanation for the presence of QS deficient strains on sites where it can be expected that biofilm formation should be favourable for colonization. Evolutionary biologists describe the phenomenon of ‘cheating’ individuals in the population (Dunny et al., 2008). Such cheaters profit from the benefits of the cooperating population, without contributing to the community. Since these cheaters do not invest in the production of the biofilm, they have a competitive advantage relative to the

biofilm producing individuals and, as a consequence, can become predominant in the community. However, when the proportion of cheaters becomes too large, this can affect the stability of the biofilm and the entire population may crash as a result (Dunny et al., 2008).

Salmonella

Several QS systems have been described in *Salmonella*. *Salmonella* has a LuxR homologue, SdiA, but does not have a luxI homologue and therefore does not produce AHLs (Walters and Sperandio, 2006). It has been suggested that SdiA senses AHLs produced by other bacterial species (Michael et al., 2001) and in this way senses the presence of the intestinal environment. SdiA regulates the expression of virulence genes with different functions, ranging from resistance to complement killing to the expression of fimbriae. In murine, poultry or bovine models, however, an *sdiA* mutant strain is not attenuated and, very recently, SdiA dependent gene expression was shown to be activated in the gut of turtles, but not in the intestines of several homoiothermic animal species (Smith et al., 2008). The role of SdiA in *Salmonella* pathogenesis therefore still remains largely unknown.

In *Salmonella enterica* subspecies *enterica* serotype Typhimurium (*Salmonella* Typhimurium), the *luxS* gene is directly involved in the AI-2 synthesis. It was recently demonstrated that *luxS* and the *Salmonella* AI-2, 4,5dihydroxy-2,3-pentanedione (DPD), are necessary for *Salmonella* virulence (Choi et al., 2007). Deletion mutants lacking the *luxS* gene are severely attenuated in the expression of the virulence genes of the *Salmonella* Pathogenicity Island 1 (SPI-1). These genes are required for the efficient invasion of intestinal epithelial cells and are therefore crucial in the pathogenesis of *Salmonella* infections in a wide variety of animal hosts, including poultry, pigs and cattle (Morgan et al., 2004; Bohez et al., 2006; Boyen et al., 2006). This finding suggests that *Salmonella* might secure the initial

infection process by producing SPI-1 virulence factors only when its population size attains a high enough level (Choi et al., 2007).

Eukaryotic cells communicate with each other using various hormones or hormone-like substances, for example epinephrine and norepinephrine. These signals can be misused, however, by bacterial pathogens, such as *Salmonella*, to colonize the host or to induce disease (Walters and Sperandio, 2006). Catecholamines may stimulate *Salmonella* Typhimurium by two mechanisms: as a quorum sensing signal or as a supplier of iron (Bearson et al., 2008). In *Salmonella*, the QseC AI-3 sensor, which is able to detect norepinephrine, has also been implicated in the regulation of virulence traits such as motility and *in vivo* competitive fitness in pigs (Bearson and Bearson, 2008). Even though the role of catecholamines or even other neurotransmitters or hormones in the pathogenesis of *Salmonella* infections is still in its infancy, the ability to respond to norepinephrine produced by the host has potential food safety consequences. The mechanism described above may be one of the factors causing the sudden burst of *Salmonella* excretion by stressed pigs, for example, during transport to the slaughter house (Bearson and Bearson, 2008).

Other veterinary pathogens

It has been shown that several Pasteurellaceae, including *Mannheimia haemolytica*, *Pasteurella multocida*, *Bibersteinia* (formerly *Pasteurella*) *trehalosi*, *Actinobacillus suis* and *Actinobacillus pleuropneumoniae*, contain LuxS homologues in their genome and are able to produce AI-2-like molecules (Malott and Lo, 2002). Also in *Histophilus somni*, QS may contribute to pathogenesis (Corbeil, 2007). A luxS deletion mutant in *Mannheimia haemolytica* did not show altered leukotoxin expression levels, but had increased expression levels of putative virulence genes such as a transferrin binding protein, an adhesin and capsule

272 biosynthesis, and was outcompeted by the wild type parent strain in a calf challenge model
273 (van der Vinne et al., 2005). Very recently, a *luxS* deletion mutant of *Actinobacillus*
274 *pleuropneumoniae* was shown to be significantly attenuated in an *in vivo* mouse model (Li et
275 al., 2008). The down-regulation of the *apxIIA* toxin, a major virulence factor of
276 *Actinobacillus pleuropneumoniae*, may contribute to the virulence attenuation of the *luxS*
277 deletion mutant (Li et al., 2008).

278 There are numerous studies dealing with the role of QS in the pathogenesis of
279 infections with EHEC (e.g. Kendall and Sperandio, 2007), but studies of the importance of
280 QS in infections with *E. coli* in veterinary medicine are scarce. Recently, a *luxS* deletion
281 mutant of a rabbit enteropathogenic *E. coli* (EPEC) strain was found to be impaired in its
282 virulence *in vitro*, but was not attenuated in experimentally infected rabbits (Zhu et al., 2007).

283 Even though QS was initially described and thoroughly examined in several *Vibrio*
284 *spp.*, reports linking the QS mechanisms to virulence in fish are much more limited, both for
285 *Vibrio spp.* (Bruhn et al., 2005; Austin and Zhang, 2006; Nelson et al., 2007; Ye et al., 2008)
286 and non-*Vibrio* fish pathogens (Morohoshi et al., 2004; Bruhn et al., 2005; Atkinson et al.,
287 2006; Bi et al., 2007; Rasch et al., 2007).

288 Quorum sensing has been described in various other veterinary or zoonotic pathogens,
289 such as *Clostridium perfringens* (Ohtani et al., 2002), *Yersinia pseudotuberculosis* (Atkinson
290 et al., 2008) and *Campylobacter jejuni* (Jeon et al., 2005; He et al., 2008), but a clear
291 correlation between these QS mechanisms and virulence is yet to be demonstrated.

FUTURE PERSPECTIVES OF QUORUM SENSING IN VETERINARY MEDICINE

Quorum sensing signal molecule detection as a diagnostic tool?

Since bacterial quorum sensing has been implicated in the onset of bacterial pathogenicity (Wu et al., 2000; Kendall and Sperandio, 2007), the signal molecules produced by the bacterial pathogens are potential biomarkers for the diagnosis and follow-up of bacterial infections (Kumari et al., 2008). Because the chemical structure of the various signal molecules differ greatly, different sensory systems for detecting these molecules have been described (Kalkum et al., 2003; Steindler and Venturi, 2007; Kumari et al., 2008). Most of the studies dealing with the detection of QS signal molecules, however, focus on the detection of AHLs, since these molecules are involved in the development of chronic bacterial infections with *P. aeruginosa* or *Burkholderia cepacia* in the lungs of cystic fibrosis patients in human medicine (Kumari et al., 2008). Despite the plethora of detection systems, only a fraction can be used to detect QS signal molecules in clinical samples (Kumari et al., 2008).

AHLs of various Gram-negative bacterial pathogens have been detected in clinical samples of sputum, mucopurulent secretions of the respiratory tract, lung, liver and spleen homogenates and feces of humans and/or experimentally infected mice (Middleton et al., 2002; Jacobi et al., 2003; Kumari et al., 2006; Kumari et al., 2008). In bronchoalveolar lavages (BALs) from transplanted human lungs, long-chain AHLs were detected, even in lungs that were clinically stable and showed no signs of bacterial infection (Ward et al., 2003). Therefore, the detection of QS signal molecules as a means to detect bacterial infections in a very early stage merits further attention. There are currently no reports of detections of QS signal molecules of veterinary bacterial pathogens in clinical samples of animal host species of veterinary importance.

Quorum sensing inhibition as a therapeutic tool?

The concept of QS inhibition, as used by a range of prokaryotic and eukaryotic organisms, is not new. For example, certain *S. aureus* strains produce auto-inducers that stimulate their own QS mechanisms, but have a cross-inhibitory effect on the QS systems of other strains, possibly excluding them from infection or colonization sites (Ji et al., 1997). Certain *Bacillus* sp. harbour the acyl-homoserine lactonase enzyme, which inactivates AHL activity by hydrolysing the lactone bond of AHLs of competing bacterial species (Dong et al., 2001). The fact that certain human cell lines are able to inactivate QS signal molecules suggests that mammalian host defences might have developed interfering QS systems against bacterial infections as well (Chun et al., 2004).

Increasing antimicrobial resistance in pathogenic bacteria has created the need for the development of novel therapeutic agents. It is clear that QS is a key regulatory system in the pathogenesis of various bacterial infections. Therefore, the targeting of the QS mechanisms provides a novel strategy for combating bacterial infections (Bjarnsholt and Givskov, 2007). These compounds ideally have no direct effect on bacterial growth, but attenuate bacterial pathogenicity, thereby increasing the susceptibility of the pathogen to the host defences. Even though the macrolides may show potential as QS inhibitors (Tateda et al., 2007), the lack of an effect of “pure” QS inhibitors on bacterial growth could mean a strong advantage relative to the “classic” antimicrobial agents, since the use of these products may not exert a strong selective pressure towards the development of resistance.

Very recently, a small molecule, LED209, was discovered using a high-throughput screening which inhibits the QseC mediated activation of virulence gene expression and subsequent *in vivo* virulence of various bacterial pathogens, such as EHEC, *Salmonella* Typhimurium and *Francisella tularensis* (Rasko et al., 2008). Being non-toxic for mammals,

having a broad spectrum and lacking a direct effect on bacterial growth, this molecule holds a promising future (Rasko et al., 2008).

Inhibition of biofilm formation has been described using QS inhibitors in *P. aeruginosa* (Bjarnsholt and Givskov, 2007), *S. aureus* (Wright et al., 2005) and *Salmonella* Typhimurium (Janssens et al., 2007).

Research aimed at the use of QS inhibitors in veterinary medicine is currently limited to their use in aquaculture. For the fish pathogens *Aeromonas salmonicida* and *Vibrio (Listonella) anguillarum*, AHL analogues reduced the virulence gene expression and the fish mortality rates, respectively (Rasch et al., 2004; Rasch et al., 2007).

CONCLUSION

Quorum sensing is a widespread phenomenon used by various bacterial pathogens of veterinary importance. Different QS mechanisms make use of diverse signal molecules, leading to intraspecies, interspecies and even interkingdom signalling. Since QS probably plays a role in the pathogenesis of many bacterial infections in animals, the detection of QS signal molecules at early stages of the infection and the use of QS inhibitors for treatment may provide new tools in future veterinary medicine.

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Figure legend

Figure 1: The principle of quorum sensing is depicted. In situations where the bacterial density is low (left), the signal molecule concentration is also low and does not exceed the quorum sensing threshold. In case the bacterial density is high (right), the signal molecule concentration is also high and the quorum sensing threshold is exceeded. As a result, the signal molecules are bound to their receptors on the bacterial cells and the gene expression of the total population is changed and synchronised.

Figure 2: Four simplified models of the described quorum sensing mechanisms.

Figure 1

Low bacterial density
Low signal molecule concentration

High bacterial density
High signal molecule concentration

Figure 2

MECHANISM 1

Quorum sensing in mainly Gr⁺ bacteria: autoinducing polypeptides (AIP)

MECHANISM 2

Quorum sensing in Gr⁻ bacteria: N-acylhomoserine lactones (AHL / AI-1)

MECHANISM 3

Quorum sensing in both Gr⁺ and Gr⁻ bacteria: autoinducer 2 (AI-2)

MECHANISM 4

Quorum sensing beyond bacterial borders: autoinducer 3 (AI-3)