Streptococcus suis infections in humans: the Chinese experience and the situation in North America

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Abstract
Infections caused by Streptococcus suis are considered a global problem in the swine industry. In this animal species, S. suis is associated with septicemia, meningitis, endocarditis, arthritis and, occasionally, other infections. Moreover, it is an agent of zoonosis that afflicts people in close contact with infected pigs or pork-derived products. Although sporadic cases of S. suis infection in humans have been reported, a large outbreak due to S. suis serotype 2 emerged in the summer of 2005 in Sichuan, China. A similar outbreak was observed in another Chinese province in 1998. Symptoms reported in these two outbreaks include high fever, malaise, nausea and vomiting, followed by nervous symptoms, subcutaneous hemorrhage, septic shock and coma in severe cases. The increased severity of S. suis infections in humans, such as a shorter incubation time, more rapid disease progression and higher rate of mortality, underscores the critical need to better understand the factors associated with pathogenesis of S. suis infection. From the 35 capsular serotypes currently known, serotype 2 is considered the most virulent and frequently isolated in both swine and humans. Here, we review the epidemiological, clinical and immunopathological features of S. suis infection in humans.

Keywords: Streptococcus suis, humans, pig, septic shock, epidemiology, pathogenesis

Introduction
Streptococcus suis infections have been considered a major problem worldwide in the swine industry, particularly during the past 15 years. The natural habitat of S. suis is the upper respiratory tract of pigs, particularly the tonsils and nasal cavities, as well as the genital and alimentary tracts (Higgins and Gottschalk, 2005). The most important clinical feature associated with S. suis infection in pigs is meningitis. However, other pathologies have also been described, such as arthritis, endocarditis, pneumonia, and septicemia with sudden death (Higgins and Gottschalk, 2005). Although S. suis is considered a major swine pathogen, it has been isolated increasingly from a wide range of mammalian species (including humans) and from birds. These findings suggest new epidemiological patterns of the infection, since other animal species might also be a source of infection of swine (Devriese et al., 1990, 1994; Devriese and Haesebrouck, 1992).

Infections in humans were considered sporadic infections in people working with pigs or pork-derived products (Arends and Zanen, 1988). However, an important outbreak that occurred during the summer of 2005 in China and affected more than 200 people with a mortality rate of nearly 20% has changed the perspective of the threat posed by this pathogen to human health.
Here, we review the most recent available data on *S. suis* infection in humans. Although we discuss some general aspects of the infection in pigs, a complete review on infection caused by this pathogen in animals can be found in a previously published book chapter (Higgins and Gottschalk, 2005).

**S. suis**: general characteristics of the microorganism

*S. suis* is an encapsulated Gram-positive coccus that possesses cell wall antigenic determinants somewhat related to Lancefield group D. There are 35 serotypes described to date and the composition of the capsule defines the serotype (Higgins and Gottschalk, 2005). There is some confusion regarding the early terminology of Lancefield groups R, S and T, and the relationship of these groups with group D streptococci and the different *S. suis* serotypes (also referred to in the literature as capsular types or serovars), especially in papers describing human infections (Tarradas et al., 2001b; Facklam, 2002; de la Hoz Adame et al., 2005). Various α-hemolytic streptococci were ascribed to Lancefield groups R, S, RS and T in 1963 by de Moor (de Moor, 1963). Years later, British researchers, working with encapsulated streptococci similar to de Moor’s groups S and R, discovered that de Moor had erroneously worked with antigens extracted from the capsular material rather than from the cell wall, and clearly demonstrated that the lipoteichoic acid present in the cell wall of these strains reacts with group D antiserum (Elliott et al., 1977). That this antigen is difficult to extract may account for the negative reaction with the existing antiserum obtained in 1963 by de Moor. In fact, the conventional method for extracting streptococcal group antigens from other group D streptococci by heating in HCl at 100°C and pH 2 yields sufficient free teichoic acid to precipitate with potent group D antiserum, but such extracts from *S. suis* may give weak or equivocal results (Elliott et al., 1977). The ‘Lancefield groups R and S’ were later identified as *S. suis* (Lancefield group D), and reclassified as capsular types 1 (formerly group S) and 2 (formerly group R) (Elliott and Tai, 1978). Some years later, groups RS and T were also reclassified as capsular types 1/2 and 15, respectively (Perch et al., 1983; Gottschalk et al., 1989). In conclusion, the Lancefield groups R, S, RS and T do not exist and, to avoid confusion, this terminology should not be used.

As noted above, *S. suis* cell wall antigen shares epitopes with Lancefield group D; however, negative reactions are often observed with some strains (Chau et al., 1983; Ho et al., 1990; Gottschalk et al., 1991; Tarradas et al., 2001b) due to either technical problems or use of low antiserum with titers of antibodies. In addition, *S. suis* is not closely related genetically to other group D streptococci (Kilpper-Bälz and Schleifer, 1987). Using 16S rRNA gene sequence analysis, Chatellier et al. described a major, well-defined group of *S. suis* reference strains which are very closely interrelated but separated from other streptococci and enterococci, with the exception of serotypes 32, 33 and 34 that showed a higher divergence (Chatellier et al., 1999). The analysis of chaperonin 60 gene sequences also revealed that serotypes 32 and 34 may belong to another species (Brousseau et al., 2001). More recently, DNA sequence data and biochemical profiles clearly indicate that these two serotypes cluster with *Streptococcus orisratti*, a species usually isolated from the teeth of rats (Hill et al., 2005).

**General aspects of *S. suis* infections in pigs**

Although the pig carrier rate is near 100%, the incidence of disease varies over time and is generally less than 5% (Clifton-Hadley et al., 1986). However, in the absence of treatment, mortality rates can reach 20% (Cloutier et al., 2003). In peracute cases, pigs may be found dead with no premonitory signs. Meningitis is the most striking feature and often the basis of a presumptive diagnosis. Other manifestations of *S. suis* infection are arthritis, endocarditis, pneumonitis, rhinitis, abortion and vaginitis (Sanford and Tilker, 1982; Sihvonen et al., 1988). In North America, *S. suis* is, by far, the infectious agent most frequently isolated from cases of endocarditis in pigs. Affected pigs may die suddenly or show various levels of dyspnea, cyanosis and wasting (Higgins and Gottschalk, 2005).

Most *S. suis* organisms isolated from diseased pigs belong to a limited number of serotypes, often between 1 and 8 (Galina et al., 1992; Kataoka et al., 1993; Reams et al., 1996; Higgins and Gottschalk, 2001). Although serotype 2 isolates predominate in most countries, the distribution may differ depending on the geographical location. For example, the prevalence of serotype 2 strains recovered from diseased animals in Canada remains relatively low (below 25%) (Higgins and Gottschalk, 2001). In some European and Asian countries, however, serotype 2 is isolated more frequently (Wisselink et al., 2000). In this regard, it may be hypothesized that Eurasian and North American serotype 2 strains of *S. suis* possess a different virulence potential (Gottschalk and Segura, 2000) (see below). Some strains belonging to less common serotypes, such as serotypes 9, 14, 7 and 5, have been associated with severe infections (Heath et al., 1996; Cloutier et al., 2003; Tian et al., 2004; Higgins and Gottschalk, 2005). Despite these differences, almost all studies on virulence factors, pathogenesis of the infection and mechanisms of protection have been conducted with serotype 2 strains. Indeed, animal models have been almost exclusively standardized using this serotype (Kataoka et al., 1991; Beaudoin et al., 1992; Quessy et al., 1994; Busque et al., 1997; Charland et al., 1997; Vecht et al., 1997; Allen et al., 2001).
Presumptive diagnosis of *S. suis* infection in pigs is based on clinical signs and macroscopic lesions. Confirmation of the infection must be achieved by the isolation of the infectious agent and the detection of microscopic lesions in tissue (Staats et al., 1997). Veterinary diagnostic laboratories easily identify *S. suis* isolates from carrier animals by observing neutrophilic granulocytosis in white blood cell counts and increases in serum enzymes (Higgins and Gottschalk, 2005). Isolation and identification of *S. suis* isolates from carrier animals is critical virulence factor described is the capsular polysaccharide (CPS) (Charland et al., 1998). However, most avirulent strains are encapsulated, indicating that other virulence factors are also essential (Gottschalk and Segura, 1999). Most studies on *S. suis* virulence factors have been performed using serotype 2 strains. One of the problems in identifying virulence factors of *S. suis* is the lack of a clear definition of virulence for this pathogen, mainly as a result of the different parameters used to define whether a strain is virulent or avirulent (Gottschalk et al., 1999). Table 1 summarizes the most important virulence factors of *S. suis* proposed so far. As of 2006, the single most critical virulence factor described is the capsular polysaccharide (CPS) (Charland et al., 1998; Smith et al., 1999, 2002; unpublished observations). In these cases, final identification of untypeable strains must be carried out with the use of *S. suis* species-specific PCR tests (Okwumabua et al., 2003). Finally, no reliable serological test has been described so far (del Campo Sepulveda et al., 1996; Higgins and Gottschalk, 2005).

**Table 1. Proposed virulence factors for *S. suis* serotype 2**

<table>
<thead>
<tr>
<th>Proposed virulence factor</th>
<th>Present only in virulent strains</th>
<th>Virulence of knockout mutants</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsule</td>
<td>No</td>
<td>Reduced</td>
<td>Charland et al., 1998; Smith et al., 1999</td>
</tr>
<tr>
<td>Muramidase-released protein (MRP)</td>
<td>Variable(^a)</td>
<td>Unaffected</td>
<td>Smith et al., 1997; Gottschalk et al., 1998</td>
</tr>
<tr>
<td>Extracellular factor (EF)</td>
<td>Variable(^a)</td>
<td>Unaffected</td>
<td>Smith et al., 1997; Gottschalk et al., 1998</td>
</tr>
<tr>
<td>Suisysin</td>
<td>Variable(^a)</td>
<td>Unaffected</td>
<td>Gottschalk et al., 1998; Allen et al., 2001; Tarradas et al., 2001a; Lun et al., 2003</td>
</tr>
<tr>
<td>Fibronectin-binding protein</td>
<td>No</td>
<td>Partially reduced</td>
<td>de Greeff et al., 2002</td>
</tr>
<tr>
<td>Serum opacity factor</td>
<td>No</td>
<td>Reduced</td>
<td>Baums et al., 2006</td>
</tr>
<tr>
<td>Proteases</td>
<td>No</td>
<td>Unavailable</td>
<td>Jobin and Grenier, 2003; Jobin et al., 2005b</td>
</tr>
<tr>
<td>Hyaluronate lyase</td>
<td>No</td>
<td>Not tested</td>
<td>Allen et al., 2004</td>
</tr>
<tr>
<td>Arginine deiminase</td>
<td>No</td>
<td>Not tested</td>
<td>Winterhoff et al., 2002</td>
</tr>
<tr>
<td>Albumin-binding protein</td>
<td>No</td>
<td>Not tested</td>
<td>Quessy et al., 1997; Brassard et al., 2001</td>
</tr>
<tr>
<td>IgG-binding protein</td>
<td>No</td>
<td>Unavailable</td>
<td>Benkirane et al., 1997, 1998</td>
</tr>
<tr>
<td>38-kDa unknown protein</td>
<td>No</td>
<td>Unavailable</td>
<td>Okwumabua and Chinnapatkakagari, 2005</td>
</tr>
<tr>
<td>2-Glyceraldehyde-3-phosphate dehydrogenase</td>
<td>No</td>
<td>Unavailable</td>
<td>Brassard et al., 2004</td>
</tr>
<tr>
<td>DNase</td>
<td>No</td>
<td>Unavailable</td>
<td>Fontaine et al., 2004</td>
</tr>
<tr>
<td>Elongation factor TS</td>
<td>No</td>
<td>Unavailable</td>
<td>Martinez et al., 2003</td>
</tr>
<tr>
<td>Proliprotein signal peptidase</td>
<td>No</td>
<td>Unaffected</td>
<td>de Greeff et al., 2003</td>
</tr>
<tr>
<td>Sortases</td>
<td>No</td>
<td>Unaffected</td>
<td>Osaki et al., 2002; unpublished observations</td>
</tr>
<tr>
<td>Glutamate dehydrogenase</td>
<td>Different protein profile</td>
<td>Unavailable</td>
<td>Okwumabua et al., 2001</td>
</tr>
<tr>
<td>O-acetylsereine lyase</td>
<td>No</td>
<td>Unavailable</td>
<td>Osaki et al., 2000</td>
</tr>
<tr>
<td>Heat-shock protein</td>
<td>No</td>
<td>Unavailable</td>
<td>Benkirane et al., 1997</td>
</tr>
<tr>
<td>1-4 Gal-binding adhesin</td>
<td>No</td>
<td>Unavailable</td>
<td>Haataja et al., 1996</td>
</tr>
<tr>
<td>52-kDa, IgG-binding protein</td>
<td>No</td>
<td>Unavailable</td>
<td>Serhir et al., 1993</td>
</tr>
<tr>
<td>Superoxide dismutase</td>
<td>No</td>
<td>Unavailable</td>
<td>Langford et al., 1991</td>
</tr>
</tbody>
</table>

\(^a\)Results vary depending on the geographical origin of the strains studied.

**Virulence factors and pathogenesis of the infection**

Most studies on *S. suis* virulence factors have been performed using serotype 2 strains. One of the problems in identifying virulence factors of *S. suis* is the lack of a clear definition of virulence for this pathogen, mainly as a result of the different parameters used to define whether a strain is virulent or avirulent (Gottschalk et al., 1999). Table 1 summarizes the most important virulence factors of *S. suis* proposed so far. As of 2006, the single most critical virulence factor described is the capsular polysaccharide (CPS) (Charland et al., 1998; Smith et al., 1999). However, most avirulent strains are encapsulated, indicating that other virulence factors are also essential (Gottschalk and Segura, 2000).
involved in virulence, other factors are not essential for virulence, are found in both virulent and avirulent strains, or could not be properly studied due to the unavailability of knockout mutants. Knockout mutants of other putative virulence candidates have been obtained, but their virulence has not been tested. Recently, a serum opacity factor has been described with structural homology to members of the MSCRAMM (microbial surface components recognizing adhesive matrix molecules) family and determined to be critical for the virulence of *S. suis* (Baums et al., 2006). However, like CPS, this factor is present in both virulent and avirulent *S. suis* strains (unpublished observations). Thus, the role in the pathogenesis of *S. suis* infections of most putative virulence factors (other than CPS) described so far remains to be confirmed. Using a novel signature-tagged mutagenesis system, Wilson et al. identified 22 mutants as attenuated in either pig or mouse model of infection. A variety of genes were thus identified, including previously known genes essential to the virulence of other organisms (Wilson et al., 2007).

The literature is also conflicting regarding the differentiation between virulence factors and virulence markers. Despite the lack of evidence that some of these putative virulence factors play a critical role in virulence, they nonetheless may serve as virulence markers. This seems to be the case for MRP and EF proteins (Vecht et al., 1991), as well as suilysin, a thiol-activated hemolysin produced by some strains of *S. suis* (Jacobs et al., 1994; Gottschalk et al., 1995). The role of MRP and EF proteins has not been clearly defined; however, suilysin has been identified as a toxic factor for various cell types (see below). Although isogenic mutants lacking either MRP and EF proteins or suilysin were shown to be as virulent to pigs as the respective parent strain (Smith et al., 1996; Allen et al., 2001; Lun et al., 2003), there is a positive association between the presence of these proteins and virulence in Euroasian strains. In addition, avirulent strains possessing MRP, EF and suilysin factors have not been described so far. On the other hand, the absence of one or both of these proteins is not necessarily associated with a lack of virulence. Indeed, some European and most North American virulent isolates do not produce these factors (Quessy et al., 1994; Galina et al., 1996; Gottschalk et al., 1998; Segers et al., 1998; Berthelot-Herault et al., 2000). As mentioned, it has been hypothesized that Euroasian virulent serotype 2 strains, especially those expressing MRP, EF and suilysin factors, are more virulent than North American virulent strains (Gottschalk and Segura, 2000). This might explain the higher prevalence of this serotype in single infections in European and Asian countries as well as the higher association of *S. suis* cases with the immunosuppressive infection caused by the porcine reproductive and respiratory syndrome virus (PRRSV) and, possibly, the higher number of human cases in those countries (see below). Indeed, higher virulence of a virulent serotype 2 European strain compared to a virulent Canadian strain was observed using a standardized experimental infection method (Berthelot-Herault et al., 2005).

The mechanisms that enable *S. suis* to disseminate throughout the animal are not well understood. The bacterium is able to spread systemically from the nasopharynx, occasionally resulting in septicemia and death (Gottschalk and Segura, 2000; Madsen et al., 2002). The palatine and pharyngeal tonsils are both potential portals of entry for *S. suis*, leading to subsequent hematogenous or lymphogenous dissemination (Madsen et al., 2002). It is not known how *S. suis*, despite its low quantities on mucosal surfaces, is able to traverse the first line of host defense to initiate disease. To accomplish this, bacteria must be able to breach mucosal epithelia in the upper respiratory tract. Very few studies have investigated the interactions between *S. suis* and epithelial cells, and many of these have produced contradictory results. For example, some studies have reported limited invasion (Norton et al., 1999), no invasion at all (Lalonde et al., 2003), or invasion only with non-encapsulated (probably avirulent) strains (Benga et al., 2004; Valentin-Weigand, 2004).

Survival of the organism in the bloodstream may be facilitated by the CPS, which efficiently hampers phagocytosis. Although an early theory, called the Trojan horse theory, suggested that the bacteria are taken up by monocytes (in the absence of specific antibodies), survive intracellularly and then invade the central nervous system (CNS) (Williams, 1990; Williams and Blakemore, 1990), studies conducted by various laboratories over the past decade indicate that bacteria travel extracellularly, not intracellularly, either free in circulation or attached to the surface of monocytes (Segura and Gottschalk, 2002). Importantly, neutrophils and monocytes are unable to kill *S. suis* in the absence of specific antibodies (Chabot-Roy et al., 2006). In addition, it has been shown that suilysin is toxic to not only epithelial and endothelial cells but also monocytes and neutrophils, thus suggesting a role in immune evasion. Moreover, suilysin appears to affect complement-dependent killing by decreasing the opsonization of *S. suis* and the bactericidal capacity of neutrophils (Charland et al., 2000; Gottschalk and Segura, 2000; Lalonde et al., 2000; Segura and Gottschalk, 2002; Chabot-Roy et al., 2006; Segura et al., 2006).

In the event that *S. suis* fails to cause acute fatal septicemia, bacteria are able to reach the CNS via mechanisms that are only partially elucidated, such as adhesion to, with or without toxicity, and invasion of brain microvascular endothelial cells (BMVEC) (Charland et al., 2000; Vanier et al., 2004; Benga et al., 2005). BMVEC, together with the choroid plexus epithelial cells (CPEC), constitute the structural basis of the blood–brain barrier (BBB). It has recently been shown that *S. suis* also affects porcine CPEC barrier function and integrity. Although apoptosis may be involved in the process of CPEC cell death, necrosis seems to be the predominant mechanism.
These and probably other mechanisms facilitate *S. suis* invasion of the CNS (Tenenbaum et al., 2005, 2006).

**Inflammation as a major player in *S. suis* pathology?**

Clinical presentation of *S. suis* infection in swine and humans varies from asymptomatic bacteremia to fulminating systemic disease similar to Gram-negative sepsis. The increased severity of *S. suis* infections in humans observed in cases of septic shock and toxic shock-like syndrome, such as a shorter incubation time, more rapid disease progression and a higher rate of mortality, is indicative of a massive inflammatory process and underscores the critical need to better understand the interactions between *S. suis* and cells of the host immune system. In addition, clinical signs of meningitis in swine have also been associated with inflammation in the CNS, and treatment with anti-inflammatory drugs contributes to the recovery of the affected animal (Higgins and Gottschalk, 2005).

Multiple lines of evidence suggest that the immune system may play an important role not only in the development of protection against disease but also in the pathology caused by the invading pathogen. Indeed, several inflammatory and infectious diseases are associated with the overproduction of pro-inflammatory cytokines and chemokines, and the recruitment and activation of different leukocyte populations are hallmarks of acute inflammation. Given that these cytokines have been detected in the blood and cerebrospinal fluid (CSF) during septic shock and invasive meningeal infections, the ability of *S. suis* to induce cytokine production may have considerable biological relevance (Verhoef and Mattsson, 1995). We previously demonstrated that *S. suis* is able to induce the production of pro-inflammatory cytokines by murine and human cells (Segura et al., 1999, 2002). More recently, we confirmed the inflammatory properties of *S. suis* in a swine whole blood culture system (Segura et al., 2006). Live bacteria induce high levels of tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β) and IL-6 and intermediate levels of IL-8 and monocyte chemotactic protein (MCP)-1 in this system. The bacterial cell wall was observed to be the major cytokine-inducing component, whereas capsule expression was important for MCP-1 activation. The presence of specific antibodies that suppress bacterial growth also causes a significant reduction in levels of cytokine production. Thus, antibody-mediated bacterial phagocytosis combined with suppressed inflammation may be beneficial for infection control strategies (Segura et al., 2006).

We further studied *in vitro* the receptors involved in cell activation by *S. suis*. We demonstrated that stimulation of human monocytes by whole encapsulated *S. suis* or its purified cell wall components influences the relative expression of Toll-like receptor (TLR) 2 and CD14 mRNA. Moreover, this stimulation triggers the release of cytokines (TNF-α, IL-1β and IL-6) and chemokines (IL-8 and MCP-1), which is significantly reduced by antibody-mediated neutralization of TLR2 but not TLR4. Mouse macrophages deficient in TLR2 also show reduced IL-6 and MCP-1 release in response to whole encapsulated bacteria. Given that this response is completely abrogated in MyD88-deficient macrophages, other TLRs might be involved in MyD88-dependent cytokine production induced by encapsulated *S. suis*. Furthermore, we demonstrated that the presence of CPS modulates *S. suis* interactions with TLRs. In the absence of CPS, uncovered cell wall components induce cytokine and chemokine production via TLR2-dependent as well as -independent pathways. However, CPS contributes to MCP-1 production in a MyD88-independent manner (Graveline et al., 2007).

A typical type 1 inflammatory response is observed following *S. suis* infection. However, the failure to control this inflammatory cascade may contribute to clinical manifestations and poor outcome (Dominguez et al., 2007). Since most of the aforementioned cytokines are believed to mediate responses associated with clinical deterioration, multi-organ system failure and death, we developed an *in vivo* mouse model to study the septic shock induced by *S. suis*. Using the Luminex multiplex system, we quantitatively measured the kinetics of several cytokines simultaneously in a small volume of plasma. High levels of the pro-inflammatory cytokines TNF-α, IL-6, IL-12 and IFN-γ and the chemoattractants MCP-1, KC and RANTES were observed *in vivo* within 24 h post-infection and might be responsible in part for the sudden death of 20% of animals. On the other hand, the anti-inflammatory cytokine IL-10 was up-regulated mainly at 24 h post-infection, following the onset of most pro-inflammatory cytokines. This may indicate a negative feedback mechanism to control the extent of the inflammatory response. Increased rate of septic shock was observed in *S. suis*-infected mice that were treated with neutralizing antibodies against IL-10 (unpublished observations).

Meningitis is also one of the most striking features of *S. suis* infection, and, as previously mentioned, the inflammatory reaction induced by this pathogen at the CNS may play an important role in pathology. Indeed, fibrin, edema and cellular infiltrates in the meninges are typically observed during *S. suis* meningitis (Madsen et al., 2002). *S. suis* can induce the release of arachidonic acid by BMEC, a mechanism suggested to facilitate the ability of bacteria to penetrate the CNS and to modulate local inflammation (Jobin et al., 2005a). In addition, bacterial CPS induces human macrophages to secrete PGE2 and matrix metalloproteinase 9, which also may be involved in disruption of the BBB (Jobin et al., 2006). Finally, other studies from our laboratory have shown that *S. suis* is able to induce the release of pro-inflammatory cytokines and chemokines by human BMEC and to...
up-regulate the expression of adhesion molecules on human monocytes with consequent increased adherence of S. suis-activated monocytes to endothelial cells (Al-Numani et al., 2003; Vadeboncoeur et al., 2003).

In vivo experiments showed that infected mice that survive the septicemic phase can develop serious signs of inflammation at the CNS, with supplicative and necrotizing lesions at the meninges and brain parenchyma, especially in the cortex, hippocampus, thalamus, hypothalamus and corpus callosum. Bacterial antigens were detected in association with microglia residing only in the affected zones. In situ hybridization combined with immunocytochemistry showed transcriptional activation of TLR2 and TLR3 as well as of CD14, NF-κB, IL-1β, MCP-1 and TNF-α at the aforementioned brain structures. Microglia/macrophage cells were probably the main cellular sources of cytokine induction in the brain. Early transcriptional activation of TLR2, CD14 and inflammatory cytokines in the choroid plexus and brain endothelial cells suggests these structures as possible bacterial portals of entry into the CNS (Dominguez et al., 2007) (Gottschalk and Segura, 2000; Vanier et al., 2004; Tenenbaum et al., 2005, 2006). These data confirm the important role of the inflammatory response in the pathogenesis of S. suis infection in mice.

S. suis infection in humans

Since the first description in Denmark in 1968 (Perch et al., 1968), nearly 250 human cases of S. suis infection have been reported. Although S. suis disease has been considered in the past as a rare event in humans, it was identified more recently as the third most common culture-confirmed cause of community-acquired bacterial meningitis in Hong Kong, following Streptococcus pneumoniae and Mycobacterium tuberculosis as the most common agents (Hui et al., 2005). In addition to Denmark, cases have been reported in The Netherlands, Italy, Spain, the United Kingdom, Belgium, Croatia, Austria, New Zealand, Sweden, Hong Kong, Singapore, Taiwan, Japan, China, Thailand, Germany, Ireland, Hungary, France, Greece, Australia, Ireland, Hungary and Argentina (Christensen and Kronvall, 1985; Colaert et al., 1985; Dickie et al., 1987; Arends and Zanen, 1988; Dupas et al., 1992; Hampson et al., 1993; Yen et al., 1994; Perseghin et al., 1995; Spiss et al., 1999; Fongcom et al., 2001; Tarradah et al., 2001b; Watkins et al., 2001; Chan et al., 2002; Kopic et al., 2002; Rosenkranz et al., 2003; Huang et al., 2005; Lopreto et al., 2005; Chang et al., 2006; Voutsadakis, 2006). Mysteriously, only two cases have been reported in Canada (Trottier et al., 1991; Michaud et al., 1996) and only one, very recently, in the USA (Willenburg et al., 2006).

Most cases of S. suis infection have been attributed to serotype 2 strains, generally on the basis of biochemical analysis obtained using commercial kits (Colaert et al., 1985; Peetermans et al., 1989; Meecham and Worth, 1992; Yen et al., 1994; Perseghin et al., 1995; Caumont et al., 1996; Asensi et al., 2001; Alonso-Socas et al., 2006). While many of these tests claim to clearly differentiate serotype 2 from serotype 1 strains, there is no evidence of a correlation between a specific serotype and its biochemical properties (Michaud et al., 1996). In addition to serotype 2 strains, cases due to serotype 4 (Arends and Zanen, 1988), serotype 14 (Gottschalk et al., 1989; Watkins et al., 2001) and serotype 16 (one case in Vietnam; C. Schultz, personal communication, 2006) strains have also been reported. Two human cases associated with S. suis serotype 1 could not be confirmed because the serotype of these strains was established using only biochemical criteria and was not confirmed with a serologic reaction using specific sera (Kopic et al., 2002). Unfortunately, these isolates are not longer viable to allow confirmation of the serotype (J. Kopic, personal communication, 2004).

In humans, S. suis usually produces a purulent or non-purulent meningitis (Arends and Zanen, 1988). In addition, endocarditis, cellulitis, peritonitis, rhombomylitis, arthritis, spondylodiscitis, pneumonia, uveitis and endophthalmitis have been reported (Walsh et al., 1992; Huang et al., 2005). Arthritis affects various joints including hips, elbows, wrists, sacroiliac, spine and thumbs (Walsh et al., 1992). In most cases, arthritis reflects generalized septicemia caused by S. suis. Recently, an association between S. suis infection and colon carcinoma, as reported for Streptococcus bovis infection, has been suggested (Voutsadakis, 2006). Finally, cases of peracute infections with shock and a high rate of mortality have been described (see below). In general, most patients with systemic S. suis infections exhibit leukocytosis and neutrophilia (Suankratay et al., 2004), and patients with meningitis have CSF with high numbers of leukocytes, a high percentage of neutrophils, and low sugar and high protein levels (Suankratay et al., 2004).

One of the most striking features of the infection is the consequence of deafness and/or vestibular dysfunction following S. suis meningitis (Lutticken et al., 1986; Huang et al., 2005). Indeed, the recorded incidence of deafness following infection caused by this pathogen is consistently higher than that reported for other meningitis-causing bacteria, such as S. pneumoniae, Neisseria meningitidis and Haemophilus influenzae, and can reach 50 and 65% in Europe and Asia, respectively (Walsh et al., 1992). The reason for these observations is unknown. The deafness (unilateral or bilateral) has been mainly high tone, and is frequently associated with vertigo. Studies have shown that the accumulation of inflammatory cells observed around the vestibular-cochlear (eighth cranial) nerve in S. suis meningitis is insufficient to impede normal neural conduction. Alternatively, cochlear sepsis, resulting from passage of the organism from the sub-arachnoid space to the perilymph...
via the cochlear aqueduct, might be primarily responsible for the hearing loss complicating bacterial meningitis (Walsh et al., 1992; Huang et al., 2005). Early administration of antibiotics does not appear to have any influence on the development of subsequent hearing loss. No cases of deafness have been reported in non-meningitis cases of S. suis infection in humans.

**Epidemiology of the infection in humans**

The route of entry of the organism in humans might be a small cut in the skin, although in some cases no wound was detected. In addition, bacteria may colonize the nasopharynx, as observed in swine, and the gastrointestinal tract, as suggested by diarrhea as a prodromal symptom (Fongcom et al., 2001). The incubation period ranges from a few hours to two days (Fongcom et al., 2001). S. suis infection in humans generally occurs sporadically without obvious seasonal change. However, serious cases in Asia (either human or swine) occur mainly during the summer (Huang et al., 2005). Since most patients acquire the disease following occupational exposure to pigs or pork products, the preponderance of affected adult males is readily explained. There is only one report of a young female patient; she was four weeks old (Vilaichone et al., 2002).

Although few facets of the epidemiology of S. suis infections in humans have been elucidated, it is apparent that nearly all cases of human infection can be ascribed to a high degree of exposure to unprocessed pork meat or to close contact with pigs. With few exceptions, most cases of infected people are pig farmers, abattoir workers, persons transporting pork, meat inspectors, butchers and veterinary practitioners (Walsh et al., 1992; Huang et al., 2005; Tang et al., 2006). In the United Kingdom and France, this infection was listed as an Industrial Disease in 1983 and 1995, respectively (Walsh et al., 1992).

In 2005, the Center for Health Protection in Hong Kong classified S. suis as a statutorily notifiable disease (Amendment to Quarantine and Prevention of Disease Ordinance Cap. 141, 2005, www.chp.gov.hk/letters.asp?lang=en&id=31&ampid=13). Although it has been suggested that manifestation of disease in pigs is not a prerequisite for infections in people in contact with pigs (which may be healthy carriers), handling diseased pigs (with high rate of bacterial shedding) would certainly increase the risk (Staats et al., 1997; Higgins and Gottschalk, 2005).

Surprisingly, in a recent report from Thailand, only three of 41 cases had a history of occupational and behavioral exposure to pigs (Wangkaew et al., 2006). However, since these cases were identified in a retrospective study, data could easily have been missed. In addition, open markets where people can buy raw pork or porcine products are widely available in Asian countries, thus it is not possible to exclude indirect exposure (Wangkaew et al., 2006). It has been shown that more than 6% of pork samples was positive for S. suis carriage in six wet markets in Hong Kong (Ip et al., 2007).

The presence of the organism would be confined not only to the tonsillar region, but also to other sites such as the head/neck, tonsils, tongue, intestines, bone and tail that are all readily available in the wet markets as ingredients for Chinese cuisine. In a risk assessment exercise, it may be possible to minimize the exposure to S. suis by avoiding handling of specific parts of the pig carcass. Although it was suggested that the bulk of meat/muscle in healthy pigs may be relatively free of this pathogen (Ip et al., 2007), S. suis was isolated from the bulk of meat in a cold storage house in Jiangxi Province during the 2005 outbreak in China (Ye et al., 2006). Thus, minced meat could potentially be another source of contamination for humans handling pork products.

In The Netherlands, the annual risk of S. suis infection among abattoir workers and pig breeders was estimated at approximately 3.0/100,000, a rate that is 1500 times higher than that among persons not working in the pork industry. For abattoir workers, it was concluded that eviscerators involved in removing the larynx and lungs from the carcasses have a significantly greater risk of exposure to S. suis (Arends and Zanen, 1988). Butchers had an annual rate of 1.2/100,000; this rate is even higher in the United Kingdom (Walsh et al., 1992). In Germany, the nasopharyngeal carriage rate of S. suis serotype 2 in the high-risk group (butchers, abattoir workers and meat processing employees) was 5.3%, while those without contact with pigs or pork consistently tested negative (Strangmann et al., 2002). It has to be noted that a selective medium was not used in this study, indicating that the number of positive samples was probably underestimated (Strangmann et al., 2002). Interestingly, some positive individuals were sampled again 3 weeks after the first study, and the presence of S. suis serotype 2 could still be confirmed, indicating that the bacteria probably remained at the tonsils of healthy people for a relatively long period of time, as demonstrated previously in pigs (Higgins and Gottschalk, 2005).

Other reports confirmed isolation from tonsils in healthy abattoir workers (Sala et al., 1989; Rojas et al., 2001). In New Zealand, a study revealed that 9% of dairy farmers, 10% of meat inspectors and 21% of pig farmers were seropositive with the S. suis serotype 2, indicating the presence of human subclinical infections (Robertson and Blackmore, 1989). However, these data should be considered with caution since no standardized serological test to detect S. suis antibodies exists and the ELISA test used might have detected false cross reactions. In general, these data indicate that high exposure to S. suis may lead to a colonization of the upper respiratory tract without producing any health consequences. Only in some cases,
clinical disease may follow. In this regard, predisposing factors may influence disease progression. As reported for Group B Streptococcus (Sims and Barton, 2006), splenectomy, alcoholism, diabetes mellitus and malignancy have been suggested as important predisposing factors for the development of serious S. suis disease (Gallagher, 2001; Watkins et al., 2001; Huang et al., 2005). Indeed, many S. suis cases have been described in individuals who had suffered splenectomy (Baddeley, 1995; Auer et al., 2001; Tambyah and Lee, 2001; Watkins et al., 2001; Kopic et al., 2002; de la Hoz Adame et al., 2005; Lopreto et al., 2005). Furthermore, the fatality rate of S. suis infection after splenectomy is nearly 80%. It has been suggested that individuals who have had a splenectomy should be excluded from the meat trade or pig farms (Gallagher, 2001). A study in Thailand reported that 75% of affected patients had a history of significant alcohol consumption (Suankratay et al., 2004). Patients with rheumatic heart disease, valvular heart disease or ventricular septal defect were more likely to have infective endocarditis (Huang et al., 2005). Finally, in addition to pigs, wild boars are a possible reservoir for S. suis and a major source of S. suis infection for hunters and poachers (Grebe et al., 1997; Halaby et al., 2000; Rosenkranz et al., 2003). Indeed, the prevalence of S. suis serotype 2 among wild boars (11%) is similar to that among domestic pigs (14%) in Germany (Baums et al., 2007).

Although there are some phenotypic differences between human and swine strains of S. suis serotype 2, most studies show that strains isolated from humans are phenotypically and genotypically similar to those recovered from swine within the same geographical region (Chatellier et al., 1999; Berthelot-Herault et al., 2002; Pedrol et al., 2003; Marois et al., 2006; Yu et al., 2006; Rehm et al., 2007). While a high molecular weight variant of the protein EF (EF*) has been associated with strains that are pathogenic to humans, other studies showed that the MRPEF profiles from human isolates were generally identical to those of the corresponding pig strains found in the same country. Interestingly, similar to most swine strains in North America, strains isolated from humans in Canada and USA were negative for MRP, EF and suilysin (Chatellier et al., 1999; unpublished observations). In 2001, Tarradas et al. reported two cases of meningitis in a butcher and an abattoir worker who had handled pork originating from the same three closed farms (Tarradas et al., 2001b). Analysis of S. suis serotype 2 strains recovered from tonsils of healthy pigs from these farms showed that they were genotypically similar but not identical to the human strains. The slight differences between isolates might reflect an adaptation to the new host or, more likely, a lack of reproducibility of the detection technique. Virulence properties of strains isolated from pigs or humans appear to be similar (Charland et al., 2000; Halaby et al., 2000; Lalonde et al., 2000; Segura et al., 2002).

**Serious outbreak of S. suis disease in humans: the Chinese experience**

In summer 2005, an important outbreak of acute disease in humans caused by S. suis serotype 2 was reported in Sichuan, China (Normile, 2005). Although several reports are available concerning this outbreak, the official report of the Sichuan and Beijing, China CDCs indicated a total of 215 cases, 66 of which were laboratory confirmed, with a total of 39 deaths (Yu et al., 2006). The most important feature of this outbreak was the high incidence of systemic disease and proportionally low number of cases of meningitis, as well as a high rate of mortality. Three clinical presentations were observed: sepsis, meningitis and streptococcal toxic shock syndrome (STSS) (Tang et al., 2006; Yu et al., 2006). The original ‘toxic shock syndrome (TSS)’ is clearly defined in clinical and laboratory data (http://www.cdc.gov/epo/dphsi/casedef/toxicsscurrent.htm). STSS is also a well-defined syndrome, usually associated with Group A streptococci (GAS) (http://www.cdc.gov/epo/dphsi/casedef/streptococcalscurrent.htm). Less frequently, it has been associated with streptococci other than GAS (Hashikawa et al., 2004). TSS and STSS are usually toxin-mediated and mainly associated with superantigens (Alouf and Muller-Alouf, 2003). In some STSS cases, M protein–fibrinogen interactions with activation of the coagulation system have also been suspected (Cohen, 2002; Herwald et al., 2004). However, the term ‘toxic shock-like syndrome’ is a more generic term referring to a clinical situation that shares many characteristics of TSS. In addition, septic shock, which is a highly lethal syndrome of cardiovascular shock with progressive organ damage of the liver, kidneys and lung that kills within 24–48 h after onset, may also present some features clinically similar to TSS (Ulloa and Tracey, 2005).

What happened in the Chinese outbreak? Cases in China were suggested as STSS based on the presence of the following criteria: sudden onset of high fever, diarrhea, hypotension, blood spots and petechia, clear erythematous blanching rash and dysfunction of multiple organs, such as acute respiratory distress syndrome, liver and heart failure, disseminated intravascular coagulation and acute renal failure (Tang et al., 2006; Yu et al., 2006). Until more information about the toxic potential of the strains responsible for the outbreak can be obtained, it would be more appropriate to classify the Chinese episode as a streptococcal toxic shock-like syndrome. Although this is the first very large human outbreak with many patients presenting these acute symptoms, there is one previous report of an ‘STSS’ caused by S. suis (Suankratay et al., 2004) and there are many other reports in the literature indicating severe cases of S. suis sepsis with shock, multiple organ failure, disseminated intravascular coagulation and associated purpura fulminans, which lead to death within hours (Arends and Zanen, 1988; Bungener and Bialek, 1989; van Jaarsveld et al., 1990;
Francois et al., 1998; Fongcom et al., 2001; Kopic et al., 2002; Strangmann et al., 2002; Pedrol et al., 2003). Interestingly, ten of 41 cases recently described in Thailand had sepsis syndrome in the absence of primary organ infection with a clinical presentation similar to that described in the Chinese outbreak (Wangkaew et al., 2006). A serious case of septic shock caused by a non-serotype 2 strain (serotype 14) has also been described (Watts et al., 2001). Although the Sichuan outbreak is the largest recorded outbreak of S. suis infection in humans, another smaller human outbreak took place in Jiangsu Province (also in China) in 1998 that affected 25 people with 14 reported deaths (Zhu et al., 2000; Yu et al., 2006).

In the Sichuan outbreak, cases occurred in association with backyard production systems where people were directly exposed to infection during the slaughtering process of pigs that had presented clinical signs of illness or had died of unknown causes (Yu et al., 2006). It is also possible that infection resulted from consumption of affected pigs as food. There was no evidence of human to human infection and none of the 417 healthcare workers who had cared for case patients were clinically infected (Yu et al., 2006). Notably, the human outbreak followed a local swine outbreak that killed more than 600 backyard pigs (Yu et al., 2006). Most patients were farmers, although five butchers and one veterinarian were also affected (Tang et al., 2006). The first suspected human case was reported on 24 June 2005, three days after the patient slaughtered a diseased goat (Yu et al., 2006). One day after the first report, his neighbor was also affected. Both men died within hours, and although no bacteriological culture was attempted, this clearly represented the beginning of an outbreak of similar cases in the same region where S. suis was later identified. Although reported to affect ruminants (Hommez et al., 1988), human infection after exposure to animal species other than swine has not been described or proven to date. In backyard farms where various animal species are kept together, S. suis infections can be transmitted from pigs to other species (Yu et al., 2006). Indeed, a dog that had been fed raw pig meat died without prior clinical signs, and S. suis type 2 was later isolated from the deceased animal’s cerebrum and liver (Keymer et al., 1983). We have isolated S. suis serotype 2 from an abortion case of a cow that had been transported in a non-disinfected truck that was typically used for swine transportation (unpublished observations). In addition, S. suis is believed to be a normal inhabitant of the intestine of a variety of ruminants (Staats et al., 1997). Nevertheless, since bacteriological cultures were not performed a cause-effect relationship cannot be formerly established between the diseased goat and the first two patients of the Sichuan outbreak. Genotypic studies comparing S. suis strains from swine, human and other animal species would give new insights into the epidemiology of S. suis infections.

Farmers in Sichuan Province have close contact with pigs. In addition, animals are illegally slaughtered at home and it is not uncommon that diseased animals are slaughtered for family consumption, and sometimes commercialized. These facts may explain the higher degree of animal to human transmission in the Sichuan outbreak, and maybe in other parts of Asia. In fact, control measures strictly applied during the outbreak, such as strict prohibition of illegal slaughtering, eating, selling and transporting diseased pigs, greatly contributed to ending the outbreak (Yu et al., 2006). However, these practices have existed for hundreds of years and are similar in other countries in Asia (Wangkaew et al., 2006), where such large outbreaks have not been reported before. Explanations such as the presence of predisposing factors (asplenia, diabetes mellitus, alcoholism or malignancy) have not been described in Sichuan patients (Dr J. Xu, unpublished observations). It has been suggested that the increased mortality was also due to delayed access to treatment (Sriskandan and Slater, 2006). Thus, why did so many cases suddenly appear? One hypothesis to explain the abrupt onset of disease and its high infectivity is that there was a new, highly virulent and more toxic strain that might possess the ability to produce superantigens. The first question to resolve was whether the presence of one or more strains was at the origin of this outbreak. Independent researchers clearly confirmed the identity of S. suis strains recovered from ill patients, and also showed that the strains belong to serotype 2 (Tang et al., 2006; Ye et al., 2006; Yu et al., 2006). Using restriction fragment length polymorphisms, ribotyping and pulsed-field gel electrophoresis, strains involved in both the human and swine outbreaks were shown to be clonal and identical to the strain responsible for the 1998 outbreak in Jiangsu Province (Tang et al., 2006; Ye et al., 2006; Yu et al., 2006). Multilocus sequence typing (MLST) is a technique that defines strains by using sequences of different housekeeping loci and has become the method of choice to compare different microbial populations. Using MLST, all but two strains from the 2005 outbreak were classified into a single sequence type (ST), called ST-7, which derives from the ST-1 complex (Ye et al., 2006). The latter has been strongly associated with cases of septicemia and meningitis in swine and humans in different parts of the world (King et al., 2002).

Since almost all cases were produced by a single clone, the next step was to study whether this new clone possesses higher virulence capacities. The presence of known virulence factors and markers in representative strains was studied. The emerging clone produces MRP, EF and suilysin proteins, a feature that is typical of Euroasian strains (Ye et al., 2006; Yu et al., 2006). After studying the structural gene clusters involved in CPS synthesis, one of the studies showed that the Chinese clone strain has a genetic pattern which differs from that of strain P1/7, an internationally well-characterized pathogenic strain (http://www.sanger.ac.uk/Projects/S_suis/). In fact, seven of 12 CPS structural genes showed some point variations (Tang et al., 2006). However, phenotypic
changes that might have resulted from these mutations have not been studied (amount of CPS expressed, composition, etc.). In fact, the strains could be serotyped as usual (Ye et al., 2006). Although the most common disease observed was a toxic shock-like syndrome, the presence of superantigens could not be identified in the ST-7 clone strain (Tang et al., 2006; unpublished data; Dr T. Profi, personal communication). Cytotoxicity studies performed with peripheral blood mononuclear cells showed that the Chinese ST-7 strain was significantly more toxic than a well-characterized European virulent strain 31533 (ST-1) (Ye et al., 2006). Although previous studies in our laboratory showed that the 31533 strain is toxic to various cells (Segura et al., 1998, 2002, 2004, 2006; Charland et al., 2000; Lalonde et al., 2000; Segura and Gottschalk, 2002; Chabot-Roy et al., 2006), the increased toxic properties of the ST-7 strain remains to be characterized. Finally, the Chinese clone strain was also shown to be pathogenic to mini-pigs (Tang et al., 2006), although it was not compared to other virulent swine strains. In conclusion, there is so far no clear explanation as to why the ST-7 clone induced such a serious outbreak of systemic disease in humans. The complete genome of a representative strain from the emerging ST-7 type, as well as another strain isolated from a human case in Vietnam, is presently under investigation at the Sanger Institute in the United Kingdom (C. Schultz and M. Holden, personal communication).

The situation in North America: are the few reported cases due to low incidence of human disease or to inadequate detection?

There are only three human cases reported in North America: two in Canada (one case of endocarditis and one of meningitis) and one case of meningitis in the United States (Trottier et al., 1991; Michaud et al., 1996; Willenburg et al., 2006). As mentioned above, the overall case fatality rate from S. suis infection has been reported to be near 13% in Europe and 20% in Asia (Huang et al., 2005). The three affected individuals in North America survived, and only one resulted in a certain degree of cochlear type hypoacusia which improved with treatment and resolved completely after six months (Michaud et al., 1996). Two hypotheses may be raised concerning the low number of human S. suis infections reported: (a) there is a serious problem in diagnostic laboratories such that this bacterial species is underdiagnosed and they usually misidentify it as other streptococci, and (b) as suggested above, North American strains of S. suis possess a lower virulence potential. In our opinion, both hypotheses are valid and may explain the low number of cases. Although S. suis field isolates readily grow on media used for culturing meningitis-causing bacteria, many laboratories are not aware of this microorganism and usually misidentify it as enterococci, S. pneumoniae, S. bovis, Group D streptococci, viridans group streptococci (Streptococcus anginosus, Streptococcus vestibularis and others) or even Listeria (Lutitckiet al., 1986; Arends and Zanen, 1988; Yen et al., 1994; Michaud et al., 1996; Huang et al., 2005; Tsai et al., 2005).

For example, Donsakul et al. reported that five of eight cases of S. suis infections had been erroneously diagnosed as Streptococcus viridans (Donsakul et al., 2003). In many cases, the initial Gram stain diagnosis of the CSF specimen is pneumococcal meningitis. This confusion may have led to missed diagnosis of S. suis meningitis in the past. At least one of the Canadian cases was diagnosed retrospectively after the isolate was initially identified as S. viridans (R. Higgins, personal communication; Trottier et al., 1991). Considering the many and very large swine operations in different parts of Canada and the United States, the number of human S. suis cases in North America is probably underestimated. Several months after the Chinese outbreak, which attracted considerable public and scientific interest (Normile, 2005), the first report in USA was published (Willenburg et al., 2006) indicating that active research may increase the number of human cases reported.

As mentioned above, most North American strains do not carry the virulence markers, MRP, EF and suilysin, and are probably less virulent to healthy pigs and, possibly, to healthy humans, as demonstrated by comparative experimental infection of piglets (Berthelot-Herault et al., 2005). The high impact of S. suis swine infections in Canada and USA is mainly associated with the presence of PRRSV infections (Halbur et al., 2000; Thanawongnuwech et al., 2000; Feng et al., 2001; Pallares et al., 2003). This situation may also explain the presence of not only serotype 2 strains but also other serotypes that cause important swine outbreaks (Gottschalk and Segura, 2000; Cloutier et al., 2003; Higgins and Gottschalk, 2005). Since serotype 2 is the most common serotype affecting humans, the low prevalence of this serotype in North America might contribute to reduced number of human cases.

Therapy and prevention of the infection in humans

S. suis strains recovered from humans are typically sensitive to penicillin, with a few exceptions (Twort, 1981; Lutitckiet al., 1986; Vilachone et al., 2000). Therefore, intravenous penicillin G has been used to successfully treat most cases. However, it should be noted that penicillin-resistant strains have been isolated in 6–28% of piglets (Higgins and Gottschalk, 2005; Huang et al., 2005). Since at least two cases of relapse have occurred after two and four weeks of treatment, antibiotics should be administered for a relatively long period of time (at least 6 weeks) (Woo and Li, 1987; Kay et al., 1995). Ampicillin and chloramphenicol, sometimes combined with an aminoglycoside, can also be used. As previously mentioned, hearing loss and vestibular
disturbances are frequently observed sequelae unrelated to antibiotic use (Lutticken et al., 1986). Resistance to norfloxacin has been reported in strains recovered from humans (Tayoro et al., 1996).

*S. suis* vaccines for humans do not exist so far. There are also no effective vaccines available even for swine (Higgins and Gottschalk, 2005). Interestingly, there is a report of a patient with recurrent septic shock, 15 years after the first episode, due to *S. suis* serotype 2 (Francois et al., 1998). The second and fatal episode was considered as a re-infection rather than a recurrence of the previous infection. The authors suggested an absence of immunity after the first infection and highlighted the importance of constant prevention in exposed workers. As mentioned above, low prevalence of antibodies against *S. suis* is also reported in healthy individuals professionally exposed to this microorganism (Robertson and Blackmore, 1989; Elbers et al., 1999). Nevertheless, more data would be required to determine the magnitude and the extent of the adaptive immune responses generated in patients affected by *S. suis*. On the other hand, in experimental infections, infected pigs become resistant to a new infection with the same or another strain belonging to the same serotype (del Campo Sepulveda et al., 1996; Higgins and Gottschalk, 2005). However, the second experimental infection was carried out within a relatively short period of time and long-term protection has not been evaluated in this model.

Despite the low incidence of *S. suis* infection in humans, some preventive measures may be justified due to the high rate of contamination of pigs with this microorganism. Individuals in close occupational contact with pigs or pork should pay special attention. As mentioned above, most infected persons are probably healthy carriers (Breton et al., 1986; Strangmann et al., 2002); however, in situations of stress or immunodeficiency, *S. suis* may become an opportunistic pathogen. *S. suis* can also survive in the environment. The organism has been shown to survive in feces for 104 days at 0°C, up to 10 days at 9°C, and up to 8 days at 22–25°C. It also survives in dust up to 54 days at 0°C and up to 25 days at 9°C, but could not be isolated from dust stored at room temperature for 24 h (Clifton-Hadley and Enright, 1984). Moreover, *S. suis* can survive in water for 10 min at 60°C, making the scalding process in abattoirs a possible source of contamination. On the other hand, the organism is rapidly inactivated by disinfectants and cleansers, commonly used in farms and laboratories at concentrations lower than those recommended for use by the manufacturers (Clifton-Hadley and Enright, 1984).

**Conclusion**

*S. suis* is the cause of an uncommon but potentially serious disease in humans. Despite wide prevalence of the infection in the pig population, a relatively low number of human cases are reported each year. The Chinese outbreak in 2005 provoked strong interest within the scientific community, clearly indicating that this zoonotic agent must be given important consideration. Given that many people worldwide are in contact with pigs daily and that *S. suis* is a common cause of disease in swine populations, it is reasonable to propose that many persons already harbor this pathogen without presenting any clinical signs. Under unusual circumstances, disease may develop. Due to close contact with pigs in certain Asian countries, it is expected that such countries report a higher number of human cases. Physicians and microbiologists, especially in North America, should be aware of this infection, and more attention should be given to streptococcal meningitis or septic shock cases in people working with pigs or pork products. Veterinarians should also be aware that there is a low but real risk during handling of *S. suis*-diseased animals that are probably shedding high numbers of this zoonotic agent.

There is some dispute regarding the preventive measures that might be justified due to the high rate of contamination of pigs with this microorganism. Some authors advise that prompt first-aid care of injuries in meat handlers might reduce the risk of *S. suis* infections, although others consider this recommendation questionable because it is evident that skin lesions have only been reported in some cases and the route of entry of the infection remains unclear (Lutticken et al., 1986). Although it is difficult to recommend effective prevention measures for employees of the food industry, people coming into close occupational contact with pigs or pork should pay special attention. As mentioned above, most infected persons are probably healthy carriers; however, in situations of stress, immunodeficiency and other predisposing factors, *S. suis* may become an opportunistic pathogen. Increased collaboration between laboratories with diverse but complementary expertise in different parts of the world is necessary to significantly increase our understanding of this intriguing pathogen (Sriskandan and Slater, 2006).

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