REVIEW ARTICLE

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Streptococcus suis: a re-emerging pathogen associated with occupational exposure to pigs or pork products. Part I – Epidemiology

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Abstract

Streptococcus suis (ex Elliot 1966, Kilpper-Bälz & Schleifer 1987) is a facultatively anaerobic Gram-positive ovoid or coccal bacterium surrounded by a polysaccharide capsule. Based on the antigenic diversity of the capsule, *S. suis* strains are classified serologically into 35 serotypes. *Streptococcus suis* is a commensal of pigs, commonly colonizing their tonsils and nasal cavities, mostly in weaning piglets between 4–10 weeks of age. This species occurs also in cattle and other mammals, in birds and in humans. Some strains, mostly those belonging to serotype 2, are also pathogenic for pigs, as well as for other animals and humans. Meningitis is the primary disease syndrome caused by *S. suis*, both in pigs and in humans. It is estimated that meningitis accounted for 68.0% of all cases of human disease reported until the end of 2012, followed by septicaemia (including life-threatening condition described as 'streptococcal toxic shock-like syndrome' – STSLS), arthritis, endocarditis, and endophthalmitis. Hearing loss and/or vestibular dysfunction are the most common sequelae after recovery from meningitis caused by *S. suis*, occurring in more than 50% of patients. In the last two decades, the number of reported human cases due to *S. suis* has dramatically increased, mostly due to epidemics recorded in China in 1998 and 2005, and the fulminant increase in morbidity in the countries of south-eastern Asia, mostly Vietnam and Thailand. Out of 1,642 cases of *S. suis* infections identified between 2002–2013 worldwide in humans, 90.2% occurred in Asia, 8.5% in Europe and 1.3% in other parts of the globe.

The human disease has mostly a zoonotic and occupational origin and occurs in pig breeders, abattoir workers, butchers and workers of meat processing facilities, veterinarians and meat inspectors. Bacteria are transmitted to workers by close contact with pigs or pig products, usually through contamination of minor cuts or abrasions on skin of hands and/or arms, or by pig bite. A different epidemiologic situation occurs in the Southeast Asian countries where most people become infected by habitual consumption of raw or undercooked pork, blood and offal products in the form of traditional dishes. Prevention of *S. suis* infections in pigs includes vaccination, improvement in pig-raising conditions, disinfection and/or fumigation of animal houses, and isolation of sick animals at the outbreak of disease. Prevention of human infections comprises: protection of skin from pig bite or injury with sharp tools by people occupationally exposed to pigs and pig products, prompt disinfection and dressing of wounds and abrasions at work, protection of the respiratory tract by wearing appropriate masks or repirators, consulting a doctor in the case of febrile illness after exposure to pigs or pork meat, avoidance of occupations associated with exposure to pigs and pork by immunocompomised people, avoidance of consumption of raw pork or pig blood, adequate cooking of pork, and health education.

Key words

Streptococcus suis, pigs, humans, carriage, disease, epidemiology, treatment, prevention

INTRODUCTION

Streptococcus suis is a primary commensal of pigs, commonly colonizing tonsils and nasal cavities of these animals [1–5]. In the course of evolution, some strains – mainly those belonging to serotype 2 – became virulent for pig hosts, causing meningitis, septicaemia and many other diseases. The disease in swine, described for the first time by Field et al. [6], occurs mainly in piglets up to 10 weeks of age [7]. It causes significant economic losses worldwide, which have been estimated in the USA alone at over 300 millions dollars *per annum* [3]. The bacterium may also infect other mammals and birds [8–10], and since 1968 is known as a zoonotic human pathogen mainly of occupational origin [11], frequently causing meningitis with subsequent hearing loss, or less often, septicaemia or other diseases in pig farmers, butchers and abbatoir workers worldwide [5, 12, 13]. The interest in human infections caused by *S. suis* has grown exponentially after two epidemics in China with high mortality that occurred in 1998 and 2005 [4, 14–16], and after disclosure of the high morbidity in other East Asia countries, often associated with oral infection by consumption of raw pork products. The organism has been classified as a re-

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emerging pathogen, posing risk for a wide population of people exposed to pigs or pork products by occupation, or by consumption of traditionally prepared raw pork or pig blood [5, 17]. This classification is substantiated by the fact that in recent decades the pork industry is the most rapidly and geometrically expanding sector of the food industry, which dramatically increases the number of humans potentially exposed to *Streptococcus suis* infection [18, 19]. The intensive research, conducted mainly in Canada, China, Japan, and The Netherlands, resulted in the discovery of the multitude of virulence factors which create prospects for the future production of an effective vaccine which could be very useful in the prevention of human diseases, as well as those related to occupation [14, 20]. As the human disease caused by *Streptococcus suis* has no name, we propose to define it as a 'porcine streptococcosis' by analogy with some other zoonotic diseases, such as 'avian influenza' [21].

The first of the presented review article focuses on the epidemiology of the disease, while the subsequent part will focus on its pathogenesis.

SPECIES CHARACTERISTICS AND IDENTIFICATION METHODS

Streptococcus suis (ex Elliot 1966, Kilpper-Bälz & Schleifer 1987) is a facultatively anaerobic Gram-positive ovoid or coccal bacterium measuring, on average, 1.0–1.5 μm, occurring in pairs, short chains, or singly (Fig. 1). It is classified within the family Streptococcaceae, order Lactobacillales, phylum Firmicutes [22–24].

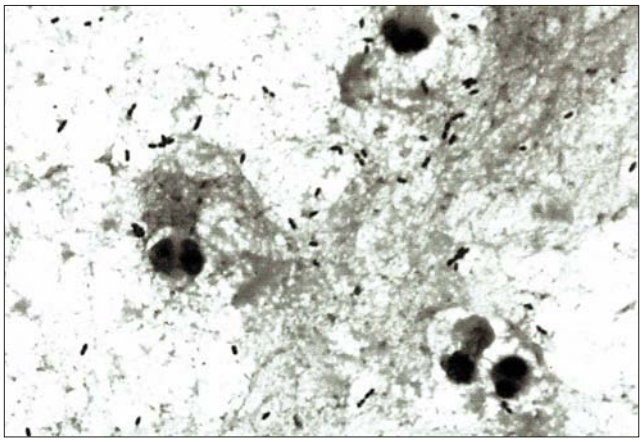

Figure 1. *Streptococcus suis* cocci, mostly in pairs, in cerebrospinal fluid of patient with meningitis. According to Manzin et al. [95]

The presence of *S. suis* in the organism of humans and animals can be ascertained by bacteriological, immunologic and molecular methods. If *S. suis* meningitis is suspected, cultures of cerebrospinal fluid (CSF) are recommended, while at the suspicion of septicaemia – blood cultures [25]. Columbia agar plates supplemented with 5% defibrinated sheep blood and Todd-Hewitt Broth are recommended for the culture of *S. suis*, both for diagnostic and research purposes [14, 26]. Colonies of *S. suis* grown on blood agar after 24 hrs of incubation at 37 °C are small (0.5–1.0 mm diameter), greyish or transparent, and slightly mucoid. Most *S suis* strains produce narrow zones of α-haemolysis on sheep or bovine blood agar plates, while on horse blood agar, β–haemolysis is noted [1, 3, 4, 23]. The biochemical differentiation from other α-hemolytic streptococci commonly occurring in vertebrate respiratory and/or gastrointestinal tracts, such as *Streptococcus pneumoniae*, viridans group streptococci (e.g., *Streptococcus anginosus*, *S. bovis*, *S. salivarius, S. sanguinis, S. mitis*), 'group D streptococci', and enterococci, may often be troublesome and/or misleading [25, 27]. Tarradas et al. [2] recommend following biochemical features distinguishing *S. suis* from similar species: no growth in 6.5% NaCl agar, a negative Voges–Proskauer test (for production of acetoine), positive test for esculin hydrolysis, production of acid from trehalose, and total absence of β–haemolysis on sheep blood agar. Another trait of *S. suis* of diagnostic importance is resistance to optochin, a derivative of hydroquinine, which is efficient in the treatment of pneumococcosis [28].

S. suis cells are surrounded by a polysaccharide capsule showing a diverse antigenicity, depending on the strain. Based on antigenic diversity, *S. suis* strains are currently classified serologically into 35 serotypes (serotypes 1–34 and serotype 1/2 which react with both serotypes 1 and 2 antisera) [24]. Serotyping of *S. suis*, mostly by the agglutination test with a panel of antiserum samples, is a basic identification method of clinical isolates, superior to biochemical tests (Fig. 2). Out of the 35 known serotypes, only a limited number are responsible for infections in pigs [28]. Serotype 2 is considered as the most virulent, both for humans and pigs [24, 28]. Based on the varied virulence of *S. suis* strains, Feng et al. [14] categorized them into highly pathogenic, weakly-pathogenic (hypo-virulent), and non-pathogenic (avirulent). A different classification, applied only to pathogenic *S. suis* strains has been presented by Ye et al. [29] who distinguished intermediate pathogenic, highly pathogenic, and epidemic strains, of which the latter are the most virulent.

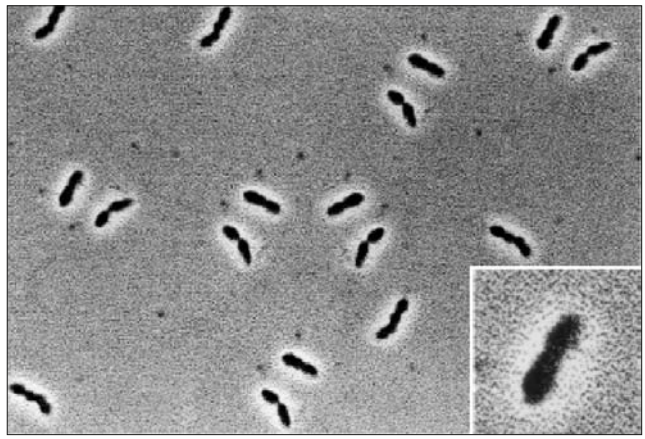

Figure 2. *Streptococcus suis* serotype 2 cocci with capsules swelled after agglutination reaction with homologous serum. Reproduced from Scientific Electronic Library Online (Scielo), Sao Paulo, Brazil: http://www.scielo.br/img/fbpe/pvb/v22n1/8864f1.gif

Besides the serotyping by agglutination, other immunologic methods have been developed for diagnosis of *S. suis* infections, including the immunocapture method, fluorescent antibody techniques, whole-cell antigen-based indirect ELISA, and purified capsular polysaccharide antigen-based indirect ELISA [4].

In addition to serotype, the genotype contributes to the virulence of *S. suis*. The *S. suis* genome, which has been completely sequenced in a number of strains, usually appears as a single, circular chromosome. Its size varies markedly

from 1,640,446–2,341,754 bp, with an average G+C content of ~41% [4, 14, 29–31]. A notable variation can also be observed in the gene number which ranged from 1,825–2,447 in 98 strains isolated by Willemse et al. [30] in The Netherlands.

A comparative genomic analysis revealed that *S. suis* is phylogenetically distinct from other *Streptococcus* species, as approximately 40% of the *S. suis* genome is unique in comparison to other *Streptococcus* species [25, 32]. Although the functions of 20–30% of the genes are unknown, many genes that may play a part in the pathogenesis of *S suis* infection have been studied, including polysaccharide production, capsular transport, iron-restriction factors, suilysin, virulence-associated proteins, various enzymes, arginine deiminase system, and IgG binding proteins. The virulence of *S suis* differs among serotypes and between different strains of the same serotype.

S. suis strains have been genotyped into many different sequence types (STs) by multilocus sequence typing (MLST). As of 2016, more than 700 STs combined in a number of clonal complexes (CCs) were known in *S. suis* [24]. Invasive *S. suis* strains are limited only to certain STs and CCs. Of which, *S. suis* serotype 2 (SS2) isolates belonging to MLST clonal complex 1 (SS2/CC1) are considered highly virulent and zoonotic [26].

The introduction of molecular, PCR-based techniques targeting 16S rRNA gene or serotype specific *cps* genes increased the sensitivity and specificity of *S. suis* detection in cerebrospinal fluid, blood and other clinical specimens [5]. Wertheim et al. [28] reports that the use of *S. suis* serotype 2–specific PCR targeting *cps2J* gene markedly improved the detection of *S. suis* cases in Asia. By use of the modern molecular techniques, it appears that a range of strains isolated from pigs, sheep, cattle and goats, and defined as '*S. suis*-like strains', show distinct differences in genome sequence and probably belong to a new species [24].

OCCURRENCE IN PIGS

Transmission among pigs and predisposing factors. *Streptococcus suis* is transmitted among pigs both vertically and horizontally. In vertical transmission, piglets born from sows with uterine or vaginal *S. suis* infections may become infected before birth, at birth, or soon after birth. The bacterium is often transferred from sow to infants during parturition with vaginal secretions to the oral cavity of the piglet, and colonizes the tonsils soon after birth [3, 28].

Horizontal transmission between the sow and piglets, as well as among piglets and among adult pigs, is considered to occur mainly via the respiratory (oro-nasal) route, although the gastrointestinal tract cannot be excluded as a secondary site of infection in piglets [5, 7]. Many modes of transmission have been proposed for the transfer of *S. suis* between swine within the herd. The most accepted relates to a transmission of *S. suis* by a 'nose-to-nose' contact between infected and uninfected pigs, especially when the animals show clinical signs of infection. Berthelot-Hérault et al. [33] first evidenced the transmission of *S. suis* virulent serotype 2 strains through aerosols from infected swine to pathogen-free swine. Their results were confirmed more recently by Dekker et al. [34] who demonstrated that *S. suis* serotype 9 strain could also be transmitted through aerosols. Bonifait et al. [35] demonstrated the presence of *S. suis*, mostly serotype 2, in the bioaerosols of swine confinement buildings, with and without recent documented infection cases. Using a quantitative-PCR (qPCR) method, the authors determined the total numbers of *S. suis* bacteria as ranging from $4–10 \times 10^5$ per 1 m^3 of air, and numbers of *S. suis* serotype 2 and 1/2 bacteria as ranging from $1–30 \times 10^3$ per 1 m^3 of air. Gauthier-Levesque et al. [36] demonstrated that the highly virulent *S. suis* serotype 2 ST1 strains are preferentially aerosolized, thereby increasing the risk of infection.

All the studies cited above indicate airborne transmission as a potential way of spreading the *S. suis* infection among pigs, and probably from pigs to humans [36]. The palatine and pharyngeal tonsils of pigs are both potential portals of entry for *S. suis*, leading to subsequent haematogenous or lymphogenous dissemination [37, 38]. Pigs of any age can be infected with *S. suis*, but susceptibility generally decreases with age following weaning [39]. Faeces, dust, water and feed may be secondary sources of infection, and also vectors such as flies and mice can play a role in disease transmission [3, 39].

As *S. suis* is a facultative pathogen, different biotic and abiotic predisposing factors such as virus infections, mainly with the Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), pseudorabies virus or influenza virus, corrosive gases, and factors evoking stress, followed by immunosuppression, mostly in young animals, overcrowding, poor housing with inadequate ventilation, mixing and moving, are regarded as promoting *S. suis* diseases in modern swine production [3, 7, 34, 40–42].

Carriage. Pigs and wild boars are considered as natural reservoirs of *S. suis*. *Streptococcus suis* occurs commonly in the upper respiratory tract of healthy pigs, mostly in their nasal cavities and nasopharyngeal and palatine tonsils (Fig. 3), and to a lesser extent in the genital and alimentary tracts [5, 28, 39]. Colonization of pigs with *S. suis* occurs usually at an early stage of life, often through vertical transmission from carrying sows, as described above [43].

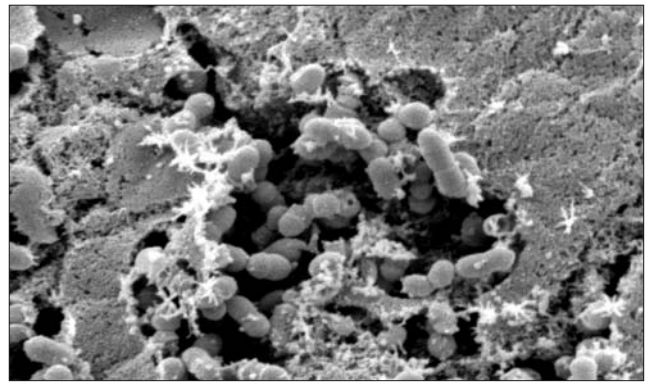

Figure 3. *S. suis* cocci in a sheet of mucus on the surface of the nasopharyngeal epithelium from a pig. Scanning Electron Micrograph (SEM) by Josh D. Slater. According to Sriskandan and Slater [74]

S. suis carriage rates may vary between herds and can range from 0% to up to 80–100% [3, 41, 43]. According to Gottschalk et al. [25, 38], the pig carrier rate is near 100%. However, this high figure applies most probably to weanlings, as the highest carrier rates are known to occur in weaning piglets between 4–10 weeks of age, and are associated with the decrease of maternal antibodies [3, 39].

In adult pigs, the carrier rates are usually much lower, and approximate 40%, as evidenced by the bacteriological examinations of tonsillar swabs from slaughterhouse pigs performed in Canada [44], Korea [45] and Vietnam [43], which revealed the prevalence of *S. suis* equal to 43.6%, 13.5%, and 41.0%, respectively, and the prevalence of the most virulent *S. suis* serotype 2 equal to 7.0%, 0.5%, and 8.0%, respectively. The corresponding figures recorded in adult pigs tended on farms in China [43], France [46] and Thailand [47] were 40.4%, 72.0% and 37.0% for total *S. suis*, and 3.0%, 1.25% and 2.0% for *S. suis* serotype 2, respectively. However, a high prevalence of *S.suis* carriage recorded in France may be due to the presence of clinical cases of swine streptococcosis on the investigated farms.

At each age, the occurrence of subclinical *S. suis* carriers among pigs must be regarded as a potential threat of infection and disease for healthy pigs and humans [39].

Disease. Some carrier piglets may develop clinical disease due to dissemination of *S. suis* from tonsils and/or other mucosal surfaces. After breaching mucosal epithelial barriers, *S. suis* can reach and survive in blood and invade multiple organs, including spleen, liver, kidney, lung, and heart, to cause exaggerated inflammation [20]. The pathogen is also able to cross the barrier made by the brain microvascular endothelial cells and/or the epithelial cells of the choroid plexus to gain access to the central nervous system to cause meningitis [7].

The disease usually peaks during weaning (about 6 weeks of age) and mixing of pigs. Pigs of any age can be affected, but susceptibility generally decreases with age following weaning [3]. Despite a high carrier rate, morbidity rarely exceeds 5 %, although it can reach more than 50 % in cases of poor hygiene and concurrent disease. With appropriate treatment, mortality is usually low (0–5%), but can be up to 20% in untreated herds [3, 28, 39]. Meningitis is the primary disease syndrome in swine caused by *S. suis* (Fig. 4), others include septicaemia, arthritis, endocarditis, pneumonia, rhinitis, encephalitis, polyserositis, abortions, vaginitis and abscesses [3, 25]. In North America, *S. suis* has been identified as the primary infectious agent causing endocarditis in pigs. Affected pigs may die suddenly or show various levels of dyspnea, cyanosis and wasting [25].

Figure 4. Typical clinical streptococcal meningitis in a piglet. According to White [103]

S. suis infection in pigs is reported worldwide, from the United States and Canada to South America (Brazil), Europe (United Kingdom, The Netherlands, France, Denmark, Norway, Spain, Poland and Germany), Asia (China, Thailand, Vietnam, and Japan), Australia, and New Zealand [28, 40, 48]. Of the 35 known *S. suis* serotypes, types 2, 1/2, 3, 4, 5, 7, 9 and 14 have been reported to cause infections in pigs [25, 49]. Among 4,711 cases of *S. suis* infections identified worldwide in pigs between 2002–2013, the most common was serotype 2 (27.9%), followed by serotype 9 (19.4%) and serotype 3 (15.9%). The majority of cases (3,162, 67.1%) were described in North America [5].

In the acute form of the disease, clinical signs may include fever (up to 42°C), depression, anorexia and lassitude, followed by one or more of the following: ataxia, incoordination, tremors, opisthotonus, blindness, loss of hearing, joint swelling, paddling, paralysis, dyspnoea, convulsions, nystagmus, arthritis, lameness, erythema, and/or abortion. Acute disease can become chronic, cause death, or result in healthy carriers. The sequelae of chronic disease include lameness and/or residual central nervous system signs [3].

There are many descriptions of the pathological and histopathological lesions in pigs infected with *S suis*. Most commonly, typical gross lesions are found in the brain, heart and joints. As predominant lesions, hyperaemia of meningeal vessels, lymphadenopathy (concerning mediastinal and/or mesenteric lymph nodes), fibrinopurulent or suppurative epicarditis are usually specified. In the pericardial and thoracic cavity, a considerable amount of serous effusion can be found. Interstitial pneumonia, relatively often described in cases of *S. suis* infections, is considered as a consequence of septicaemia. Other gross lesions observed in *S. suis* infection are congestion and/or oedema of the brain, congestion of parenchymatous organs, most commonly the spleen and liver, and reddening or discoloration of the skin. Some of these lesions may also be due to generalized septicaemia [3, 40].

The most common histopathological findings occur within the choroidal plexus. In the central nervous system, lesions associated with meningitis and choroiditis may be observed, including oedema of the leptomeninges and the dura mater, hyperaemic meningeal blood vessels, and an increased quantity of cerebrospinal fluid. The most characteristic histopathological lesion of acute *S suis* meningitis is a diffuse neutrophilic infiltrate [3, 4].

The earliest detectable change in arthritis associated with *S. suis* is dilation of the synovial blood vessels and hyperaemia. A fibrinous polyserositis without changes in the articular surfaces may occur. In affected joints, the capsules may be thickened and synovial membranes may be erythematous. Cardiac lesions are common, including, next to pericarditis, vegetative valvular endocarditis, and to a lesser extent, haemorrhagic necrotizing myocarditis, which resembles mulberry heart disease. Pulmonary lesions may include: interstitial fibrinous and fibrinohaemorrhagic pneumonia, fibrinous or suppurative bronchopneumonia, bronchiolitis, bronchitis, alveolar haemorrhage, lobular consolidation, interlobular emphysema, and fibrinopurulent pleuritis [3, 40].

OCCURRENCE IN OTHER ANIMALS

Although *Streptococcus suis* is mostly adapted to pigs, it occurs in a wide range of animal species. Wild boar (*Sus*

scrofa), the closest relative of domesticated pig, is regarded as an important reservoir of this bacterium and a potential hazard for hunters and poachers who become infected while butchering boars. This view was confirmed by Baums et al. [50] who found by PCR that 92% of wild boars from Northwestern Germany carried *S. suis* and 11% – *S. suis* type 2, known to be virulent for humans. These values were higher compared to those recorded in domestic pigs, tested in parallel by the authors.

Streptococcus suis is believed to be a commensal in the intestinal biota of cattle, sheep, goats and horses [3, 8], and in the biota of tonsils of cattle, cats and dogs [51, 52]. *S. suis* was also reported as a causative agent of various diseases in these animals, such as meningitis, arthritis, pneumonia, peritonitis, and septicaemia in cattle [3, 8], meningitis, guttural pouch infection, purulent pneumonia and osteomyelitis in horses [3, 53, 54] and pneumonia and/or moist dermatitis in cats [3]. This species has been also identified as a cause of fatal disease in wild mammals, such as raccoon dog (*Nyctereutes procyonoides*) and fallow deer (*Dama dama*) [3, 55]. Recently, Okwumabua et al. [10] isolated 16 strains of *Streptococcus suis* from clinical cases of diverse conditions in cattle, and expressed the opinion that this bacterium may be an important pathogen of bovine calves. Although exposure to cattle and other animals is most probably a rare cause of porcine streptococcosis in humans, compared to exposure to swine, such a possibility should not be underestimated, as recently proved by Ishigaki et al. [56] who described a case of *S. suis* type 2 endocarditis in a farmer exposed to calves.

Meaningful results were obtained by Devriese et al. [9] who evidenced that *Streptococcus suis* should be regarded as a common cause of septicemia in various bird species. They described fatal *S. suis* infections in: 4 species of psittacine birds, including spectacled parotlets (*Forpus conspillatus*), budgerigars (*Mellopsittacus undulatus* f. dorn.), black-collared lovebird (*Agapornis swindemiana*), and peach-faced lovebird *Agapornis roseicollis*); 3 species of passerine birds, including zebrafinches *(Taeniopygia guttata costanatis),* bullfinches *(Pyrrhula pyrrhuld)* and canaries *(Serinus canaria* f. dom.); and in one species of domestic duck *(Anas platyrhynchos)*. Lethal infections occurred often in a large proportion of the examined birds, e.g. in 6 of 18 spectacled parotlets, 7 of 7 bullfinches (entire shipment), and 10 of 40 canaries.

The quoted results indicate that *Streptococcus suis* is probably widespread in nature and its circulation among various species of mammals and birds contributes to the persistence of endemic foci of streptococcosis in pigs.

OCCURRENCE IN HUMANS

Epidemiology worldwide. In the last 2 decades, the number of reported human cases due to *S. suis* has dramatically increased, mostly due to epidemics recorded in China in 1998 and 2005, and the fulminant growth of morbidity in the countries of southeastern Asia, mostly Vietnam and Thailand. Contrary to Western countries, where almost all cases were caused by occupational contact with pigs or pork products, a considerable part of Asian cases were due to consumption of the raw pig meat or blood.

According to Goyette-Desjardins et al. [5], 1,642 cases of *S. suis* infections were identified between 2002–2013 worldwide in humans, in a total of 34 countries. The majority of human cases (90.2%) were identified in Asian countries, of which Vietnam, Thailand and China alone accounted for 83.6% of all cases worldwide [5]. The disease poses a severe health problem for China, which has a pig population of 700 million, and produces more than half (51.7 million tons of meat annually) of the total global pork for consumption [18].

In Europe, 8.5% of all reported human cases were described, of which 71.4% were in countries with a highly developed pig industry: The Netherlands, United Kingdom, France and Spain. Cases were also reported in Austria, Belgium, Croatia, Denmark, Germany, Greece, Ireland, Italy, Poland, Portugal, Serbia and Sweden. Surprisingly, no cases have yet been reported in Russia, a country with high pig production. In spite the highest number of *S. suis* infection reports from diseased pigs, only a few cases of *S. suis* infection in humans have been reported in North America. Sporadic cases have also been reported from South America and Oceania, but when combined, they account for only 0.8% of all reported cases [5].

According to Huong et al. [17], the highest cumulative prevalence rate was in Thailand (8.21 cases/million population), followed by Vietnam (5.40) and The Netherlands (2.52). In most European countries, including Poland, Germany, France, Sweden, Austria, Czech Republic and Greece, as well as in China and Australia, the prevalence rate was 0.11–0.45 cases/million population, in the United Kingdom, Denmark and Serbia – 0.46–1.08, in Italy, Portugal, USA, Canada, Argentina, Japan – 0.00–0.10. The pooled mean age of the patients was 51.4 years, of whom 76.6% were men. All case-patients were adults, with the exception of one female infant reported in Thailand.

Most probably, the real morbidity due to *S. suis* in the countries with officially reported low or no numbers of disease is greatly underestimated. An example could be Poland, where Bojarska et al. [57], after conducting a retrospective analysis, identified 21 cases of disease caused by *S. suis*, none of which had been included in earlier official reports, and nearly half (10 cases, 48%) had been misdiagnosed by a microbiological laboratory. The authors expressed the opinion that the real morbidity due to *S. suis* in Poland, a country with a well-developed swine industry (over 10 million heads), is very likely underestimated.

The second example is Argentina, where Callejo et al. [58] recently described 17 cases of disease caused by *S. suis* isolated between 1995–2016, and also indicated an underestimation of the morbidity. It is noteworthy that after recognition of 2 above-cited reports, Poland and Argentina, together with The Netherlands, United Kingdom and France, were among the 5 Western countries with the highest numbers of disease caused by *S. suis* [58].

Among 1,642 cases of *S. suis* infections identified in humans between 2002–2013 worldwide, the most common was serotype 2 (74.7% of all cases), followed by serotype 14 (2.0%). Other serotypes (4, 5, 16, 21, 24) accounted for 0.3% and unidentified for 23.0%. Among the sequence types (STs), ST1 is mostly associated with disease in both pigs and humans in Europe, Asia and Argentina. ST7, responsible for the 1998 and 2005 epidemics, is mostly endemic to China, the ST101 – ST104 are endemic to Thailand, and the ST25 or ST28 to North America [5].

Some authors, such as Callejo et al. [58], estimate that the *S. suis* serotype 2 most commonly isolated from diseased pigs represents more than 95% of human cases worldwide.

Human disease – clinical signs and symptoms. Human infections with *S suis* are most frequently manifested as purulent meningitis, the other reported syndromes include septicaemia, streptococcal toxic shock-like syndrome (STSLS) with multiple organ failure, endocarditis, cellulitis, rhabdomyolysis, pneumonia, arthritis, peritonitis, spondylodiscitis, uveitis and endophthalmitis [4, 14, 25]. Arthritis affects various joints including hips, elbows, wrists, sacroiliac, spine and thumbs, and in most cases reflects generalized septicaemia caused by *S. suis* [38].

According to Huong et al. [17], who analysed 1,584 cases of porcine streptococcosis reported until the end of 2012, the main clinical syndrome was meningitis (pooled rate -68.0%), followed by the other (co-existing or not) syndromes: septicaemia (25.0%), arthritis (12.9%), endocarditis (12.4%), and endophthalmitis (4.6%). Toxic shock-like syndrome was also reported as a distinct severe clinical feature at high rates in 2 outbreaks in China (64.0% and 28.9% of patients) and in Thailand (37.7%), but at a rate of only 2.9% among the total case reports. The pooled case-fatality rate for the total analysed cases of porcine streptococcosis was 12.8% [17].

Van Samkar et al. [13] also report meningitis as the most frequently described presentation of *S. suis* infection, but estimate its occurrence somewhat lower, as present in approximately 50–60% of reported *S. suis* infected patients. The case fatality rate reported by these authors was 17 out of 581 analysed cases of meningitis caused by *S. suis* (2.9%), and was much lower compared to fatality rates reported for meningitis caused by *Streptococcus pneumoniae* (20%) or *Listeria monocytogenes* (36%) [13].

It is noteworthy that *S. suis* has recently been identified as the leading cause of adult meningitis in Vietnam, the second in Thailand, and the third in Hong Kong [20, 59]. According to Ho et al. [60], *Streptococcus suis* causes approximately 40% of all adult acute bacterial meningitis cases recorded in the Vietnamese cities of Ho Chi Minh City and Hanoi, more than the combined number of cases evoked by *Streptococcus pneumoniae* and *Neisseria meningitidis*.

In the acute form of meningitis, symptoms include high fever, headache, chills, nausea, vomiting, and vertigo, followed by one or more of the following: hearing loss, walking ataxia, neck stiffness, petechia, articular pain, peripheral and facial paralysis, severe myalgia, ecchymosis, rashes, rhabdomyolysis and coma [4]. According to Gottschalk et al. [25], the incubation period ranges from a few hours to 2 days, whereas Wertheim et al. [28] estimate the duration of illness before hospital admission at 2–5 days. One striking feature is subjective hearing loss, which may be reported by up to one-half of patients at presentation or a few days later. In general, most patients with *S. suis* infections exhibit leukocytosis and neutrophilia, and patients with meningitis have subarachnoid cerebrospinal fluid with a high numbers of leukocytes, a high percentage of neutrophils, low sugar and high protein levels [25].

In some cases, *S. suis* type 2 infects the bloodstream and the meninges at the same time. As a result, meningitis is often accompanied by septicaemia, similar to *Streptococcus pneumoniae* and *Neisseria meningitidis* meningitis. Due to the rapid progression of septicaemia, it can evolve into irreversible toxic shock, and even acute death, if the sufferers do not receive urgent treatment [14].

Hearing loss and/or vestibular dysfunction are the most common sequelae after recovery from purulent meningitis caused by *S. suis*. The recorded incidence of deafness following infection caused by this pathogen is consistently higher than that reported for other meningitis-causing bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae*, and can reach 50% and 73% in Europe and Asia, respectively. The deafness (unilateral or bilateral) has been mainly high tone, and is frequently associated with vertigo [25]. It can be profound – 180 dB on audiometric testing of Vietnamese patients [28]. According to Gottschalk et al. [38], the accumulation of inflammatory cells observed around the vestibularcochlear (8th 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.

Van Samkar et al. [13] estimated hearing loss as a common sequela of *S. suis* meningitis, occurring in 259 of 489 patients (53%). Other neurological sequelae observed by these authors were present in 35 of 286 patients (12%) and consisted of ataxia in 19 patients, cognitive impairment in 2, tinnitus in 2, and were not specified in 12. Huong et al [17] also reported hearing loss as the most common sequela of porcine streptococcosis in an investigated group of 1,584 patients (39.1%, with a low recovery equal to 15.4%), followed by vestibular dysfunction (22.7%).

Improvement of hearing is variable. Wertheim et al. [28] report that 93 (66.4%) of 140 evaluated Vietnamese adult patients with *S. suis* meningitis had mild-to-severe hearing loss at hospital discharge, compared with 41 (47.7%) of 86 patients evaluated at 6 months after hospital discharge. Notably, no cases of deafness have been reported in non-meningitis cases of *S. suis* infection in humans [25].

The most severe form of porcine streptococcosis in humans is toxic shock, recorded for the first time in a greater number of patients during the Chinese outbreaks caused by serotype 2 of *S. suis*. The outbreaks occurred in Jiangsu Province in 1998–1999, with 25 reported cases and 14 deaths, and in Sichuan Province in 2005, with 204 reported cases and 38 deaths according to Tang et al. [61], and 215 cases and 39 deaths according to Yu et al.[62]. The outbreaks in human populations were closely related to a large outbreak of *S suis* infection in pigs, affecting approximately 80,000 pigs. Almost all the human patients had a history of direct occupational contact with infected pigs or pork [4].

The shock symptoms observed during these outbreaks resembled in almost all details the condition described as Streptococcal Toxic Shock Syndrome (STSS), which is caused by *Streptococcus pyogenes* and *Staphylococcus aureus* producing so-called superantigens (e.g., streptococcal and staphylococcal exotoxins), that trigger a nonspecific, uncontrolled activation of T cells and massive cytokine release. Initially, the STSS name was adopted for the Sichuan cases caused by *S. suis*. Nevertheless, because the presence of superantigens has not been confirmed in these cases, implying that a different mechanism could be involved, the toxic shock caused by *S. suis* serotype 2 was named Streptococcal Toxic Shock-Like Syndrome (STSLS) [14, 21, 25, 63].

The clinical criteria for diagnosis of STSLS disease can be described as follows: 1) clear erythematous blanching rash, 2) sudden onset of high fever, 3) hypotension diarrhea, 4) blood spots and petechiae, and 5) dysfunction of multiple organs, such as: disseminated intravascular coagulation, acute renal failure, acute respiratory distress syndrome and

liver and heart failure [14, 63]. The presence of rash and petechiae (Fig. 5) is most probably due to the action of *S. suis* toxins released into the blood, that break down the walls of blood vessels which allows blood to leak out under the skin [14, 61, 62].

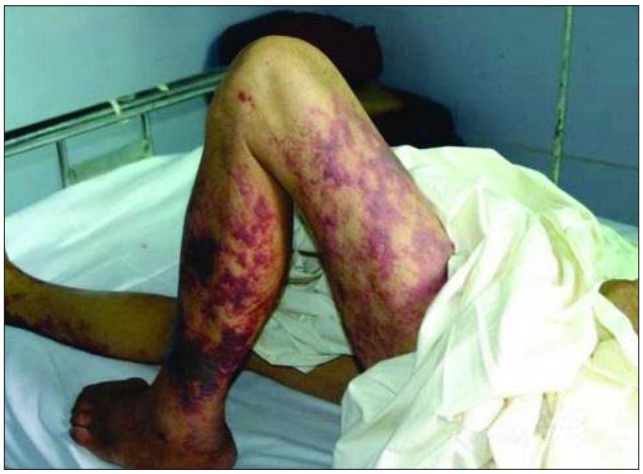

Figure 5. Patient from Sichuan epidemics with the diagnosis of STSLS, featuring purpura and evidence of gangrenous changes in the leg. According to Yu et al. [62]

Lun et al. [4] report that in an analysed group of 81 patients with septic shock, 100% had high fever, 93% – subcutaneous haemorrhage, 93% – disseminated intravascular coagulation, 82% – acute renal failure, 79% – chills, 77% – hypotension, 67% – vomiting, 63% – abnormal liver function, 52% – diarrhea, and 49% – headache. Tang et al. [61] in one of the first detailed reports on Sichuan epidemics, reported that among 204 patients the diagnosis of STSLS was established in 59 persons with an extremely high mortality rate of 62.7%, whereas in 104 persons with the established diagnosis of meningitis, the mortality rate was only 1.0%.

On necropsy examination of patients who died from STSLS or meningitis caused by *S. suis*, gross lesions were found, including widespread haemorrhage, especially in the stomach and adrenal glands, leptomeningeal congestion, oedema of cerebrum, hyperaemia of myocardium, disseminated intravascular coagulation, and lack of coagulation of whole blood, as well as septicaemia. Additionally, degeneration or necrosis of hepatocytes and kidney cells was observed. Inside the Kupffer-Browicz cells of the liver, pathogenic bacteria surrounded by glycocalyx could be seen (Fig. 6). The nature of pathological changes was similar to that observed in the organs of sick pigs [4, 61].

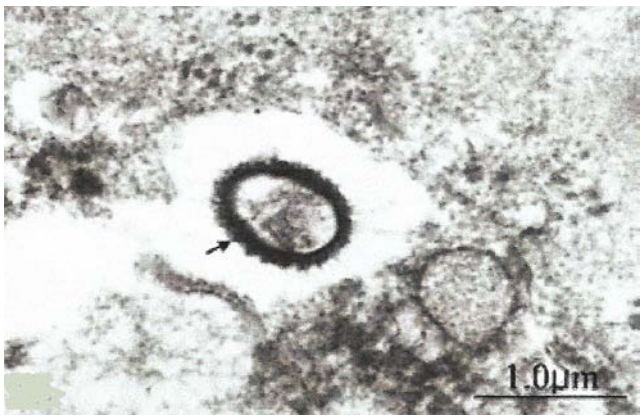

Figure 6. Transmission Electron Microscopy (TEM) of the liver section from the patient who died on STSLS during Sichuan epidemics. Single *S. suis* cell (indicated by an arrow), surrounded by glycocalyx, is visible inside a Kupffer-Browicz cell. According to Tang et al. [61], modified

RELEVANCE TO OCCUPATION

Occurrence in the working environment. The working environment on farms or in abattoirs may be a source of infection, as *S suis* can survive in dust, manure, and pig carcasses for days or even weeks under optimal conditions. *S suis* type 2 is resistant to various environmental conditions. The bacterium can survive in water for 10 minutes at 60°C, and for 2 hrs at 50°C, making the scalding process in abattoirs a possible source of contamination. At 4°C, *S. suis* type 2 can survive in carcasses for 6 weeks. At 0°C, the organism can survive for one month in dust and for over 3 months in faeces, whereas at 25°C, it can survive for 24 hrs in dust and for 8 days in faeces. Fomites, such as manure-covered work boots and needles, have also been shown to transmit *S. suis* [3, 4, 64].

Breton et al. [44] examined by culture the samples taken from the hands and knives of abattoir workers in Canada and revealed the presence of *S. suis* on 33.3% of eviscerators' knives in the killing room, and in only 4.8% of butchers' knives in the cutting room, while the corresponding figures for *S. suis* type 2 were 3.0% and 2.4%, respectively. *S. suis* was isolated from 18.9% of eviscerators' hands and from 4.8% of butchers hands, while no *S. suis* type 2 strains were isolated from workers' hands. The authors proved that eviscerators involved in removing the larynx and lungs from the carcasses had a significantly higher ($p < 0.05$) risk of exposure to *Streptococcus suis* than other abattoir workers.

Soares et al [65] demonstrated with the use of PCR that *Streptococcus suis* was present in 25% of environmental samples taken in swine abattoirs in Brazil, including carcasses, knives, and hands of employees. This suggests that all employees are at risk of infection.

S. suis may be present in raw or cured pork products sold in markets and shops, posing a risk for salesmen and consumers. The bacterium was isolated from 6.1% of raw pork meat samples collected from wet markets in Hong Kong [28]. Surprisingly, the data on the occurrence and persistence of *S. suis* in various pork products are very scarce, and it remains virtually unknown just how long the bacterium may survive in various pork products, such as raw meat, ham, sausages and cutlets.

Transmission in working environments. *S. suis* can be transmitted to workers by close contact with pigs or pig products [4], usually through contamination of minor cuts or abrasions on the skin of hands and/or arms causing a breach of skin integrity [5, 7, 13, 41, 61, 66–68]. Such injuries have frequently been recorded as having occurred 2–3 days prior to the onset of clinical signs [69]. It is noteworthy that both Strangmann et al. [66] in Germany and Tramontana and al. [27] in Australia noted the presence of multiple scars and cuts on the hands of the patients who developed septic shock syndrome caused by *S. suis* after handling pigs or animal carcasses.

The other possible route of infection, usually neglected by the authors reviewing occupational aspects of *S. suis* infection, is through a wound caused by pig bite or piercing

by a boar's tusk, often in the posterior aspect of the thigh of a pig farmer. Most probably, this is a common mode of transmission, as *S. suis* often colonizes oral mucosa of the healthy and diseased pigs. This way of transmission has been recently suggested by Ishigaki et al. [56] who described a case of *S. suis* endocarditis of bovine origin in a cattle farmer who had been frequently bitten in the fingers by calves during feeding. The authors suggested a similar route of transmission in 5 of 8 pig farmers in Japan with diagnosed porcine streptococcosis. Pig bite is regarded by many authors as an important transmission route of zoonotic pathogens [70–73], mostly Gram-negative species *Pasteurella multocida* and *Pasteurella aerogenes* [72, 73]. Nevertheless, Barnham [70], who analyzed 7 cases of febrile infections in pig farmers caused by pig bite or boar's tusk gore, isolated from these patients, together with *Pasteurella* spp., also the haemolytic *Streptococcus* strains (identified as *S. anginosus*, *S. agalactiae* and *S. dysagalactiae* subsp. *equisimilis*), *Bacteroides* spp., *Proteus* spp. and *Escherichia coli*. Accordingly, pig farmers should be protected from pig bite by appropriate gloves and boots, and in the case of severe injuries should receive surgical management of the wound and broad-spectrum antibiotics effective against *S. suis*, such as penicillin G, ampicillin or flucloxacillin.

The respiratory route with subsequent colonization of the tonsils which is the basic way of transmission among pigs seems to be less significant among humans. Some authors, based on the relatively common presence of *S. suis* in tonsils of exposed workers, suggest that the workers may become infected by the inhalation of bioaerosols emitted by swine [3, 35, 66, 74], while others regard the airborne transmission to humans as doubtful [7]. According to Fulde and Valentin [39], bacteria may also enter the organism of workers through the conjunctiva. The gastro-intestinal route, common in the Asian rural communities by eating raw pork, seems rather uncommon in the working environment.

Carriage. The carriage of *S. suis* has been evidenced in various occupational populations by the culture of bacteria from the upper respiratory tract of exposed abattoir workers or swine breeders [35, 66, 76, 77], or by the detection of seropositive reactions to antigen of this bacterium [69, 77, 78]. In Italy, *S. suis* serotype 2 was isolated from tonsil swabs of 20% abattoir workers [75], while in Mexico, serotypes 2, 27, and unidentified serotypes were isolated from tonsil swabs of 5.8% abattoir workers [76]. In Germany, *S. suis* serotype 2 was isolated from pharyngeal swabs of 5.3% slaughtering and meat processing workers, while none of the non-exposed controls showed the presence of the pathogen [66]. More recently, Bonifait et al. [35] in Canada, using a more sensitive molecular method (quantitative PCR), detected the presence of *S. suis* in nasal swabs from 14 of 21 workers (66.7%) in a swine confinement building. The latter results show that the earlier ones obtained with the use of a routine culture method could probably have been underestimated [7]. Nevertheless, even the use of sensitive molecular methods do not always ensures positive results, as demonstrated by Soares et al. [65] who recently did not detect *S. suis* in tonsil samples taken from 139 pig-slaughtering employees in Brazil, and tested by PCR.

Serological studies on the occurrence of antibodies against the virulent serotype 2 of *S. suis* in different occupational groups were performed in 3 countries. In New Zealand, the study was carried out with indirect ELISA (enzyme-linked immunosorbent assay test), and the presence of specific antibodies detected in 21.4% of pig farmers, 10.3% of meat inspectors, and 9.4% of dairy farmers [69]. In the study performed in the USA by the same method, antibodies to *S. suis* were found in 9.6% of pig workers and 1.5% of controls not exposed to pigs [77]. In both studies, antibody titers were related to longer occupational exposure. Researchers in The Netherlands performed Western blot analysis, targeting 2 virulence-related markers of *S. suis* – the MRP and EF proteins. Results showed that 6% of veterinarians and 1.1% of pig farmers were positive for anti-MRP, while 2% of veterinarians and 0.5% pig farmers were positive for anti-EF [78].

As can be seen from the studies cited above, workers exposed to pigs or pork could be asymptomatic carriers of *Streptococcus suis*, mostly in the upper respiratory tract. Although the localization of bacteria is similar to that in pigs, the epidemiological significance of human carriage is most probably much less compared to swine. To-date, there is no evidence for a possibility of the transmission of *S. suis* among humans, and most probably bacteria are not shed by humans into the environment in significant quantities. The only potential health hazard associated with human carriage relies on the possibility of the transformation of subclinical infection into disease in the case of the depression of an individual's immunity. Such depression may follow medical procedures, such as splenectomy, a malignant disease (such as colon carcinoma), diabetes mellitus, and acute alcoholism. Patients with rheumatic heart disease, valvular heart disease or ventricular septal defect are also more likely to have infective endocarditis. Accordingly, immunocompromised people should not perform any work associated with a massive exposure to pigs, animal carcasses and/or pork [25, 38].

Occupational disease. Porcine streptococcosis in humans in most cases is a typical occupational disease. Already in 1988, Arends and Zanen [12] estimated that the annual risk for developing *S. suis* meningitis among Dutch abattoir workers and pig breeders was approximately 3.0/100,000, being the highest in the group of slaughterhouse workers (3.5/100,000), lower in pig breeders (2.7/100,000) and the lowest in butchers (1.2/100,000). Compared to the general population non-exposed to pigs and pork (0.002/100, 000), the risk for workers of the pig industry was about 1,500 times higher. More recently, Dr Constance Schultsz from Amsterdam reported that the annual incidence rate of 3–5 per 100,000 individuals at risk in The Netherlands is an underestimate. The National Institute of Public Health of The Netherlands recently placed *S. suis* among its top 10 priority zoonotic pathogens for which increased awareness and disease surveillance is warranted (cited after Segura et al. [15]).

There are at least 5 big occupational groups exposed to *Streptococcus suis* [3, 5, 13, 25, 39, 67]:

1) Pig breeders, comprising both farmers breeding hundreds or even thousands of pigs on an industrial scale, and rural inhabitants, mostly in developing countries, tending pigs on a small scale as 'backyard production'.
2) Abattoir workers, among whom several categories may be distinguished, depending on the production process.

3) Butchers and workers of meat processing facilities, restaurants and food shops having contact with pork or animal carcasses.
4) Veterinarians and meat inspectors.
5) Hunters having contact with killed wild boars.

In most Western countries, the infection rates among the occupationally-exposed groups are poorly known because *S. suis* infection is not a notifiable disease. Only 2 countries consider *S. suis* infections in humans as an industrial disease: the United Kingdom and France, since 1983 and 1995, respectively. This recognition led to legislation and regulations which may have contributed to reducing the number of cases in both of these countries, with the last human case in the United Kingdom being reported in 2001. In France, although few cases have been reported since 1995, they were mostly not related to people engaged in the pig industry, but to wild boar hunters [5].

The incidence of the occupational porcine streptococcosis in Asian countries is probably distinctly greater than in Europe. Thus, the annual incidence in Hong Kong was 32/100,000 [25], over 350-times higher that that of the general population (0.09/100,000), and over 10-times higher compared to the analogous group in The Netherlands, analyzed by Arends and Zanen [12]. Nevertheless, in the countries of southeast Asia, such as Thailand and Vietnam, the differences in *S. suis* morbidity between the occupationally-exposed people and the general population are much smaller. This is due to the traditional consumption of raw pig products which appears to be a major cause of infection in Thailand [79].

The situation is different in China, where cases of the disease distinctly related to occupation prevail. The best example is the big epidemics by *S. suis* in Sichuan province in 2005 and affected 204 patients, all of whom were occupationally exposed to live or dead pigs or pork. The group consisted of 198 farmers, 5 butchers, and one veterinarian. Most of them were found to have cuts in the skin of their hands and/or feet, and all of them reported a history of direct contact with ill or dead pigs before developing symptoms [61]. Huong et al. [17] estimated the prevalence of the cases with occupational exposure among 1,584 analysed cases of porcine streptococcosis as 38.1%, which seems to be an underestimate due to imprecise qualification and reflecting the situation in southeastern Asia rather than worldwide.

The worldwide significance of porcine streptococcosis as an occupational disease is evident from an analysis of the 22 case reports published in this century in 16 countries, each describing one case (19 reports) or two cases (3 reports). The cases included: meningitis (13 persons), septic disease comprising septic shock, septicemia and septic arthritis (10), endocarditis (1), and peritonitis (1). The occupational origin of the disease was reported in 19 cases from the United Kingdom [80], Germany [66, 81], USA [82–84], Australia [27], Canada [67], Korea [85], Japan [56, 86], Chile [87], Poland [88], Sweden [89], Greece [90], Italy [91], and Malaysia [92], whereas in the remaining 6 cases, from Croatia [93], Argentina [94], Italy [95], Vietnam [96] and Korea [97], no association could be found between the occupation and disease. The patients who contracted *S. suis* infection at work included: pig farmers (11 persons), truck drivers transporting pigs (2), butchers (2), pet-food processor (1), worker of the restaurant serving raw meat (1), hunter (1), and cattle farmer (1). The total incidence of work-related cases among the analysed 25 infections caused by *S. suis* was 76%. Although the group of above-reported cases does not correspond exactly to the world profile of porcine streptococcosis morbidity (because of under-representation of *S. suis* type 2 and some countries with high morbidity indices), the authors of the presented study believe that a value between 75–80% probably well reflects the real proportion of work-related cases among the total human infections caused by *S. suis* worldwide, with the exclusion of the countries of southeastern Asia.

Specificity of porcine streptococcosis in the population of southeastern Asia. Ma et al. [21] classified *Streptococcus suis* serotype 2 as one the most hazardous zoonotic agents that has recently emerged in Southeast Asia, including China, together with such pathogens as severe acute respiratory syndrome-associated coronavirus (SARS-CoV), avian influenza viruses H5N1 and H9N2, Nipah virus, and enterohaemorrhagic *Escherichia coli* O157:H7. This region of the world is considered to be an epicentre of newly-emerging or re-emerging infectious diseases, which is most probably associated with the presence of yet unknown animal vector and/or reservoir species. This may also apply to *S. suis*, although the leading role of swine as main reservoir of the disease seems unquestionable.

The morbidity rate of porcine streptococcosis in southeast Asia is the highest in the world; for example, the incidence rate noted in 2010 in the general population in the Phayao Province of Thailand in 2010 (6.2 per 100,000) was 69 times higher than that in Hong Kong (0.09 per 100,000), which is the only available data for the general population in southeast Asian countries, and 3,100 times higher than that in the general population of The Netherlands (0.002/100,000). A high morbidity in this region has been accompanied by a high case fatality rate of 16.1% [79]. There are at least 4 main reasons for such a catastrophically high incidence of porcine streptococcosis in the countries of southeast Asia:

1) Habitual consumption of raw or undercooked pork, blood and offal products in the form of traditional dishes, such as 'Loo' (raw pork meat and blood), 'Lap' (raw pork meat), and fermented raw pork (all examples from Thailand) [79], or 'tiêt canh' (pudding of raw pig blood) in Vietnam [15], mostly in Thailand, Vietnam, and Laos, and to the less extent in China [60, 79, 98]. As a result of widespread consumption of such 'high risk' dishes, the infection with *S. suis* by the oral route prevails over the work-related infection route through skin abrasions, which also occurs in these countries. For example, recent consumption of raw pork products declared 22 out of 31 patients from Phayao Province in Thailand with confirmed diagnosis (71.0%), whereas recent contact with pig or pig products was declared by only 2 out of 31 (6.5%) [79]. In China, however, a reverse situation occurs, as noted during the Sichuan outbreak where directly occupation-related cases distinctly prevailed [61].
2) Widespread pig breeding, mostly in the form of small-scale 'backyard farming' [21].
3) Low level of hygiene at pig slaughtering and preparing of dishes [98].
4) Poor meat inspection and unsatisfactory health care [98].

Most probably, the proper execution of sanitary rules and food safety control at points 1. and 3, combined with intense health education, could radically improve the situation

and cause a significant decrease in porcine streptococcosis morbidity, not only in the countries of southeast Asia, but also worldwide.

Treatment. *Streptococcus suis* is generally susceptible to beta-lactam antibiotics, including penicillin, ampicillin, amoxicillin, flucloxacillin, cephalosporin and ceftriaxone [3, 4, 25, 28]. These antibiotics are effectively applied for treatment in both diseased humans and pigs. Van Samkar et al. [13] reports that out of 453 patients with diagnosed *S. suis* meningitis and known therapy, analysed worldwide by meta-analysis, 250 (55.2%) were treated with ceftriaxone alone, 102 (22.5%) with penicillin alone and 101 (22.3%) with either ceftriaxone or penicillin; no antibiotic resistance to these antibiotics was found in the 182 cases where the resistance pattern was determined. As many as 157 of 300 analysed patients (52%) received adjunctive dexamethasone (a corticosteroid) which was shown to reduce hearing loss in a part of treated individuals. Gottschalk et al. [38] expressed an opinion that in the treatment of *S. suis* infections in humans, antibiotics should be administered for a relatively long period of time (at least 6 weeks) because of the threat of relapse.

Penicillin G (benzylpenicillin) given intravenously is commonly used to treat infections caused by *S. suis* in humans [4, 25]. However, penicillin-resistant strains have been isolated, and strains highly resistant to other commonly used antibiotics have also been reported [4]. According to Paptsiros et al. [41], the sensitivity rate to amoxicillin and ampicillin in the treatment of pigs is circa 90%. Gottschalk et al. [38] report that penicillin-resistant strains have been isolated in 6–28% of examined piglets. *S. suis* strains are usually resistant to tetracyclines, aminoglycosides, erythromycin, chloramphenicol and clindamycin [28, 41].

A high susceptibility of *S. suis* to beta-lactams has been confirmed in Poland on strains isolated from pigs. Pejsak et al. [99] tested for sensitivity to antibiotics 393 *S. suis* strains isolated from pathologically-changed lungs of pigs with respiratory symptoms, and found that over 98.5–99% of isolates were sensitive to ampicillin and amoxicillin, 96.% to ceftiofur and 91.9% to penicillin, while only 47–56% were sensitive to tetracyclines. Similarly, Szczotka et al. [100] demonstrated that out of 242 pig isolates, 99.5–100% proved sensitive to penicillin, ampicillin and ceftiofur, 98% to florphenicol and 95% each to gentamicin and a combination of sulphamethoxazole and trimethoprim, while only 40–50% were sensitive to tetracyclines and erythromycin.

Among antibiotics belonging to other groups, vancomycin and trimethoprim-sulfamethoxazole are reported to be effective against *S. suis* [28, 41]. According to Wertheim et al. [28], the same treatment dose and duration used for pneumococcal meningitis is also recommended for *S. suis* meningitis in humans, e.g. ceftriaxone with or without vancomycin. Antibiotic treatment has only limited effect for severely ill patients who developed STSLS [4]. According to Gottschalk et al. [25], early administration of antibiotics does not appear to have any influence on the development of post-meningitis hearing loss.

According to Papatsiros et al. [41], affected pigs should be treated for 3–5 days. As an effective prevention measure, these authors recommend a prophylactic injection of piglets with long-acting penicillin at birth [41]. According to Staats et al. [3], the use of penicillin or tiamulin in drinking water or feed has been beneficial in decreasing the incidence of *S. suis* type 2 infection in pigs.

Because an increased antibiotic resistance in *S. suis* has been reported recently, the search for new antimicrobials effective against this bacterium is progressing. Thus, Lebel et al. [101] demonstrated that nisin, a bacteriocin produced by *Lactobacillus lactis* and used commonly as a food preservative, effectively killed *S. suis*, causing breakdown of the cytoplasmic membrane and lysis of bacteria.

Synergistic effects of nisin were observed in combination with several antibiotics used for the treatment of *S. suis*, which creates prospects for use of this bacteriocin in the treatment and prevention of porcine streptococcosis.

Jiao et al. [102] have recently shown that the antimicrobial peptide NZ2114, a derivative of fungal defensin plectasin, displayed a potent antimicrobial activity against *S. suis* type 2, both *in vitro* and *in vivo* which was stronger compared to ampicillin.

PREVENTION

Prevention of porcine streptococcosis in pigs. The following measures could be applied for prevention of the disease in pigs:

- **Vaccination.** Currently, both commercial vaccines and inactivated autogenous vaccine generated each time from virulent strains isolated from sick pigs are used [4]. Although the use of commercial vaccines is more comfortable, they usually provide protection only against the most important capsular type 2 of *S. suis* [4, 103], but not against a number of other capsular types that can also evoke the disease. In contrast, the use of autogenous vaccines is troublesome because each new batch needs empirical checking on animals, but in the end they provide better protection and prevent the spread of the disease in herds during outbreaks of *S. suis* infection [4, 102]. Nevertheless, a polyvalent commercial vaccine that would protect pigs from infection with all *S. suis* types is strongly required [74].
- **Injection of piglets at birth with long-acting penicillin.** Such an injection may prevent disease [41], but this method should be used with caution to avoid the risk of appearance of antibiotic-resistant strains.
- **Improvement of pig-raising conditions.** The risk of disease can be minimized by avoiding overcrowding, maintaining proper ventilation, minimizing mixing and moving (particularly at weaning), control of other pig diseases, incorporating pest control measures, cleaning and drying the housing areas adequately, and using disinfectants and/or fumigants between housing groups [3, 103]. The latter measure is strongly recommended as *S. suis* type 2 has been shown to be susceptible to commonly used disinfectants, soaps and cleansers, such as 5% bleach at 1:800 dilution [3, 38, 44]. The use of fumigants is important in preventing airborne transmission of bacteria among animals [35]. Farrowing sows should be kept in isolation. According to some authors, the use of all-in, all-out husbandry methods can reduce the spread of infection [41].
- **Isolation of sick animals at disease outbreak.** Affected pigs should be moved to quiet pens with no draughts and an adequate heat source [3]. The back marking of previously affected but recovered older pigs is also very

important [103]. Eradication of disease by slaughter, followed by disinfection and repopulation, may be effective in controlling the disease but may not be economically feasible [3].

Prevention of porcine streptococcosis in humans. For prevention of disease in humans, following measures could be applied:

- **Protection of skin from pig bite or injury with sharp tools.** Should be achieved by pig farmers, slaughterhouse and meat industry workers, veterinarians, and cooks handling pork, by wearing stout gloves, and in the case of farmers, by wearing high boots protecting the posterior aspect of the thigh from pig bite or goring with boar's tusk. In the case of severe injuries at work, people occupationally-exposed to pigs and/or pig products should receive surgical management of the wound and broad-spectrum antibiotics effective against *S. suis*. Because of the known ability of *S. suis* to spread within the bloodstream, minor wounds or abrasions of skin (especially on hands) and mucous membranes should be promptly disinfected and dressed to prevent infection [13, 66]. After work with pigs or pig products, hands should be thoroughly washed.
- **Protection of respiratory tract by wearing appropriate masks or repirators.** Such apparel should be worn by pig farmers, especially in the case of *S. suis* epizootics, as well as during tasks linked to higher bioaerosol exposure (swine handling, moving, and vaccination) [35].
- **Consulting a doctor.** Such consultations should take place in the case of febrile illness after exposure to pigs or pork meat [41].
- **Avoidance of occupations associated with exposure to pigs and pork by immunocompomised people.** Necessary for all immunocrompromised persons after splenectomy or immunosuppresive treatment, and by individuals with some types of heart diseases, as such people are especially predisposed to contract porcine streptococcosis [25].
- **Avoidance of consumption of raw pork or pig blood.** Especially applies in southeast Asia, where such dishes are traditionally prepared.
- **Adequate cooking of pork.** According to the WHO recommendations, pork should be cooked to reach an internal temperature of 70 °C, or until the juices are clear rather than pink [4, 41].
- **Health education.** Should be applied to all people exposed to pigs and/or pork as both the cheapest and most effective preventive measure [16].
- **Proper execution of sanitary rules and food safety control.** Especially applies to southeast Asia.
- **As a vaccine for use in humans is still unavailable, continuation of research on production of an effective and safe vaccine is important**. Positive examples of such studies are the results obtained recently by Chinese scientists. Jiang et al. [49] identified a natural low-virulence *S. suis* type 5 strain XS045 as a live vaccine candidate, and demonstrated its safety and effectiveness by providing cross-protection against challenges by type 2 and type 9 *S. suis* strains. In another study, Wang et al. [31] detected significant genomic differences between the avirulent *S. suis* strain 05HAS68 and the highly virulent strain 05ZYH33. Piglets vaccinated with the avirulent strain were fully protected from challenge infection with the virulent strain.

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