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REVIEW

Streptococcus suis, an important pig pathogen and emerging zoonotic agent—an update on the worldwide distribution based on serotyping and sequence typing

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Streptococcus suis **is an important pathogen causing economic problems in the pig industry. Moreover, it is a zoonotic agent causing severe infections to people in close contact with infected pigs or pork-derived products. Although considered sporadic in the past, human *S. suis* infections have been reported during the last 45 years, with two large outbreaks recorded in China. In fact, the number of reported human cases has significantly increased in recent years. In this review, we present the worldwide distribution of serotypes and sequence types (STs), as determined by multilocus sequence typing, for pigs (between 2002 and 2013) and humans (between 1968 and 2013). The methods employed for *S. suis* identification and typing, the current epidemiological knowledge regarding serotypes and STs and the zoonotic potential of *S. suis* are discussed. Increased awareness of *S. suis* in both human and veterinary diagnostic laboratories and further establishment of typing methods will contribute to our knowledge of this pathogen, especially in regions where complete and/or recent data is lacking. More research is required to understand differences in virulence that occur among *S. suis* strains and if these differences can be associated with specific serotypes or STs.**
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INTRODUCTION

Streptococcus suis is one of the most important pathogens in the porcine industry causing septicemia, meningitis and many other infections.[1] In addition, it is an emerging zoonotic agent responsible for septicemia with or without septic shock, meningitis and other less common infections in humans.[1] During the last decade, the number of reported human cases due to *S. suis* has dramatically increased, and while most sporadic human cases of infection appear to be due to close occupational contact with pigs/pork products, particularly in Western countries (farmers, veterinarians, butchers, food processing workers, *etc.*), two epidemics were recorded in China in 1998 and 2005.[1] As of 2006, the number of human cases reported in Asia has increased.[2,3] In fact, in some Asian countries, the general population is at risk.[2] However, an update on the distribution of the different serotypes and sequence types (STs), as determined by multilocus sequence typing (MLST), of strains responsible for infections in both pigs and humans from around the world have not been recently compiled. Yet, knowledge of this distribution is necessary in order to not only understand the current situation regarding *S. suis*, but also to evaluate areas where knowledge is lacking. This review covers the global distribution of the *S. suis* serotypes and STs responsible for infections reported in pigs from 1 January 2002 to 31 December 2013. A complete review on serotypes from humans since the first description in 1968 was also carried out. However, data of the STs from human cases are available only since 2002. Complete reviews have already covered the different virulence factors implicated in the pathogenesis of the infection caused by this important pathogen,[4,5] and this will not be further addressed in this review.

Brief description of the general aspects of infection in pigs and human

The natural habitat of *S. suis* is the upper respiratory tract of pigs, more particularly the tonsils and nasal cavities, but also the genital and digestive tracts.[6] With almost 100% of pig farms worldwide having carrier animals, *S. suis* is one of the most important bacterial pig pathogens. Transmission of *S. suis* among animals is considered to be mainly through the respiratory route.[6] Of the various manifestations of the disease, septicemia and meningitis are by far the most striking features, but endocarditis, pneumonia and arthritis can also be observed.[7] Nevertheless, in peracute cases of infection, pigs are often found dead with no premonitory signs of disease.[7] Presumptive diagnosis of infection in pigs is usually based on clinical signs and macroscopic lesions.[8] Confirmation of the infection is mandatory and must be achieved by isolation and characterization of the pathogen.[8]

Since first described in Denmark in 1968,[9] over 1600 human cases of *S. suis* infection have been reported with many more probably never diagnosed or misdiagnosed. *S. suis* is the most common cause of adult meningitis in Vietnam, the second most common in Thailand and the

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third most frequent cause of community-acquired bacterial meningitis in Hong Kong.[10–12] Different from pigs, the main route of entry of *S. suis* in humans is thought to be through contact of cutaneous lesions, most usually on the hands and arms, with contaminated animals, carcasses or meat.[3] However, this situation seems to be different in some Asian countries where the oral route is taken into consideration since many cases of infection have been reported after ingestion of contaminated raw pork products.[13] In Western countries, infections in humans most usually occur sporadically.[1] After an incubation period that ranges from a few hours to days,[13] *S. suis* usually produces meningitis in humans, but is also responsible for cases of endocarditis, pneumonia, peritonitis, arthritis and other less common diseases usually related to generalized septicemia.[14,15] In addition, peracute infections with shock and a high mortality rate have been described, particularly in the case of the streptococcal toxic shock-like syndrome (STSLS) closely associated with the 2005 Chinese epidemic, but also observed independently of this outbreak.[16]

IDENTIFICATION OF *S. suis*

S. suis is an encapsulated gram-positive bacterial coccus that occurs singly, frequently in pairs, or occasionally in short chains. The organism grows well in aerobiosis, but growth is enhanced by microaerophilic conditions. The majority of strains are alpha-hemolytic on bovine and sheep blood agar plates after 24 h of incubation at 37℃.

Pig and human strains isolated from clinical cases of infection

For clinical cases in pigs, isolation and identification of strains is relatively easy since successful identification can be achieved by a minimum of biochemical tests and confirmed by serotyping (see below).[17] However, the use of rapid multi-test biochemical kits may be misleading as some strains of *S. suis* can be misidentified.[18] Although *S. suis* field isolates readily grow on media used for culturing meningitis-causing bacteria and veterinary diagnostic laboratories easily identify this pathogen, many human diagnostic laboratories are less aware of this pathogen and may misidentify it as enterococci, *Streptococcus pneumoniae*, *Streptococcus bovis*, viridans group streptococci (e.g., *Streptococcus anginosus* and *Streptococcus vestibularis*) or even *Listeria monocytogenes*.[14,18–22] In many cases, the initial gram stain presumptive diagnosis of the cerebrospinal fluid specimen is pneumococcal meningitis. This confusion may have led to the misdiagnosis of *S. suis* infections in the past. Many cases were diagnosed retrospectively after the isolates were initially misidentified.[23] More recently, polymerase chain reaction (PCR) tests have been used to directly detect *S. suis* DNA from cerebrospinal fluid samples with a sensitivity considerably higher than direct culture, especially if antibiotics have been used.[2] However, most PCR tests used for humans detect serotype 2 strains only and will not detect infections caused by other *S. suis* serotypes (see below). Instead of the serotype 2 PCR test, it is advisable to use other validated PCR tests that allow the detection of the *S. suis* species (see below).

Strains isolated from clinically healthy pigs

S. suis is a normal inhabitant of the oral cavity of pigs. The biochemical identification of isolates recovered from clinically healthy pigs (mainly from tonsil samples) is difficult to achieve due to the presence of other streptococci that are part of the normal oral microflora and that are phenotypically similar to *S. suis*. For this reason, molecular biology techniques have been developed during the last decade to allow the detection and identification of *S. suis* strains, such as a PCR assay targeting the specific house-keeping gene encoding for the glutamate dehydrogenase (*gdh*).[24] Although widely used, the *gdh* PCR test can sometimes fail to correctly identify certain *S. suis* isolates.[25] Using this test, it has also been reported that there was a risk of misidentifying *Streptococcus gallolyticus* as *S. suis*.[26]

SEROTYPING

Definition of serotypes

Serotyping, which should be a part of the routine identification of *S. suis* strains recovered from diseased pigs and humans, will provide further confirmation regarding the pathogen's identity. A total of 35 serotypes of *S. suis* have been described and are defined based on the antigenicity of their capsular polysaccharide (CPS).[6] Evidence accumulated throughout the years has demonstrated a high level of genetic diversity in the *S. suis* species, as shown by sequence analysis of the 16S rRNA and *cpn60* genes: these two methods suggested that serotypes 32 and 34 were divergent, being clustered together at a significant distance from the other serotypes. This led to the suggestion that these two serotypes might be reclassified as a different species (*Streptococcus orisratti*).[27,28] However, field strains belonging to these serotypes have been isolated from diseased pigs in recent years in Canada and China.[25,29,30] More recently, further studies have suggested that the reference strains of additional serotypes (20, 22, 26, and 33) do not belong to the *S. suis* species.[31] As such, there is an urgent need for a consensus in defining whether a serotype belongs to *S. suis* or not.[32]

In order to understand the important roles of the CPS in serotyping and in the interactions of *S. suis* with the host, knowledge regarding the specific structure that confers capsular properties to each individual serotype is necessary. Van Calsteren *et al.*[33,34] have described the composition and structures of the *S. suis* serotypes 2 and 14 CPS. Still, the chemical composition and structure of the CPS of the serotypes other than 2 and 14 are presently unknown.

Serological methods

Proper serological typing, which is one of the most important features of the *S. suis* infection diagnosis, must be performed using either a co-agglutination test, capillary precipitation test or with Neufeld's capsular reaction using reference antisera.[35,36] Details on how to perform the co-agglutination test have already been published.[37] This test is preferred by many laboratories, especially in North America.[17] Some serotypes cross-react, indicating the presence of common antigenic determinants. This cross-reaction is probably due to similar or closely related structural features of the CPS. To date, the following cross-reactions have been described: serotype 1/2 with serotypes 1 and 2, serotypes 6 and 16, serotypes 2 and 22, and serotypes 1 and 14.[35,38] In some cases, absorption is recommended in order to obtain monospecific antisera.[17] However, levels of cross-reactions for some serotypes vary with field strains (Gottschalk M, unpublished data, 2014).

Serotyping by multiplex PCR

The idea of molecular serotyping by PCR amplification of serotype specific *cps* genes using either a simplex or multiplex PCR is attractive due to the fact that animals are not used for serum production, ease of development and effectiveness. Early studies reported the use of assays targeting some serotypes.[39,40] Liu *et al.*[41] reported a new protocol using four multiplex PCR assays allowing the detection of the 33 serotypes of *S. suis* (serotypes 1 to 31, 33 and 1/2), but not those related to *S. orisratti* (serotypes 32 and 34). Strains reacting in serology with more than one serotype could be confirmed using this technique. More recently, Okura *et al.* developed a PCR for all 35 described

serotypes of *S. suis*.[42] Regardless of the PCR test used, a major disadvantage is the fact that the serotypes 2 and 14 cannot be distinguished from serotypes 1/2 and 1, respectively, since both of these serotype pairs do not possess unique *cps* genes.[43] This represents a major problem for pig isolates since serotypes 1, 1/2, 2 and 14 are commonly isolated in swine.[3,10] The use of specific antisera is mandatory for such strains. For this reason, only serologically confirmed isolates of serotypes 2 and 14 recovered from pigs were considered in the present review. Although it is also necessary to confirm isolates from humans, it may represent a less important drawback since serotype 1/2 has never been isolated from humans and serotype 1 has been reported in only three non-serologically confirmed cases (at least with both serotypes 1 and 14 antisera), which is important considering these serotypes cross-react (see above).[44,45] For this reason, isolates from humans reported in the literature as being serotype 2 or 14 based only on PCR reactions (although not serologically confirmed) will be considered as such in the present review.

'Serotyping' by biochemical identification

In the past, some reported cases of *S. suis* infection in humans have been attributed to serotype 2 based on the biochemical analyses obtained using the rapid multi-test commercial kits. While many of these kits claim to differentiate between serotype 1 and 2 strains based on sugar fermentation, there is still no evidence of a correlation between a specific serotype and its biochemical properties.[17,20,46] As a result, some human cases have been reported as serotype 2, while others were reported as serotype 1, but since the serotypes of these strains have not been confirmed using antisera (and not even by PCR), their serotypes are herein reported as 'unconfirmed by reference antisera or PCR tests'.

Non-typable strains

Some *S. suis* isolates do not agglutinate with any of the typing antisera directed against the 35 serotypes and are identified as non-typable isolates.[29] Non-typable *S. suis* strains may correspond to either truly encapsulated strains that belong to novel, not yet described, encapsulated serotypes, or to non-encapsulated strains, which are impossible to serotype using the serological methods based on CPS antigens. The proportion of non-typable isolates varies between studies depending on the number of serotypes detected using antisera.

Using antisera against all 35 serotypes, Gottschalk *et al.*[25,47] demonstrated that 89% of non-typable *S. suis* strains presented high surface hydrophobicity, suggesting that they were poorly or non-encapsulated. This was confirmed using transmission electron microscopy, demonstrating that highly hydrophobic strains (74%–93%) were non-encapsulated.[25] More than 40% of these non-encapsulated strains have been recently shown to belong to known serotypes using a multiplex PCR for all 35 serotypes.[42] It is also difficult to be certain if these strains were already non-encapsulated when causing disease, or if they lost their CPS during isolation and culture. It has been previously reported that 34% of isolates belonging to serotype 1/2 or 2 recovered from cases of endocarditis in Japan were non-encapsulated due to deletions and insertions in the genes of the CPS locus.[48] It was concluded that although the CPS is considered an important virulence factor for *S. suis*, loss of capsular production might be beneficial to *S. suis* in the course of infective endocarditis. In fact, non-encapsulated strains were shown to possess not only high adhesion properties to mammalian cells, but also a capacity to form biofilms.[47] Since the sites of isolation of these non-typable strains were similar to those of the most important serotypes (meninges/brain, joints, heart and lungs), their potential virulence capacity should not be disregarded.

MULTILOCUS SEQUENCE TYPING

Being a pathogen capable of causing sporadic cases of infection and epidemics in both pigs and humans, the global surveillance of *S. suis* is very important in order to better understand the epidemiology of this bacterial species.[49] Though different methods based on DNA have been used for the surveillance of *S. suis*, these methods are effective for short-term epidemiology only as they are based on non-characterized genomic differences between isolates.[49] In contrast, MLST distinguishes a large number of genotypes while using genetic variations that accumulate very slowly, in housekeeping genes, and has allowed global and long-term epidemiology for many important meningitis-causing bacteria by determining the STs present within a population.[49,50]

In 2002, King *et al.*[51] established a model of MLST for *S. suis* using seven different house-keeping genes (*cpn60*, *dpr*, *recA*, *aroA*, *thrA*, *gki* and *mutS*). Since being established, this MLST model has been used by multiple laboratories throughout the world to determine the STs of *S. suis* strains isolated from pig and human cases of infection. When used alongside serotyping, MLST allows gathering further information about the genetic diversity of the *S. suis* strains within the different serotypes. The popularity of this typing method for *S. suis* continues to increase due to the ease in carrying out the technique (PCR and sequencing) and due to the fact that the data are transferrable and comparable from one laboratory to another. Thanks to the *S. suis* MLST Database, the global distribution of the different *S. suis* STs can be shared and compared. When the MLST data take into consideration the serotypes, it is important that a trustable and complete serotyping system has been applied to the field strains; otherwise, the final data are difficult to interpret. More recently, studies have begun combining data obtained from MLST with the presence or absence of different *S. suis* virulence-associated markers at the gene and protein levels including the suilysin (SLY, encoded by the *sly* gene), muramidase-released protein (MRP, encoded by the *mrp* gene), extracellular factor (EF, encoded by the *epf* gene) and different pili in order to compare STs data with phenotypic characteristics.[52,53]

METHODOLOGY USED IN THE PRESENT REVIEW

In the present review, literature searches were completed using the following databases: Medline (PubMed; http://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (http://thomsonreuters.com/web-of-science-core-collection/) and Science Direct (http://www.sciencedirect.com/). Relevant articles in English were used, while references in other languages were considered when available. MLST results were obtained from the *S. suis* MLST Database (http://ssuis.mlst.net/). Regarding the distribution of serotypes, the results reported for clinical cases in pigs correspond only to those where serotyping was carried out using antisera and not PCR, while for human cases, reports where serotyping was performed by either antisera or PCR (for serotypes 2 and 14) are both reviewed. This consideration is primarily based on the fact that serotype 1 and serotype 1/2 isolates have not yet been recovered (or confirmed) from human cases of infection. It is important to note that when the correlation between STs and serotypes are reported in this review, it is impossible to confirm the methodology used for the serotyping for many cases.[51] We decided to take the data into consideration, especially for those included in the *S. suis* MLST Database, since the number of cases used for this review would otherwise have been highly limited. For the distribution of STs, the ST complexes represent hyperinvasive lineages to which two or more STs belong as a result of genetic proximity and are based on the MLST phylogeny diagram presented by Lachance *et al.*[54] STs considered to be unrelated to another ST according to this phylogeny diagram are identified as being 'unrelated' to any

known ST complex. With the exception of the serotype distribution of *S. suis* human cases, which comprises all cases reported since first described in 1968, distribution of serotypes for clinical cases in pigs and distribution of all STs are based on data published between 1 January 2002 to 31 December 2013.

WORLDWIDE DISTRIBUTION OF SEROTYPES

Diseased pigs

In order to fully appreciate the prevalence of human infections and the zoonotic potential of *S. suis*, one must understand the situation at the farm level since transmission from diseased pigs or pork-derived products is a prerequisite for infection of humans. The data compiled from studies since 1 January 2002 are shown in Table 1.

While *S. suis* is part of the normal microflora of pigs and many studies have focused on carriage in healthy pigs, these studies were not included in this review since the serotype distribution in healthy carriers greatly differs from that of clinical strains, with serotype 2 being much less frequently isolated.[65–71] In addition, since *S. suis* is a normal inhabitant of the upper respiratory tract,[6] most of these studies identified only a small part of the real population of each carrier. Finally, in the case where species-specific PCR tests were not used, many of the 'untypable' strains detected probably did not belong to the *S. suis* species. The contribution of these commensal strains to the risk posed to humans in close-contact with pigs or with pork-derived products remains to be further studied[14,72,73] and seems to occur particularly in immunocompromised patients. The situation may be different when animals are not really 'healthy carriers' but rather convalescent animals, carrying in their tonsils virulent strains. However, this situation is almost impossible to define in field studies.

During the last 12 years, more than 4500 serologically confirmed strains recovered from diseased pigs have been reported (Table 1). Globally, the predominant *S. suis* serotypes isolated from clinical cases in pigs are, in decreasing order, serotypes 2, 9, 3, 1/2 and 7, along with 15.5% of the strains being non-typable by serotyping. However, there is a clear geographical effect on the distribution of serotypes (see below) and these figures are influenced by the number of published studies.

Almost 70% of studies on worldwide isolates recovered from diseased pigs are from North America (Table 1). Nevertheless, this is not an indication of a higher number of cases but simply of a higher number of published reports and studies. In fact, 97% of North American data are from Canada and the rest from the United States, with no data from Mexico. In North America, serotype 2 is the most prevalent in Canada, while in the United States, it is serotype 3. Meanwhile, the second most prevalent serotype in Canada is serotype 3 and is serotype 2 in the United States. However, only slight differences in percentages have been observed in both countries, demonstrating a similar distribution when the data are combined: both serotypes 2 and 3 are the two most prevalent serotypes isolated from clinical pig cases in North America with 24.3% and 21.0% of prevalence, respectively, followed by serotypes 1/2, 8 and 7. Similar distributions of serotypes in Canada and the United States may be explained by a fluid movement of animals between the two countries.

In South America, only two studies have been published, both from Brazil, which report serotype 2 as being the most prevalent with a mean of 57.6% of cases, followed by, in decreasing order of prevalence, serotypes 1/2, 14, 7 and 9 (Table 1). Interestingly, although no clinical cases in pigs have been published, human cases have been reported in other South American countries (see below).[74–77] On the other hand, no human cases have yet been reported in Brazil.

In Asia, where the vast majority of human cases have been reported (see below), studies on clinical cases in pigs account for only 14.0% of the data available and are provided from China and South Korea only. The most prevalent serotypes in infected pigs are, in decreasing order of prevalence, serotypes 2, 3, 4, 7 and 8 (Table 1). The South Korean study surprisingly reported serotypes 3 and 4 as being predominant, followed by serotype 2 at a low prevalence of only 8.3%. This anomaly may be due to the fact that the paper reported a relatively low number of cases (only 20 isolates) from animals with acute polyserositis only.[61] Even more disturbing is the fact that the information available regarding the status of *S. suis* infections in pigs in Asia is the most scarce of the three continents, while this is the continent where cases of zoonosis occur the most frequently in the general population. Although many hospitals and microbiologists in both Thailand and Vietnam are aware of *S. suis* infections when it comes to diagnosis,[2] the four veterinary studies published from these countries investigated healthy or slaughterhouse pigs only.[69,70,78,79] Similarly, there have been 10 human *S. suis* cases reported in Japan between 1994 and 2009, but no complete study on the distribution of isolates from clinically ill pigs including all serotypes has been recently published. In fact, data from the last epidemiological studies in Japan date back to between 1987 and 1991, more than 20 years ago, which predate the human cases reported in this country and illustrate the necessity to gather data in order to increase our knowledge of the current epidemiological situation.[80] In Hong Kong, where *S. suis* has been reported as the third most common culture-confirmed cause of community-acquired bacterial

Table 1 Worldwide distribution of serotypes for reported clinical *S. suis* cases of infection in pigs by country from 1 January 2002 to 31 December 2013

Country	Clinical cases	Predominant serotypes[a] (frequency in %)			Reference
Worldwide	4711	2 (27.9%)	9 (19.4%)	3 (15.9%)	
North America	3162 (67.1%)	2 (24.3%)	3 (21.0%)	1/2 (13.0%)	
Canada	3 065	2	3	1/2	25, 29
United States	97	3	2	7	55
South America	125 (2.7%)	2 (57.6%)	1/2 (9.6%)	14 (8.8%)	
Brazil	125	2	1/2	14	56,57
Asia	659 (14.0%)	2 (44.2%)	3 (12.4%)	4 (5.6%)	
Mainland China	639	2	3	4	30,58–60
South Korea	20	3	4	2, 8, 22	61
Europe	765 (16.2%)	9 (61.0%)	2 (18.4%)	7 (6.7%)	
Netherlands	99	9	2	7	62
Spain	666	9	2	7	63–65

[a] Only the three most predominant serotypes, which were identified by co-agglutination (or an equivalent method using reference antisera), are shown in this table.

meningitis, there have been 47 human cases from 1983 to 2001 and 21 from 2003 to 2005,[12] yet there is a complete absence of epidemiological data regarding *S. suis* in pigs, with the exception of two studies investigating the prevalence of *S. suis* in pork meat sold in wet markets.[81,82] In Singapore, the Philippines, Laos and Cambodia, where human cases have occurred during the last decade (Table 2), there are no data available on the epidemiology of *S. suis* infections in pigs.

Important pig producing European countries, such as Denmark, Belgium, France, Germany, Italy and the United Kingdom, have not recently reported the distribution of serotypes recovered from clinical cases in pigs: the last reports from these countries regarded strains isolated between 1990 and 2000.[66,83] Before the year 2000, serotype 2 was the most common serotype recovered in Italy, France and Spain, whereas serotype 9 was more frequently found in the Netherlands, Germany and Belgium.[76] This lack of information is of high importance. The only two countries with more recent data are Spain and the Netherlands. In fact, in Spain, serotype 2 is no longer the most prevalent serotype, but the second behind serotype 9, followed by serotypes 7, 8 and 3.[63–65] In the Netherlands, between 2002 and 2007, serotype 9 was still the most prevalent, followed by serotypes 2, 7, 1 and 4.[62] Although serotype 9 is the most prevalent serotype in Spain and in the Netherlands and was also prevalent in many European countries before the year 2000, no human cases associated with this serotype have yet been reported. Taken together, these two European

Table 2 Worldwide distribution of reported clinical *S. suis* cases of infection in humans by country until 31 December 2013

		Confirmed serotypes[a]			Unconfirmed[c] or unknown serotypes[d]	
Country	Reported cases	2	14	Others[b]		Reference
Worldwide	1642	1227 (74.7%)	33 (2.0%)	5 (0.3%)	377 (23.0%)	
North America	8 (0.5%)	7 (87.5%)	1 (12.5%)	0	0	
Canada	5	4	1	—	—	7,20,94,95
United States	3	3	—	—	—	96–98
South America	9 (0.5%)	2 (22.2%)	0	1 (11.1%)	6 (66.7%)	
Argentina	4	1	—	1	2	74,77,99,100
Chile	4	—	—	—	4	75,76
French Guiana	1	1	—	—	—	101
Asia	1481 (90.2%)	1133 (76.5%)	29 (2.0%)	3 (0.2%)	316 (21.3%)	
Cambodia	13	13	—	—	—	102
Mainland China	245	245	—	—	—	16,103–107
Hong Kong	69	53	—	—	16	12,82,108–113
Japan	11	10	—	—	1	114–118
Laos	1	—	—	—	1	Unpubl.[e]
Philippines (United States)	1	—	—	—	1	119
Singapore	3	—	—	—	3	120–122
South Korea	4	—	—	—	4	123–126
Taiwan	7	2	2	—	3	21,22,127
Thailand	553	292	21	2	238	11,13,23,26,45,73,128–143
Vietnam	574	518	6	1	49	10,72,144–149
Europe	140 (8.5%)	84 (60.0%)	3 (2.1%)	1 (0.7%)	52 (37.1%)	
Austria	1	—	—	—	1	150
Belgium	4	3	—	—	1	151–154
Croatia	2	—	—	—	2	44
Denmark	8	6	1	—	1	9,155–159
France	19	8	—	—	11	160–177
Germany	9	8	—	—	1	19,92,178–184
Greece	2	—	—	—	2	185,186
Ireland	1	—	—	—	1	187
Italy	3	2	—	—	1	188–190
Netherlands	51	39	1	1	10	14,191–199
Poland	1	—	—	—	1	200
Portugal	1	—	—	—	1	201
Serbia	5	—	—	—	5	202
Spain	13	4	—	—	9	203–214
Sweden	1	1	—	—	—	215
United Kingdom	19	13	1	—	5	216–230
Oceania	4 (0.2%)	1 (25.0%)	0	0	3 (75.0%)	
Australia	3	—	—	—	3	231,232
New Zealand	1	1	—	—	—	91

[a] Serotypes were identified by co-agglutination (or an equivalent method using reference antisera) or by PCR specific reaction for serotype 2 (and 1/2) or for serotype 14 (and 1).
[b] Serotypes other than serotypes 2 and 14. See main text and Table 3 for details.
[c] Serotypes were determined based on biochemical identification so are reported as 'unconfirmed'.
[d] Strain serotype was not mentioned in the publication and is thus considered as 'unknown'.
[e] Wertheim H, unpublished data (2014).

countries provide a relatively similar serotype distribution with serotypes 9, 2, 7, 8 and 3 in order of importance (Table 1). In studies previous to 2002, serotype 1 also appeared to be prevalent in countries such as Belgium and the United Kingdom;[76] however, it is not clear if this is the current situation. The situation is similar in Denmark where only serotype 7 isolates were characterized during the last twelve years and where the last serological study regarded isolates recovered in 1995–1996.[84,85] For the time period covered in this review, two reports, from France and Italy, have been published, although the data from none of these was considered since one of them used serotyping by PCR, detecting serotypes 1 (and 14), 2 (and 1/2), 7 and 9 only and, thus, did not meet the inclusion criterion (see above), while the other studied the distribution of serotypes in healthy animals.[67,86] Interestingly, human cases have emerged in other European countries in many of which few or no studies on *S. suis* isolation from diseased pigs have been conducted. In Serbia, a recent prevalence study was published using isolates from swab samples taken from dead animals, clinically healthy pigs, slaughterhouse pig carcasses and butchers' knives, but it was impossible to associate corresponding serotypes to the diseased animals only.[87] In Croatia, only one study pertaining to the antimicrobial susceptibility of *S. suis* type 2 isolates was published,[88] but no epidemiological studies on the distribution of serotypes is available. Moreover, in Greece and Poland, where human cases have been reported, there are still no pig data available. As such, there is an urgent need to evaluate fresh data on the prevalence of *S. suis* in clinical isolates from pigs in Europe where many countries are among the more important pig producers in the world.

Finally, there is also a lack of relatively recent serotyping data from Australia and New Zealand. In Australia, where three human cases have been recently reported, the studies concerning serotype distribution in pigs predate these human cases, thus showing that there were once active surveillance studies in this country.[89,90] One human case of *S. suis* was also reported in New Zealand,[91] but no recent studies regarding isolates recovered from diseased pigs have been published in this country.

In summary, there are countries where the serotype distribution of field strains recovered from diseased pigs has been systematically undertaken during the last 12 years, generating data that may influence any analysis of the worldwide distribution of serotypes. There is an urgent need for new data from European countries on the serotype distributions of *S. suis* strains isolated from diseased pigs, especially considering the fact that currently available vaccines are bacterins, which are supposed to confer serotype-specific protection. Some countries with an important pig production, such as Brazil, have few studies on pig disease and no human cases declared. Other countries commonly report human cases, but data from diseased animals are almost absent.

Human cases

One of the goals of this review was to compile the serotype distribution of *S. suis* infections in humans, which has not been completed since 1989,[92] and to update the total number of cases from recent reviews on human cases, all of which are excellent comprehensive reviews regarding the clinical features of *S. suis* infections in humans.[3,18,93] In the present study, and differently from clinical pig isolates, serotype 2 and 14 isolates were considered to be as such even if identified by PCR, which is unable to differentiate them from serotypes 1/2 and 1, respectively. This consideration is primarily based on the fact that serotype 1 and serotype 1/2 isolates have not yet been recovered (or confirmed) from human cases. A total of 1642 cases have been reported worldwide as of 31 December 2013 (Table 2).

Of these cases, serotype 2 was the most frequently reported with 74.7%, followed by serotype 14 with 2.0%. It is important to note that 262 (21.5%) serotype 2 strains and two (6.0%) serotype 14 strains were identified by PCR only. The most striking aspect regarding human cases of infection is that 377 cases (23.0%) of all reported cases either do not specify the serotype in the case report or employed a method for serotype identification that was judged inadequate ('biochemical serotyping'). Even though many of these reports claim to be caused by serotype 2, which is probably true, serotyping, or at the very least PCR, should be performed if the strains are still available in order to increase our knowledge of *S. suis* infections in humans. Meanwhile, the remaining five human cases of infection were caused by the following serotypes: 4,[14] 5,[133] 16,[146] 21[77] and 24.[133] Since 2011, human *S. suis* cases of infection have been reported for the first time in Cambodia, Chile, French Guiana, Poland and South Korea.

The vast majority of human cases have occurred in Asia, which account for more than 90% of all reported cases, particularly in Vietnam, Thailand and China. These three countries alone account for 83.6% of all cases worldwide. However, in China, almost all cases were described during the 1998 and 2005 outbreaks.[16,105] In East and Southeast Asia, *S. suis* zoonosis should be considered endemic due in part to the high density of pigs, relatively high number of backyard-type production farms, slaughtering practices with the use of few preventive measures, presence of wet markets and consumption of ill pigs and/or consumption of uncooked or undercooked pork products.[3] In Thailand, most of the reported cases were caused by serotype 2, while serotype 14 is the second highest, the latter accounting for 21 cases of meningitis and sepsis out of a total of 530 cases. However, infections by other serotypes, such as a serotype 5 peritonitis and a serotype 24 sepsis, have also been reported. In Vietnam, where *S. suis* is now the most frequent cause of adult bacterial meningitis,[10] most cases are also due to serotype 2, six cases of meningitis were caused by serotype 14, and one case of peritonitis by serotype 16. The diversity of infections caused by serotypes other than serotype 2 could be explained by the awareness of diagnosticians to *S. suis* infections. Consequently, this could also explain why Vietnam and Thailand have the largest number of reported cases and a higher probability of encountering atypical cases on a more regular basis. It is also interesting that the patients who suffered infections by serotypes 5, 16 and 24 were also suffering from cirrhosis: a likely explanation is that these infections were the result of immunocompromisation. The compilation of human cases in China includes sporadic cases and the two *S. suis* serotype 2 epidemics, the first in Jiangsu province in 1998, where 14 deaths out of 25 cases occurred,[16] and the second in Sichuan province in 2005, where 38 deaths out of 215 cases were reported. This second epidemic remains the largest outbreak of *S. suis* in humans.[105] These epidemics were unprecedented for *S. suis* infections in humans considering the high incidence of systemic disease, the low number of cases of meningitis, and the high rate of mortality observed.[1] The patients presented cases consisting of either sepsis, meningitis, or STSLS, based on the presence of the following symptoms: sudden onset of high fever, diarrhea, hypotension, blood spots and petechial, clear erythematous blanching rash and dysfunction of multiple organs, such as acute respiratory distress syndrome, liver and heart failure, disseminated intravascular co-agulation, and acute renal failure.[1] Even though China has the largest pig production in the world and is the site of the 1998 and 2005 outbreaks that attracted much

attention from the scientific community, the number of reported cases is considerably lower than in Thailand and Vietnam. One possible explanation is that dishes containing raw pork and blood, very popular in Thailand and Vietnam, are uncommon in China. In fact, since the last outbreak in 2005, only four other sporadic human cases were reported in mainland China.[107,113]

Human cases were also reported in Cambodia, Hong Kong, Japan, Laos, Singapore, South Korea and Taiwan. It is of interest to note that in Hong Kong, *S. suis* serotype 2 was reported as the third most frequent cause of adult bacterial meningitis.[12,108] There is also a human case of infection from the Philippines, although it was not officially reported in this country. In fact, even though the infection was diagnosed as *S. suis* serotype 2 meningitis and treated in the United States, the patient had just returned from a seven-month vacation in the Philippines where he had consumed raw pork, making this an Asian case and considered as such in this study.[119]

The second continent where most human infections have been described is Europe, accounting for 8.5% of all reported human cases (Table 2), with approximately 71.4% of all European human cases occurring 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 an increased developing pig production. Human cases of *S. suis* infection were reported for the first time in Europe, with the first ever case in Denmark, in 1968. It is interesting to note that all cases reported before 1983 were from Western Europe.[9,108] Only two countries consider *S. suis* infections in humans as an industrial disease: the United Kingdom and France since 1983 and 1995, respectively.[18] 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, most were related to wild boar hunters. It is known that wild boars also carry *S. suis*.[163] Consequently, hunters should be aware of the necessary precautions when preparing the carcasses, which present the greatest risk.[176,177] Most human cases of infection contracted from wild boars were serotype 2, with two cases of meningitis caused by serotypes 4 and 14 in the Netherlands, one case of meningitis by serotype 14 in Denmark, and one case of septicemia by serotype 14 in the United Kingdom.[14,158,226]

Although being the continent with the highest number of *S. suis* infection reports from diseased pigs (Table 1), only a few sporadic cases of *S. suis* infection in humans have been reported in North America. As previously mentioned, the isolation rate of *S. suis* serotype 2 from diseased pigs is considerable lower than that of Europe or Asia. The lower number of pig cases of disease due to this serotype may be a reason for the lower number of human cases of infection. It has been suggested that *S. suis* strains of serotype 2 from Canada and the United States present lower virulence properties than those from Europe and Asia.[54] For these two countries, confirmed human cases were all serotype 2, with the exception of one serotype 14 case of meningitis in Canada.[95] In the United States, two of the cases were from the continent while the third was from Hawaii, an island in the Pacific Ocean importing pigs from Asia. While the case in Hawaii is considered American (unlike the case from the Philippines), it would perhaps be more appropriate to compare the features of this infection with those from Asia. In fact, the strain recovered from Hawaii presents phenotypic characteristics typical of Asian strains (Gottschalk M, unpublished data, 2014).

Sporadic cases were also reported elsewhere throughout the world, such as those in South America (Argentina, Chile and French Guiana), and Oceania (Australia and New Zealand), but when combined, they only account for 0.8% of all reported cases. As was shown by Wertheim *et al.*,[3] sporadic cases of *S. suis* infections in humans are encountered in most regions where pig rearing is important, with notable exceptions being Mexico and Brazil. In the case of Mexico, even though one study evaluated upper respiratory tract colonization of slaughterhouse workers[233] (see below), no official reports on clinical pig cases or human infections are available, which is alarming, knowing full well that in previous studies, clinical strains of *S. suis* isolated from pig and human cases were included.[83,234] Despite the lack of available reports, this infection is very common in Mexican farms (Gottschalk M, unpublished data, 2014). As such, action is required in order to remedy the troubling situation in this country which has well-developed veterinary diagnostic laboratories. It remains to be seen if the absence of human cases is due to a lack of awareness of *S. suis* as a zoonotic pathogen in these regions when diagnosing bacterial infections, or if these strains are of lower virulence, as with some strains from Canada and the United States.

Table 3 shows the frequency of the clinical manifestations of infection by confirmed serotype, illustrating that the serotypes 2 and 14 are involved in similar proportions in meningitis (50%–70%) and septicemia (20%–25%). Septic shock was defined as a category comprising sepsis, septicemia, bacteremia and/or STSLS, while meningitis comprises all meningeal-related symptoms. Serotype 2 infections also represented 2.9% of the cases where other afflictions where diagnosed such as endocarditis, septic arthritis, pneumonia, peritonitis, pulmonary edema, myocarditis and other infections. Serotypes 4 and 21 were isolated from cases of meningitis, serotypes 5 and 16 from cases of peritonitis, and serotype 24 from a case of sepsis.

Table 3 Clinical manifestations of reported clinical *S. suis* cases of infection in humans by serotypes confirmed by co-agglutination

		Clinical manifestations			
Confirmed serotypes	Reported cases	Meningitis	Septic shock[a]	Other[b]	Unknown[c]
2	867	590 (68.1%)	233 (26.9%)	25 (2.9%)	19 (2.2%)
14	28	14 (50.0%)	6 (21.4%)	—	8 (28.6%)
4	1	1	—	—	—
5	1	—	—	1	—
16	1	—	—	1	—
21	1	1	—	—	—
24	1	—	1	—	—

[a] Septic shock includes bacteremia, sepsis, septicemia and streptococcal toxic shock-like syndrome cases.
[b] Other clinical manifestations such as endocarditis, septic arthritis, pneumonia, peritonitis, pulmonary edema, myocarditis, *etc.*
[c] Clinical manifestations were either not specified or could not be associated with a particular serotype.

Why reported strains isolated from human cases are almost exclusively serotypes 2 and 14 is puzzling. While the serotypes 3, 9 and 1/2 are among the most highly prevalent in diseased pigs after serotype 2, at least in North America, no human infections due to these serotypes have yet been reported in any country. These differences in virulence between pig and human isolates may be partially due to serotype-specific CPS structural features, for which the CPS structures are still unknown, except for serotypes 2 and 14, and/or due to other serotype-specific bacterial factors involved in the pathogenesis. We could speculate that the serotypes 2 and 14 are more virulent than the other serotypes based on the observation that three out of the five cases caused by other serotypes (5, 16 and 24) occurred in patients suffering from cirrhosis, which in turn may have immunocompromised them and made them susceptible to serotypes uncommon in human infections.[133,146] These differences could also be explained by varying serotype-specific colonization abilities. However, many cases caused by serotypes 2 and 14 have also been described in individuals with predisposing conditions. More research is required in order to understand how differences in virulence of *S. suis* strains occurs and if these differences can be associated with specific serotypes.

Subclinically infected humans: zoonotic potential to workers?

Subclinically infected pigs are carriers of *S. suis* mainly in the tonsils.[6] However, this information is not clearly available for humans. Only a handful of studies have investigated *S. suis* subclinical infections in humans as displayed in Table 4, either by serology (antibodies) or by bacterial detection.

Three of these were serological studies, with two using an indirect enzyme-linked immunosorbent assay (ELISA) with *S. suis* serotype 2 whole bacteria (formalin-inactivated or not) as antigen (Table 4). In New Zealand, the authors examined sera from 70 pig farmers, 96 dairy farmers, 107 meat inspectors and 16 veterinary students.[235] Twenty-one percent of pig farmers, 10% of meat inspectors and 9% of dairy farmers (most of them also raising pigs on their farms) were positive for 'anti-*S. suis* serotype 2 antibodies'. It is impossible to be certain if these titers were specific for serotype 2 since cross-reacting antibodies with other *S. suis* serotypes and/or with other bacterial species were probably detected. Antibody titers were associated with longer occupational exposure for both pig farming and meat inspection. In the United States, using a similar antigen, sera from 73 pig-exposed and 67 non-pig-exposed adults from Iowa were titrated. Ten percent of pig-exposed workers were found to be positive compared to only one positive individual (1.5%) from the non-pig-exposed group.[237] Once again, the authors concluded that positive titers were associated with either working with pigs or living on a pig farm for more than 10 years, and also found that study participants who worked with both finishing and nursery pigs had 8.8 times the odds of having a positive titer when compared to non-exposed participants. The third serological study, from the Netherlands, is interesting since the authors chose to perform Western blot analysis, with higher specificity, targeting two virulence-related markers of *S. suis* serotype 2 that are widely present among virulent strains in that country, the MRP and EF proteins, in sera from 102 veterinarians and 191 pig farmers.[236] Results showed that 6% of veterinarians were positive for anti-MRP and 2% were positive for anti-EF, while 1% of pig farmers were positive for anti-MRP and 0.5% were positive for anti-EF. It is important to note that these antigens have not been reported to be present in bacterial species other than *S. suis*. These three serological studies, while the titers obtained cannot be directly compared, illustrate the zoonotic potential of *S. suis* based on the presence of antibodies possibly generated through long-term exposure and/or exposure-related subclinical infections. It should be noted that the presence of antibodies does not guarantee a carriage status for positive individuals.

In addition to these serological studies, three studies have directly focused on carriage in the upper respiratory tract of humans by trying to isolate *S. suis* from pharyngeal or tonsil swabs of pig-exposed workers (Table 4). In Italy, 10 volunteer slaughterhouse workers were swabbed and two were found to be positive for *S. suis* serotype 2.[238] In Mexico, the tonsils from 69 slaughterhouse workers were swabbed and four were found to be positive.[233] Of the four strains isolated, one was serotype 2, another was serotype 27 and two were non-typable by serotyping. The virulence of these four strains was also evaluated in mice and it was determined that three of them were mildly virulent (30%–80% mortality) and one of the non-typable strains was highly virulent (70%–90% mortality). Finally, in Germany, the tonsils from 132 meat workers (from either a slaughterhouse or meat processing factory) and 140 controls were swabbed and seven workers were found to be positive carriers of *S. suis* serotype 2, while none of the controls showed positive results. For the seven workers found to be positive carriers, four were retested 3 weeks later and were confirmed to still be

Table 4 Studies exploring human carriage and exposure to *S. suis* in risk groups

Study (reference)	Technique employed/target	Risk groups	Positive carriage or exposure (positive/tested)	Serotypes found
Serological				
New Zealand, 1989[235]	Indirect ELISA/serotype 2 whole bacteria	Pig farmers	15/70 (21.4%)	—
		Meat inspectors	11/107 (10.3%)	
		Dairy farmers	9/96 (9.4%)	
Netherlands, 1999[236]	Western blot/serotype 2 MRP/EF	Veterinarians	MRP: 6/100 (6.0%)	—
			EF: 2/100 (2.0%)	
		Pig farmers	MRP: 2/190 (1.1%)	
			EF: 1/190 (0.5%)	
United States, 2008[237]	Indirect ELISA/serotype 2 whole bacteria	Pig workers	7/73 (9.6%)	—
Upper respiratory tract colonization (isolation)				
Italy, 1989[238]	Tonsil swabs	Slaughterhouse workers	2/10 (20%)	2
Mexico, 2001[233]	Tonsil swabs	Slaughterhouse workers	4/69 (5.8%)	2, 27, NT[a]
Germany, 2002[181]	Pharyngeal swabs	Slaughtering and meat processing workers	7/132 (5.3%)	2

[a] Non-typable strain (NT).

positive carriers, indicating that the bacteria probably remained in the tonsils of healthy individuals for a relatively long period of time, which was also shown to be the case in pigs.[6] However, since these individuals were continuously exposed to pork products, repeated recolonization could not be ruled out.[2] All of the positive workers were employed for an average of 9.9 years ranging from three to 21 years. These three studies regarding the nasopharyngeal carriage all report positive samples in pig-related meat workers and none in the population without occupational exposure to pig. It is also very important to note that of the 13 strains isolated from healthy workers, 84.6% were serotype 2.

Taken together, these studies illustrate the zoonotic potential through long-term exposure, either by demonstrating the presence of antibodies towards *S. suis* or by isolating *S. suis* from tonsils or pharynx in pig-exposed workers. It must be noted that the positive rates in the studies of carriers of the upper respiratory tract are probably underestimated since detection of the pathogen was achieved using isolation methods, which are considered as having low sensitivity. Studies using molecular techniques (species-specific PCR) would probably present a significantly higher sensitivity. Exposure to *S. suis* may lead to subclinical infections, induction of antibodies, serious disease, as was the case in the human cases discussed previously, or just an insignificant and transitory atypical colonization of the mucosal membranes within the respiratory route.[110,181] The annual risk of developing meningitis due to *S. suis* in the Netherlands was estimated to be 3.5/100 000 for slaughterhouse workers, 2.7/100 000 for pig breeders and 1.2/100 000 for butchers.[14] Compared to the non-exposed general population (0.002/100 000), the risk for slaughterhouse workers is 1500 times higher. In the United Kingdom, the risk for butchers is even higher.[239] The annual incidence for the occupational group (direct contact with pigs) in Hong Kong was 32/100 000, 350 times higher than that of the general population (0.09/100 000) and 30 times higher than the homologous group in the Netherlands.[82] In addition, a less dramatic difference between the occupational group and the general population was observed in Hong Kong (350 times higher in Hong Kong versus 1500 times in the Netherlands). All these differences may be due, at least in part, to a closer contact between people and pork carcasses in Asia.[2] Also, a case–control study conducted in Vietnam from 2006 to 2009 showed that eating high risk dishes common in Vietnam, such as fresh (Tiết Canh) or undercooked blood, tonsils, tongue, stomach, intestines and uterus from pigs within 2 weeks prior to admission was the most significant risk factor for *S. suis* infection, followed by exposure to pigs, pork products and preparation of pork in the presence of skin lesions within two weeks prior to admission.[72] The authors also investigated the presence of *S. suis* in pork by-products collected from slaughterhouses and wet/retail markets in Vietnam, and found an 11% contamination rate with *S. suis* serotype 2 in internal organ samples. Unfortunately, they were unable to demonstrate *S. suis* carriage rates in 1022 healthy individuals or patients without *S. suis* infection using a PCR targeting *S. suis* serotype 2 and 1/2. A PCR for the detection of *S. suis* may have been more sensitive and could possibly have identified potential carriers of other serotypes.[233] The authors suggested that their results, which include six positive rectal swabs from patients, strengthen the hypothesis that the gastrointestinal tract may be a route of entry for *S. suis*, which is in agreement with cases following the ingestion of raw pork meat. Similarly, data from Thailand suggest a high incidence rate (6.2/100 000) of *S. suis* infection in the general population in 2010, mostly related to consumption of raw pork products.[130]

WORLDWIDE DISTRIBUTION OF SEQUENCE TYPES

Global distribution of sequence types

As presented in Figure 1, different serotype 2 STs predominate in different regions of the world. The ST1 is mostly associated with disease in both pigs and humans in Europe (though the ST20 is important in the Netherlands), Asia (Cambodia, mainland China, Hong Kong, Japan, Thailand and Vietnam) and Argentina (Tables 5 and 6). Meanwhile, the ST7, responsible for the 1998 and 2005 epidemics, is mostly endemic to mainland China (Tables 5 and 6). North American cases greatly vary from those in Eurasia, with most strains being either ST25 or ST28, two STs also recovered in Thailand and Japan, respectively (Tables 5 and 6). Finally, the ST101 to 104 are endemic to Thailand and appear to be more and more commonly isolated from human cases, especially the ST104 (Table 6). As such, it can be easily observed that the current distribution of the *S. suis* serotype 2 STs greatly varies throughout the world, though data have only been available for a little over a decade, from only a few countries and mostly only for the serotype 2.

Nevertheless, there is an important issue regarding the serotypes attributed to the different strains typed by MLST. Many of the studies, including most of the strains from the *S. suis* MLST Database, do not specify the method used for serotyping. In other cases, such as the study of King *et al.*,[51] the authors did not necessarily confirm the serotypes of the strains used. As explained above, the use of PCR for serotyping of serotypes 2 and 14 strains is an inappropriate method, especially for clinical pig cases, even though cases serotyped using this

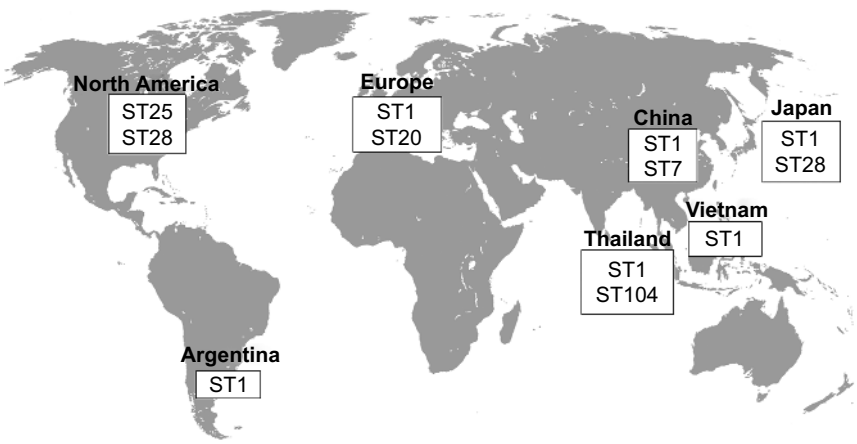

Figure 1 Worldwide distribution of the most important *S. suis* serotype 2 sequence types isolated from both clinical pig and human cases of infection.

Table 5 Determined sequence types of reported clinical *S. suis* cases of infection in pigs from 1 January 2002 to 31 December 2013

Country	Serotypes[a]	ST	ST complex	Number of cases	Reference
North America					
Canada	2	1	1	2	240
		25	25	28	52,240
		28	28	18	52
		145	25	1	MLST Database
	23	80	Unrelated	1	51
	24	68	Unrelated	1	51
	25	69	Unrelated	1	51
	27	72	Unrelated	1	51
	28	75	Unrelated	1	51
	29	92	Unrelated	1	51
	30	77	Unrelated	1	51
	31	70	Unrelated	1	51
	Not specified	13	13/149	Not specified	51
United States	2	1	1	3	52
		25	25	28	52
		28	28	33	52
Europe					
Denmark	4	54	53/54	1	51
	5	53	53/54	1	51
	6	55	Unrelated	1	51
	8	87	87	1	51
	9	82	Unrelated	1	51,240
	10	78	Unrelated	1	51
	11	91	Unrelated	1	51
	12	74	Unrelated	1	51
	13	71	Unrelated	1	51,241
	16	73	Unrelated	1	51
Finland	2	37	Unrelated	1	51
	Not specified	27	27	Not specified	51
		38	Unrelated	1	51
France	2	1	1	4	242
		140	Unrelated	1	MLST Database
		141	1	1	MLST Database
		142	28	1	MLST Database
		143	1	1	MLST Database
		144	1	1	MLST Database
		229	25	1	MLST Database
		230	25	1	MLST Database
	14	231	Unrelated	1	MLST Database
	15	81	Unrelated	1	MLST Database
Germany	1/2	100	Unrelated	1	243
	2	1	1	5	243
		25	25	1	243
		28	28	2	243
		97	Unrelated	1	243
	3	95	Unrelated	1	243
	7	29	29	7	240,243
		89	16	1	243
	9	93	Unrelated	1	243
		96	Unrelated	1	243
		98	16	2	243
		99	16	1	243
Italy	2	1	1	1	86
	9	138	Unrelated	1	MLST Database
Netherlands	1	1	1	4	62,240
		13	13/149	2	51,62
		149	13/149	1	62
		156	1	1	62
	1/2	1	1	1	62,240
	2	1	1	21	62,240
		20	147	19	62

Table 5 Continued

Country	Serotypes[a]	ST	ST complex	Number of cases	Reference
		29	29	1	62
		134	1	1	MLST Database
		146	1	1	MLST Database
	3	15	16	1	62
		35	27	1	51
	4	17	147	3	62
	7	29	29	5	62
		135	29	1	MLST Database
		136	16	1	62
		150	Unrelated	1	62
		153	Unrelated	1	MLST Database
		218	Unrelated	1	62
	8	87	87	1	62
		198	16	1	62
	9	1	1	2	62,240
		15	16	1	62
		16	16	38	62
		136	16	2	62
		148	1	1	62
		151	16	1	62
		152	16	1	MLST Database
		154	16	1	MLST Database
		155	16	1	62
		182	Unrelated	1	62
		184	Unrelated	1	MLST Database
		189	Unrelated	1	62
		220	Unrelated	1	62
	15	81	Unrelated	1	51
	Not specified	183	Unrelated	1	MLST Database
Spain	1	1	1	2	244
					MLST Database
	1/2	1	1	2	244
					MLST Database
		28	28	1	MLST Database
		64	94	1	51
	2	1	1	31	244
		5	1	1	51
		27	27	1	MLST Database
		28	28	1	MLST Database
		86	1	1	MLST Database
		124	1	1	244
	3	14	147	1	51
		15	16	1	51
		27	27	1	MLST Database
		89	16	1	51
	4	16	16	1	51,240
	5	17	147	1	51
	9	16	16	2	51,240
		59	123	1	51
		123	123	8	244
		125	123	9	244
		361	Unrelated	1	MLST Database
		367	Unrelated	1	MLST Database
	14	1	1	1	244
					MLST Database
	15	65	Unrelated	2	51
	27	65	Unrelated	2	51
United Kingdom	1	1	1	5	240,242
					MLST Database
		12	11	1	51
		13	13/149	1	51
	1 or 14	10	1	1	51
	2	1	1	37	240,242
					MLST Database

Table 5 Continued

Country	Serotypes[a]	ST	ST complex	Number of cases	Reference
		2	1	5	51
		9	1	1	51
		25	25	7	MLST Database
		28	28	5	MLST Database
		29	29	1	MLST Database
		30	28	1	MLST Database
	3	27	27	2	51
		29	29	1	MLST Database
		31	28	2	51
		33	27	1	51
		42	Unrelated	1	51
	4	23	87	3	51
	5	39	Unrelated	1	MLST Database
		44	Unrelated	1	51
	7	29	29	6	MLST Database
		34	225	1	51
		83	29	1	51
	8	1	1	1	MLST Database
	9	46	Unrelated	1	51
		48	Unrelated	2	51
		50	Unrelated	1	51
	11	88	Unrelated	1	51
	14	1	1	14	MLST Database
	15	43	43/52	1	51
		45	Unrelated	1	51
		49	Unrelated	1	51
		52	43/52	1	51
	16	41	Unrelated	2	51
					MLST Database
		47	Unrelated	1	51
	28	21	87	1	51
	Not specified	40	Unrelated	1	MLST Database
		51	Unrelated	1	MLST Database
		90	Unrelated	1	MLST Database
Asia					
Mainland China	2	1	1	49	59,245,246
		7	7	216	59,241,242,245–247
		25	25	1	246
		28	28	31	59,245,246
		86	1	1	245
		117	27	27	MLST database
		162	28	1	245
		223	1	1	MLST Database
		228	7	1	MLST Database
		242	1	1	MLST Database
		244	7	1	MLST Database
		245	28	1	MLST Database
		289	1	1	59
		290	Unrelated	1	MLST Database
		352	Unrelated	1	MLST Database
		353	Unrelated	1	MLST Database
		354	Unrelated	1	MLST Database
		355	Unrelated	1	MLST Database
		418	Unrelated	1	MLST Database
		419	Unrelated	1	MLST Database
	3	224	Unrelated	1	MLST Database
	7	129	29	1	MLST Database
		225	225	1	MLST Database
		335	Unrelated	1	MLST Database
		420	Unrelated	1	MLST Database
	9	222	Unrelated	1	MLST Database
		226	226/227	1	MLST Database
		227	226/227	1	MLST Database

Table 5 Continued

Country	Serotypes[a]	ST	ST complex	Number of cases	Reference
		239	239/241	1	MLST Database
		241	239/241	1	MLST Database
		417	Unrelated	1	MLST Database
	11	260	Unrelated	1	MLST Database
		263	Unrelated	1	MLST Database
	13	262	Unrelated	1	MLST Database
	27	258	Unrelated	1	MLST Database
	31	261	27	1	MLST Database
		265	27	1	MLST Database
	Not specified	29	29	1	59
		118	Unrelated	1	59
		156	1	2	59
		264	Unrelated	1	MLST Database
		266	Unrelated	1	MLST Database
		267	Unrelated	1	MLST Database
		303	Unrelated	1	MLST Database
		383	Unrelated	2	MLST Database
		421	Unrelated	1	MLST Database
		422	Unrelated	1	MLST Database
Japan	1	1	1	1	53,248
	2	1	1	5	53,248
		28	28	48	53,248
		324	28	1	248
	3	108	94	1	53
		117	27	1	53
	7	29	29	1	53
		118	Unrelated	1	53
	11	108	94	1	53
Vietnam	9	390	Unrelated	1	MLST Database

[a] Serotypes were identified by co-agglutination (or an equivalent method using reference antisera), by PCR or, sometimes, by undefined methods.

method were still considered for this part of the review. As such, in the cases where more than one serotype was identified for a single ST, it is possible that the serotypes were misidentified and remain to be confirmed using reference antisera. Hence, it is important to keep in mind these discrepancies when analyzing the distribution of STs, particularly for the clinical pig cases. On the other hand, if confirmed, it would be extremely interesting to study strains of different serotypes sharing the same ST, since capsular switching has not been clearly demonstrated for this pathogen.

Diseased pigs

In contrast to the serotype distribution of diseased pigs (the section on '**Diseased pigs**' under '**WORLDWIDE DISTRIBUTION OF SEROTYPES**'), results where the serotype was identified by either serological methods, PCR or unidentified methods and where the ST was determined using the MLST method described by King *et al.*,[51] were taken into consideration for the worldwide distribution of the STs of clinical cases in pigs.

In North America, the majority of MLST studies conducted on *S. suis* strains isolated from diseased pigs have been serotype 2 (Table 5). It was determined that 44% of North American strains are ST25, 51% ST28 and only 5% are ST1.[52] In Canada, the proportions of ST25 and ST28 are similar to 54% and 46%, respectively, but in the United States, 75% of strains were shown to be ST28 and only 10% ST25, while the remaining 15% are ST1.[52] As with North American *S. suis* strains, the majority of European studies have been conducted using serotype 2 strains (Table 5). Most of these studies have demonstrated that ST1 strains are predominately isolated from diseased pigs in the Netherlands, Spain and the United Kingdom.[51,62,244] King *et al.* had already associated the serotype 2 ST1 strains with invasive infections.[51] Nevertheless, many strains of serotype 9 have also been recovered from diseased pigs and typed.[62,244] In both the Netherlands and Spain, serotype 9 isolates were identified as belonging to the ST16, where they represent 43% of strains in the Netherlands.[62] Unlike some countries in Europe, where the serotype 9 is as important as the serotype 2, most *S. suis* strains isolated from diseased pigs in Asia are serotype 2, representing 90% of cases in mainland China.[59] However, as mentioned above, there are relatively few reports of isolation from diseased pigs in Asia. Of these serotype 2 cases, the predominant STs are ST1, ST7 and ST28 (Table 5). In mainland China, Chen *et al.*[59] demonstrated that 22% of serotype 2 strains are ST1 and 77% are ST7. Meanwhile, the few ST28 strains recovered in that country were mostly associated with cases of pneumonia.[246] Regarding Japan, ST1 and ST28 strains isolated from cases of endocarditis in diseased pigs account for 8% and 76% of serotype 2 strains, respectively.[248]

Human cases

With 97% of all serotype confirmed human cases of *S. suis* infection due to serotype 2, the determination of the STs responsible for these cases becomes highly important (Table 6). Globally, ST1 strains have been described as mostly responsible for *S. suis* serotype 2 human cases, particularly in South America, Europe and Asia, but also one case in North America.[10,62,86,129,242,249] Nevertheless, multiple other STs have been described worldwide, though these appear to be endemic to certain geographical regions. For example, the ST20 is important in the Netherlands and France but not in the rest of Europe.[62] ST7 strains, to which belong the strains responsible for the 1998 and 2005 Chinese epidemics, were isolated from human patients only in mainland China and Hong Kong.[242,249] Meanwhile, ST25 and ST28 strains have been particularly associated with human

Table 6 Determined sequence types of reported clinical *S. suis* cases of infection in humans from 1 January 2002 to 31 December 2013

Country	Serotype[a]	ST	ST complex	Number of cases	Reference
North America					
Canada	2	25	25	3	53,242
	14	6	1	1	51
United States	2	1	1	1	53
		25	25	1	98
South America					
Argentina	2	1	1	1	Unpubl.[b]
French Guiana	2	1	1	1	101
Europe					
France	2	20	147	2	53,242
Italy	2	1	1	1	86
		134	1	2	86,188
Netherlands	2	1	1	14	62,240
		20	147	11	62,240
		134	1	1	62
		146	1	1	62
	14	6	1	1	51
Spain	2	3	1	1	204
United Kingdom	2	1	1	1	53
	14	2	1	1	MLST Database
Asia					
Cambodia	2	1	1	13	102
Mainland China	2	1	1	11	242,247
		7	7	210	242,240,247
	14	1	1	1	241
Hong Kong	2	1	1	14	51,249
		9	1	12	51,249
		25	25	1	249
Japan	2	1	1	7	53,116
		28	28	1	116
Thailand	2	1	1	123	53
		25	25	17	53,129
		28	28	4	53,129
		101	225	1	128
		102	25	2	53
		103	25	6	53,129
		104	225	45	53
		126	1	3	129
	5	181	Unrelated	1	133
	14	11	11	1	53
		105	1	19	130,132
		127	1	1	132
	24	221	221/234	1	133
Vietnam	2	1	1	56	10,240
		107	1	1	10
	14	105	1	1	10
	16	106	Unrelated	1	146

[a] Serotypes were identified by co-agglutination (or an equivalent method using reference antisera) or by PCR. However, it is impossible to distinguish between serotypes 1 and 14 and serotypes 1/2 and 2 by PCR, so serotypes remain to be confirmed.
[b] Gottschalk M, unpublished data (2014).

cases in North America and Japan, respectively.[53,116,242] The situation is particular in Thailand, where ST1 and ST104 strains are predominant, causing mainly meningitis and non-meningitis cases, respectively.[53,128,129] A few cases of ST25, ST28, ST101, ST102 and ST103 have also been described.[129] Interestingly, ST101–104 are so far endemic to Thailand only.

Though *S. suis* serotype 14 infections are less frequent in humans than serotype 2 cases, representing 2% of all the serotype-confirmed cases, the number of human infections caused by this serotype appears to be increasing. The ST105 is prevalent in Southeast Asia, particularly in Vietnam and Thailand. In the latter country, 92% of human serotype 14 cases are caused by this ST (Table 6).[10,132]

Only three human *S. suis* cases, other than those caused by serotypes 2 and 14, have been typed by MLST (Table 6), and all three were described as newly identified STs. Serotype 5, 16 and 24 human cases of infection were identified as ST181, ST106 and ST221, respectively.[133,146] Interestingly, no data have yet been published on the possible presence of these three newly identified STs for human isolates in diseased pigs.

Association between pig and human sequence types

Albeit no study has yet associated STs of strains isolated from human cases with those from diseased pigs in the same geographical region, it would seem reasonable to suggest that this association exists, particularly for the serotype 2, as most human strains appear to originate from contact with either pigs or pork by-products. In North America, where serotype 2 ST25 and ST28 strains are predominately isolated from diseased pigs, it is of no surprise that human ST25 cases were identified.[52,98,242] Interestingly, no cases due to ST28 have been diagnosed in humans. It has been suggested that ST25 strains from pigs are more virulent than their ST28 counterparts,[52] which may explain this situation. Moreover, it is interesting to note that even though ST1 strains account for only 5% of isolates from diseased pigs, a human case caused by an ST1 strain was reported in the United States.[96] It is possible that ST1 strains were imported from pigs from Europe and Asia. Being more virulent than their ST25 and ST28 counterparts, it may be hypothesized that a higher number of cases in pigs due to ST1 strains will appear in the near future in North America. Furthermore, similar STs have been described in some Asian countries for both diseased pigs and humans. For example, in Japan, ST1 and ST28 strains have been isolated from both species, while ST1 and ST7 strains have been identified for human and pig isolates in mainland China.[53,59,116,128,241,242,248] The situation is similar in Europe where serotype 2 ST1 clonal complex strains are predominately isolated from diseased pigs in Spain, Italy, the Netherlands and the United Kingdom and where most human cases have also been typed as belonging to this complex.[51,62,86,204,240,244]

This association between pig and human strains within a geographical region, though not definitive and currently only reflecting the situation for the serotype 2, confirms the results obtained by Chatellier *et al.*[250] whereby using randomly amplified polymorphic DNA, they concluded that strains isolated from pigs and humans could not be genotypically distinguished and were similar.

Association between sequence types and virulence markers

Presently, the most popular virulence markers used in association with STs are the SLY (*sly*), MRP (*mrp*) and EF (*epf*). It is important to note that although the genotypes of strains belonging to other serotypes have been reported, these factors are mainly associated with serotype 2 strains.

Serotype 2 ST1 strains recovered from both clinical pig and human cases have for the most part been genotyped/phenotyped as *sly*+ *mrp*+*epf*+/SLY+MRP+EF+, regardless of the geographic origin (whether it be mainland China, Japan, North America or Spain for both diseased pigs and human cases), which is identical to the serotype 2 ST7 strains isolated from diseased pigs and humans in mainland China.[52,242,244–246,248] Nevertheless, other important genetic differences vary between ST1 and ST7 strains including the presence of a 89K pathogenicity island in ST7 strains.[251] These ST1 complex strains interestingly differ from not only the human serotype 2 ST104 strains of Thailand which are *sly*+*mrp*-*epf*- but also from the human serotype 2 ST20 strains recovered in the Netherlands that were *epf*-.[62,129,242] Also of interest is a human case from Spain where the serotype 2 strain isolated was typed as being a ST3, and presented a large variant of the *mrp*, identified as *mrp** (which has a higher molecular weight), though being *sly*+*epf*+.[204,252] In Europe, it was determined that strains isolated from diseased pigs belonging to the ST16 complex differ from the ST1 complex strains in being *mrp** rather than *mrp*, while in Spain, the endemic ST123 and ST125 are both *mrp*- and *epf*-.[244] As for ST25 strains isolated from diseased pigs in North America, these were identified as being *SLY-MRP-EF*-, while the ST28 isolated from North America, mainland China and Japan were *sly*-*mrp*+*epf*- or *SLY*-MRP+*EF*-.[52,246,248] Though currently not as widely used as the above mentioned virulence markers, different pili (*srtB*, *srtC*, *srtD*, *srtF* and *srtG*) have also been associated with different STs. It was identified that ST1 strains isolated from both diseased pigs and human cases of serotype 2 infections in Japan and Thailand were *srtBCD*+ and *srtF*+ but *srtG*-.[53] Meanwhile North American ST25 strains isolated from diseased pigs and human cases were *srtF*- and *srtG*+ and ST28 strains isolated from diseased pigs and human cases from North America and Japan were *srtF*+ and *srtG*+.[52,248]

It remains difficult to be certain of the association between STs and virulence markers as being universal, but it appears to be representative of populations within a region and may be a useful diagnostic tool with methods identifying the genotypic or phenotypic presence or absence of the different virulence markers.

CONCLUDING REMARKS

S. suis serotype 2 remains the most isolated serotype and the one most associated with disease in both pigs and humans in most parts of the world. Due to its endemic status in Southeast Asia and the two epidemics it caused in Jiangsu (1998) and Sichuan (2005), China, characterized by STSLS and high mortality rates, this bacterium should no longer be considered merely an important pig pathogen, but also an important and emerging zoonotic agent. Many avenues of research remain regarding the definition of a 'true' *S. suis* serotype and the adoption and use of a complete serotyping system. In this regard, the recent availability of new complete PCR serotyping systems will allow any laboratory in the world to serotype *S. suis* isolates without the need of specific antibodies. The identification of this pathogen by medical and veterinary laboratories significantly varies among countries, and in only a few regions both are well developed. In some important pig producing countries in the Americas, such as Canada, the United States, Mexico and Brazil, diagnostic laboratories in human medicine should be more aware of the zoonotic potential of *S. suis* due to occupational exposure to pigs and/or pork-derived products. The scientific community should request that the specific serotype of each reported case in humans be identified using acceptable techniques to keep useful epidemiological data. On the other hand, in some countries in Asia where human cases are routinely reported, the number of studies provided by diagnostic laboratories working in veterinary medicine should be significantly increased, since there are almost no data regarding strains recovered from diseased animals. The same applies to European countries which are important pig producers and from which no data regarding the distribution of serotypes from diseased animals were reported in the last 12 years, hampering the use of species-specific protective bacterins.

Though the MLST data currently available for *S. suis* strains isolated from both diseased pigs and human cases of infection come from different countries throughout the world, there remains a long way to go before a complete picture of the current situation of *S. suis* can be obtained. Yet, this picture is necessary as it could hint at both dominating and emerging STs and could possibly help identify epidemic strains quickly and categorize the zoonotic potential of specific STs. With the dissemination of information about STs across the internet, particularly thanks to the *S. suis* MLST Database, it would be important to set up a complete and reliable serotype identification of the different strains added. Although this database is a great tool that facilitates the sharing of knowledge, the lack of many details pertaining to each strain such as the serotype, method used for serotyping, health status of the host, and host itself, limit the full potential of the STs as

was demonstrated in this review where many strains could not be included. Furthermore, in the absence of identification of the serotyping method, it is impossible to confirm if the serotype indicated is correct. Nevertheless, the global distribution of *S. suis*, particularly serotype 2 strains, greatly varies, an aspect that could be useful in developing diagnostic and preventive tools specific for a particular geographical distribution. Despite the fact that studies have recently associated virulence markers and profiles with given STs, the biological significance of these associations still needs to be studied, as only a handful of studies have compared STs from different geographical origins. In fact, some STs found in North America and described as low virulent are frequently isolated from patients in Asia. There is an urgent need to compare virulence properties of strains of similar STs from different geographical origins. Finally, though still tentative, the possibility of associating strains from diseased pigs and human cases in a given region, as determined based on serotypes and STs, would provide further epidemiological support for the zoonotic potential of this pig pathogen, demonstrating the need for proper hygiene practises in order to reduce the risk of zoonotic infections. With more and more laboratories using a complete serotyping system and MLST as a tool for *S. suis* classification, we will one day have the complete picture regarding the *S. suis* distribution.

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