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Streptococcus suis, an emerging drug-resistant animal and human pathogen

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Streptococcus suis, a major porcine pathogen, has been receiving growing attention not only for its role in severe and increasingly reported infections in humans, but also for its involvement in drug resistance. Recent studies and the analysis of sequenced genomes have been providing important insights into the *S. suis* resistome, and have resulted in the identification of resistance determinants for tetracyclines, macrolides, aminoglycosides, chloramphenicol, antifolate drugs, streptothricin, and cadmium salts. Resistance gene-carrying genetic elements described so far include integrative and conjugative elements, transposons, genomic islands, phages, and chimeric elements. Some of these elements are similar to those reported in major streptococcal pathogens such as *Streptococcus pyogenes, Streptococcus pneumoniae,* and *Streptococcus agalactiae* and share the same chromosomal insertion sites. The available information strongly suggests that *S. suis* is an important antibiotic resistance reservoir that can contribute to the spread of resistance genes to the above-mentioned streptococci. *S. suis* is thus a paradigmatic example of possible intersections between animal and human resistomes.

Keywords: *Streptococcus suis*, zoonotic pathogen, resistome, integrative and conjugative element, transposon, genomic island, phage, chimeric element

The massive use of antibiotics by the livestock industry, either for growth promotion (a practice recently banned in Europe) or for prophylaxis and therapy, contributed to the emergence, and spread of antibiotic resistance (McEwen and Fedorka-Cray, 2002). Antimicrobials for veterinary use are the same or belong to the same classes as those for human use and exert a constant pressure on the animal microflora, selecting for resistance (Witte, 1997). *Streptococcus suis*, an emerging zoonotic pathogen, has been receiving growing attention for its involvement not only in severe and increasingly reported human infections, but also in drug resistance. Here we outline the current knowledge about the *S. suis* resistome and assess its role as a possible reservoir of antibiotic resistance determinants for streptococcal pathogens.

S. SUIS AND *S. SUIS* INFECTIONS

Streptococcus suis is a major porcine pathogen worldwide, endemic in all countries where intensive pig farming is practiced. Moreover, it is increasingly being isolated from mammalian species other than pigs, from birds, and from the environment (Gottschalk et al., 2010). In humans, *S. suis* is now considered as an emerging zoonotic pathogen, causing systemic infection: meningitis with possible residual deafness or vestibular dysfunctions is the most frequent clinical presentation; endocarditis, cellulitis, peritonitis, rhabdomyolysis, arthritis, spondylodiscitis, pneumonia, uveitis, and endophthalmitis have also been reported (Lun et al., 2007; Wertheim et al., 2009a). The human infection is mainly an occupational disease that may affect those who come into contact with animal infected blood or secretions or with pork-derived products. Thirty-three capsular serotypes are currently recognized (Staats et al., 1997; Hill et al., 2005). Serotype 2 is the most virulent and is responsible for severe infections in both swine and humans worldwide.

After the first reported human case of *S. suis* infection in Denmark in 1968 (Perch et al., 1968), sporadic cases (mainly of meningitis) have been reported in Europe and South-East Asia in the following decades (Lun et al., 2007; Wertheim et al., 2009a). In 2005, a severe epidemic caused by *S. suis* serotype 2 broke out in China's Sichuan Province, preceded by a small outbreak in 1998 (Yu et al., 2006). From 2005 onward, an increasing number of *S. suis* human infections have been reported worldwide, also in countries where the infection had been rarely or never reported before (Gottschalk et al., 2010). Currently, the majority of cases occur in South-East Asia where *S. suis* is a leading cause of adult meningitis, in particular in Vietnam (Mai et al., 2008; Wertheim et al., 2009b). A multilocus sequence typing scheme (King et al., 2002) disclosed a high genetic diversity of *S. suis* isolates with over 250 sequence types (ST) identified (http://ssuis.mlst.net). Four major ST clonal complexes (CC; CC–ST1, CC–ST16, CC–ST25, and CC–ST27) dominate the population; CC–ST1, the most virulent, includes ST1, found throughout the world, and ST7, responsible for the Chinese epidemic (Ye et al., 2006). It has been suggested that the increase in human cases may also reflect the recent awareness of *S. suis* as an emerging agent of meningitis and the improvement of microbiological diagnostic techniques (Gottschalk et al., 2010). Actually, the fact that *S. suis* does share several characteristics with other bacteria causing meningitis can result in misdiagnosis. Indeed, many isolates that had originally been identified as *Streptococcus pneumoniae,* enterococci, *Streptococcus bovis,* viridans streptococci, or even *Listeria* spp. were re-identified as *S. suis* in retrospective studies. In addition, recent

serologic data suggest that human infection occurs more frequently than previously believed (Smith et al., 2008). Altogether these findings suggest that *S. suis* disease has been under diagnosed in the past. The growing interest in this pathogen is reflected by recent (2007–2011) whole-genome sequencing studies. So far, eight strains have been sequenced (Chen et al., 2007; Holden et al., 2009; Ye et al., 2009; Hu et al., 2011a,b), showing that ∼40% of the ∼2 Mb genome is unique. This suggests that *S. suis* is phylogenetically distinct from other *Streptococcus* species whose genome sequences are currently available. Intraspecies genomic comparisons have shown high levels of sequence conservation. However, these data may be influenced by the clonal relatedness of the sequenced strains, six of eight being serotype 2 strains belonging to the CC–ST1.

CURRENT KNOWLEDGE OF THE *S. SUIS* RESISTOME

High rates of *S. suis* resistance to tetracyclines (up to >90%) and macrolides (up to >70%) have been reported in pig isolates worldwide (Wisselink et al., 2006; Hendriksen et al., 2008; Zhang et al., 2008; Princivalli et al., 2009). In the 1990s, a retrospective study of historic pig isolates in Denmark demonstrated that the increase in tetracycline and macrolide resistance had begun in the early 1980s (Aarestrup et al., 1998). Resistances to tetracyclines and macrolides in human strains were first reported in the second half of the first decade of 2000, but retrospective studies showed that they were already widespread in previous decades (Ye et al., 2008; Chu et al., 2009; Hoa et al., 2011). The genetic basis of tetracycline and macrolide resistance in *S. suis* has been extensively investigated.

Tetracycline resistance in streptococci is mainly due to ribosomal protection genes *tet*(M) and *tet*(O), and less frequently *tet*(Q), *tet*(T), and *tet*(W), and to efflux genes *tet*(K) and *tet*(L) (Chopra and Roberts, 2001; Roberts, 2005). Until a few years ago, *tet*(M) and *tet*(O) were the only tetracycline resistance determinants reported in *S. suis*; further determinants have lately been detected, such as ribosomal protection genes *tet*(W) and mosaic *tet*(O/W/32/O) and efflux genes *tet*(L), *tet*(B), and *tet*(40). Of these, *tet*(O/W/32/O), *tet*(B), and *tet*(40) had never been described in the genus *Streptococcus* before. *tet*(W) is an emerging tetracycline resistance determinant whose host range, including Gram-positive and Gram-negative, aerobic and anaerobic bacteria, is second only to that of *tet*(M) among ribosomal protection *tet* genes (Roberts, 2005). In *S. suis, tet*(W) was first detected in 2008, in an isolate from a case of meningitis in Italy (ST1 strain SsCA) (Manzin et al., 2008); it was subsequently described in other Italian strains (ST1 human strain SSUD and three pig isolates) (Princivalli et al., 2009), in the sequenced genome of the Chinese ST1 human strain GZ1 (Ye et al., 2009), and in two Vietnamese human isolates (Hoa et al., 2011). *tet*(O/W/32/O) is a new mosaic gene reported in 2009 in clonally unrelated pig isolates of *S. suis* (Princivalli et al., 2009). Mosaic *tet* genes are a recently discovered class of hybrids of ribosomal protection genes (Thaker et al., 2010). Mosaic derivatives of *tet*(O) and *tet*(W) were first detected in 2003 in anaerobic Gram-negative *Megasphaera elsdenii* from swine intestine (Stanton and Humphrey, 2003). Other mosaic genes, also including portions of *tet*(32), were later detected in *Clostridium difficile* (Patterson et al., 2007) and *Clostridium saccharolyticum* (Kazimierczak et al., 2008). *tet*(L), commonly carried in streptococci by small transmissible plasmids (Chopra and Roberts, 2001), has recently been detected in a sequenced genome of *S. suis*, where it is carried by a Tn*916*-like element (Holden et al., 2009), and lately, still outside plasmids, in Vietnamese human isolates (Hoa et al., 2011). *tet*(B), which had never been described in Gram-positive bacteria, was detected in 2010 in Chinese pig isolates of *S. suis* (Chander et al., 2011). *tet*(40) is a novel efflux gene recently detected in *C. saccharolyticum* in tandem with a mosaic *tet* gene [*tet*(O/32/O)] (Kazimierczak et al., 2008).

Macrolide resistance in streptococci is mainly due to methylase-mediated target site modification by *erm* genes and to active efflux by *mef* genes. *erm*(B), the old-established *erm* determinant in streptococci, can be expressed either constitutively or inducibly and is usually associated with high-level resistance; *erm*(TR), an *erm*(A) subclass, is normally inducible and is widely distributed in *S. pyogenes* isolates; *erm*(T) was detected in inducibly erythromycin-resistant isolates of group D streptococci and in *S. pyogenes* (Varaldo et al., 2009), and more recently in *Streptococcus dysgalactiae* subsp. *equisimilis* (Palmieri et al., 2011b). *mef*-class genes, which include some variants, are associated to a low-level resistance pattern affecting, among MLS antibiotics, only 14- and 15-membered macrolides (M phenotype) (Sutcliffe et al., 1996). *mef*(A) and *mef*(E) are widespread in *S. pyogenes* and *S. pneumoniae,* respectively, but they are also common in other streptococcal species (Varaldo et al., 2009). In *S. suis*, while *mef*(A) (Martel et al., 2003; Chu et al., 2009) and *mef*(E) (Hu et al., 2011a,c) have only occasionally been reported, *erm*(B) is found in >90% of macrolide-resistant pig isolates (Martel et al., 2001, 2003; Princivalli et al., 2009; Hoa et al., 2011); it has recently been reported also in human isolates (Manzin et al., 2008; Holden et al., 2009; Princivalli et al., 2009; Hoa et al., 2011). Although no further macrolide resistance determinants have been documented, the isolation of macrolide-resistant strains negative for the above genes (Martel et al., 2003; Princivalli et al., 2009; Hoa et al., 2011) suggests that other genetic determinants or target site mutations may occur.

Strains resistant to other antibiotics, such as β-lactams, aminoglycosides, trimethoprim–sulfamethoxazole, chloramphenicol, and fluoroquinolones, have been reported. The genetic basis of resistance to these antibiotics has only occasionally been investigated. Penicillin resistance was first reported in a human isolate in UK in 1980 (Shneerson et al., 1980) and more recently among pig isolates (Marie et al., 2002; Higgins and Gottschalk, 2005; Huang et al., 2005; Zhang et al., 2008). Penicillin-binding protein modifications (altered molecular weight and/or decreased affinity for penicillin) are involved in the resistance mechanism (Cain et al., 1995). Quite recently, resistance also to third-generation cephalosporins has been reported (Hu et al., 2011c). Aminoglycoside resistance has frequently been reported in *S. suis* (Touil et al., 1988; Wasteson et al., 1994; Marie et al., 2002; Tian et al., 2004; Wisselink et al., 2006; Hendriksen et al., 2008). Recently, genes coding for resistance to kanamycin [aminoglycoside-3′-phosphotransferase (*aphA*)] and to streptomycin [aminoglycoside-6′-adenyltransferase (*aadE*)] have been detected in multiresistant strains (Chen et al., 2007; Holden

et al., 2009; Hu et al., 2011a; Palmieri et al., 2011a). Resistance to antifolate drugs has frequently been reported (Mengelers et al., 1989; Wisselink et al., 2006; Zhang et al., 2008). A dihydrofolate reductase (*dhfr*) resistance gene has been detected in the sequenced strain BM407 (Holden et al., 2009). Chloramphenicol resistance has rarely been reported (Takamatsu et al., 2003). However, a recent increase in chloramphenicol-resistant strains has been noted among human isolates in Vietnam (Hoa et al., 2011). Fluoroquinolone resistance has occasionally been described (Aarestrup et al., 1998; Escudero et al., 2007, 2011; Hendriksen et al., 2008; Hu et al., 2011c). Resistance is associated with single point mutations in the quinolone resistance-determining regions of ParC and GyrA (Escudero et al., 2007; Hu et al., 2011c), but a novel efflux pump has recently been described (Escudero et al., 2011).

CONTRIBUTION OF EXOGENOUS GENETIC ELEMENTS TO THE *S. SUIS* RESISTOME

Recent studies (Li et al., 2011; Palmieri et al., 2011a,c) and the analysis of sequenced genomes (Chen et al., 2007; Holden et al., 2009; Ye et al., 2009; Hu et al., 2011a,b,c) have provided significant insights into the *S. suis* resistome, leading to the identification of several genetic elements carrying resistance determinants for tetracyclines, macrolides, aminoglycosides, chloramphenicol, antifolate drugs, streptothricin, and cadmium salts. These elements, that include integrative and conjugative elements (ICEs), transposons, genomic islands (GIs), phages, and chimeric elements, are illustrated in **Figure 1**. A scheme of their integration sites into the *S. suis* core chromosome is shown in **Figure 2**.

Five ICEs have been described in the sequenced genomes of ST7 (98HAH33, 05ZYH33, and SC84) and ST1 (BM407) human strains (Chen et al., 2007; Holden et al., 2009). Of these, four – ICE$_{Ssu98HAH33}$, ICE$_{Ssu05ZYH33}$, and ICE$_{SsuSC84}$ (∼90 kb, three virtually identical elements), and ICE$_{SsuBM407.2}$ (∼80 kb) – are closely related, except for cargo genes, to ICE$_{Sde3396}$ of *S. dysgalactiae* subsp. *equisimilis* (Davies et al., 2009): they are integrated immediately downstream of the 50S ribosomal gene L7/L12 (*rplL*), they harbor a tyrosine family integrase, and share an almost identical set of genes for the conjugative machinery. ICE$_{Ssu98HAH33}$, ICE$_{Ssu05ZYH33}$, and ICE$_{SsuSC84}$ bear three distinct cargo regions: (i) a putative bacteriocin biosynthesis cluster that is disrupted by a putative integron containing the *aadE* gene; (ii) a Tn*916* transposon, regularly carrying *tet*(M); and (iii) a cluster of genes associated with lantibiotic export/resistance. ICE$_{SsuBM407.2}$ contains three distinct cargo regions: (i) a Tn*916*-like element carrying,

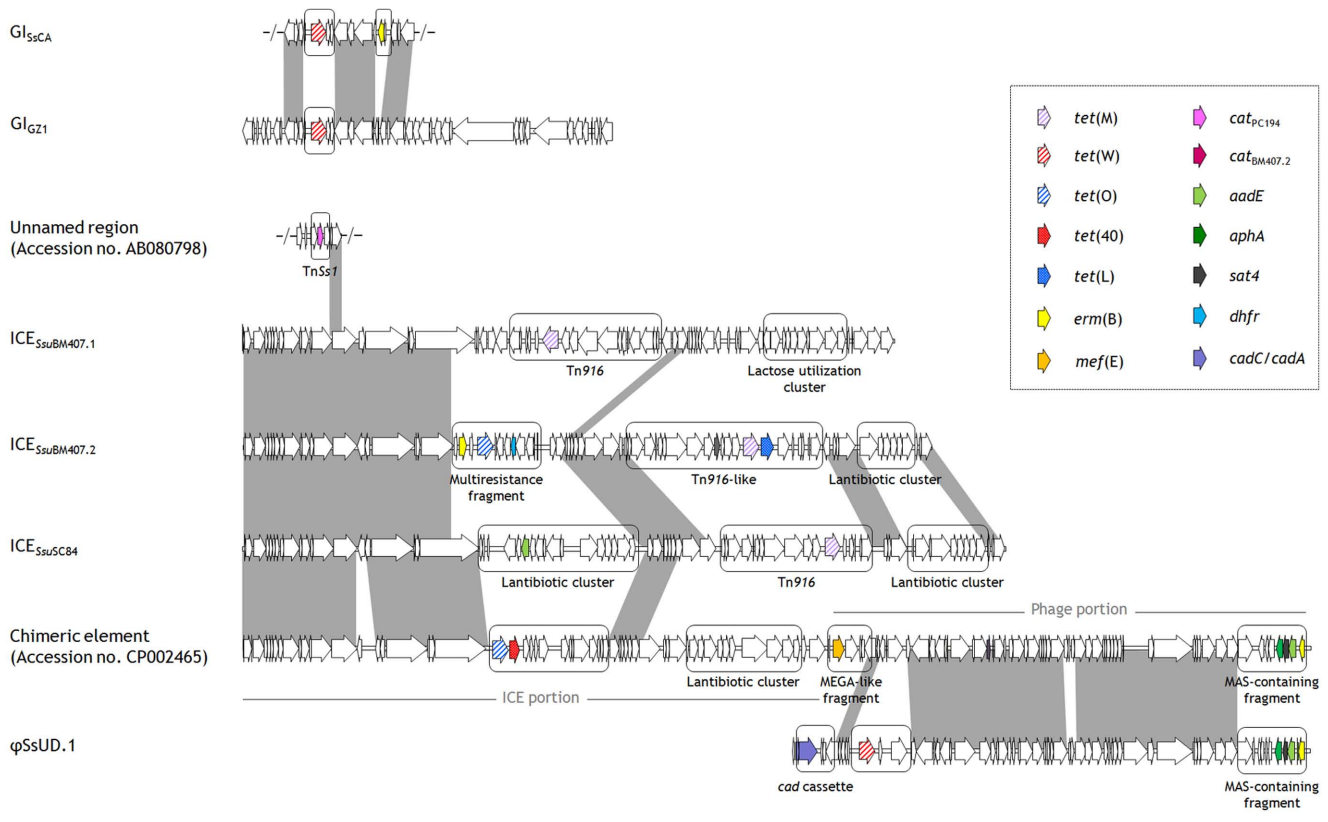

FIGURE 1 | ORF maps and genome organization of recognized *S. suis* genetic elements carrying resistance genes. ICE$_{SsuSC84}$ was chosen as a representative of the ICEs of ST7 strains. The ORFs, indicated as'arrows pointing in the direction of transcription, are depicted as white arrows, except for resistance genes which are specified in the box. Cargo regions are enclosed in rounded rectangles. Gray areas between ORF maps denote >90% DNA identity (identities between cargo regions are not shown).

besides *tet*(M), *tet*(L) and a novel chloramphenicol acetyltransferase (*cat*) gene; (ii) a multiresistance fragment bearing *tet*(O), *erm*(B), and a *dhfr* gene; and (iii) a lantibiotic cluster similar to the one mentioned above. The fifth ICE ($ICE_{SsuBM407.1}$) displays a similar scaffold but contains a different integrase, belonging to serine recombinase family, which directs the insertion of this element into a luciferase-like monooxygenase gene (Holden et al., 2009). $ICE_{SsuBM407.1}$ contains two cargo regions: (i) a Tn*916* transposon, regularly carrying *tet*(M), and (ii) a lactose utilization cluster. Structural and compositional analysis strongly suggests that all five ICEs have the potential to undergo excision and transfer. In particular, $ICE_{Ssu05ZYH33}$ was transferred at high frequency to *S. suis* recipients in conjugation assays (Li et al., 2011). Another ICE ($ICE_{Ssu32457}$, ∼56 kb), recently identified in a pig isolate in Italy and shown to carry *tet*(O/W/32/O), is the first reported genetic support for a mosaic *tet* gene in streptococci (Palmieri et al., 2011c). $ICE_{Ssu32457}$ is transferable to *S. suis, S. pyogenes, S. agalactiae,* and *S. pneumoniae*, and similar to $ICE_{Ssu98HAH33}$, $ICE_{Ssu05ZYH33}$, $ICE_{SsuSC84}$, and $ICE_{SsuBM407.2}$ mentioned above, it is closely related to $ICE_{Sde3396}$ of *S. dysgalactiae* subsp. *equisimilis* except for cargo genes (Palmieri et al., submitted).

A *tet*(W)-carrying ∼47 kb GI (here designated GI_{GZ1}), located immediately downstream of the lysyl-tRNA synthetase chromosomal gene (*lysS*), has been identified in the sequenced genome of the Chinese strain GZ1 (Ye et al., 2009). An almost identical, non-transferable, *tet*(W)-carrying GI (GI_{SsCA}), differing from GI_{GZ1} only for the presence of an *erm*(B)-containing insertion, has recently been detected in an Italian human strain (Palmieri et al., 2011a).

In another Italian human strain, the presence of *tet*(W) has been reported in a phage (φSsUD.1, ∼61 kb) (Palmieri et al., 2011a). φSsUD.1 carries a unique combination of antibiotic and heavy metal resistance genes resulting from the presence, besides *tet*(W), of an *erm*(B)-containing MAS (macrolide–aminoglycoside–streptothricin) – like fragment and a *cadC/cadA* cadmium efflux cassette. The MAS-like fragment closely resembles the one recently described in the pneumococcal transposons Tn*6003* and Tn*1545* (Cochetti et al., 2007, 2008). The resistance genes fitting in the φSsUD.1 phage scaffold differ from, but are in the same position as, the cargo genes carried by *S. pyogenes* phages such as φ10394.4 (Banks et al., 2003) and φm46.1 (Brenciani et al., 2010). φSsUD.1 is integrated at the 3′ end of a conserved RNA uracil methyltransferase (*rum*) gene and is transferable to *S. pyogenes*.

A ∼124 kb chimeric element constituted of two portions, an ICE (∼69 kb) and a phage (∼55 kb), has recently been detected in the sequenced genome of JS14 (Hu et al., 2011a), integrated at the 3′ end of the *rum* gene. The ICE portion harbors a site-specific integrase, it displays a scaffold similar to the *S. suis* ICEs mentioned above, and contains two cargo regions, one bearing *tet*(O) in tandem with *tet*(40) and the other a bacteriocin gene cluster. The phage portion displays the typical modular organization of tailed phages, and closely resembles φSsUD.1 (Palmieri et al., 2011a). The right end of the phage portion bears an *erm*(B)-containing MAS-like fragment, like φSsUD.1; the left end bears a mega-like genetic structure, similar to the *mef*(E)-carrying mega element originally described in *S. pneumoniae* (Gay and Stephens, 2001), in the same position as the *cadC/cadA* cassette in φSsUD.1.

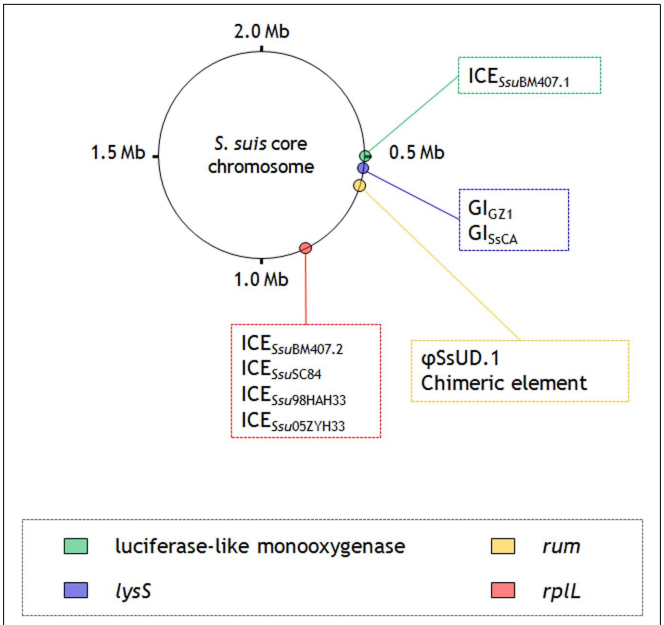

FIGURE 2 | Schematic illustration showing the *S. suis* core chromosome with the insertion sites of recognized genetic elements carrying resistance genes.

Beside the Tn*916*-family elements, only another transposon carrying resistance genes, Tn*Ss1*, has been described in *S. suis* (Takamatsu et al., 2003). It contains a *cat* gene showing 97% identity with cat_{PC194} (Widdowson et al., 2000) flanked by direct repeats of an IS6-family element.

CONCLUDING REMARKS

Although the emergence of *S. suis* as a human pathogen has caused a flurry of research, current knowledge on the *S. suis* resistome is still fairly sketchy. This is mainly due to the so far limited number of studies of the genetic basis of resistance and to the redundancy of data from the strains sequenced, many of which are clonally related. Next-generation DNA sequencing will probably provide a wealth of new data in the next few years. The available information suggests that *S. suis* may contribute to the spread of antibiotic resistance genes to streptococcal human pathogens such as *S. pyogenes, S. pneumoniae,* and *S. agalactiae*, acting as a resistance reservoir. The notion is supported by studies demonstrating that *S. suis* harbors mobile resistance genetic elements, similar to those of the above-mentioned streptococci, that share the same conserved chromosomal insertion sites. Thus, *S. suis* is a paradigmatic example of possible intersections between animal and human resistomes.

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