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Antimicrobial resistance and prudent drug use for *Streptococcus suis*

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Abstract

This paper reviews information on antimicrobial resistance patterns and prudent use of antimicrobials to reduce the impact and spread of resistant *Streptococcus suis* strains. *S. suis* is an important pathogen in swine, which can cause significant economic loss. Prudent use of antimicrobials for *S. suis* is essential to preserve the therapeutic efficacy of broad-spectrum antimicrobials and to minimize selection of resistant *S. suis* strains. Resistance of *S. suis* to antimicrobials commonly used in swine, including lincosamides, macrolides, sulphonamides, and tetracycline, has been documented worldwide, with resistance in up to 85% of strains. Among antimicrobials examined, resistance of *S. suis* has been demonstrated to be relatively low for penicillin (0–27%), ampicillin (0.6–23%), and ceftiofur (0–23%). For penicillin, this result may be due in part to the unique mechanism by which resistance is acquired through modifications in the structure of penicillin-binding proteins. Recommendations to control *S. suis* infection include focused and careful choice and appropriate use of antimicrobials, together with preventive measures intended to improve swine management.

Keywords: *Streptococcus suis*, prudent use, antimicrobial resistance, serotype 2

Introduction

Streptococcus suis is widely considered as one of the most important pathogens causing an economic impact in the swine industry. A survey conducted in the USA on common diseases in large commercial swine operations (producing greater than 150,000 pigs per year) found that *S. suis* was the fourth most significant pathogen in the breeder and weaner site, and the tenth in the finisher site (Holtkamp *et al.*, 2007). The US National Animal Health Management Survey (2006) reported confirmed cases of *S. suis* infection in 39 and 50% of sites with pre-weaned and nursery-age pigs, respectively. This pathogen is frequently isolated in cases of arthritis, encephalitis, meningitis, pneumonia, polyserositis, and septicemia (Osweiler, 2003; National Animal Health Monitoring System, 2006). The costs of a potential *S. suis* outbreak in a farrow-to-finish operation can include (1) associated neonatal septicemia or 'fading piglet syndrome' (Sanford *et al.*, 1988), (2) involvement in porcine respiratory disease complex (PRDC) (Higgins *et al.*, 1990; Gottschalk *et al.*, 1991a), (3) post-weaning meningitis or septicemia causing mortality of approximately 20% in untreated animals (Cloutier *et al.*, 2003), (4) extra carcass trim as a result of arthritis, which can mean losses in excess of $20,000 per year for a 300-sow operation (Keenliside *et al.*, 2006), (5) a 15% decrease in farrowing rate in 3 months (Sanford *et al.*, 1988), and (6) costs associated with animal welfare actions such as treatment of meningitis and arthritis, hospital pen management, and euthanasia for poor-doers surviving septicemia

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(Blackwell, 2005; Keenliside *et al.*, 2006). Sporadic human cases of infection resulting from contact with swine have been reported in North America (Michaud *et al.*, 1996; Willenburg *et al.*, 2006; Haleis *et al.*, 2009).

S. suis is a capsulated, Gram-positive facultative anaerobic coccus. Capsular type 2, the most common of 35 known serotypes, is associated with disease and is the serotype most likely to express virulence (Gottschalk and Segura, 2000; Higgins and Gottschalk, 2000; Gottschalk, 2004; Messier *et al.*, 2008). Virulence of European and Asian strains, but not North American strains, has been associated with the genes *mrp*, *epf* and *sly*, which encode muramidase-released protein (MRP), extracellular factor (EF), and suilysin (SLY), respectively (Smith *et al.*, 1996; Wisselink *et al.*, 1999, 2000).

The spectrum of disease caused by *S. suis* includes the asymptomatic carrier state, clinical infection and peracute fatal disease (Higgins and Gottschalk, 1999; Gottschalk, 2012). *S. suis* is the most common inhabitant of the tonsils of healthy pigs, with isolation rates as high as 98% (Brisebois *et al.*, 1990; MacInnes *et al.*, 2008; Gottschalk, 2012). Pigs harboring *S. suis* in their nasal cavities and tonsils play the most important role in airborne transmission to other pigs (Berthelot-Herault *et al.*, 2001). A rise in rectal temperature (up to 42°C) is typically the earliest clinical sign of *S. suis* infection, accompanied by inappetence, depression, and lassitude. More severe clinical signs follow, which may include abortion, ataxia, erythema, meningitis, pneumonia, shifting lameness, septicemia, and tremors (Clifton-Hadley *et al.*, 1984; Staats *et al.*, 1997; Higgins and Gottschalk, 1999; Keenliside *et al.*, 2006). In peracute cases, sudden death may occur with no previous signs. Arthritis, endocarditis, meningitis, pneumonia and septicemia with sudden death are usually observed in pigs under 12 weeks of age, although the disease has also been reported in pigs up to 32 weeks of age (MacInnes and Desrosiers, 1999; Reams *et al.*, 1996; Gottschalk, 2012).

Pathological manifestations of *S. suis* are usually limited to the brain, heart, lungs, and joints (Reams *et al.*, 1994). *S. suis* has been recognized as the dominant agent for porcine endocarditis, a sequel to bacteraemia, with bacteria lodging on the valvular endothelium (Jones, 1981; Jensen *et al.*, 2010; Karstrup *et al.*, 2011). Other predominant lesions include arthritis, endocarditis, myocarditis, pericarditis, and suppurative bronchopneumonia (Reams *et al.*, 1994). Presumptive diagnosis is based on clinical signs and pathological lesions. Diagnosis is confirmed by biochemical and serological characterization of *S. suis* isolated from affected pigs (Higgins and Gottschalk 1999; Neumann *et al.*, 2009; Gottschalk, 2012).

S. suis is not only a major problem in the swine industry (Holtkamp *et al.*, 2007): but it has also been recognized as an emerging zoonotic pathogen (Lun *et al.*, 2007; Smith *et al.*, 2008; Feng *et al.*, 2009). After the first reports of zoonosis in the Netherlands and England in the early 1950s (Jensen and Dorseen van, 1957), the disease has been documented worldwide (Walsh *et al.*, 1992; The Government of the Hong Kong Special Administrative Region, 2005; Lun *et al.*, 2007; Gottschalk *et al.*, 2007, 2010). *S. suis* has been recognized as a sporadic cause of human meningitis and septicemia, with significant hearing loss a common sequel (Wertheim *et al.*, 2009a; Feng *et al.*, 2010). Outbreaks in Asia have been widely reported, with occupational exposure a common risk factor (Wertheim *et al.*, 2009a, b). In North America, sporadic cases resulting from contact with swine have also been reported (Michaud *et al.*, 1996; Willenburg *et al.*, 2006; Haleis *et al.*, 2009).

Highly effective measures to control *S. suis* do not exist; thus, interventions to minimize the impact and spread of the disease and to improve response to treatment should be considered. Management practices such as all-in/all-out pig flow, with emphasis on age segregation, proper ventilation, avoiding overcrowding, and strict sanitation of facilities and fomites, are recommended (Staats *et al.*, 1997; Higgins and Gottschalk, 1999; Neumann *et al.*, 2009). The objective of this review is to describe antimicrobial resistance patterns and measures to reduce the impact and spread of resistant *S. suis* strains in swine.

Antimicrobial resistance in *S. suis*

Antimicrobial resistance patterns

The emergence of resistance to macrolides and lincosamides and the use of these antimicrobial agents in animal husbandry were connected for the first time in Denmark, where the prevalence of antimicrobial resistance among *S. suis* isolates increased from 0 to 20% over a 15-year period (Aarestrup *et al.*, 1998). In contrast, no resistance to macrolides or lincosamides was reported in Sweden, where the use of antibiotics as growth promoters had been banned since 1986 (Aarestrup *et al.*, 1998). After introduction of the macrolide tylosin into the Danish swine industry in 1982, it became the most widely used swine growth promoter in Denmark (Aarestrup, 1999). The difference in bacterial resistance observed between Danish and Swedish isolates suggests a link between antibiotic resistance and antibiotic use and points to selective pressure specific for the type of antibiotic used and the bacterial species (Kolar *et al.*, 2001). Resistance to macrolides and lincosamides has also been observed among *S. suis* isolates from other countries. In Quebec, Canada, up to 91 and 82% of *S. suis* isolates were resistant to clindamycin and erythromycin, respectively (Cantin *et al.*, 1992). Lower resistance rates were found in western Canada: 40 and 27% of *S. suis* isolates were resistant to clindamycin and erythromycin, respectively (Cantin *et al.*, 1992). In the USA, a retrospective study of 256 cases over a four-year period (1985–1989) reported that 42 and 45% of 65 serotype 2 isolates were resistant to clindamycin and

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erythromycin, respectively (Reams *et al.*, 1993). In Spain, more than 87% of *S. suis* isolates were resistant to tetracycline and oxytetracycline, sulphadimethoxine and sulphathiazole, the macrolides erythromycin and tylosin tartrate, and clindamycin (Vela *et al.*, 2005). In France, 70% of 110 *S. suis* isolates from healthy and diseased swine were shown to be resistant to erythromycin, spiramycin, tylosin, and lincomycin (Marie *et al.*, 2002). A slightly lower rate of resistance (71%) was reported among isolates from the Netherlands (Martel *et al.*, 2001). In a European study, the percentage of resistance among 2553 *S. suis* isolates from six countries ranged from 29% in Denmark to 75% in Portugal (Hendriksen *et al.*, 2008). Macrolide and lincosamide resistance is also prevalent in *S. suis* isolates from clinically healthy pigs, where rates up to 67% have been reported (Zhang *et al.*, 2008). In humans, resistance of clinical *S. suis* isolates to clindamycin and macrolides has also been acknowledged, with higher prevalence in recent studies in Asia (approximately 20%) (Ma *et al.*, 2008; Hoa *et al.*, 2011) than in an older study in Canada (8%) (Cantin *et al.*, 1992). In contrast, *S. suis* strains isolated from healthy German workers occupied in the pig slaughtering, pork dissecting, and processing industries were highly susceptible to most antibiotics tested, including erythromycin (Strangmann *et al.*, 2002).

Tetracycline resistance among *S. suis* isolates is well documented worldwide. In Denmark, the proportion of isolates resistant to this antimicrobial increased by 39% between 1981 and 1997, while considerably lower levels of resistance were found among isolates from Sweden, where use of tetracycline as a growth promoter for livestock has been prohibited since 1986 (Aarestrup *et al.*, 1998). Recent studies reported higher levels of tetracycline resistance among *S. suis* isolates from Europe, ranging from 52% of 557 isolates in Denmark (Hendriksen *et al.*, 2008) to 95% of 151 isolates in Spain (Vela *et al.*, 2005). In North America, levels of resistance to tetracycline range from 95% of 65 serotype 2 isolates in the USA (Reams *et al.*, 1993) to 100% in some capsular types among 92 isolates in Canada (Cantin *et al.*, 1992). In Asia, tetracycline resistance in *S. suis* isolates from both diseased and healthy pigs is also common (up to 92%) (Kataoka *et al.*, 2000; Zhang *et al.*, 2008). High levels of tetracycline resistance (up to 90%) have also been reported among *S. suis* isolates from diseased and clinically healthy persons (Strangmann *et al.*, 2002; Ma *et al.*, 2008; Hoa *et al.*, 2011). In contrast, a 1992 report showed that only 8% of 12 *S. suis* isolates from human cases in the Netherlands were resistant to tetracyclines (Cantin *et al.*, 1992).

The prevalence of penicillin resistance among *S. suis* isolates from pigs varies among countries, but is generally low. *S. suis* isolates were reported to be 100% susceptible to penicillin in Denmark (120 strains), Sweden (13 strains) (Aarestrup *et al.*, 1998), the Netherlands (87 and 762 strains isolated in 2000 and 2003, respectively) (Martel *et al.*, 2001; Hendriksen *et al.*, 2008), western Canada (15 strains) (Cantin *et al.*, 1992), North and West Japan (303 strains) (Kataoka *et al.*, 2000), England and Wales (87 strains), and France (711 strains) (Hendriksen *et al.*, 2008). In contrast, 0.9 to 13% of isolates were reported resistant to penicillin in Denmark (357 strains), Poland (412 strains), Portugal (24 strains) (Hendriksen *et al.*, 2008), Spain (151 strains) (Vela *et al.*, 2005), Quebec (15 strains) (Cantin *et al.*, 1992), Central Japan (386 strains) (Kataoka *et al.*, 2000), and China (421 strains) (Zhang *et al.*, 2008). In a US study, 25% of 65 isolates of *S. suis* were resistant to penicillin (Reams *et al.*, 1993). Human studies report that *S. suis* isolates from both diseased and clinically healthy persons are highly susceptible to penicillin, with 0% resistance (Cantin *et al.*, 1992; Strangmann *et al.*, 2002; Ma *et al.*, 2008; Hoa *et al.*, 2011).

A detailed listing of resistance patterns for *S. suis* isolates from different countries for the most commonly used antimicrobial agents in pig production is shown in Table 1.

Many antimicrobials used in veterinary medicine belong to the same classes as antimicrobials used to treat humans (McEwen and Fedorka-Cray, 2002). Use of antimicrobials in livestock may allow transfer of resistant bacteria among animals, and resistance genes may be transferred to both commensal organisms and animal or human pathogens (McEwen and Fedorka-Cray, 2002). Increased human morbidity and mortality associated with failure of standard treatments are indirect costs associated with antimicrobial resistance. Treatment failure also initiates a need for newer, typically more expensive, antibiotics to replace those that become ineffective (Hawkey, 2008). It has been suggested that *S. suis* may act as an antibiotic resistance reservoir contributing to the spread of resistance genes to streptococcal human pathogens such as *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Streptococcus agalactiae* (Palmieri *et al.*, 2011). Thus, occurrence of relatively high levels of resistance of *S. suis* to some antimicrobials (e.g. macrolides, lincosamides, tetracyclines, and sulphonamides) may represent a human health concern.

Mechanisms of resistance

Resistance of *S. suis* to lincosamides (lincomycin and clindamycin), macrolides (erythromycin, spiramycin, and tylosin), tetracycline, and sulphonamides has been acknowledged in many countries, with reporting rates up to 85% (Strangmann *et al.*, 2002; Vela *et al.*, 2005; Zhang *et al.*, 2008; Hoa *et al.*, 2011). Although mechanisms of resistance of *S. suis* have not been well documented, recent studies have reported on the determinants that may be involved in resistance of *S. suis* to different antibiotics. For instance, *S. suis* resistance to tetracycline is most often mediated by ribosomal

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Table 1. A detailed listing of resistance patterns for *S. suis* isolates from various countries for the most commonly used antimicrobial agents in pig production

		Percentage resistance (%)															
Country	Research dates	AMP	CEPH	CLI	ENR	ERY	GEN	LIN	MAC	PEN	SPY	STR	SUL	TET	TMP	TMP sulfa	TYL
Asia																	
China	2005–2007	4	22.1	68.4	32.8	22.2	–	–	–	9.5	–	–	86.7	91.7	–	59.1	–
Hong Kong*	2003–2005	S	S	–	–	90.7	–	–	20	S	–	–	–	–	–	–	–
Japan	1987–1996	0.6	0.9	–	–	27	–	–	–	0.9	–	29.5	–	86.9	–	0	–
Korea		–	S	–	–	–	–	–	–	S	–	–	–	–	–	–	–
Northern Thailand		23	0	–	21	–	–	100	–	27	–	–	–	96	–	37	–
Vietnam*	1997–2008	–	0	–	–	S	–	–	–	0	–	–	–	88.6	–	–	–
Europe																	
Denmark*	1995–1997	0	0	–	1	20.4	0	20.4	–	0	20.4	3.1	57.1	43.9	0	–	20.4
Denmark*	1995–1996	0	0	–	1.6	0	–	9.7	–	0	12.9	–	–	40.3	–	3.2	–
Denmark	2003	–	–	–	–	–	–	–	–	0.9	–	–	–	52.2	–	51.5	–
England/Wales	2003	–	–	–	–	29.1	–	–	–	0	–	–	–	68	–	3	–
England/Wales	2004	–	–	–	–	36	–	–	–	0	–	–	–	68	–	8	–
France	2002	–	–	–	–	50	0	–	–	0	–	–	–	57.8	–	22.4	–
France	2004	–	–	–	–	64.6	0	–	–	0	–	–	–	62.5	–	13	–
Germany*	2002	S	–	–	–	–	–	–	–	S	–	–	–	90	–	–	–
Netherlands*	1992	–	–	8	–	35	17	–	–	0	–	8	100	8	–	–	–
Netherlands	2003	–	–	–	–	58.1	–	–	–	0	–	–	–	48	–	8	–
Poland	2002	–	–	–	–	8	28	–	–	10.6	–	–	–	73.3	–	30	–
Poland	2004	–	–	–	–	–	53.2	–	–	8.1	–	–	–	64	–	14.4	–
Portugal	2004	–	–	–	–	30.6	100	–	–	13	–		–	92	–	–	–
Spain	1999–2001	–	0.7	87.4	2	75	4.6	–	–	4	–	11.3	95	95.4	–	0	89.4
Sweden*	1992–1997	0	0	–	0		0	0	–	0	0	7.7	15.4	7.7	0	–	0
North America																	
Canada (Quebec)*	1992	–	–	91	–	78	2	–	–	3	–	42	67	100	–	–	–
Canada (Western)*	1992	–	–	40	–	82	0	–	–	0	–	13	7	87	–	–	–
USA	1998–2001	2.3	23.1	86.8	–	67.2	7.6	86.8	–	14.5	–	–	~57.8	97.8	–	1.2	79.9
USA (Iowa)	2003	3	1	81	–	81.9	7	–	–	14	–	–	~46.7	–	–	1	79

*: Serotype 2.

-: No data available; S: Reported as sensitive but no percentage provided.

Abbreviations: AMP=ampicillin; CEPH=cephalosporins (ceftiofur); CLI=clindamycin; ENR=enrofloxacin; ERY=erythromycin; GEN=gentamicin; LIN=lincomycin; MAC=macrolides (erythromycin, spiramycin, and tylosin); PEN=penicillin; SPY=spiramycin; STR=streptomycin; SUL=sulphonamides; TET=tetracycline; TMP=trimethoprim; TMPsulfa=trimethoprim/sulphamethoxazole; TYL=tylosin.

protection genes *tet*(M) and *tet*(O) and less frequently by *tet*(Q), *tet*(T), *tet*(W) and by efflux pump genes *tet*(K) and *tet*(L) (Hoa *et al.*, 2011; Palmieri *et al.*, 2011). The mechanisms of resistance to macrolides are modification of the methylase-mediated target site by the product of *erm*(B) and less frequently active efflux by products of *mef* (A) and *mef* (E) (Palmieri *et al.*, 2011). Resistance to fluoroquinolones is mainly due to single-point mutations in the quinolone-resistance determining regions *parC* and *gyrA* (Escudero *et al.*, 2007, 2011; Palmieri *et al.*, 2011), and to *satAB*, encoding an efflux pump (Escudero *et al.*, 2011). The mechanism of *S. suis* resistance to penicillin, a β-lactam, is modification of penicillin-binding proteins, either altered molecular weight or decreased affinity for penicillin or both (Cain *et al.*, 1995). The relatively low levels of penicillin resistance in *S. suis* strains may be related to this unusual mechanism (Gottschalk *et al.*, 1991b; Cain *et al.*, 1995). Recent studies (Hu *et al.*, 2011; Ge *et al.*, 2012) have shown that resistance of *S. suis* multi-drug resistant strain R61 to cefuroxime, a β-lactam and second generation cephalosporin, is mediated by mutations in key sites of the penicillin-binding protein PBP2x. Limited information exists on the genetic bases of resistance to other classes of antimicrobials, including aminoglycosides, trimethoprim-sulfamethoxazole, and chloramphenicol (Palmieri *et al.*, 2011).

Prudent drug use and measures to reduce the impact and spread of antimicrobial-resistant S. suis in swine

Specific strategies to ensure prudent use of antimicrobials in swine do not exist. Approaches to reduce the impact and spread of *S. suis* and antimicrobial resistance should be focused on measures that improve the management and environment of the pigs, together with strategic medication of clinically diseased animals (Amass *et al.*, 1996b). The main goal of prudent use of antimicrobials in agriculture is to 'maximize therapeutic efficacy while minimizing bacterial resistance' (Health Canada, 2002). The 'choice' and the 'use' of the right antimicrobial are two important aspects of this principle. Choice of the right antimicrobial should be based on an accurate diagnosis, including clinical evaluation, past experience, farm epidemiological status, and sensitivity testing. The selected antimicrobial should be approved for the species and indicated for the disease of concern. In addition, drug pharmacokinetic parameters, immune system of the diseased animal (e.g. bactericidal antimicrobials preferred for immune-suppressed patients), and spectrum of activity should be considered (i.e. broad-spectrum antimicrobials exert selection pressure for resistance on more non-target bacterial species) (Federation of Veterinarians of Europe, 2012). The appropriate use of the right antimicrobial depends on carefully following the label instructions together with veterinarian prescription and advice regarding dosage regimen, duration of treatment, group of animals to be treated (sick only versus both sick and healthy animals), withdrawal time, and disposal of unused antimicrobials and containers (Federation of Veterinarians of Europe, 2012).

Preventive measures for optimization of management and the environment of pigs are described under five categories.

Good environmental and handling practices

Implementation of good environmental and handling practices are encouraged to reduce stress caused by excessive temperature fluctuation, high relative humidity, crowding, and mixing pigs differing by $\geq$2 weeks of age (Dee *et al.*, 1993). Co-infection with PRRS virus results in more severe clinical *S. suis* disease (Thanawongnuwech *et al.*, 2000). Thus, strategies that prevent introduction of PRRS virus into a herd or reduce incidence of clinical signs of PRRS may reduce incidence and severity of clinical *S. suis*.

Continuous-flow facilities, fomites (surfaces in contact with manure), rodents, flies, and nutritional deficiencies have been associated with farms carrying high rates of *S. suis* (Dee *et al.*, 1993). All-in/all-out pig flow schemes help to reduce the microbial load in an existing facility when appropriate disinfectants and hot water, power washer equipment are used (Dee and Corey, 1993). Periodic disinfection of mechanical vectors, use of unique needles in the stoppers of bottles containing drugs or vaccines, prompt removal and appropriate disposal of dead pigs (Dee and Corey, 1993), and fly and rodent control strategies are recommended, together with supplementation of pigs with selenium and vitamin E.

Creating S. suis-free herds

Several strategies have been investigated, including deriving pigs via caesarean section, which is effective (Amass *et al.*, 1996a) but impractical for the swine industry. Removal of pigs from dams at birth is ineffective (Amass *et al.*, 1997). Absence of clinical signs due to *S. suis* serotype 2 has been considered successful in eradicating the organism. However, several antimicrobial regimens were unable to eliminate the carrier state (Amass *et al.*, 1996b), and the lack of sensitive tools to monitor for *S. suis* serotype 2 in tonsils of clinically healthy pigs is problematic.

Prophylactic antimicrobial therapy at times of potential stress

Factors to be considered when initiating prophylactic antimicrobial therapy in a herd with a history of clinical *S. suis* include prior or concurrent efforts to reduce risk factors and pharmaco-kinetic considerations such as bioavailability, route of administration, and serum concentration of the drug required to kill *S. suis* (Amass *et al.*, 1997; Gottschalk, 2004). Given the reported prevalence of susceptible isolates, penicillins may be considered for prophylaxis. Historically, in-feed procaine

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penicillin significantly reduced prevalence of *S. suis* meningitis in an affected herd (McKellar *et al.*, 1987). This is noteworthy, since studies in swine suggest that absorption of penicillin G is very limited when administered orally, and that penicillin V is the only form sufficiently absorbed to achieve therapeutic serum levels (McKellar *et al.*, 1987; Friendship, 2006). However, there is no commercially available form of penicillin V for oral administration in animals in Canada. Water-soluble penicillin G at a dose of 40,000 IU kg^{-1} body weight continues to be successfully used, possibly as a result of achieving therapeutic levels on the tonsils where colonization first occurs (P. Dowling, personal communication). Other water solubles such as tetracyclines (tetracycline, chlortetracycline, or oxytetracycline at a dose of 55–110 mg L^{-1}) or sulphamethazine (80–130 mg L^{-1}) may be used if recent on-farm culture and susceptibility results suggest that resident potentially pathogenic strains are sensitive (Friendship, 2006).

Vaccination

After several decades of investigation, the limited acceptance of *S. suis* vaccines is noteworthy, given the prevalence and burden of the pathogen. The National Animal Health Monitoring System (2006) has reported that less than 7% of US herds use a vaccine. Although a few *S. suis* vaccines are licensed and commercially available in Canada, most published studies investigate use of autogenous vaccines and report inconsistent findings (Reams *et al.*, 1996; Halbur *et al.*, 2000; Gottschalk, 2004). Possible explanations include weak antigenicity of the capsulated bacteria (del Campo Sepulveda *et al.*, 1996), deterioration of antigenicity during heat or formalin processing (Holt *et al.*, 1990), and interference of maternal antibodies with the immune response (Lapointe *et al.*, 2002). While multiple serotypes are frequently present in a herd, all of them may not be pathogenic. Diligent sampling and diagnostics, preferably including identification of virulent strains, are required to select the strains needed in the farm's vaccine (J. Gallant, personal communication). The most common population studied has been piglets (Holt *et al.*, 1990; Busque *et al.*, 1997; Amass *et al.*, 1999); however, immunization of sows has also been reported as an effective control strategy in reducing depression and neurological signs in weaned pigs (Amass *et al.*, 2000).

Capsular polysaccharides have been investigated as immunogens with variable results (del Campo Sepulveda *et al.*, 1996; Wisselink *et al.*, 2002). Bacterial MRP and EF proteins (Wisselink *et al.*, 2002) have protected piglets against challenge; however, Jacobs *et al.* (1996) reported that only the suilysin protein offered effective protection. Complicating matters, multiple investigators report that suilysin proteins are not present in all virulent strains, especially North American strains (Quessy *et al.*, 1994; Galina *et al.*, 1996; Gottschalk *et al.*, 1998). Li *et al.* (2006) reported that the Sao protein elicited good humoral antibody response, but piglets challenged endotracheally with a virulent strain were not protected.

Other control measures

Other *S. suis* control measures include prompt treatment of both sick and clinically healthy animals, as *S. suis* infection is an invasive disease that can kill pigs very quickly (MacInnes and Desrosiers, 1999). Every farm should have established treatment protocols, with specific guidelines of when and how to treat ailments and whether it is appropriate to remove an affected pig to a hospital pen, together with strict instructions regarding medication and appropriate nursing care (Blackwell, 2005). For instance, pigs affected with meningitis may die of dehydration if adequate water is not offered during the treatment period; it may appear that treatment failed, when in fact the cause of death was dehydration (Blackwell, 2005). Rules for stopping treatments and culling and euthanizing pigs should also be included in the protocols (Blackwell, 2005).

Individual pigs affected with *S. suis* infection should be treated with injectable antibiotics (Neumann *et al.*, 2009). In-feed or in-water medication is recommended to treat a group of sick pigs, at the same time medicating others in the group to prevent the disease (Neumann *et al.*, 2009). As sick pigs are more likely to drink than to eat, in-water medication is preferred over in-feed medication. Penicillin G, amoxicillin, trimethoprim/sulfa, gentamicin, and ceftiofur (a third generation cephalosporin) have been recommended as the antimicrobials of choice to treat diagnosed or suspected cases (MacInnes and Desrosiers, 1999; Halbur *et al.*, 2000; Done and Burch, 2007). Antimicrobial treatment based on bacterial culture and sensitivity is recommended (Reams *et al.*, 1993; Gottschalk *et al.*, 1998), with the understanding that treatment is unlikely to eliminate the carrier state (Amass *et al.*, 1996b). In a study conducted on a commercial farrow-to-finish operation with a history of *S. suis* serotype 2 infection, mortality and tonsillar carriage of *S. suis* were significantly reduced with in-water treatment with potassium penicillin G (Byra *et al.*, 2011). A close second choice is amoxicillin, followed by trimethoprim/sulfa and ceftiofur (Done and Burch, 2007). Complementary therapy should be considered, such as anti-inflammatories for treatment of *S. suis* meningitis (MacInnes and Desrosiers, 1999) and analgesics for severe arthritis, together with encouragement to eat, drink, and move while infection is resolving (Blackwell, 2005). In addition, regular monitoring of antimicrobial resistance of *S. suis* isolates provides valuable data for prescribing practices and prudent use recommendations.

Disease prevention and growth promotion are common goals for antimicrobial use in farm animals. In these instances, development of resistance is a major concern, as is the potential transfer of resistant bacteria from animals to humans through the food chain or direct animal contact (McEwen and Fedorka-Cray, 2002).

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Conclusions

(**1**) *S. suis,* a zoonotic pathogen causing significant economic loss in the swine industry, represents a threat to human health. *S. suis* infection causes a spectrum of diseases in pigs, including an asymptomatic carrier state, clinical infection, and peracute fatal disease.

(**2**) Resistance to macrolides, lincosamides, tetracyclines, and sulphonamides has been reported, with up to 85% of strains resistant. *S. suis* isolates are uniformly sensitive to penicillin and ampicillin. Relatively low levels of resistance are reported when resistance is observed.

(**3**) It has been suggested that the unusual mechanism by which resistance to penicillin is acquired (modifications in the structure of penicillin-binding proteins) is the reason that low levels of resistance are observed in *S. suis* isolates from various countries.

(**4**) Prudent use of antimicrobials in agriculture is important to preserve the therapeutic efficacy of antibiotics used in animals and humans. Strategies to control *S. suis* infection in pigs should be focused on the right choice of antimicrobial and its appropriate use, together with preventive measures intended to improve the management and environment of pigs.

References

Aarestrup FM (1999). Association between the consumption of antimicrobial agents in animal husbandry and the occurrence of resistant bacteria among food animals. *International Journal of Antimicrobial Agents* **12**: 279–285.

Aarestrup FM, Rasmussen SR, Artursson K and Jensen NE (1998). Trends in the resistance to antimicrobial agents of *Streptococcus suis* isolates from Denmark and Sweden. *Veterinary Microbiology* **63**: 71–80.

Amass SF, Struve R, Clark LK and Wu CC (1996a). Cesarean section: a surgical method to derive pigs free of *Streptococcus suis*. *Swine Health and Production* **4**: 196–198.

Amass SF, Wu CC and Clark LK (1996b). Evaluation of antibiotics for the elimination of the tonsillar carrier state of *Streptococcus suis* in pigs. *Journal of Veterinary Diagnostic Investigation* **8**: 64–67.

Amass SF, SanMiguel P and Clark LK (1997). Demonstration of vertical transmission of *Streptococcus suis* in swine by genomic fingerprinting. *Journal of Clinical Microbiology* **35**: 1595–1596.

Amass SF, Stevenson GW, Knox KE and Reed AJ (1999). Efficacy of an autogenous vaccine for preventing streptococcosis in piglets. *Veterinary Medicine* **94**: 480–484.

Amass SF, Stevenson GW, Bryan D, Vyverberg BD, Huxford TW, Knox KE and Grote LA (2000). Administration of a homologous bacterin to sows prefarrowing provided partial protection against streptoccosis in their weaned pigs. *Journal of Swine and Health Production* **8**: 217–219.

Berthelot-Herault F, Gottschalk M, Labbe A, Cariolet R and Kobisch M (2001). Experimental airborne transmission of *Streptococcus suis* capsular type 2 in pigs. *Veterinary Microbiology* **82**: 69–80.

Blackwell T (2005). Effective treatment and handling of poor doing pigs in the finishing barn. In: *Conference Proceedings, London Swine Conference*, London, Ontario, p. 167.

Brisebois LM, Charlebois R, Higgins R and Nadeau M (1990). Prevalence of *Streptococcus suis* in four to eight week old clinically healthy piglets. *Canadian Journal of Veterinary Research* **54**: 174–177.

Busque P, Higgins R, Caya F and Quessy S (1997). Immunization of pigs against *Streptococcus suis* serotype 2 infection using a live avirulent strain. *Canadian Journal of Veterinary Research* **61**: 275–279.

Byra C, Gadbois P, Cox WR, Gottschalk M, Farzan V, Bauer SA and Wilson JB (2011). Decreased mortality of weaned pigs with *Streptococcus suis* with the use of in-water potassium penicillin G. *Canadian Veterinary Journal* **52**: 272–276.

Cain D, Malouin F, Dargis M, Harel J and Gottschalk M (1995). Alterations in penicillin-binding proteins in strains of *Streptococcus suis* possessing moderate and high levels of resistance to penicillin. *FEMS Microbiology Letters* **130**: 121–127.

Cantin M, Harel J, Higgins R and Gottschalk M (1992). Antimicrobial resistance patterns and plasmid profiles of *Streptococcus suis* isolates. *Journal of Veterinary Diagnostic Investigation* **4**: 170–174.

Clifton-Hadley FA, Alexander TJ, Enright MR and Guise J (1984). Monitoring herds for *Streptococcus suis* type 2 by sampling tonsils of slaughter pigs. *Veterinary Record* **115**: 562–564.

Cloutier G, D'Allaire S, Martinez G, Surprenant C, Lacouture S and Gottschalk M (2003). Epidemiology of *Streptococcus suis* serotype 5 infection in a pig herd with and without clinical disease. *Veterinary Microbiology* **97**: 135–151.

Dee SA and Corey MM (1993). The survival of *Streptococcus suis* on farm and veterinary equipment. *Swine Health and Production* **1**: 17–20.

Dee SA, Carlson AR, Winkelman NL and Corey MM (1993). Effect of management practices on the *Streptococcus suis* carrier rate in nursery swine. *Journal of the American Veterinary Medical Association* **203**: 295–299.

del Campo Sepulveda EM, Altman E, Kobisch M, D'Allaire S and Gottschalk M (1996). Detection of antibodies against *Streptococcus suis* capsular type 2 using a purified capsular polysaccharide antigen-based indirect ELISA. *Veterinary Microbiology* **52**: 113–125.

Done S and Burch D (2007). Prevention and control of respiratory diseases excluding *Mycoplasma Hyopneumoniae*. *Thai Journal of Veterinary Medicine* **37**: 9–20.

Escudero JA, San Millan A, Catalan A, de la Campa AG, Rivero E, Lopez G, Dominguez L, Moreno MA and Gonzalez-Zorn B (2007). First characterization of fluoroquinolone resistance in *Streptococcus suis*. *Antimicrobial Agents and Chemotherapy* **51**: 777–782.

Escudero JA, San Millan A, Gutierrez B, Hidalgo L, La Ragione RM, AbuOun M, Galimand M, Ferrandiz MJ, Dominguez L, de la Campa AG and Gonzalez-Zorn B (2011). Fluoroquinolone efflux in *Streptococcus suis* is mediated by SatAB and not by SmrA. *Antimicrobial Agents and Chemotherapy* **55**: 5850–5860.

Federation of Veterinarians of Europe (2012). *Antibiotic resistance & prudent use of antibiotics in veterinary medicine*. [Available online at http://www.fve.org/news/publications/pdf/antibioen.pdf] [accessed 5 June 2012].

Feng Y, Shi X, Zhang H, Zhang S, Ma Y, Zheng B, Han H, Lan Q, Tang J, Cheng J, Gao GF and Hu Q (2009). Recurrence of human *Streptococcus suis* infections in 2007: three cases of meningitis and implications that heterogeneous *S. suis* 2 circulates in China. *Zoonoses and Public Health* **56**: 506–514.

Feng Y, Zhang H, Ma Y and Gao GF (2010). Uncovering newly emerging variants of *Streptococcus suis*, an important zoonotic agent. *Trends in Microbiology* **18**: 124–131.

https://doi.org/10.1017/S1466252313000029 Published online by Cambridge University Press

Friendship RM (2006). Antimicrobial drug use in swine. In: Giguere S, Prescott JF, Baggot JD, Walker RD and Dowling PM (eds) *Antimicrobial Therapy in Veterinary Medicine*. Iowa: Blackwell Publishing, p. 538.

Galina L, Vecht U, Wisselink HJ and Pijoan C (1996). Prevalence of various phenotypes of *Streptococcus suis* isolated from swine in the U.S.A. based on the presence of muraminidase-released protein and extracellular factor. *Canadian Journal of Veterinary Research* **60**: 72–74.

Ge Y, Wu J, Xia Y, Yang M, Xiao J and Yu J (2012). Molecular dynamics simulation of the complex PBP-2x with drug cefuroxime to explore the drug resistance mechanism of *Streptococcus suis* R61. *PLoS ONE* **7**: e35941.

Gottschalk M and Segura M (2000). The pathogenesis of the meningitis caused by *Streptococcus suis*: the unresolved questions **76**: 259–272.

Gottschalk M (2004). Porcine *Streptococcus suis* strains as potential sources of infections in humans: an underdiagnosed problem in North America? *Journal of Swine and Health Production* **12**: 197–199.

Gottschalk M (2012). Streptococcosis. In: Zimmerman JJ, Karriker LA, Ramirez A, Schwartz KJ and Stevenson GW (eds) *Diseases of Swine*, 10th edn. Iowa: Blackwell Publishing, pp. 841–855.

Gottschalk M, Higgins R, Jacques M, Beaudoin M and Henrichsen J (1991a). Isolation and characterization of *Streptococcus suis* capsular types 9–22. *Journal of Veterinary Diagnostic Investigation* **3**: 60–65.

Gottschalk M, Turgeon P, Higgins R, Beaudoin M and Bourgault AM (1991b). Susceptibility of *Streptococcus suis* to penicillin. *Journal of Veterinary Diagnostic Investigation* **3**: 170–172.

Gottschalk M, Lebrun A, Wisselink H, Dubreuil JD, Smith H and Vecht U (1998). Production of virulence-related proteins by Canadian strains of *Streptococcus suis* capsular type 2. *Canadian Journal of Veterinary Research* **62**: 75–79.

Gottschalk M, Segura M and Xu J (2007). *Streptococcus suis* infections in humans: the Chinese experience and the situation in North America. *Animal Health Research Reviews* **8**: 29–45.

Gottschalk M, Xu J, Calzas C and Segura M (2010). *Streptococcus suis*: a new emerging or an old neglected zoonotic pathogen? *Future Microbiology* **5**: 371–391.

Halbur P, Thanawongnuwech R, Brown G, Kinyon J, Roth J, Thacker E and Thacker B (2000). Efficacy of antimicrobial treatments and vaccination regimens for control of porcine reproductive and respiratory syndrome virus and *Streptococcus suis* coinfection of nursery pigs. *Journal of Clinical Microbiology* **38**: 1156–1160.

Haleis A, Alfa M, Gottschalk M, Bernard K, Ronald A and Manickam K (2009). Meningitis caused by *Streptococcus suis* serotype 14, North America. *Emerging Infectious Diseases* **15**: 350–352.

Hawkey PM (2008). The growing burden of antimicrobial resistance. *Journal of Antimicrobial Chemotherapy* **62**: 1–9.

Health Canada (2002). *Strategies to ensure prudent use of antimicrobial drugs*. [Available online at http://www.hc-sc.gc.ca/dhp-mps/pubs/vet/amr-ram_final_report-rapport_06-27_cp-pc-eng.php#a8] [accessed 5 June 2012].

Hendriksen RS, Mevius DJ, Schroeter A, Teale C, Jouy E, Butaye P, Franco A, Utinane A, Amado A, Moreno M, Greko C, Stark KD, Berghold C, Myllyniemi AL, Hoszowski A, Sunde M and Aarestrup FM (2008). Occurrence of antimicrobial resistance among bacterial pathogens and indicator bacteria in pigs in different European countries from year 2002–2004: the ARBAO-II study. *Acta Veterinaria Scandinavica* **50**: 19.

Higgins R and Gottschalk M (1999). Streptococcal diseases. In: Straw BE, D'Allaire S, Mengeling WL and Taylor DJ (eds) *Diseases of Swine*, 8th edn. Iowa: Blackwell Publishing, pp. 563–578.

Higgins R and Gottschalk M (2000). Distribution of *Streptococcus suis* capsular types in 1999. *Canadian Veterinary Journal* **41**: 414.

Higgins R, Gottschalk M, Mittal KR and Beaudoin M (1990). *Streptococcus suis* infection in swine. A sixteen month study. *Canadian Journal of Veterinary Research* **54**: 170–173.

Hoa NT, Chieu TT, Nghia HD, Mai NT, Anh PH, Wolbers M, Baker S, Campbell JI, Chau NV, Hien TT, Farrar J and Schultsz C (2011). The antimicrobial resistance patterns and associated determinants in *Streptococcus suis* isolated from humans in southern Vietnam, 1997–2008. *BMC Infectious Diseases* **11**: 6.

Holt ME, Enright MR and Alexander TJ (1990). Protective effect of sera raised against different fractions of *Streptococcus suis* type 2. *Journal of Comparative Pathology* **103**: 85–94.

Holtkamp D, Rotto H and Garcia R (2007). The economic cost of major health challenges in large US swine production systems. In: *Conference Proceedings, American Association of Swine Veterinarians*. Orlando, FL, 3–6 March 2007. p. 85.

Hu P, Yang M, Zhang A, Wu J, Chen B, Hua Y, Yu J, Chen H, Xiao J and Jin M (2011). Comparative genomics study of multi-drug-resistance mechanisms in the antibiotic-resistant *Streptococcus suis* R61 strain. *PLoS ONE* **6**: e24988. doi:10.1371/journal.pone.0024988.

Jacobs AA, van den Berg AJ and Loeffen PL (1996). Protection of experimentally infected pigs by suilysin the thio-activated haemolysin of *Streptococcus suis*. *Vetinary Record* **139**: 225–228.

Jensen HE, Gyllensten J, Hofman C, Leifsson PS, Agerholm JS, Boye M and Aalbaek B (2010). Histologic and bacteriologic findings in valvular endocarditis of slaughter-age pigs. *Journal of Veterinary Diagnostic Investigation* **22**: 921–927.

Jensen J and Dorseen van CA (1957). Meningo-encephalitis bij vafkens door streptococcen. *Tijdschrift voor diergeneeskunde* **76**: 815–832.

Jones JE (1981). Experimental streptococcal endocarditis in the pig: the development of lesions 3 to 14 days after inoculation. *Journal of Comparative Pathology* **91**: 51–62.

Karstrup CC, Jensen HE, Aalbaek B, Leifsson PS, Boye M and Agerholm JS (2011). Endocarditis-associated brain lesions in slaughter pigs. *Journal of Comparative Pathology* **144**: 289–295.

Kataoka Y, Yoshida T and Sawada T (2000). A 10-year survey of antimicrobial susceptibility of *Streptococcus suis* isolates from swine in Japan. *Journal of Veterinary Medical Science* **62**: 1053–1057.

Keenliside J, Gamroth A, Bystrom J and Perry A (2006). Carcass trims – a look at arthritis and adhesions trims from severely affected herds. *Advances in Pork Production* **17**: 187–192.

Kolar M, Urbanek K and Latal T (2001). Antibiotic selective pressure and development of bacterial resistance. *International Journal of Antimicrobial Agents* **17**: 357–363.

Lapointe L, D'Allaire S, Lebrun A, Lacouture S and Gottschalk M (2002). Antibody response to an autogenous vaccine and serologic profile for *Streptococcus suis* capsular type 1/2. *Canadian Journal of Veterinary Research* **66**: 8–14.

Li Y, Martinez G, Gottschalk M, Lacouture S, Willson P, Dubreuil JD, Jacques M and Harel J (2006). Identification of a surface protein of *Streptococcus suis* and evaluation of its immunogenic and protective capacity in pigs. *Infection and Immunology* **74**: 305–312.

https://doi.org/10.1017/S1466252313000029 Published online by Cambridge University Press

Lun ZR, Wang QP, Chen XG, Li AX and Zhu XQ (2007). *Streptococcus suis*: an emerging zoonotic pathogen. *Lancet Infectious Diseases* **7**: 201–209.

Ma E, Chung PH, So T, Wong L, Choi KM, Cheung DT, Kam KM, Chuang SK and Tsang T (2008). *Streptococcus suis* infection in Hong Kong: an emerging infectious disease? *Epidemiology and Infection* **136**: 1691–1697.

MacInnes JI and Desrosiers R (1999). 'Agents of the ' *S. suis*-ide diseases' of swine: Actinobacillus *S. suis*, Haemophilus para *S. suis*, and *Streptococcus suis'*. *Canadian Journal of Veterinary Research* **63**: 83–89.

MacInnes JI, Gottschalk M, Lone AG, Metcalf DS, Ojha S, Rosendal T, Watson SB and Friendship RM (2008). Prevalence of *Actinobacillus pleuropneumoniae*, *Actinobacillus suis*, *Haemophilus parasuis*, *Pasteurella multocida*, and *Streptococcus suis* in representative Ontario swine herds. *Canadian Journal of Veterinary Research* **72**: 242–248.

Marie J, Morvan H, Berthelot-Hérault F, Sanders P, Kempf I, Gauthier-Bouchardon AV, Jouy E and Kobisch M (2002). Antimicrobial susceptibility of *Streptococcus suis* isolated from swine in France and from humans in different countries between 1996 and 2000. *Journal of Antimicrobial Chemotherapy* **50**: 201–209.

Martel A, Baele M, Devriese LA, Goossens H, Wisselink HJ, Decostere A and Haesebrouck F (2001). Prevalence and mechanism of resistance against macrolides and lincosamides in *Streptococcus suis* isolates. *Veterinary Microbiology* **83**: 287–297.

McEwen SA and Fedorka-Cray PJ (2002). Antimicrobial use and resistance in animals. *Clinical Infectious Diseases* **34**: 93–106.

McKellar QA, Baxter P, Taylor D and Bogan JA (1987). Penicillin therapy of spontaneous streptococcal meningitis in pigs. *Veterinary Record* **121**: 347–350.

Messier S, Lacouture S and Gottschalk M (2008). Distribution of *Streptococcus suis* capsular types from 2001 to 2007. *Canadian Veterinary Journal* **49**: 461–462.

Michaud S, Duperval R and Higgins R (1996). *Streptococcus suis* meningitis first case reported in Quebec. *Canadian Journal of Infectious Diseases* **7**: 329–331.

National Animal Health Monitoring System (2006). *Swine 2006 Part II: Reference of swine health and health management practices in the United States*. [Available online at http://www.aphis.usda.gov/animal_health/nahms/swine/downloads/swine2006/Swine2006_dr_PartII.pdf] [accessed 10 April 2012].

Neumann EJ, Ramirez A and Schwartz KJ (2009). Streptococcal infections. In: Neumann EJ, Ramirez A and Schwartz KJ (eds) *Swine Disease Manual*, 4th edn. Iowa: American Association of Swine Veterinarians, pp. 39–40.

Osweiler G (2003). Summary of selected swine assays and results for 2003 from the Iowa State University Veterinary Diagnostic Laboratory. In: *Conference Proceedings, 11th Annual Swine Disease Conference for Swine Practitioners*, Iowa, p. 188.

Palmieri C, Varaldo PE and Facinelli B (2011). *Streptococcus suis*, an emerging drug-resistant animal and human pathogen. *Frontiers in Microbiology* **2**: 235.

Quessy S, Dubreuil JD, Caya M, Letourneau R and Higgins R (1994). Comparison of pig, rabbit and mouse IgG response to *Streptococcus suis* serotype 2 proteins and active immunization of mice against the infection. *Canadian Journal of Veterinary Research* **58**: 220–223.

Reams RY, Glickman LT, Harrington DD, Bowersock TL and Thacker HL (1993). *Streptococcus suis* infection in swine: a retrospective study of 256 cases. Part I. Epidemiologic factors and antibiotic susceptibility patterns. *Journal of Veterinary Diagnostic Investigation* **5**: 363–367.

Reams RY, Glickman LT, Harrington DD, Thacker HL and Bowersock TL (1994). *Streptococcus suis* infection in swine: a retrospective study of 256 cases. Part II. Clinical signs, gross and microscopic lesions, and coexisting microorganisms. *Journal of Veterinary Diagnostic Investigation* **6**: 326–334.

Reams RY, Harrington DD, Glickman LT, Thacker HL and Bowersock TL (1996). Multiple serotypes and strains of *Streptococcus suis* in naturally infected swine herds. *Journal of Veterinary Diagnostic Investigation* **8**: 119–121.

Sanford SE, Schultz R and Straw B (1988). *Streptococcus suis disease in pigs*. [Available online at http://www.animalgenome.org/edu/PIH/118.html [accessed 10 April 2011].

Smith HE, Vecht U, Wisselink HJ, Stockhofe-Zurwieden N, Biermann Y and Smits MA (1996). Mutants of *Streptococcus suis* types 1 and 2 impaired in expression of muramidase-released protein and extracellular protein induce disease in newborn germfree pigs. *Infection and Immunity* **64**: 4409–4412.

Smith TC, Capuano AW, Boese B, Myers KP and Gray GC (2008). Exposure to *Streptococcus suis* among US swine workers. *Emerging Infectious Diseases* **14**: 1925–1927.

Staats JJ, Feder I, Okwumabua O and Chengappa MM (1997). *Streptococcus suis*: past and present. *Veterinary Research Communications* **21**: 381–407.

Strangmann E, Froleke H and Kohse KP (2002). Septic shock caused by *Streptococcus suis*: case report and investigation of a risk group. *International Journal of Hygiene and Environmental Health* **205**: 385–392.

Thanawongnuwech R, Brown GB, Halbur PG, Roth JA, Royer RL and Thacker BJ (2000). Pathogenesis of porcine reproductive and respiratory syndrome virus-induced increase in susceptibility to *Streptococcus suis* infection. *Veterinary Pathology* **37**: 143–152.

The Government of the Hong Kong Special Administrative Region (2005). *Amendment to the Quarantine and Prevention of Disease Ordinance, Cap. 141*. [Available online at http://www.chp.gov.hk/en/content/9/24/3648.html [accessed 3 April 2012].

Vela AI, Moreno MA, Cebolla JA, Gonzalez S, Latre MV, Dominguez L and Fernandez-Garayzabal JF (2005). Antimicrobial susceptibility of clinical strains of *Streptococcus suis* isolated from pigs in Spain. *Veterinary Microbiology* **105**: 143–147.

Walsh B, Williams AE and Satsangi J (1992). *Streptococcus suis* type 2: pathogenesis and clinical disease. *Reviews in Medical Microbiology* **3**: 65–71.

Wertheim HF, Nghia HD, Taylor W and Schultsz C (2009a). *Streptococcus suis*: an emerging human pathogen. *Clinical Infectious Diseases* **48**: 617–625.

Wertheim HF, Nguyen HN, Taylor W, Lien TT, Ngo HT, Nguyen TQ, Nguyen BN, Nguyen HH, Nguyen HM, Nguyen CT, Dao TT, Nguyen TV, Fox A, Farrar J, Schultsz C, Nguyen HD, Nguyen KV and Horby P (2009b). *Streptococcus suis*, an important cause of adult bacterial meningitis in northern Vietnam. *PLOS ONE* **4**: e5973.

Willenburg KS, Sentochnik DE and Zadoks RN (2006). Human *Streptococcus suis* meningitis in the United States. *New England Journal of Medicine* **354**: 1325.

Wisselink HJ, Reek FH, Vecht U, Stockhofe-Zurwieden N, Smits MA and Smith HE (1999). Detection of virulent strains of *Streptococcus suis* type 2 and highly virulent strains of *Streptococcus suis* type 1 in tonsillar specimens of pigs by PCR. *Veterinary Microbiology* **67**: 143–157.

Wisselink HJ, Smith HE, Stockhofe-Zurwieden N, Peperkamp K and Vecht U (2000). Distribution of capsular types and production of muramidase-released protein (MRP) and

https://doi.org/10.1017/S1466252313000029 Published online by Cambridge University Press

extracellular factor (EF) of *Streptococcus suis* strains isolated from diseased pigs in seven European countries. *Veterinary Microbiology* **74**: 237–248.

Wisselink HJ, Stockhofe-Zurwieden N, Hilgers LA and Smith HE (2002). Assessment of protective efficacy of live and killed vaccines based on a non-encapsulated mutant of *Streptococcus suis* serotype 2. *Veterinary Microbiology* **84**: 155–168.

Zhang C, Ning Y, Zhang Z, Song L, Qiu H and Gao H (2008). In vitro antimicrobial susceptibility of *Streptococcus suis* strains isolated from clinically healthy sows in China. *Veterinary Microbiology* **131**: 386–392.

https://doi.org/10.1017/S1466252313000029 Published online by Cambridge University Press