UNIVERSITI PUTRA MALAYSIA

SYSTEMATIC REVIEW ON STREPTOCOCCUS SUIS ZOONOTIC POTENTIAL

LEE CHYE TUNG

SYSTEMATIC REVIEW ON *STREPTOCOCCUS SUIS* ZOONOTIC POTENTIAL

LEE CHYE TUNG

FACULTY OF VETERINARY MEDICINE
UNIVERSITI PUTRA MALAYSIA
SERDANG, SELANGOR
2021/2022

SYSTEMATIC REVIEW ON *STREPTOCOCCUS SUIS* ZOONOTIC POTENTIAL

LEE CHYE TUNG

A project paper submitted to the
Faculty of Veterinary Medicine, Universiti Putra Malaysia
In partial fulfilment of the requirement for the
DEGREE OF DOCTOR OF VETERINARY MEDICINE
FACULTY OF VETERINARY MEDICINE
Universiti Putra Malaysia
Serdang, Selangor Darul Ehsan.

December 2021

DEDICATION

To

My dearest family and friends

ACKNOWLEDGEMENTS

First and foremost, I would like to express my greatest gratitude to my supervisor, Assoc. Prof Dr. Ooi Peck Toung, for his guidance and patience throughout this systematic review and preparation of this project paper. I would like to thank my co-supervisor, Assoc. Prof Dr. Gayathri Thevi Selvarajah, for her guidance and support for this systematic review as well. Furthermore, a very special thank to Dr. Michelle Fong Wai Cheng for guiding me throughout the process of searching, extracting, and analysing data in this systematic review.

Next, I would like to thank my beloved final year project mates, Yi Ling, Sin Lin, Betty, and Hui San, for their supports throughout the systematic review. Moreover, a big thank to my DVM2022 classmates who assisted me directly or indirectly in this project.

Last but not least, I would also like to thank my parents and siblings for their encouragement and unconditional supports. This project would not have been possible without them.

Thank you.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABBREVIATIONS

°C	Degree Celsius
cps	Capsular Polysaccharide
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
S. suis	*Streptococcus suis*
ml	Millilitre
m-PCR	Multiplex polymerase chain reaction
no.	Number
PCR	Polymerase Chain Reaction
RFLP	Restriction fragment length polymorphism
rRNA	Ribosomal ribonucleic acid
RNase	Ribonuclease
UK	United Kingdom
USA	United States of America

ABSTRAK

Abstrak daripada kertas projek yang dikemukakan kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripada keperluan kursus VPD 4999-Projek.

Kajian Sistematik mengenai Potensi Zoonotik *Streptococcus Suis*

Oleh

Lee Chye Tung

2021

Penyelia: Profesor Madya Dr. Ooi Peck Toung

Streptococcus suis (*S. suis*) ialah bakteria Gram-positif fakultatif anaerobik, yang hidup sebagai flora normal dalam saluran pernafasan atas, saluran gastrousus dan saluran pembiakan babi. Manifestasi klinikal dalam babi termasuk meningitis, septikemia dengan kematian mengejut, arthritis, dan radang paru-paru. *S. suis* boleh menjangkiti manusia dan membawa kepada tanda klinikal yang serupa dengan babi. Objektif kajian sistematik ini adalah untuk mengkaji dan mengenal pasti potensi zoonotik dan risiko terdedah dalam jangkitan *S. suis* pada manusia. Artikel dikenal pasti dari tiga pangkalan data pencarian, iaitu Scopus, PubMed, dan Science Direct. Tiada sekatan tahun dalam carian, artikel dimasukkan jika ditulis dalam bahasa Inggeris. Artikel dikecualikan jika dicari duplikasi atau di luar skop. Antara 264 artikel yang dikenal pasti, 38 artikel dimasukkan untuk kajian sistematik ini. Sebanyak 718 kes telah dikenal pasti dari 24 negara antara tahun 1968 dan 2021. Purata umur adalah 51 tahun dan 561 (78.13%) pesakit adalah lelaki. Risiko terdedah yang dikenal pasti termasuk pendedahan kepada babi atau daging babi, pekerjaan yang berkaitan dengan babi, kecederaan kulit, keadaan kesihatan asas, dan ketagihan alkohol. Kadar kematian kes adalah 11.42%. Pencegahan jangkitan *S. suis* dalam manusia boleh dilakukan dengan kesedaran dan pendidikan awam. Dalam kajian sistematik ini, kami menyimpulkan bahawa *S. suis* mempunyai potensi zoonotik terhadap manusia dan risiko terdedah yang paling kerap adalah pendedahan kepada babi atau daging babi. Walau bagaimanapun, penyelidikan lanjut diperlukan untuk mengetahui sumber jangkitan atau risiko terdedah yang lain, serta untuk penciptaan vaksin untuk manusia.

Kata kunci: *Streptococcus suis*; potensi zoonotik; faktor-faktor risiko

ABSTRACT

An abstract of the project paper presented to the Faculty of Veterinary Medicine in partial fulfilment of the course VPD 4999-Project.

Systematic Review on *Streptococcus Suis* Zoonotic Potential

By

Lee Chye Tung

2021

Supervisor: Associate Professor Dr. Ooi Peck Toung

Streptococcus suis (*S. suis*) is a facultatively anaerobic Gram-positive bacteria, which lives as a normal flora in the upper respiratory tract, gastrointestinal tract, and genital tract of pigs. Clinical manifestations in swine include meningitis, septicaemia with sudden death, arthritis, and pneumonia. Interestingly, *S. suis* can infect humans and lead to clinical signs similar to pigs. The objective of this systematic review is to review and identify the zoonotic potential and the predispose risks of *S. suis* infection in humans. Articles were identified from three databases, namely Scopus, PubMed, and Science Direct. No time restriction was set in the searching, articles were included if they were written in English. Articles were excluded if they were duplicates or out of scope. Among 264 articles identified, 38 articles were included for this systematic review. A total of 718 cases were identified from 24 countries between 1968 and 2021. The mean age was 51 years old and 561 (78.13%) patients were male. Predispose risks identified include exposure to pigs or pork, pig-related occupations, skin injuries, underlying health conditions, and alcoholism. The case-fatality rate was 11.42%. Prevention of human *S. suis* infection can be done by public awareness and education. In this systematic review, we concluded that *S. suis* has zoonotic potential towards humans and the most frequent predispose risks was pigs or pork exposure. Nevertheless, further researches are needed to find out other possible source of infection or predispose risks, as well as for development of vaccine for humans.

Keywords: *Streptococcus suis*; zoonotic potential; risk factors

INTRODUCTION

Streptococcus suis (*S. suis*) is a facultatively anaerobic Gram-positive ovoid or coccal bacterium surrounded by a polysaccharide capsule. Based on the antigenic diversity of the capsule, *S. suis* strains can be classified serologically into 35 serotypes (Dutkiewicz *et al*., 2017). *S. suis* infections mainly caused by serotype 2, but infections due to other serotypes such as serotype 1 and 5 had been reported. *S. suis* is a colonizing agent in the upper respiratory tract, gastrointestinal tract, and genital organs of various animals including pigs, ruminants, cats, dogs, deer and horses (Németh *et al*., 2019). *S. suis* is predominantly animal pathogenic, however it has zoonotic potential towards human (Németh *et al*., 2019). In both animal and human cases, clinical manifestations of *S. suis* infection include meningitis, septicaemia, arthritis, endocarditis, pneumonia, and occasionally, other infections. In human, more than 50% of patients suffer from vestibular dysfunction and/or hearing loss after recovery from meningitis caused by *S. suis* (Dutkiewicz *et al*., 2017). Furthermore, *S.suis* can cause high morbidity and mortality in both pigs and humans, not to mention the economic impact in swine industry brought by the disease (Lun *et al*., 2007; Segura *et al*., 2020).

In the past, number of reported human cases due to *S. suis* has increased significantly. Most of these cases related to their occupations which have close contact with pig or pig products, for example, veterinarians, pig farmers, pig breeders, abattoir workers, meat inspectors, and butchers (Gottschalk *et al*., 2007). Transmission of *S. suis* from pigs to humans can occur through close contact, cut or abrasions on skin, pig bite, consumption of raw or under-cooked pork, or even pig blood (Goyette-Desjardins *et al.*, 2014; Huong *et al.*, 2014; Segura *et al.*, 2016; Papatsiros *et al.*, 2011). The transmission of *S. suis* are different between Asian and European countries. In Asian countries, *S. suis* infections are mainly due to cultural and eating habits, whereas in European countries, *S. suis* is primarily an occupational disease (Németh *et al.*, 2019).

Nevertheless, there are existence of gaps in the existing studies. For instance, the association of different *S. suis* serotypes and their pathogenicity in human infections need to be studied in the future. Besides, route of transmission except close contact with pigs and ingestion of raw pork need to be further identified. Furthermore, although vaccination against *S. suis* in pigs is developed, the protective efficacy varies (Lun *et al.*, 2007). Commercial vaccine only protect the pigs against the most common serotype 2, but not other serotypes (Lun *et al.*, 2007; White, 2016); whereas the inactivated autogenous vaccine although provide better protection, but it requires empirical checking on each batch of animals, which is labor intensive (Lun *et al.*, 2007; Jiao *et al.*, 2017). Thus, future research is required to develop a polyvalent vaccine which is effective in protection of pigs against a wide range of serotypes. Moreover, vaccine against *S. suis* in humans is not available yet. Antimibrobial resistance in *S. suis* infection is also an important issue that need to be concerned, development of new antimicrobial in the coming time is helpful in treatment and control of this disease in pigs and humans.

1.1 Objective

The objective of this review was

1. To review and identify *S. suis* zoonotic potential from pigs to humans and its predisposing factors.

1.2 Hypothesis

The hypothesis proposed was

1. *Streptococcus suis* have zoonotic risk towards humans from pigs contact.

LITERATURE REVIEW

2.1 Aetiology

Streptococcus suis (*S. suis*) is a major porcine pathogen, causing economical health worldwide problems in the global swine industry. It is also an important emerging zoonotic pathogen which can cause severe invasive disease in humans exposed to pigs or pork products (Papatsiros *et al.*, 2011). *S. suis* is a facultatively anaerobic Gram-positive ovoid or coccal bacterium surrounded by a polysaccharide capsule. *S. suis* strains can be classified serologically into 35 serotypes according to its antigenic diversity of the capsule (Dutkiewicz *et al.*, 2017). *S. suis* has a wide host range, it is a colonizing agent in the upper respiratory tract, gastrointestinal tract, and genital organs of a wide variety of animals including pigs, ruminants, cats, dogs, deer and horses (Németh *et al.*, 2019).

2.2 Epidemiology

S. suis is distributed worldwide and is most adapted to domesticated pigs, but is also occasionally recovered from wild boars, horses, dogs, and cats (Staats *et al.*, 1997). Serotype 2 is the most common serotype that lead to infections in pigs and human beings, and is the most frequently reported serotype worldwide (Costa *et al.*, 2005; Higgins *et al.*, 1990; Wisselink *et al.*, 2000). Piglets and weaners are most susceptible to *S. suis* infections, however other age groups can also be affected. *S. suis* usually colonize in the upper respiratory tract, particularly the tonsils and nasal cavities (Gottschalk and Segura, 2000), and the genital and alimentary tracts of pigs (Higgins and Gottschalk, 1999). *S. suis* type 2 will colonize the palatine tonsils of clinically ill and apparently healthy pigs (Arends *et al.*, 1984), therefore asymptomatic pigs remain as a potential source of infection to the herds and humans. Some infected pigs that show no illness may show signs in the presence of predisposing factor such as poor housing with inadequate ventilation. The situation can be further aggravated if pigs are raised under stress conditions or in an immunosuppressed status (Staats *et al.*, 1997).

On top of that, *S. suis* carried zoonotic risk towards human. In human, *S. suis* infection is largely due to close contact with infected pigs, asymptomatic carrier pigs, and raw pork or contaminated products. The transmission of *S. suis* can be happen through wounds on skin or mucosa of the mouth and nasal cavity (Francois *et al.*, 1998). Thus, *S. suis* infections in human are usually occupational-related, for instance, pig farmers, abattoir workers, meat-processing workers, and veterinarians are having higher risk of getting infected by *S. suis* (Arends *et al.*, 1988; Tang *et al.*, 2001; Francois *et al.*, 1998; Wang *et al.*, 2000). Besides, individuals who are immunosuppressed, including those who are splenectomized, posing a higher risk of *S. suis* infections (Auer *et al.*, 2001). In addition, there had been case reported in which hunters become infected by *S. suis* due to contact with wild boars (Mazokopakis *et al.*, 2005). To date, no human-to-human transmission reported. Direct contact with sick pigs or other infected animals, as well as contaminated products, is necessary for *S. suis* infection (Zhao *et al.*, 2007).

S. suis infection in human in Asian and European countries results from different predisposing factors. In Asian countries, *S. suis* infections are mainly caused by their cultural and eating habits, such as consuming raw pork and pig blood; whereas in European countries, infected individuals are largely related to occupations that have close contact with pigs, for example, veterinarians, pig farmers, and abattoir workers. Nevertheless, imported cases may occur, due to the emerging tourism (Németh *et al.*, 2019).

2.3 Clinical Signs

The most important clinical manifestation in *S. suis* infected pigs is meningitis. Meanwhile, other pathological conditions such as endocarditis, septicaemia with sudden death, arthritis and pneumonia, abortions, and abscesses, have also been described (Gogolewski *et al.*, 1990; Higgins and Gottschalk, 1999; King *et al.*, 2001; Smith *et al.*, 2001). Clinical signs usually seen in weaners or growers, less frequently in suckling piglets (Touil *et al.*, 1988). Since *S. suis* is a primary commensal in pigs, pigs may carry the bacterium without showing signs. However, under situations like stress or immunosuppression, asymptomatic carriers may start to show signs. Morbidity, mortality and case fatality rates that associated with *S. suis* in pigs vary (John *et al.*, 1982).

Manifestations of *S. suis* infections in humans are mostly similar to those observed in swine, including meningitis, septicaemia, arthritis, pneumonia, endocarditis, toxic shock syndrome, vestibular dysfunction, and hearing loss (Avril *et al.*, 1977; Cheng *et al.*, 1987; Hickling *et al.*, 1976; Doube *et al.*, 1988).

Permanent deafness or severe hearing loss is a sequela to infections in 50 to 75% of human cases after recovery from purulent meningitis caused by *S. suis* (Dupas *et al*., 1992). The possibility of humans may also be healthy carriers cannot be excluded (Gottschalk *et al*., 2007; Smith *et al*., 2008; Wertheim *et al*., 2009), *S.suis* may become an opportunistic pathogen in the presence of certain circumstances such as stress, immunodeficiency or cancer (Gottschalk *et al*., 2007; Manzin *et al*., 2008).

2.4 Pathology

There are various of descriptions of the pathological and histopathological lesions in pigs infected with *S. suis* (Staats *et al*., 1997). Most commonly, gross lesions shown in an infected pigs include congestion of the meninges, lymph nodes, and lungs. Lesions such as encephalitis, oedema of leptomeninges and the dura mater, hyperaemia of meningeal blood vessels, and increased quantity of cerebrospinal fluid may be observed. In histopathology, findings mainly found within the choroidal plexus. Diffuse neutrophilic infiltrate is one of the most characteristic histopathological findings in *S. suis* infected pigs.

In human cases, pathological and histopathological lesions are examined during necropsy of patients who died from septic shock syndrome or meningitis syndrome. Based on Zhu and colleagues (2000), gross lesions reported in human *S. suis* cases include widespread haemorrhage, especially in stomach and adrenal glands, leptomeningeal congestion, oedema of cerebrum, hyperaemia of myocardium, disseminated intravascular coagulation, and lack of coagulation of whole blood, as well as septicaemia. Apart from that, degeneration or necrosis of hepatocytes and kidney cells was observed. Similar with infected pigs, increased cerebrospinal fluid has been reported in human meningitis cases (Rosenkranz *et al.*, 2003; Mazokopakis *et al.*, 2005). In short, the pathology observed in organs of human patients and sick pigs were almost similar.

2.5 Pathogenesis

Pathogenesis of *S. suis* infections in pigs and humans basically divided into four stages: adherence to and colonisation of mucosal and/or epithelial surface(s) of the host, invasion into deeper tissue and translocation in the bloodstream, breaching of the blood-brain barrier, and inflammation (Gottschalk *et al.* 2010; Fittipaldi *et al.*, 2012; Fulde & Valentin-Wiegand, 2013; Feng *et al.*, 2014).

The first stage is adherence to and colonisation of mucosal and/or epithelial surface(s) of the host. *S. suis* gains its route of entry through oronasal route, and reside in palatine and pharyngeal tonsils. In contrast, the main route of entry in human S. suis infections are mostly through small injuries causing a breach of the skin integrity, or by gastrointestinal route, through consumption of raw pig meat or blood (Gottschalk *et al.*,2010; Segura *et al.*, 2016).

The second stage is invasion into deeper tissue and translocation in the bloodstream. *S.suis* is able to disseminate in the blood circulation and maintain bacteraemia for certain time. This step is crucial in causing meningitis. There are few mechanisms that assist S. suis in this stage: (i) invasion of *S. suis* through the epithelial cell barriers, (ii) evasion of killing by complement and phagocytosis, and (iii) invasion into the cerebrospinal fluid (CSF) or other target sites (Fulde & Valentin-Wiegand, 2013).

Next, in order to cause central nervous system (CNS) infections, *S. suis* must cross the blood–brain barrier and/or the blood–cerebrospinal fluid (CSF)- barrier (Fittipaldi *et al.*, 2012). *S. suis* was not only to attach, but also to invade immortalized porcine brain microvascular endothelial cells (BMEC) (Vanier *et al.*, 2004). This increases the permeability of blood-brain barriers.

It has been shown that *S. suis* can induce the release of arachidonic acid by BMEC, a mechanism that may facilitate the ability of bacteria to penetrate the CNS and to modulate local inflammation (Jobin *et al.*, 2005). Besides, studies have shown that purified suilysin able to induce the release of several proinflammatory cytokines by human and porcine BMEC, and the upregulation of adhesion molecules on human monocytes, which lead to inflammation of the meninges (Vanier *et al.*, 2009; Vadeboncoeur *et al.*, 2003; Al-Numani *et al.*, 2003).

2.6 Classification of *S. suis* Strains

In 1998, Chatellier *et al.* reported a 16S rRNA sequencing analysis of 35 *S. suis* serotype reference strains, namely serotypes 1–34 and 1/2. However in their data, the reference strains of serotypes 20, 22, 26, and 32–34 were located distant from the other 29 reference strains on the 16S rRNA-based phylogenetic tree.

These reference strains exhibited 16S rRNA sequence similarity values with the other 29 reference strains of less than 97% (serotypes 32–34) or 96.76%–98.27% (serotypes 20, 22, and 26). According to the generally accepted or recommended taxonomic criteria of 16S rRNA sequence similarity, these six serotype reference strains are suggested to be distinct species from *S. suis*. Chatellier *et al.* then demonstrated that on the 16S rRNA-based phylogenetic tree, the serotype 33 reference strain was more related to *Streptococcus acidominimus*, whereas serotypes 32 and 34 have since been proven to be *Streptococcus orisratti* (Hill *et al.*, 2005). More recently, it was proposed to remove serotypes 20, 22, 26 and 33 from the *Streptococcus suis* taxon (Tien *et al.*, 2013; Okura *et al.*, 2013). Hence, it is currently considered that there are 29 "true" *S. suis* serotypes (Kerdsin *et al.*, 2014).

Serotype 2 is the most frequent reported serotype worldwide. Most of the *S. suis* infections in human and pigs are associated with serotype 2. Nevertheless, other serotypes such as serotype 1 and 14 had been reported in human cases (Kopic *et al.*, 2002; Watkins at al., 2001). On the other hand, *S. suis* isolates from diseased pigs were categorized under a limited number of serotypes, including serotypes 2, 3, 7, and 9, although infections by other serotypes had been described (Goyette-Desjardins *et al.*, 2014).

2.7 Diagnostic Methods

In cases of meningitis, cerebrospinal fluid (CSF) cultures are the most important. Field isolates of *S. suis* readily grow on media used for culturing meningitis-causing bacteria can help to identify the pathogen. Moreover, sheep blood agar plates can be used to identify *S. suis*. Most *S. suis* strains will produce narrow zone of α-haemolysis on the agar plate. Based on Staats *et al.* (1997), *S. suis* type 2 colonies produce α-haemolysis on sheep blood agar plates and β-haemolysis on horse blood agar plates.

The initial routine laboratory examination is essential for diagnosis of S. suis infection (Du *et al.*, 2000; Rosenkranz *et al.*, 2003; Mazokopakis *et al.*, 2005). An elevated white blood cell counts and high C-reactive protein concentrations may be observed (Rosenkranz *et al.*, 2003; Halaby *et al.*, 2000; Mazokopakis *et al.*, 2005). Under certain conditions where liver is damaged, increased alanine aminotransferase and aspartate aminotransferase can be detected (Mazokopakis *et al.*, 2005). When examining the CSF, turbidity and polymorphonuclear pleocytosis, associated with very low concentrations of protein and glucose are the common findings (Rosenkranz *et al.*, 2003; Halaby *et al.*, 2000; Mazokopakis *et al.*, 2005).

Gram staining of the CSF, blood or joint fluid, will show pairs or short chains of Gram-positive coccoid rods. Confirmation of the isolated bacterium is then done by biochemical and serological procedures, and sometimes by molecular techniques.

Next, presumptive identification also can be made based on four biochemical tests, namely Voges-Proskauer, salicin, trehalose, and 6·5% NaCl. These tests can be applied for almost all capsular types of *S. suis* (Higgins & Gottschalk, 1990). A combination of biochemical reactions, followed by confirmative serotyping may be required (Durand *et al.*, 2001; Zhu *et al.*, 2000).

Furthermore, PCR is one of the important and rapid diagnostic technique used to detect specific serotypes or strains of *S. suis* in sick animals, animal carriers, or even sick human beings. PCR based on the *S. suis*-specific 16S ribosomal RNA (rRNA) region and a species-specific probe (serotypes 1–31) targeting 16S rRNA gene can be used to identify *S. suis* strains (Rasmussen & Andresen, 1998; Boye *et al.*, 2000). Multiplex PCR was used to identify different *S. suis* strains (Okwumabua *et al.*, 2003). In addition, other diagnostic methods such as immunocapture method, fluorescent antibody techniques, whole-cell antigen-based indirect ELISA, and purified capsular polysaccharide antigen-based indirect ELISA have been developed to identify S. suis (Gottschalk *et al.*, 1999; Davies & Ossowicz, 1991; Paterson *et al.*, 1993; Robertson & Blackmore, 1989).

On top of that, molecular methods such as RFLP (Okwumabua *et al.*, 1995), genome fingerprinting (Mogollon *et al.*, 1990), pulsed-field gel eletrophoresis (Berthelot-Herault *et al.* 2002; Allgaier *et al.*, 2001; Vela *et al.*, 2003), and multilocus sequence typing (King *et al.*, 2002) have been used to study the genetic diversity of *S. suis* strains, the colonial relations between the strains, and pathogenicity of particular clones.

2.8 Treatment

Generally, in both pig and human infections, *S. suis* is susceptible to beta-lactam antibiotics, such as penicillin, ampicillin, amoxicillin, flucloxacillin, cephalosporin, and ceftriaxone (Staats *et al*., 1997; Lun *et al*., 2007; Gottschalk *et al*., 2010; Wertheim *et al*., 2009).

Papatsiros et al. (2011) reported that the sensitivity rate to amoxicillin and ampicillin in the treatment of pigs is circa 90%. Based on a study done by Pejsak *et al*. (2005), 393 *S. suis* strains isolated from pathologically-changed lungs of pigs with respiratory symptoms were tested for the sensitivity of antibiotics. From the result, over 98.5–99% of isolates were sensitive to ampicillin and amoxicillin, 96% to ceftiofur and 91.9% to penicillin, while only 47–56% were sensitive to tetracyclines. Another study was done by Szczotka *et al*. (2007), similarly, out of 242 pig isolates, 99.5–100% proved sensitive to penicillin, ampicillin and ceftiofur, 98% to florphenicol and 95% each to gentamicin and a combination of sulphamethoxazole and trimethoprim, while only 40–50% were sensitive to tetracyclines and erythromycin.

Next, according to Gottschalk *et al*. (2007), among the examined piglets, 6-28% are carrying the penicillin-resistant strains. Additionally, *S. suis* strains are usually resistant to tetracyclines, aminoglycosides, erythromycin, chloramphenicol and clindamycin (Wertheim *et al*., 2009; Papatsiros *et al*., 2011) .

Infected pigs should be treated for 3 to 5 days. Prophylactic injection of piglets with long-acting penicillin at birth is recommended as a preventive measure (Papatsiros *et al.*, 2011). Staats *et al.* (1997) suggested that the use of penicillin or tiamulin in drinking water or feed has been beneficial in reducing the incidence of *S. suis* type 2 infection in pigs.

2.9 Control and Prevention

Vaccine is used as one of the preventive and control measure. Both commercial vaccines and inactivated autogenous vaccine generated each time from virulent strains isolated from sick pigs are used (Lun *et al.*, 2007). Commercial vaccine is convenient but only protect the pigs against the most important capsular type 2 of S. suis (Lun *et al.*, 2007; White, 2016). On the contrary, autogenous vaccine requires empirical checking on each new batch of animals, which is labour intensive and time consuming, however they provide better protection and prevent the spread of the disease in herds during outbreaks of *S. suis* infection (Lun *et al.*, 2007; Jiao *et al.*, 2017).

As mentioned above, prophylactic antibiotic injection of piglets at birth using long-acting penicillin is also adopted by farmers. Another way to prevent S. suis infection outbreak is by improving the pig-raising conditions, reduce stress, and prevent immunosuppression. This can be done by avoiding overcrowding, maintaining proper ventilation, and controlling other pig diseases. Next, disinfect the pens between each housing groups by using disinfectants, soaps and cleansers, such as 5% bleach at 1:800 dilution is beneficial (Staats *et al.*, 1997; Gottschalk *et al.*, 2007; Breton *et al.*, 1986). All-in-all-out husbandry methods are useful to reduce the spread of infection. Furthermore, isolation of sick animals is indeed needed to prevent further spread of the disease. The last choice to control the disease is by culling, followed by disinfection, and repopulation, however this method is economically feasible (Staats *et al.*, 1997).

In human aspects, prevention of *S. suis* infection can be done by protection of skin from pig bite or injury with sharp tools. This needs to be achieved by individuals that work closely with pigs or pig products. By wearing gloves and boots, chance of getting infected by *S. suis* is greatly reduced. After work with pigs or pig products, hands should be thoroughly washed (Dutkiewicz *et al.*, 2017). Besides, appropriate masks or respirators are used to protect respiratory tract, these apparel are crucial especially in the case of *S. suis* epizootics (Bonifait *et al.*, 2014).

Any febrile illness after exposure to pigs or pork meat must be referred to a doctor immediately (Papatsiros *et al.*, 2011). Wound that created during working with pigs also need to be treated promptly.

Immunocompromised people especially those underwent splenectomy or on immunosuppresive treatment, or those with comorbidities, should avoid occupations associated with exposure to pigs or pig products (Gottschalk *et al.*, 2010). Moreover, pork should be cooked adequately before served. Avoid consuming raw pork or pig blood, especially applies in southeast Asia, where such dishes are traditionally prepared.

According to Segura *et al.* (2014), health education, especially to those exposed to pigs or pig products, is the cheapest and most effective way to prevent *S. suis* infection. Vaccine for human *S. suis* infection is still unavailable. Hence, continuation of research is required to fill this gap.

METHODOLOGY

Published articles describing zoonotic potential of *Streptococcus suis* (*S. suis*) were identified from the following search databases: Scopus, PubMed, and Science Direct. The searches were limited from 1981 to September 2021 (40 years time frame).

Search terms were used to generate a search string. The following search terms were involved: *Streptococcus suis*, zoonotic, zoonosis, zoonoses, emerging, public health, risk, factor, occupation, contact, exposure, pig, swine, porcine, pork, and animal. Search string were generated as below:

Search Database	Search Criteria / Limitations	Search String	Search Results
Scopus	Title/Abstract	((("streptococcus suis" OR "S. suis" OR "Strep suis") AND (zoono* OR emerging OR "public health" OR risk OR factor)) AND (occupation* OR contact OR exposure)) AND (pig OR pigs OR swine OR porcine OR pork OR animal*)	135
PubMed	Title/Abstract		88
Science Direct	All fields	"streptococcus suis" AND ("streptococcus suis meningitis" OR "streptococcus suis infection")	41

Table 1. Search string used in different search databases

Next, search results were identified through the databases used. The process of study selection was described in the PRISMA flow chart as shown in **Figure 1**. Duplicates within and between databases were removed. Then, the titles and abstracts were screened. Articles with no abstract, does not involved the species studied, and irrelevant to the topic were excluded. After screening, the articles left are sought for retrieval. Only articles written in English were included. Reviews, articles with no full text available, and articles in languages other than English, were excluded. Next, the articles retrieved were assessed for eligibility. Articles or journals related to zoonotic potential of *S. suis*, cases caused by *S. suis* in humans, and the predisposing factors of *S. suis* infections in humans were included.

All articles meeting the inclusion criteria were read, and the related information and data were extracted in Excel forms: Year of study, country, study design, species involved, serotypes, clinical manifestations, sample collected, diagnostic methods, occupation of the patients, predisposing factors, and outcome of the disease. Lastly, the information and data were analyzed for the writing of systematic review.

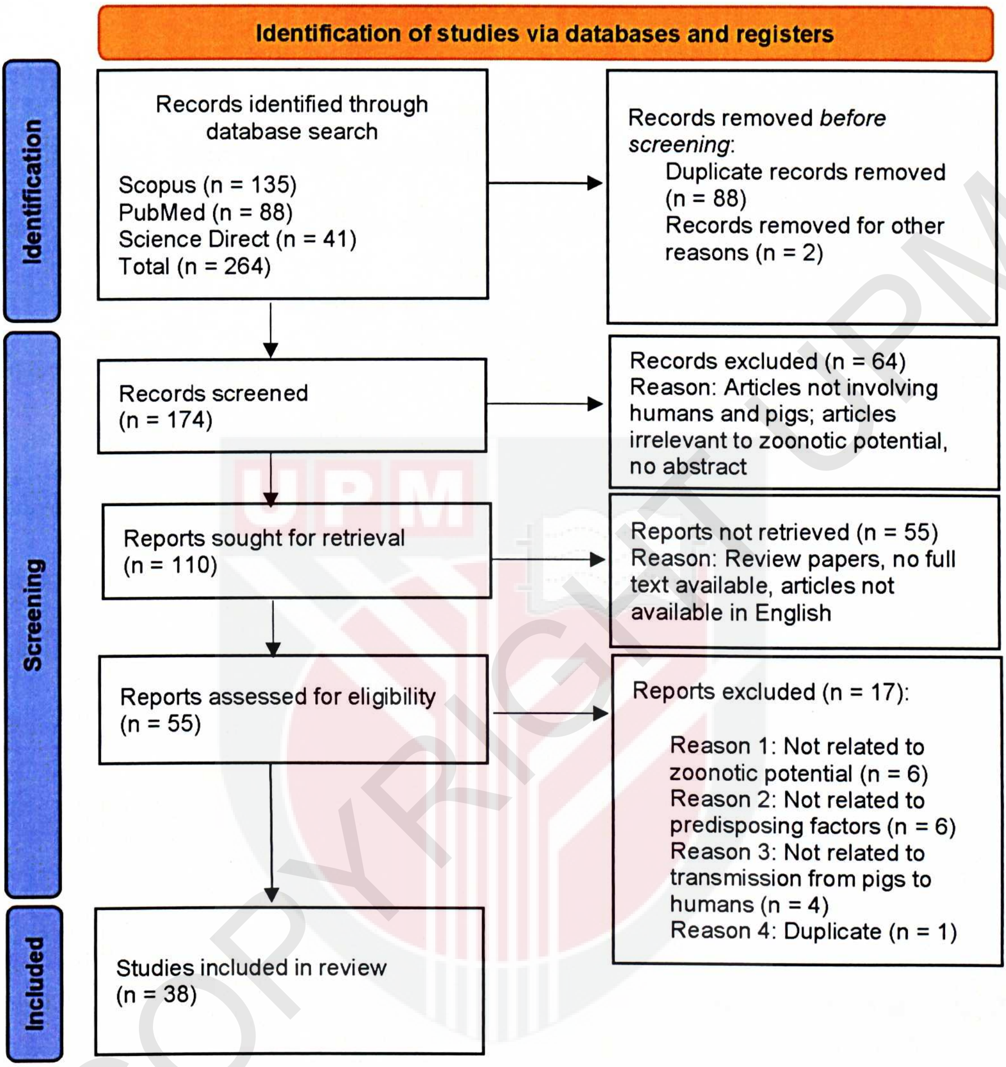


Figure 1. PRISMA flow chart of study selection process

RESULTS

4.1 Study Selection

In total, 264 articles were identified through three search databases. After removing the duplicates, there were 174 articles remained. 64 articles were further excluded by screening through the title and abstract, whereas the remained 110 articles were sought for retrieval. 55 articles were not retrieved, including the articles with no full text available, articles in foreign languages, and review papers. Next, the remaining 55 articles were assessed for eligibility. 17 articles were further excluded due to out of scope, do not including predispose risk, and duplicate articles. Lastly, 38 articles were included in systematic review after full text evaluation. The process of study selection was described in **Figure 1**.

4.2 Study Characteristics

The 38 articles included 28 case reports or case series, 6 retrospective studies, 2 prospective studies, and 2 surveillance studies. A total of 718 cases were described in the 38 articles. The 718 cases were from 24 countries, including China, Thailand, Vietnam, Hong Kong, the Netherlands, Togo, Denmark, Japan, Taiwan, United Kingdom, France, Malaysia, Croatia, Germany, Hungary, Brazil, Korea, Belgium, Poland, Portugis, Sweden, Switzerland, United States, and Canada.

In the 24 countries included, China has the highest number of cumulative cases, 219 cases, followed by Thailand and Vietnam, which reported 190 and

151 cases, respectively. Next, 55 cases were reported in Hong Kong, 34 cases in the Netherlands, and 16 cases in Togo. The rest of the countries reported a number of less than 10 cases in each of the countries. The distribution of human *S. suis* cases was shown in **Figure 2**.

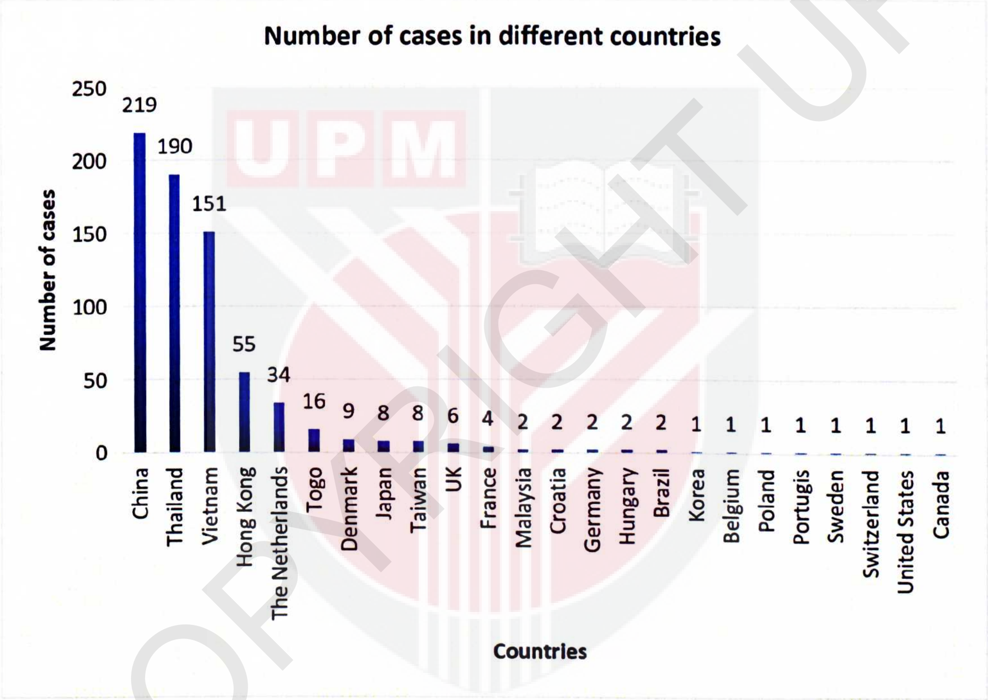


Figure 2. Number of human *S. suis* cases in different countries

Among 718 cases, a mean age of 51 years old (ranged from 19 to 89 years old) was reported in 700 cases. In the other 18 cases, neither age nor mean age were reported. 561 (78.13%) among 718 patients were male, whereas 157 (21.87%) patients were female.

4.3 Predispose Risks

The predispose risks of *S. suis* infection in these patients consisted of exposure to pigs or pork in 473 patients (65.88%), pig-related occupations in 346 patients (48.19%), skin injuries in 130 patients (18.11%), alcoholism in 56 patients (7.80%), and underlying health conditions in 69 patients (9.61%). Exposure to pigs or pork including pig rearing in 282 patients (39.28%), pig butchering in 201 patients (27.99%), handling or processing pork in 117 patients (16.30%), raw pork consumption in 81 patients (11.28%), contact with sick pigs in 18 patients (2.51%), and selling pigs or pig products in 4 patients (0.56%). Some patients were concurrently associated with more than one predispose risks. The number and percentage of cases associated with each predispose risk factor were described in **Figure 3 and 4**.

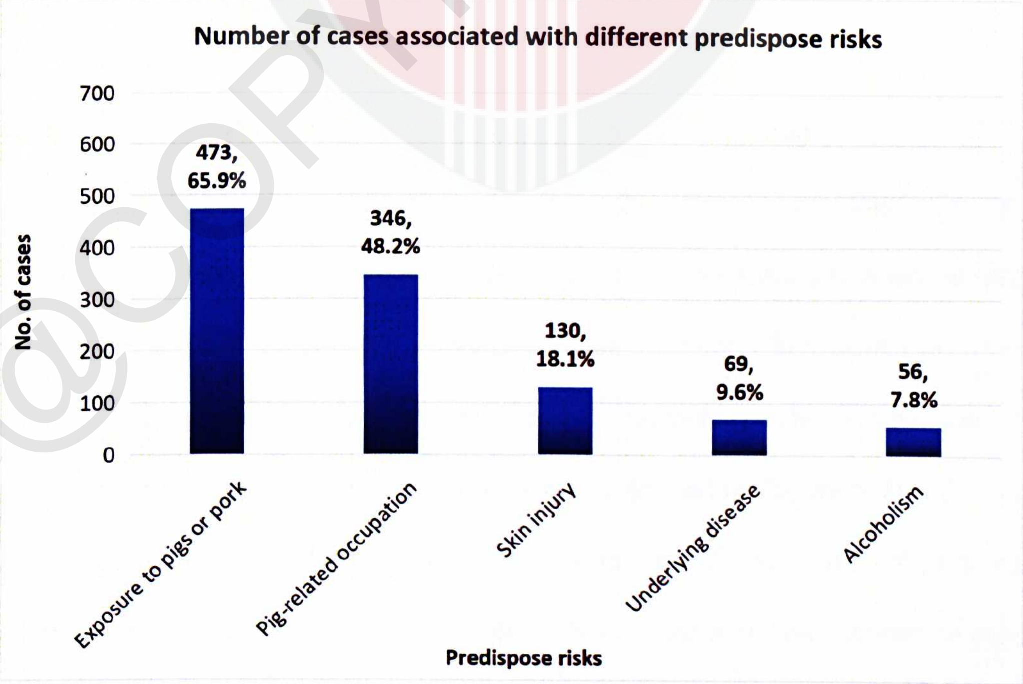


Figure 3. Number and percentage of cases associated with different predispose risks

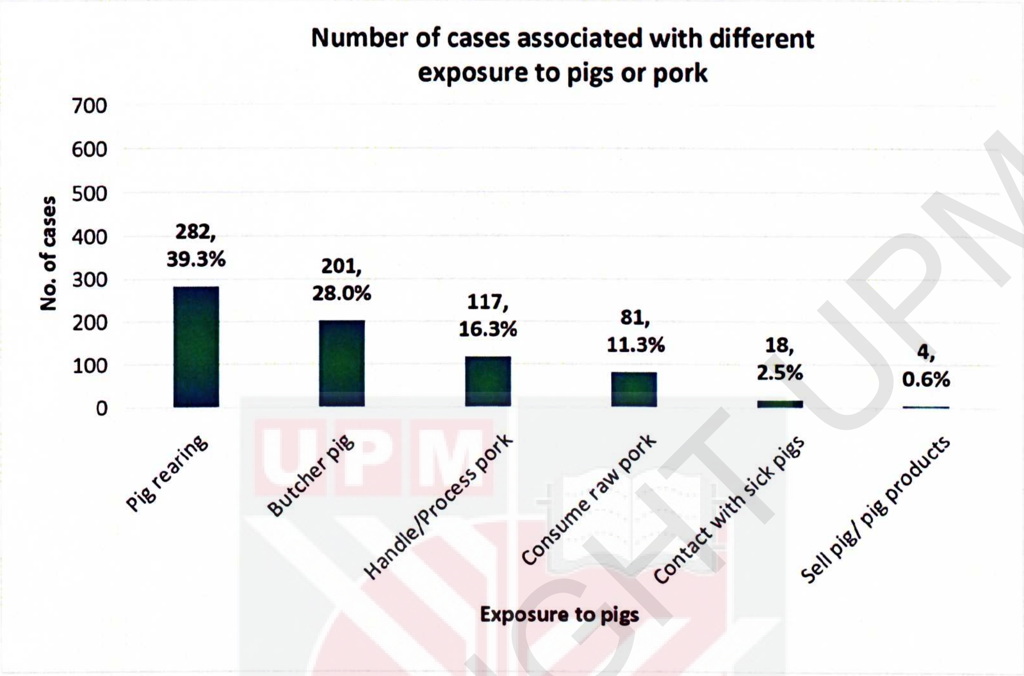


Figure 4. Number and percentage of cases associated with different exposure to pigs or pork

4.4 Comparison of Predispose Risks between Asia and Europe

There were some differences in predispose risks affecting patients in Asian countries and European countries. In Asian countries, the highest predispose risk that causes *S. suis* infection in humans was pig rearing; whereas in European countries, the highest predispose risk was pig butchering. The comparison of predispose risks between Asia and Europe was described in **Figure 5**. Besides, in European countries, 79.69% of cases were associated with pig-related occupations, while only 44.32% of cases in Asian countries were related to pig-related occupations. The comparison of cases associated with pig-related occupations in Asia and Europe was described in **Figure 6**.

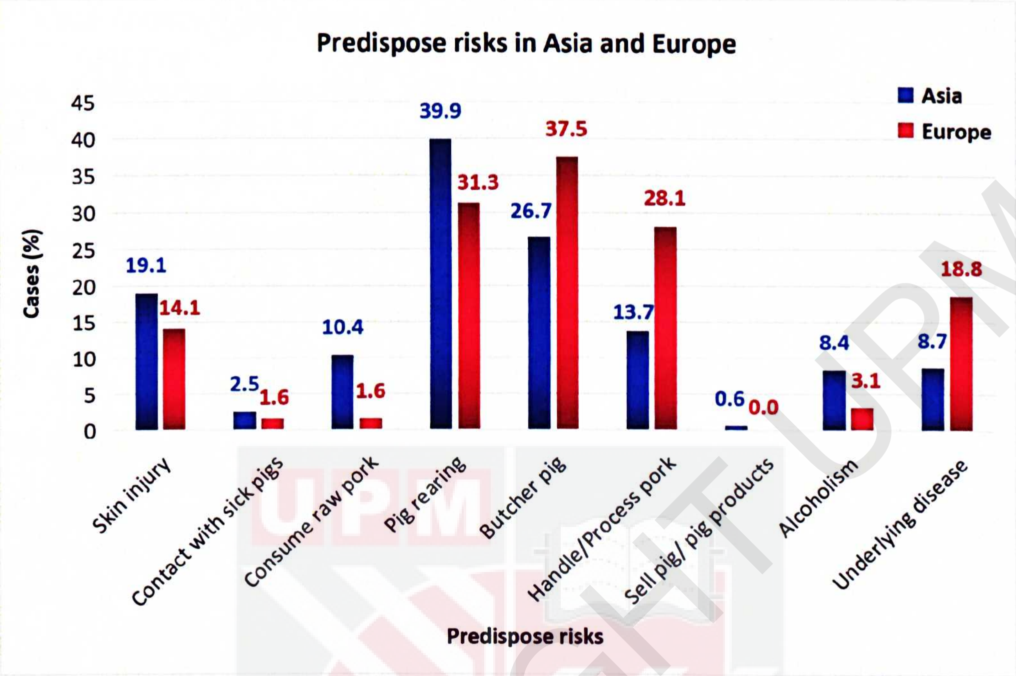


Figure 5. The comparison of predispose risks between Asia and Europe

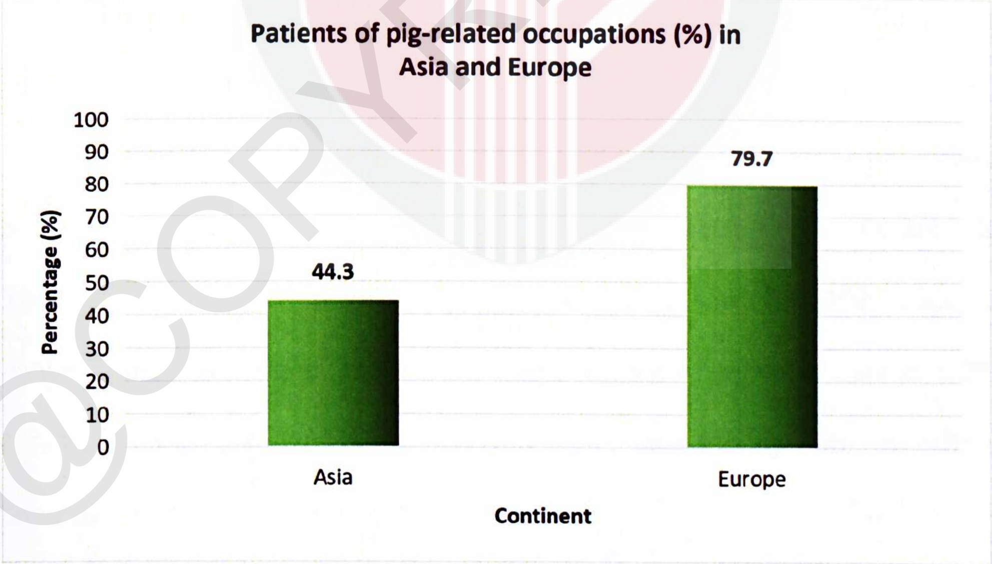


Figure 6. The comparison of cases associated with pig-related occupations in Asia and Europe

Asian countries had relatively higher percentage of cases that related to raw pork consumption, alcoholism, and underlying health conditions. Most of these cases were reported in Thailand. When compared to other countries, Thailand had relatively high number of patients who had history of raw pork consumption (n=66), alcoholism(n=48), and underlying health conditions(n=39).

4.5 Mortality

The case-fatality rate of *S. suis* infection in humans was 11.42% (81 of 709 patients). Another 9 patients were not reported about the outcome of the disease. Out of the 81 deaths, 40 cases were from China, 27 cases from Thailand, and 4 cases from Vietnam. Hong Kong and the Netherlands each reported 2 deaths, whereas Japan, Croatia, Denmark, Hungary, Togo, and United States each reported 1 death. The other countries did not report any mortality. The number of mortality was described in **Figure** 7. Besides, the case-fatality rate were different between countries. China reported the highest case-fatality rate, 18.26%, and Thailand reported the second highest case-fatality rate, 14.21%. Togo, the Netherlands, Hong Kong, and Vietnam reported the case-fatality rate as 6.25%, 5.88%, 3.63%, and 2.65%, respectively. The case-fatality rate in different countries was shown in **Figure 8**.

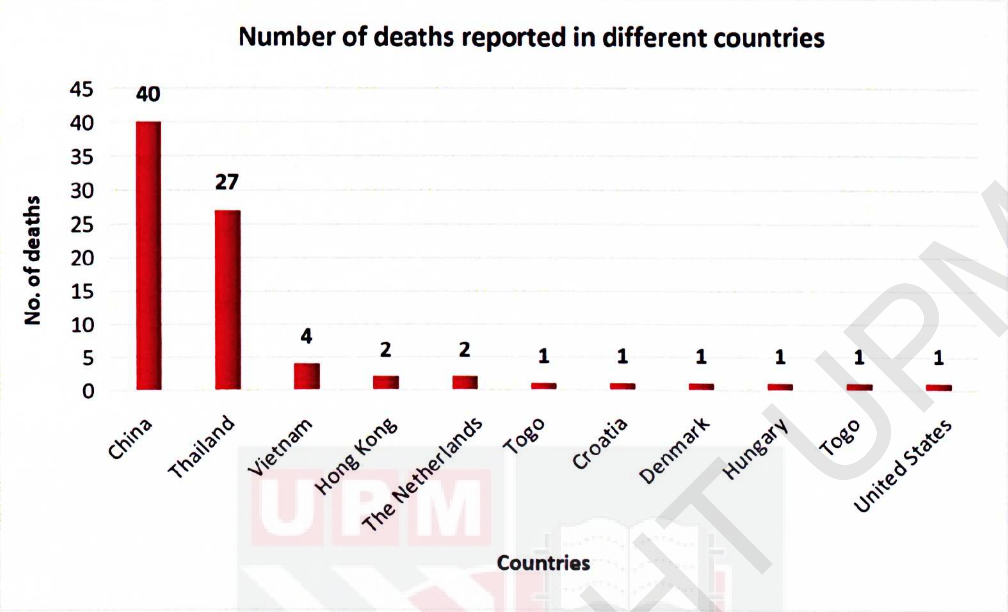


Figure 7. The number of death caused by human *S. suis* infection in different countries

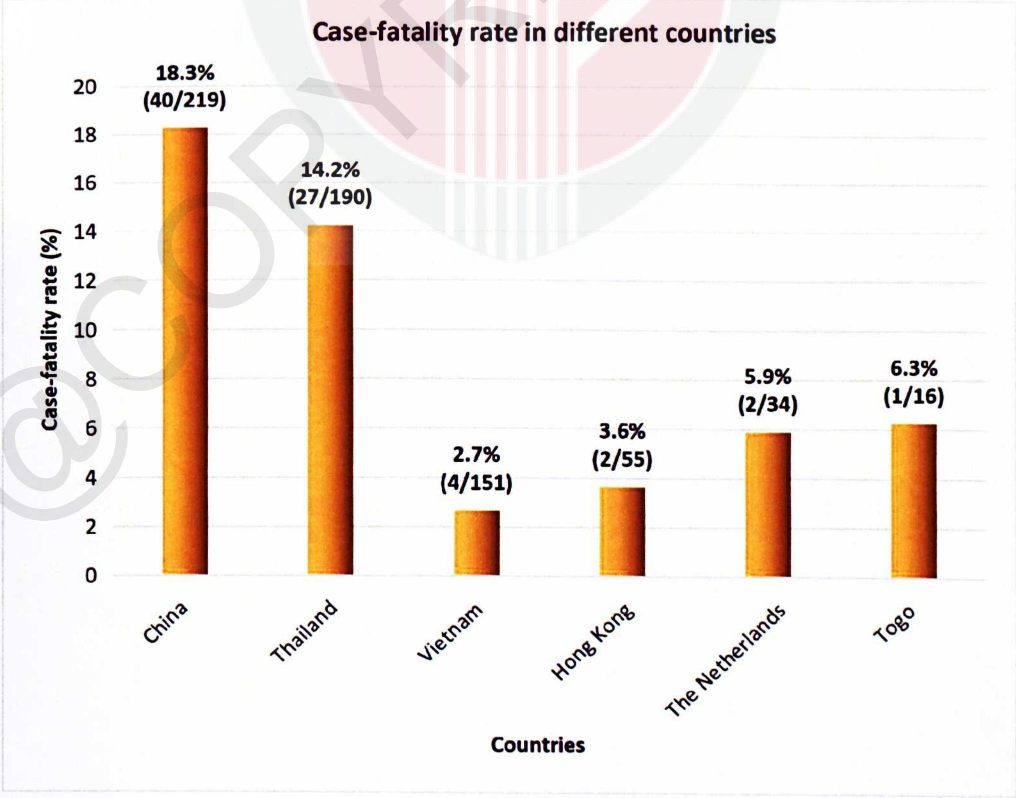


Figure 8. Case-fatality rate of human *S. suis* infection in different countries

4.6 Human *S. suis* Infection transmitted from Wild Boars

Besides domestic pigs, four cases described were related with transmission of *S. suis* from wild boars to humans. Hungary and the Netherlands each reported 1 case, and France reported 2 cases. All patients were exposed to wild boar or wild boar meat, 3 of the patients had history of butchering wild boar, 2 out of these 3 patients had skin injuries on their hands; the remaining 1 patient had history of handling and processing wild boar meat. No mortality was reported among these 4 patients.

DISCUSSION

5.1 Epidemiology of Human *S. suis* Infection

24 countries were included in this systematic review, with China recorded the highest number of human *S. suis* infection cases, 219 cases. The second and third highest number of cases were from Thailand and Vietnam, with 190 and 151 cases, respectively. Two outbreaks of human *S. suis* infection in China previously which cause high number of cases (Huang *et al.*, 2005; Yu *et al.*, 2006; Lun *et al.*, 2007; Feng *et al.*, 2009) . Human *S. suis* infection were reported in Thailand and Vietnam endemically (Teekakirikul & Wiwanitkit, 2003; Mai *et al.*, 2008). Other countries such as Hong Kong, the Netherlands, and Togo, reported 55, 34, and 16 cases, respectively. The remaining 18 countries each reported less than 10 cases. These indicated that *S. suis* infection in humans can occur sporadically with predominately around Asia territory. All of the cases above showed that *S. suis* has zoonotic potential towards human, and it can exist endemically, epidemically, or sporadically.

5.2 Predispose Risks associated with Human *S. suis* Infection

Human *S. suis* infection could be related to different predispose risks, or different combination of predispose risks. The predispose risk that associated with most of the cases in this systematic review was exposure to pigs or pork, followed by pig-related occupations, skin injuries, underlying health conditions, and alcoholism, accordingly. The first two predispose risks were supported by different literature evidence, which indicated that individuals exposed to pigs or pork, especially in occupational setting, have higher risk to get infected with *S.*

suis. Farmers, slaughterhouse workers, butchers, and meat sellers are the risk groups that predisposed to *S. suis* infection (Dupas *et al.*, 1992; Staats *et al.*, 1997; Charland *et al.*, 2000; Lalonde *et al.*, 2000). A case-control study in Vietnam on 101 patients with *S. suis* infection also reported that pig-related occupations have an odd ratio of 6.33 (Nghia *et al.*, 2011). However, in our systematic review, Thailand and Vietnam did not show evidence that their cases were highly related to pigs or pork exposure. Less than half of the cases in these two countries were associated to pigs or pork exposure. This could be explained by the reason that the cases from Thailand were from retrospective studies, which have high chance of recall bias from the patients. Besides, Thailand and Vietnam have the traditions of eating raw pork, some of the patients might unaware of their exposure to pork due to the commonness of pork consumption in these regions (Dinh *et al.*, 2005). Furthermore, indirect exposure infections cannot be excluded out in human *S. suis* cases. Therefore, systemic investigation need to be conducted to identify the route of infection thus enhance prevention method..

Besides, skin injury also would lead to *S. suis* infection in humans. In a multivariate analysis, *S. suis* infection was independently associated with exposures to pigs or pork in the presence of skin injuries in the 2 weeks prior to infection (Nghia *et al.*, 2011). However, in the same multivariate analysis, alcoholism and underlying disease were not associated with *S. suis* infection. In contrast, based on two case series reported by Fongcom *et al.* (2009) and Wangkaew *et al.* (2006), there were around 50.00% and 83.00% of *S. suis* patients had underlying diseases or alcohol-drinking habits, which lead them to immunocompromised conditions. Underlying diseases or alcoholism may not be independent predispose risk, however it can increase the risk of infection and may cause more unfavourable outcome.

Exposure to pigs or pork was further subdivided into different groups, most of the cases were related to pig rearing, followed by butchering pigs, handling or processing pork, consuming raw pork, contact with sick pigs, and selling pigs or pig products. According to a case-control study conducted in Sichuan, China slaughtering pigs carried an odd ratio of 11.9 (95% CI, 3.4–42.8), and cutting carcasses and processing sick or dead pigs had an odd ratio of 3.0 (95% CI, 1.0–8.8) (Yu *et al.*, in 2005). Some farmers reared pigs in their house area, and slaughtered them at home (Sriskandan *et al.*, 2006). Hence, exposure to pigs could be occurred in occupational or household setting. Moreover, Hong Kong and Vietnam reported a significant number of housewives who presumably infected by *S. suis* as a result of contact with contaminated pork (Kay *et al.*, 1995; Mai *et al.*, 2008; Ip *et al.*, 2007). Humans can get *S. suis* infection due to different predispose risks. Some patients may get infected by only exposed to one predispose risk; whereas some patients may associated with several predispose risks at a same time, for example, butchering pigs or processing pork in the presence of skin injury. Nevertheless, there were cases that patients denied history of contact with swine or other predispose risks. Therefore, more research are required to discover other source of infection or predispose risks in human *S. suis* infection.

5.3 Differences of Predispose Risks between Asia and Europe

Almost all cases in Western countries were caused by occupational contact with pigs or pork products, whereas a considerable number of Asian cases were due to consumption of raw pork or pig blood (Dutkiewicz *et al.*, 2017). In our systematic review, 79.69% of patients in European countries, and all patients from United States and Canada that included in this review, were having history of working with pigs. This concur with findings by Dutkiewicz *et al.* in 2017. However, in this systematic review, most of the patients from Asian countries were associated with pig rearing (39.91%), followed by butchering pigs (26.66%), and skin injuries(19.09%); whereas consumption of raw pork only contributed to 10.41% of Asian cases, which contradict the statement of "Asian cases were due to consumption of raw pork or pig blood". This could be due to the recall bias in retrospective studies conducted in Thailand, or the unawareness of exposure to pigs or pork in these regions, such as Vietnam, that have more than 98% household consuming pork (Dinh *et al.*, 2005).

Interestingly, when compared to European countries (n=1), Asian countries, especially Thailand, had a significant higher number of cases (n=66) associated with raw pork consumption. This could be explained by the habitual consumption of raw and under-cooked pork, blood and offal products in traditional dishes in Thailand. In Thailand, there are traditional dishes called "Loo" (raw pork meat and blood), "Laab" (raw pork meat), and fermented raw pork (Takeuchi *et al.*, 2012), which may serve as a cause of infection.

Furthermore, in Thailand, there was also a marked higher number of cases related to alcoholism (n=48) and underlying diseases (n=39). The explanation include people in Thailand loves to serve raw pork with alcohol, and alcoholism may lead to alcoholic liver disease and other underlying diseases. Although alcoholism and underlying diseases were not identified as independent predispose risks, it can increase the risk of infection.

In comparison with European countries, this systematic review only included 2 cases from North America, each from United States and Canada. This is a surprisingly low number of cases, especially for United States, which is the second largest pig producer country in the world (Wint & Robinson, 2007). Other European countries which also practice high industrialization of pig farming systems as United States, had far more cases. Therefore, other reasons of low cases of human *S. suis* infection in North America should be considered, such as the *S. suis* strains that have lower virulence, hygiene measure and food culture in North America (Gottschalk *et al.*, 2007).

5.4 Mortality varies between Countries

Among 718 *S. suis* cases included in this systematic review, mortality were recorded in 709 patients. There were 81 deaths occurred in these 709 *S. suis*-infected patients, resulted in a case-fatality rate of 11.42%. Based on a systematic review and meta-analysis conducted by Huong *et al.* in 2014, the pooled case-fatality rate for *S. suis*–infected patients was 12.8% (95% CI 9.0%–18.0%), which was similar to the case-fatality rate in this systematic review. Nevertheless, case-fatality rate varies in different countries. From our findings, China reported 18.26% case-fatality rate, which is the highest among other countries. The second highest case-fatality rate in this systematic review was 14.21% in Thailand. As an evidence, Takeuchi *et al.* (2012) also stated that Thailand had high case-fatality rate of 16.10%. Some countries had low case-fatality rate or no mortality reported,. Difference in country health care, public awareness and food culture might play a significant role.

5.5 Wild Boars as Source of Human *S. suis* Infection

Apart from transmission through domestic pigs, humans can get *S. suis* infection from wild boars as well. In this systematic review, 4 cases of human *S. suis* infection from wild boars were detected. Wild boars can be the source of infection in occupations such as foresters, hunters and poachers (Rosenkranz et al., 2003). Hunters contact with their game meat such as wild boars would be another occupation hazard group for *S. Suis* exposure (Staats *et al.*, 1997; Goyette *et al.*, 2014; Samkar *et al.*, 2015; Gottschalk *et al.*, 2010). In fact, all these 4 patients in this systematic review were exposed to wild boars, either by poaching, or handling the wild boar game meat with presence of skin injury. This emphasized the zoonotic potential of *S. suis* infection from wild boars and their roles as second reservoir or carrier of *S. suis* (Rosenkranz *et al.*,2003). Hence, potential zoonotic risk of *S. suis* infection from the exposure to wild boars shall not be neglected, and precautions should be taken in those high risk groups who working or contacting with wild boars.

CONCLUSIONS

In this systematic review, it was concluded that *S. suis* has zoonotic risk from pigs towards humans. Humans infected by *S. suis* will show signs such as high fever, neck stiffness, and sometimes changes in mental status.

It was found that several predispose risks can increase the risk of human *S. suis* infection, which included exposure to pigs or pork, pig-related occupations, skin injuries, alcoholism, and underlying health conditions. Furthermore, exposure to pigs or pork was subdivided into different groups, such as pig rearing, pig butchering, handling or processing pork, raw pork consumption, contact with sick pigs, and selling pigs or pig products. Among these predispose risks, exposure to pigs or pork associated with the highest number of cases, whereas pig-related occupations and skin injuries were the second and third highest predispose risks.

By knowing the predispose risks of *S. suis* infection in humans, people able to prevent and control this disease more efficiently. Public awareness and education are the simplest and cheapest way to prevent the disease. For instance, workers should be thought about the importance of wearing proper protective gears when working with pigs; people should avoid consumption of raw or under-cooked pork; one must seek for medical treatment as early as possible if injury happened during handling pigs or pork.

Besides the known predispose risks, *S. suis* was believed to infect humans by other route, such as indirect exposure. However, the evidence on this statement is limited. Therefore, future studies are recommended to involve more detailed patient history so that other possible predispose risks can be identified. Lastly, vaccine against *S. suis* infection in humans is still absent, hence development of vaccine is one of the important field to be paid attention to.

REFERENCES

Allgaier A, Goethe R, Wisselink HJ, Smith HE, Valentin-Weigand P. Relatedness of *Streptococcus suis* isolates of various serotypes and clinical backgrounds as evaluated by macrorestriction analysis and expression of potential virulence traits. *J Clin Microbiol* 2001; 39: 445–53.

Al-Numani D, Segura M, Dore M, Gottschalk M. Up-regulation of ICAM-1, CD11a/CD18 and CD11c/CD18 on human THP-1 monocytes stimulated by *Streptococcus suis* serotype 2. *Clin. Exp. Immunol.* 133(1), 67–77 (2003).

Arends JP, Hartwig N, Rudolphy M, Zanen HC. Carrier rate of *Streptococcus suis* capsular type 2 in palatine tonsils of slaughtered pigs. *J Clin Microbio*l 1984; 20: 945–47

Arends JP, Zanen HC. Meningitis caused by *Streptococcus suis* in humans. Rev Infect Dis 1988; 10:131–7.

Auer J, Berent R, Porodko M, Eber B. Streptococcus infection and splenectomy. *Lancet* 2001; 357: 1130.

Auger JP, Gottschalk M. The *Streptococcus suis* factor H-binding protein: A key to unlocking the blood-brain barrier and access the central nervous system? *Virulence.* 2017; 8 (7): 1081–1084, doi: 10.1080/21505594.2017.1342027

Avril MF, Ghanassia JP, Leger JM, Bure A, Modai J. Les meningites a streptocoque du groupe R. A propos de deux observations. Medecine et Maladies Infectieuses 1977; 12:53 1-534.

Berthelot-Herault F, Marois C, Gottschalk M, Kobisch M. Genetic diversity of *Streptococcus suis* strains isolated from pigs and humans as revealed by pulsed-fi eld gel electrophoresis. *J Clin Microbiol* 2002; 40: 615–19.

Bonifait L, Veillette M, Létourneau V, Grenier D, Duchaine C. Detection of *Streptococcus suis* in bioaerosols of swine confinement buildings. *Appl Environ Microbiol.* 2014; 80(11): 3296–3304.

Boye M, Feenstra AA, Tegtmeier C, Andresen LO, Rasmussen SR, Bille-Hansen V. Detection of *Streptococcus suis* by in situ hybridization, indirect immunofl uorescence, and peroxidase-antiperoxidase assays in formalin-fi xed, paraffi n-embedded tissue sections from pigs. *J Vet Diagn Invest* 2000; 12: 224–32.

Breton J, Mitchell WR, Rosendal S. *Streptococcus suis* in slaughter pigs and abattoir workers. *Can J Vet Res.* 1986; 50(3): 338–341.

Charland N, Nizet V, Rubens CE, Sik Kim K, et al. *Streptococcus suis* serotype 2 interactions with human brain microvascular endothelial cells. Infect Immun 2000; 68:637–643.

Chatellier S., Harel J., Zhang Y., Gottschalk M., Higgins R., Devriese L.A., Brousseau R. Phylogenetic diversity of *Streptococcus suis* strains of various serotypes as revealed by 16S rRNA gene sequence comparison. *Int. J. Syst. Bacteriol.* 1998;48:581–589. doi: 10.1099/00207713-48-2-581.

Cheng AF, Khin-Thi-Oo, Li EK, French GL. Septic arthritis caused by *Streptococciis suis* serotype 2. Journal of Infection 1987; 14:237-241.

Costa AT, Lobato FC, Abreu VL, Assis RA, Reis R, Uzal FA. Serotyping and evaluation of the virulence in mice of *Streptococcus suis* strains isolated from diseased pigs. *Rev Inst Med Trop Sao Paulo* 2005; 47: 113–15.

Davies PR, Ossowicz CJ. Evaluation of methods used for detecting *Streptococcus suis* type 2 in tonsils, and investigation of the carrier state in pigs. *Res Vet Sci* 1991; 50: 190–94.

del Campo Sepulveda EM, Altman E, Kobisch M, D'Allaire S, Gottschalk M. Detection of antibodies against *Streptococcus suis* capsular type 2 using a purifi ed capsular polysaccharide antigenbased indirect ELISA. *Vet Microbiol* 1996; 52: 113–25.

Dinh XT, Nguyen TT, Tran C. Current status and prospects for the pig sector in Vietnam: a desk study. Research Report from Pro-Poor Livestock Policy Initiative. Hanoi, Vietnam: Pro-Poor Livestock Policy Initiative, 2005. Available at: http://www.fao.org/ag/againfo/programmes/en/pplpi/docarc/rep-psd_pigmarkets_desk.pdf. Accessed 8 July 2007.

Doube A, Calin A. Bacterial endocarditis presenting as acute monoarthritis. Annals of the Rheumatic Diseases 1988;47:598-599.

Du YP, Qian WJ, Xu GB. Investigation on 8 human cases with meningitis caused by *Streptococcus suis* type 2. *Chin J Prev Med* 2000; 34: 305 (in Chinese).

Dupas D, Vignon M, Geraut C. *Streptococcus suis* meningitis a severe noncompensated occupational disease. American College of Occupational and Environmental Medicine 1992;34: 1102-1 105

Durand F, Perino CL, Recule C, et al. Bacteriological diagnosis of *Streptococcus suis* meningitis. *Eur J Clin Microbiol Infect Dis* 2001; 20: 519–21

Feng Y, Zhang H, Wu Z, Wang S, Cao M, Hu D, Wang C. *Streptococcus suis* infection: an emerging/reemerging challenge of bacterial infectious diseases? *Virulence*. 2014; 5(4): 477–497.

Fittipaldi N, Segura M, Grenier D, Gottschalk M. Virulence factors involved in the pathogenesis of the infection caused by the swine pathogen and zoonotic agent *Streptococcus suis*. *Future Microbiol.* 2012; 7(2): 259–79

Fongcom, A., Pruksakorn, S., Netsirisawan, P., Pongprasert, R. & Onsibud, P. *Streptococcus suis* infection: a prospective study in northern Tailand. *The Southeast Asian journal of tropical medicine and public health* 40, 511–517 (2009).

Francois B, Gissot V, Ploy MC, Vignon P. Recurrent septic shock due to *Streptococcus suis*. *J Clin Microbiol* 1998; 36: 2395.

Fulde M, Valentin-Weigand P. Epidemiology and pathogenicity of zoonotic streptococci. *Curr Top Microbiol Immunol.* 2013; 368: 49–81.

Gallagher F. Streptococcus infection and splenectomy. *Lancet* 2001; 357: 1129–30.

Gottschalk M, Higgins R, Jacques M, Mittal KR, Henrichsen J. Description of 14 new capsular types of *Streptococcus suis*. *J Clin Microbiol* 1989; 27: 2633–36.

Gottschalk M, Xu J, Calzas C, Segura M. *Streptococcus suis*: a new emerging or an old neglected zoonotic pathogen? *Future Microbiol.* 2010; 5(3): 371–391.

Gottschalk M, Lacouture S, Odierno L. Immunomagnetic isolation of *Streptococcus suis* serotypes 2 and 1/2 from swine tonsils. *J Clin Microbiol* 1999; 37: 2877–81.

Gottschalk M, Segura M, Xu J. *Streptococcus suis* infections in humans: the Chinese experience and the situation in North America. *Anim Health Res Rev.* 2007; 8(1): 29–45.

Goyette-Desjardins G, Auger JP, Xu J, Segura M, Gottschalk M. *Streptococcus suis*, an important pig pathogen and emerging zoonotic agent-an update on the worldwide distribution based on serotyping and sequence typing. Emerg Microbes Infect. 2014; 3(6):e45. doi: 10.1038/emi.2014.45.

Halaby T, Hoitsma E, Hupperts R, Spanjaard L, Luirink M, Jacobs J. *Streptococcus suis* meningitis, a poacher's risk. *Eur J Clin Microbiol Infect Dis* 2000; 19: 943–45.

Hickling P, Cormack FCV. Meningitis caused by group R haemolytic streptococci. British Medical Journal 1976;2:1299-1300.

Higgins R, Gottschalk M, Mittal KR, Beaudoin M. *Streptococcus suis* infection in swine. A sixteen month study. *Can J Vet Res* 1990; 54: 170–73.

Higgins R, Gottschalk M. An update on *Streptococcus suis* identification. *J Vet Diagn Invest* 1990; 2: 249–52.

Hill JE, Gottschalk M, Brousseau R, Harel J, Hemmingsen SM, Goh SH. Biochemical analysis, cpn60 and 16S rDNA sequence data indicate that *Streptococcus suis* serotypes 32 and 34, isolated from pigs, are Streptococcus orisratti. *Vet Microbiol* 2005; 107: 63–69.

Huong VT, Ha N, Huy NT, Horby P, Ho DTN, Thiem VD, Zhu X, Hoa NT, Hien TT, Zamora J et al. Epidemiology, clinical manifestations, and outcomes of *Streptococcus suis* infection in humans. *Emerg Infect Dis*. 2014; 20(7): 1105–1114.

Ip M, Fung KS, Chi F, et al. *Streptococcus suis* in Hong Kong. Diagn Microbiol Infect Dis 2007; 57:15–20.

Jiao J, Mao R, Teng D, Wang X, Hao Y, Yang N, Wang, Feng X, Wang J. In vitro and in vivo antibacterial effect of NZ2114 against *Streptococcus suis* type 2 infection in mice peritonitis models. AMB Expr. 2017; 7(1):44. doi: 10.1186/s13568–017–0347–8.

Jobin MC, Fortin J, Willson PJ, Gottschalk M, Grenier D. Acquisition of plasmin activity and induction of arachidonic acid release by *Streptococcus suis* in contact with human brain microvascular endothelial cells. FEMS Microbiol. Lett. 252(1), 105–111 (2005).

Kay R, Cheng AF, Tse CY. *Streptococcus suis* infection in Hong Kong. QJM 1995; 88:39–47.

King SJ, Leigh JA, Heath PJ, et al. Development of a multilocus sequence typing scheme for the pig pathogen *Streptococcus suis*: identification of virulent clones and potential capsular serotype exchange. *J Clin Microbiol* 2002; 40: 3671–80.

Kopic J, Paradzik MT, Pandak N. *Streptococcus suis* infection as a cause of severe illness: 2 cases from Croatia. Scand J Infect Dis 2002; 34: 683–84.

Kouki A, Pieters RJ, Nilsson UJ, Loimaranta V, Finne J, Haataja S. Bacterial adhesion of *Streptococcus suis* to host cells and its inhibition by carbohydrate ligands. *Biology (Basel)*. 2013; 2(3): 918–935.

Lalonde M, Segura M, Lacouture S, Gottschalk M. Interactions between *Streptococcus suis* serotype 2 and different epithelial cell lines. Microbiology 2000; 146:1913–1921.

Lebel G, Piché F, Frenette M, Gottschalk M, Grenier D. Antimicrobial activity of nisin against the swine pathogen *Streptococcus suis* and its synergistic interaction with antibiotics. *Peptides*. 2013; 50: 19–23.

Lun ZR, Wang QP, Chen XG, Li AX, Zhu XQ. *Streptococcus suis*: an emerging zoonotic pathogen. *Lancet* Infect Dis. 2007; 7(3): 201–209.

Lutticken R, Temme N, Hahn G, Bartelheimer EW. Meningitis caused by *Streptococcus suis*: case report and review of the literature. *Infection* 1986; 14: 181–85

Mai NT, Hoa NT, Nga TV, Linh D, et al. *Streptococcus suis* meningitis in adults in Vietnam. Clin Infect Dis 2008; 46: 659–667.

Mazokopakis EE, Kofteridis DP, Papadakis JA, Gikas AH, Samonis GJ. First case report of *Streptococcus suis* septicaemia and meningitis from Greece. *Eur J Neurol* 2005; 12: 487–89.

Mogollon JD, Pijoan C, Murtaugh MP, Kaplan EL, Collins JE, Cleary PP. Characterization of prototype and clinically defined strains of *Streptococcus suis* by genomic fingerprinting. *J Clin Microbiol* 1990; 28: 2462–66.

Nghia HD, Tule TP, Wolbers M, Thai CQ, Hoang NV, Nga TV, le TP T, Phu NH, Chau TT, Sinh DX, Diep TS, Hang HT, Truong H, Campbell J, Chau NV, Chinh NT, Dung NV, Hoa NT, Spratt BG, Eur J Clin Microbiol Infect Dis (2019) 38:1003–1014 1011 Hien TT, Farrar J, Schultsz C (2011) Risk factors of *Streptococcus suis* infection in Vietnam. A case-control study. PLoS One 6(3): e17604. https://doi.org/10.1371/journal.pone.0017604

Okwumabua O, O'Connor M, Shull E. A polymerase chain reaction (PCR) assay specific for *Streptococcus suis* based on the gene encoding the glutamate dehydrogenase. *FEMS Microbiol Lett* 2003; 218: 79–84.

Okwumabua O, Staats J, Chengappa MM. Detection of genomic heterogeneity in *Streptococcus suis* isolates by DNA restriction fragment length polymorphisms of rRNA genes (ribotyping). *J Clin Microbiol* 1995; 33: 968–72.

Papatsiros VG, Vourvidis D, Tzitzis AA, Meichanetsidis PS, Stougiou D, Mintza D, PS Papaioannou PS. *Streptococcus suis*: an important zoonotic pathogen for human – prevention aspects. *Vet World*. 2011; 4(5): 216–221.

Paterson RA, Robertson ID, Sanders RC, Siba PM, Clegg A, Hampson DJ. The carriage of *Streptococcus suis* type 2 by pigs in Papua New Guinea. *Epidemiol Infect* 1993; 110: 71–78.

Pejsak Z, Jabłoński A, Żmudzki J. Drug sensitivity of pathogenic bacteria isolated from the respiratory system of swine. *Med Wet*. 2005; 61: 664–668.

Rasmussen SR, Andresen LO. 16S rDNA sequence variations of some *Streptococcus suis* serotypes. *Int J Syst Bacteriol* 1998; 48 (pt 3): 1063–65.

Robertson ID, Blackmore DK. Occupational exposure to *Streptococcus suis* type 2. *Epidemiol Infect* 1989; 103: 157–64.

Rosenkranz M, Elsner HA, Sturenburg HJ, Weiller C, Rother J, Sobottka I. *Streptococcus suis* meningitis and septicemia contracted from a wild boar in Germany. *J Neurol* 2003; 250: 869–70.

Segura M, Calzas C, Grenier D, Gottschalk M. Initial steps of the pathogenesis of the infection caused by *Streptococcus suis*: fighting against nonspecific defenses. *FEBS Lett*. 2016; 590(21): 3772–3799.

Segura M, Zheng H, de Greeff A, Gao GF, Grenier D et al. Latest developments on *Streptococcus suis*: an emerging zoonotic pathogen: part 2. Future Microbiol. 2014; 9(5): 587–591.

Segura M, Zheng H, de Greeff A, Gao GF, Grenier D, Jiang Y et al. Latest developments on *Streptococcus suis*: an emerging zoonotic pathogen: part 1. Future Microbiol. 2014; 9(4): 441–444.

Sriskandan S, Slater JD. Invasive disease and toxic shock due to zoonotic *Streptococcus suis*: an emerging infection in the East? PLoS Med 2006; 3:e187.

Staats JJ, Feder I, Okwumabua O, Chengappa MM. *Streptococcus suis*: past and present. *Vet Res Commun* 1997; 21: 381–407.

Szczotka A, Markowska-Daniel I, Pejsak Z. Antibiotic susceptibility of Polish *Streptococcus suis* isolates. *Med Wet*. 2007; 63: 1077–1080.

Takeuchi D, Kerdsin A, Pienpringam A, Loetthong P, Samerchea S, Luangsuk P, Khamisara K, Wongwan N, Areeratana P, Chiranairadul P et al. Population-based study of *Streptococcus suis* infection in humans in Phayao Province in northern Thailand. PLoS One. 2012; 7(2):e31265. doi: 10.1371/journal.pone.0031265.

Tambyah PA, Lee KO. Streptococcus infection and splenectomy. *Lancet* 2001; 357: 1130–31.

Tang JQ, Zhu J, Hu XS, Zhu FC, Nou GZ. Epidemiological and pathogenic study on the outbreak of toxic shock syndrome and meningocephalitis caused by swine streptococcus. *Acta Acad Med Miltaris Tertiae* 2001; 23: 1292–95 (in Chinese).

Teekakirikul P, Wiwanitkit V. *Streptococcus suis* infection: Overview of case reports in Thailand. Southeast Asian J Trop Med Public Health 2003; 34(Suppl 2):178–183.

Vadeboncoeur N, Segura M, Al-Numani D, Vanier G, Gottschalk M. Pro-inflammatory cytokine and chemokine release by human brain microvascular endothelial cells stimulated by *Streptococcus suis* serotype 2. *FEMS Immunol. Med. Microbiol.* 35(1), 49–58 (2003).

van Samkar, A., Brouwer, M. C., Schultsz, C., van der Ende, A., & van de Beek, D. (2015). *Streptococcus suis* meningitis: a systematic review and meta-analysis. PLoS neglected tropical diseases, 9(10), e0004191.

Vanier G, Segura M, Friedl P, Lacouture S, Gottschalk M. Invasion of porcine brain microvascular endothelial cells by *Streptococcus suis* serotype 2. *Infect. Immun.* 72(3), 1441–1449 (2004).

Vanier G, Segura M, Lecours MP, Grenier D, Gottschalk M. Porcine brain microvascular endothelial cell-derived interleukin-8 is first induced and then degraded by *Streptococcus suis*. Microb. Pathog. 46(3), 135–143 (2009).

Vela AI, Goyache J, Tarradas C, et al. Analysis of genetic diversity of *Streptococcus suis* clinical isolates from pigs in Spain by pulsed-fi eld gel electrophoresis. *J Clin Microbiol* 2003; 41: 2498–502.

Wang H, Hu XS, Zhu FC, Chen SY, Sun JZ, Hua CT. An epidemiological study on the human streptococcal infective syndrome among men and pigs. *Mod Prev Med* 2000; 27: 312–14 (in Chinese).

Watkins EJ, Brooksby P, Schweiger MS, Enright SM. Septicaemia in a pig-farm worker. *Lancet* 2001; 357: 38.

Wertheim HF, Nghia HD, Taylor W, Schultsz C. *Streptococcus suis*: an emerging human pathogen. *Clin Infect Dis*. 2009; 48(5): 617–625.

White M. Pig health – streptococcal meningitis. NADIS (National Animal Disease Information Service) 2016. Available at: www.nadis. org.uk

Wint W, Robinson T. Gridded livestock of the world 2007. Rome: Food and Agriculture Organization; 2007. p. 131.

Wisselink HJ, Smith HE, Stockhofe-Zurwieden N, Peperkamp K, Vecht U. Distribution of capsular types and production of muramidase-released protein (MRP) and extracellular factor (EF) of *Streptococcus suis* strains isolated from diseased pigs in seven European countries. *Vet Microbiol* 2000; 74: 237–48

Yu HJ, Liu XC, Wang SW, et al. Matched case-control study for risk factors of human *Streptococcus suis* infection in Sichuan Province, China. Zhonghua Liu Xing Bing Xue Za Zhi 2005; 26:636–9.

Yu, H., Jing, H., Chen, Z., Zheng, H., Zhu, X., Wang, H., Wang, S., Liu, L., Zu, R., Luo, L., Xiang, N., Liu, H., Liu, X., Shu, Y., Lee, S. S., Chuang, S. K., Wang, Y., Xu, J., Yang, W., & Streptococcus suis study groups (2006). Human Streptococcus suis outbreak, Sichuan, China. *Emerging infectious diseases*, 12(6), 914–920. https://doi.org/10.3201/eid1206.051194

Zanen HC, Engel HWB. Porcine streptococci causing meningitis and septicaemia in man. The Lancet 1975;l: 1286-1288.

Zhu J, Tang JQ, Guo HB, Zhang Y, Tao KH. Epidemiologic and pathogenic study on an outbreak of acute streptococcal disease in pigs. *J Prev Med Chin PLA* 2000; 18: 257–59 (in Chinese).

APPENDIX 1.1: Screening of the records identified through search databases (Scopus, PubMed, Science Direct)

No.	Exclusion criteri	Year	Location	Type of Study	Cases	Species	Patient/ Study S	Serotype	Clinical Sign	Mortality/ mort	Sample collecte	Diagnostic r
1	Cant find online	2021	Japan	Case report	26	human			Sudden hearing loss, severe low back		blood and spinal fluid cultures	
2	Chicken					chicken						
3		2020	Hungary	Case report, Review		human		serotype 2	severe systemic inf	High rate mortality and morbidity		
4		2020		Review		human and pig						
5		2002–2019	East-Central Europ	Case report, Reviev	34	human	patients who had at least one positive		purulent meningitis, sepsis, uveitis-er		blood culture (63.5%) and cere	
6		2020		Update on recent findings		human				Increased mortality		
7		2020	China	Case report	2	human		sporadic ST7 and S	meningitis and sepsis, mild hearing loss			Whole-genc
8		2020 (case in 2007	Phayao province, T	cross-sectional?		human and pig						
9		2019		Review		human			purulent meningitis			
10		2019	Vietnam	Review		human						
11		2019	Israel	Case report		cat	7-year-old, castrated male, Persian ca		Severe mid lumbar back pain and extr		Blood test: mild lymphopenia a	
12	article in hungaria	2019		Case report		human			purulent meningitis			
13		2018	Spain	Review		urban wild boars		strains with the cps2 gene				
14		2018		Review: pathogenesis		pig						
15		2017		Review		human and pig						
16		2017	Sabah, Borneo, Ma	Case report	2	human			-			
17		2017		Review: epidemiology		human and pig			meningitis, septicaemia, arthritis, endocarditis, and endophthalmitis			
18		2016	Togo, Africa	Case report	1	human	32-year-old man	serotype 2, ST1	meningitis, severe hearing disorders after recovery			specific imr
19		2016	Argentina	Case report, Reviev	17 human and 14	human and pig		serotype 2, 5 (mostly ST1, two ST28)				
20		2016	Netherlands	study		human and pig						To identify
21		2016	Japan	Case report, Reviev	4	human		serotype 5				Virulence-a
22		2016	Vietnam	case-control: association between hu		human and pig	Human: 90 S. suis case-patients and 183 non-S. suis sepsis controls					
23		2015		report		pig						
24		2014		Review		human and pig						multilocus
25		2014		cross-sectional?	302	pig	pigs from slaughte	serotype 2			tonsil	antibiograr
26	article in portugue	2014	Portugal	Case report	1	human	44 years old male		acute bacterial meningitis		blood and CSF	

Sheet1 | ALL | Scopus | PubMed | CABI | PubMed (2)

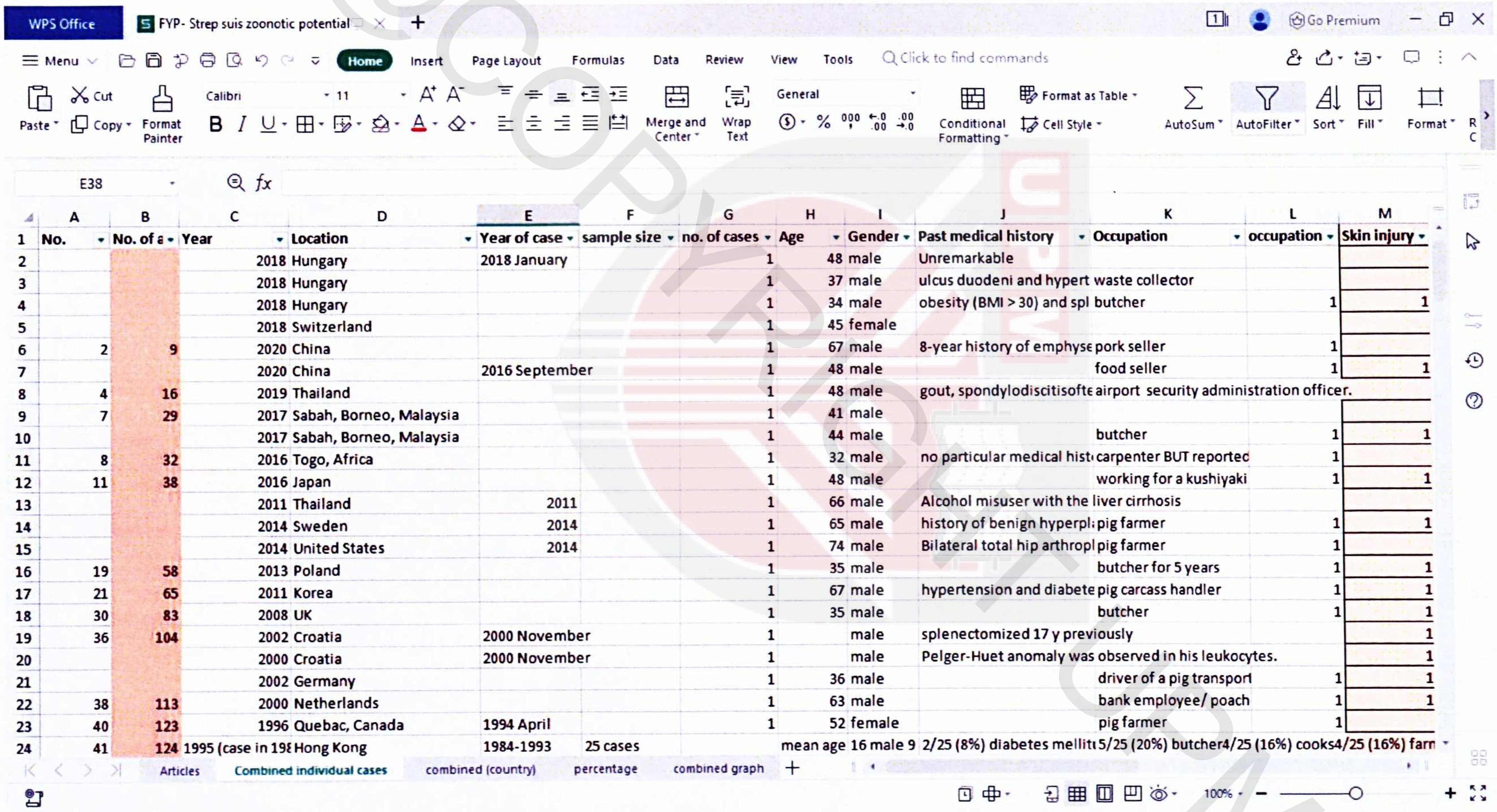
APPENDIX 1.2: Screening of the records identified through search databases (Scopus, PubMed, Science Direct)

Strep Suis 20210922 Chye Tung

	M	N	O	P	Q	R	S	
1	Diagnostic meth	Occupational?	Risk factor / Pre	Epidemiology	Impact	Control methods	Keywords / main points	Title
2	uid cultures	Restaurant busine	A cut wound while cooking raw pork				https://www.scopus.com/re	A case of sensorineural hearing loss associated with streptococcus suis menir
3							https://www.scopus.com/re	Carriage of the zoonotic organism Streptococcus suis in chicken flocks in Vietr
4		pig breeders, veter	close contact with infected pigs or contaminated pork product				https://www.scopus.com/re	Fatal case of bacteremia caused by Streptococcus suis in a splenectomized ma
5			AMR, mechanisms	swine population demographics and r		reducing the prophylactic use	https://www.scopus.com/re	Streptococcus suis research: Progress and challenges
6	%) and cerebrospi	Traditional agricul	Traditional agricul	number of affected patients was 1.89 ± 1.53/year (range: 0–5)			https://www.scopus.com/re	Streptococcus suis: An underestimated emerging pathogen in Hungary?
7			new regulations in	pathogenesis and	Decreased performance, increased mortality, ecc		https://www.scopus.com/re	Update on streptococcus suis research and prevention in the era of antimicrob
8	Whole-genome sec	work in relation to	two sporadic ST7 S	distribution and evolution of the S. su		prolonged ceftriaxone therap	https://www.scopus.com/re	Human infection caused by Streptococcus suis serotype 2 in China: Report of t
9			occupational expo	prevalence and diversity of S. suis car		Food safety, hygiene, and hea	https://www-scopus-com.ez	Genotypic comparison between streptococcus suis isolated from pigs and hur
10			occupationally exposed to contact with pigs and/or pork			therapeutic protocol should b	https://www-scopus-com.ez	Streptococcus suis Meningitis: Epidemiology, Clinical Presentation and Treatn
11		more than 50% Vie	close contact with the infected animals, their infected			residues, contaminated water, sc	https://www-scopus-com.ez	The possible zoonotic diseases transferring from pig to human in Vietnam
12	nphopenia and mildly increased serur		s.suis should be considered as such, even when there is r			oral amoxicillin-clavulanic a	https://www-scopus-com.ez	Case report: Spinal meningitis associated with streptococcus suis infection in
13			occupational dise	prevalence of the disease is very diverse in the continents, the highe			https://www-scopus-com.ez	[Special case of purulent meningitis caused by Streptococcus suis: Case report
14				Urban wild boars (Sus scrofa) from Barcelona, Spain, harbor great c			https://www-scopus-com.ez	Urban wild boars and risk for zoonotic streptococcus suis, Spain
15				pathogenesis: 4 stages (mucosal, dee		elaboration of a vaccine, effic	https://www-scopus-com.ez	Streptococcus suis: A re-emerging pathogen associated with occupational expo
16				over 100 'putative virulence factors or traits' (surface-associated or			https://www-scopus-com.ez	Critical Streptococcus suis Virulence Factors: Are They All Really Critical?
17			~	~		accurate epidemiological sur	https://www-scopus-com.ez	Case report: Two human Streptococcus suis infections in Borneo, Sabah, Mala
18	phthalmitis, heari	pig breeders, abatt	close contact with	Some strains, mostly those belonging		Pig: vaccination, improvemen	https://www-scopus-com.ez	Streptococcus suis: A re-emerging pathogen associated with occupational exp
19	specific immunological and molecula		regular contact with pork products			adapted antibiotic therapy, a	https://www-scopus-com.ez	Human meningitis due to Streptococcus suis in Lomé, Togo: A case report
20			Close contact with	ST1 strains clustered together with three strains from Vietnam and t			https://www-scopus-com.ez	Streptococcus suis serotype 2 strains isolated in Argentina (South America) ar
21	To identify genomic differences that c		food-borne transm	Zoonotic isolates have smaller genomes than non-zoonotic isolates,			https://www-scopus-com.ez	An emerging zoonotic clone in the Netherlands provides clues to virulence and
22	Virulence-associated gene profiling		handling raw pork or having close contact with infected pigs				https://www-scopus-com.ez	Human case of bacteremia due to Streptococcus suis serotype 5 in Japan: The f
23				more S. suis patients were reported re		strengthen control of PRRS	https://www-scopus-com.ez	Temporal and spatial association of Streptococcus suis infection in humans a
24			close contact with	nine draft genome sequences of S. suis			https://www-scopus-com.ez	Draft genome sequences of nine Streptococcus suis strains isolated in the Unit
25	multilocus sequence typing		close contact with	worldwide distribution of serotypes a		More research is required to i	https://www-scopus-com.ez	Streptococcus suis, an important pig pathogen and emerging zoonotic agent-a
26	antibiogram was performed using the		prevention and tre	high degree of resistance to tetracycline (90.2%) and erythromycin (			https://www-scopus-com.ez	[Antimicrobial resistance profile of Streptococcus suis type 2 isolates from to
27		pig griller	mostly men	exposed to pig or pork:	alcohol consumption	14 days of ceftriaxone	https://www-scopus-com.ez	[Acute bacterial meningitis as an occupational disease]

Sheet1 ALL Scopus PubMed CABI PubMed (2)

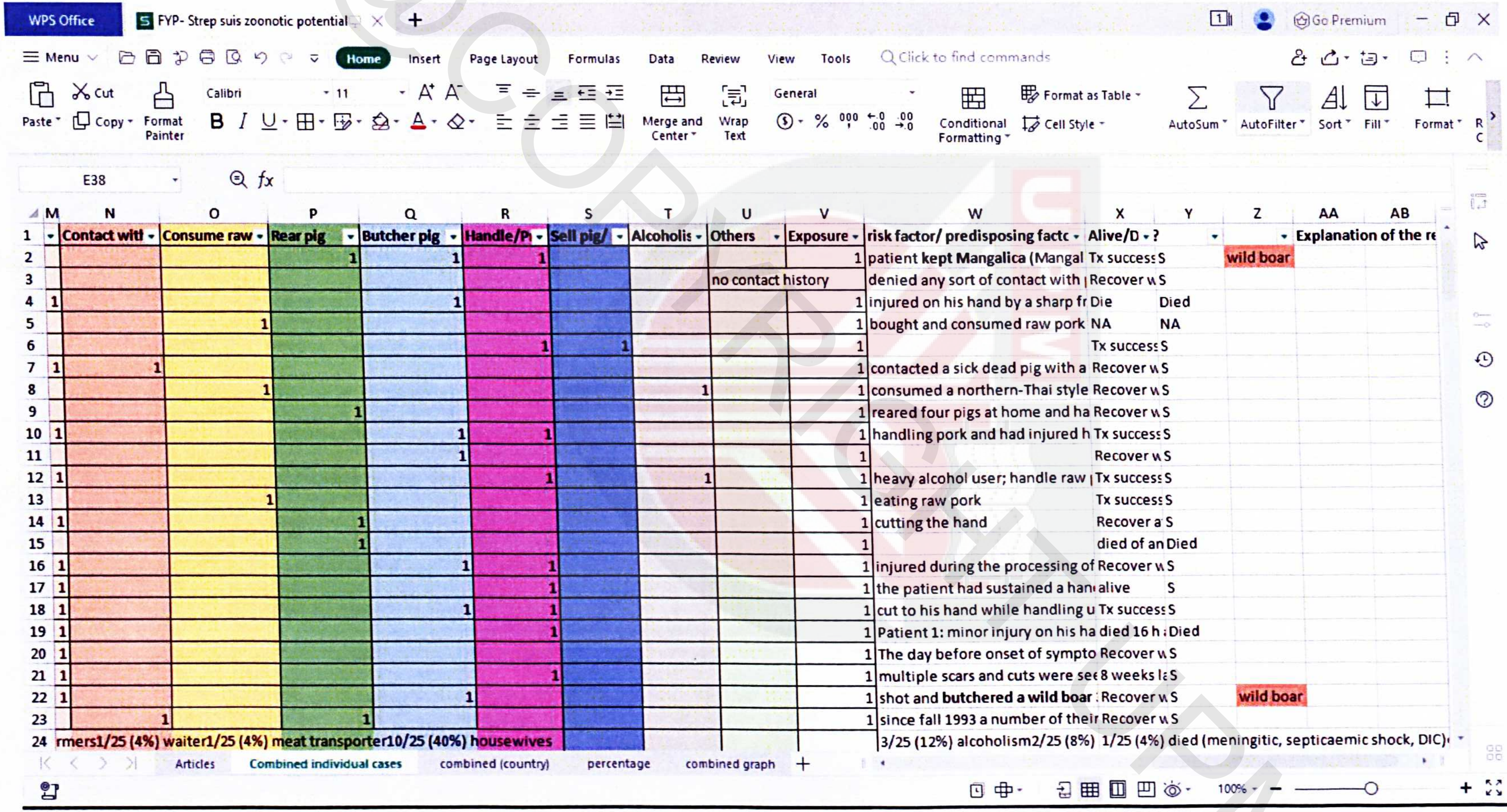
APPENDIX 2.1: Data extraction in Excel based on histories and predispose risks of human *S. suis* infection



	A	B	C	D	E	F	G	H	I	J	K	L	M
1	No.	No. of a	Year	Location	Year of case	sample size	no. of cases	Age	Gender	Past medical history	Occupation	occupation	Skin injury
2			2018	Hungary	2018 January		1	48	male	Unremarkable			
3			2018	Hungary			1	37	male	ulcus duodeni and hypert	waste collector		
4			2018	Hungary			1	34	male	obesity (BMI > 30) and spl	butcher	1	1
5			2018	Switzerland			1	45	female				
6	2	9	2020	China			1	67	male	8-year history of emphyse	pork seller	1	
7			2020	China	2016 September		1	48	male		food seller	1	1
8	4	16	2019	Thailand			1	48	male	gout, spondylodiscitisofte	airport security administration officer.		
9	7	29	2017	Sabah, Borneo, Malaysia			1	41	male				
10			2017	Sabah, Borneo, Malaysia			1	44	male		butcher	1	1
11	8	32	2016	Togo, Africa			1	32	male	no particular medical hist	carpenter BUT reported	1	
12	11	38	2016	Japan			1	48	male		working for a kushiyaki	1	1
13			2011	Thailand	2011		1	66	male	Alcohol misuser with the liver cirrhosis			
14			2014	Sweden	2014		1	65	male	history of benign hyperpl	pig farmer	1	1
15			2014	United States	2014		1	74	male	Bilateral total hip arthropl	pig farmer	1	
16	19	58	2013	Poland			1	35	male		butcher for 5 years	1	1
17	21	65	2011	Korea			1	67	male	hypertension and diabete	pig carcass handler	1	1
18	30	83	2008	UK			1	35	male		butcher	1	1
19	36	104	2002	Croatia	2000 November		1		male	splenectomized 17 y previously			1
20			2000	Croatia	2000 November		1		male	Pelger-Huet anomaly was observed in his leukocytes.			1
21			2002	Germany			1	36	male		driver of a pig transport	1	1
22	38	113	2000	Netherlands			1	63	male		bank employee/ poach	1	1
23	40	123	1996	Quebac, Canada	1994 April		1	52	female		pig farmer	1	
24	41	124	1995 (case in 19	Hong Kong	1984-1993	25 cases		mean age	16 male 9	2/25 (8%) diabetes mellit	5/25 (20%) butcher	4/25 (16%) cooks	4/25 (16%) farn

Articles | Combined individual cases | combined (country) | percentage | combined graph

APPENDIX 2.2: Data extraction in Excel based on histories and predispose risks of human *S. suis* infection



	M	N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB
1		Contact witl	Consume raw	Rear pig	Butcher pig	Handle/P	Sell pig/	Alcoholis	Others	Exposure	risk factor/ predisposing factc	Alive/D	?			Explanation of the re
2				1	1	1				1	patient kept Mangalica (Mangal	Tx success	S	wild boar		
3									no contact history		denied any sort of contact with	Recover w	S			
4	1				1					1	injured on his hand by a sharp fr	Die	Died			
5			1							1	bought and consumed raw pork	NA	NA			
6						1	1			1		Tx success	S			
7	1	1								1	contacted a sick dead pig with a	Recover w	S			
8			1					1		1	consumed a northern-Thai style	Recover w	S			
9				1						1	reared four pigs at home and ha	Recover w	S			
10	1				1	1				1	handling pork and had injured h	Tx success	S			
11					1					1		Recover w	S			
12	1					1		1		1	heavy alcohol user; handle raw	Tx success	S			
13			1							1	eating raw pork	Tx success	S			
14	1			1						1	cutting the hand	Recover a	S			
15				1						1		died of an	Died			
16	1				1	1				1	injured during the processing of	Recover w	S			
17	1					1				1	the patient had sustained a han	alive	S			
18	1				1	1				1	cut to his hand while handling u	Tx success	S			
19	1					1				1	Patient 1: minor injury on his ha	died 16 h a	Died			
20	1									1	The day before onset of sympto	Recover w	S			
21	1					1				1	multiple scars and cuts were see	8 weeks la	S			
22	1				1					1	shot and butchered a wild boar	Recover w	S	wild boar		
23		1		1						1	since fall 1993 a number of their	Recover w	S			
24	rmers1/25 (4%) waiter1/25 (4%) meat transporter10/25 (40%) housewives										3/25 (12%) alcoholism2/25 (8%)	1/25 (4%) died (meningitic, septicaemic shock, DIC)				

APPENDIX 3: Excel data arrangement of human *S. suis* infection based on countries

Country	Year	Case	Gender		Age	Occupation		Predispose risks										Outcome	
			Male	Female		Pig-related	Non pig-related	Skin injury	Contact w	Consume	Rear pig	Butcher pi	Handle/Pr	Sell pig/ p	Alcoholisn	Underlyin	Exposure	Survived	Died
China	2005-202	219	183	36	26-82 (mean 54)	210	9	106	16	0	207	141	61	1	0	1	218	179	40
Hong Kon	1983-200	55	41	14	20-89 (mean 56.6)	27	28	6	0	0	6	10	15	2	4	8	34	53	2
Japan	1994-201	8	5	3	47-58 (mean 53)	3	5	6	0	0	1	0	2	0	1	0	8	7	1
Korea	2011	1	1	0	67	1	0	1	0	0	0	0	1	0	0	1	1	1	0
Malaysia	2017	2	2	0	41-44 (mean 42.5)	1	1	1	0	0	1	1	1	0	0	0	1	2	0
Taiwan	2000-201	8	3	5	38-72 (mean 55.4)	1	7	1	0	0	0	0	1	1	0	3	1	NA	NA
Thailand	2000-201	190	137	53	27-80 (mean 49.5)	25	165	0	0	66	0	4	6	0	48	39	84	163	27
Vietnam	1996-200	151	117	34	19-84 (mean 46.5)	13	138	0	0	0	38	13	0	0	0	3	50	147	4
Belgium	1985	1	1	0	37	0	1	0	0	0	0	0	0	0	0	0	0	1	0
Brazil	2021	2	2	0	60-68 (mean 64)	2	0	0	0	0	1	1	0	0	1	1	2	2	0
Croatia	2000	2	2	0	NA	0	2	2	0	0	0	0	1	0	0	2	2	1	1
Denmark	1968-197	9	8	1	38-68 (mean 54.9)	7	2	0	0	0	5	2	0	0	0	0	7	8	1
France	1977-198	4	4	0	30-58 (48.5)	3	1	1	0	0	0	2	1	0	0	1	3	4	0
Germany	1986-200	2	1	1	36-69 (mean 52.5)	2	0	1	0	0	1	0	1	0	0	0	2	2	0
Hungary	2018	2	2	0	34-37 (mean 35.5)	1	1	1	0	0	0	1	0	0	0	2	1	1	1
The Nethe	1969-200	34	29	5	26-76 (mean 49.5)	29	5	0	0	0	13	15	10	0	1	6	31	32	2
Poland	2013	1	1	0	35	1	0	1	0	0	0	1	1	0	0	0	1	1	0
Portugis	2017	1	1	0	48	1	0	1	0	0	0	1	0	0	0	0	1	1	0
Canada	1994	1	0	1	52	1	0	0	1	0	1	0	0	0	0	0	1	1	0
Sweden	2014	1	1	0	65	1	0	1	0	0	1	0	0	0	0	1	1	1	0
Switzerlar	2018	1	0	1	45	0	1	0	0	1	0	0	0	0	0	0	1	NA	NA
UK	1976-200	6	6	0	30-62 (mean 49)	6	0	1	1	0	0	2	4	0	1	0	6	6	0
Togo	2010-201	16	13	3	5 - >50	10	6	0	0	14	6	7	12	0	0	0	16	15	1
United Sta	2014	1	1	0	74	1	0	0	0	0	1	0	0	0	0	1	1	0	1

Articles | Combined individual cases | combined (country) | percentage | combined graph

APPENDIX 4: Percentage of predispose risks of human *S. suis* infection based on countries

Country	Yea	Case	Gender		Age	Occupation			
			Male	Femal		Pi	elatec	Non	-relat
China	2005-202	219	183	36	26-82 (mean 54)	210	95.89	9	4.11
Hong Kong	1983-200	55	41	14	20-89 (mean 56.6	27	49.09	28	50.91
Japan	1994-201	8	5	3	47-58 (mean 53)	3	37.50	5	62.50
Korea	2011	1	1	0	67	1	100.00	0	0.00
Malaysia	2017	2	2	0	41-44 (mean 42.5	1	50.00	1	50.00
Taiwan	2000-201	8	3	5	38-72 (mean 55.4	1	12.50	7	87.50
Thailand	2000-201	190	137	53	27-80 (mean 49.5	25	13.16	165	86.84
Vietnam	1996-200	151	117	34	19-84 (mean 46.5	13	8.61	138	91.39
Belgium	1985	1	1	0	37	0	0.00	1	100.00
Croatia	2000	2	2	0	NA	0	0.00	2	100.00
Denmark	1968-197	9	8	1	38-68 (mean 54.9	7	77.78	2	22.22
France	1977-198	4	4	0	30-58 (48.5)	3	75.00	1	25.00
Germany	1986-200	2	1	1	36-69 (mean 52.5	2	100.00	0	0.00
Hungary	2018	2	2	0	34-37 (mean 35.5	1	50.00	1	50.00
The Netherlands	1969-200	34	29	5	26-76 (mean 49.5	29	85.29	5	14.71
Poland	2013	1	1	0	35	1	100.00	0	0.00
Portugis	2017	1	1	0	48	1	100.00	0	0.00
Sweden	2014	1	1	0	65	1	100.00	0	0.00
Switzerland	2018	1	0	1	45	0	0.00	1	100.00
UK	1976-200	6	6	0	30-62 (mean 49)	6	100.00	0	0.00
Togo	2010-201	16	13	3	5 - >50	10	62.50	6	37.50
United States	2014	1	1	0	74	1	100.00	0	0.00
Canada	1994	1	0	1	52	1	100.00	0	0.00
Brazil	2021	2	2	0	60-68 (mean 64)	2	100.00	0	0.00
Total		718	561	157		346	48.19	372	51.81

Country	Predispose risks																				Outcome			
	Sk	njury	ontact	h sick	Consu	raw p	f	r pig	Bu	er pig	handle	ocess	ell pig	g prod	Alc	olism	Under	g dise	xposur	pigs or	S	ived	ed	
China	106	48.40	16	7.31	0	0.00	207	94.52	141	64.38	61	27.85	1	0.46	0	0.00	1	0.46	218	99.54	179	81.74	40	
Hong Kong	6	10.91	0	0.00	0	0.00	6	10.91	10	18.18	15	27.27	2	3.64	4	7.27	8	14.55	34	61.82	53	96.36	2	
Japan	6	75.00	0	0.00	0	0.00	1	12.50	0	0.00	2	25.00	0	0.00	1	12.50	0	0.00	8	100.00	7	87.50	1	
Korea	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	0	0.00	0	0.00	1	100.00	1	100.00	1	100.00	0	
Malaysia	1	50.00	0	0.00	0	0.00	1	50.00	1	50.00	1	50.00	0	0.00	0	0.00	0	0.00	1	50.00	2	100.00	0	
Taiwan	1	12.50	0	0.00	0	0.00	0	0.00	0	0.00	1	12.50	1	12.50	0	0.00	3	37.50	1	12.50	NA	#VALUE!	NA	#V.
Thailand	0	0.00	0	0.00	66	34.74	0	0.00	4	2.11	6	3.16	0	0.00	48	25.26	39	20.53	84	44.21	163	85.79	27	
Vietnam	0	0.00	0	0.00	0	0.00	38	25.17	13	8.61	0	0.00	0	0.00	0	0.00	3	1.99	50	33.11	147	97.35	4	
Belgium	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	0	
Croatia	2	100.00	0	0.00	0	0.00	0	0.00	0	0.00	1	50.00	0	0.00	0	0.00	2	100.00	2	100.00	1	50.00	1	
Denmark	0	0.00	0	0.00	0	0.00	5	55.56	2	22.22	0	0.00	0	0.00	0	0.00	0	0.00	7	77.78	8	88.89	1	
France	1	25.00	0	0.00	0	0.00	0	0.00	2	50.00	1	25.00	0	0.00	0	0.00	1	25.00	3	75.00	4	100.00	0	
Germany	1	50.00	0	0.00	0	0.00	1	50.00	0	0.00	1	50.00	0	0.00	0	0.00	0	0.00	2	100.00	2	100.00	0	
Hungary	1	50.00	0	0.00	0	0.00	0	0.00	1	50.00	0	0.00	0	0.00	0	0.00	2	100.00	1	50.00	1	50.00	1	
The Netherlands	0	0.00	0	0.00	0	0.00	13	38.24	15	44.12	10	29.41	0	0.00	1	2.94	6	17.65	31	91.18	32	94.12	2	
Poland	1	100.00	0	0.00	0	0.00	0	0.00	1	100.00	1	100.00	0	0.00	0	0.00	0	0.00	1	100.00	1	100.00	0	
Portugis	1	100.00	0	0.00	0	0.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	1	100.00	0	
Sweden	1	100.00	0	0.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	1	100.00	1	100.00	0	
Switzerland	0	0.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	NA	#VALUE!	NA	#V.
UK	1	16.67	1	16.67	0	0.00	0	0.00	2	33.33	4	66.67	0	0.00	1	16.67	0	0.00	6	100.00	6	100.00	0	
Togo	0	0.00	0	0.00	14	87.50	6	37.50	7	43.75	12	75.00	0	0.00	0	0.00	0	0.00	16	100.00	15	93.75	1	
United States	0	0.00	0	0.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	1	100.00	0	0.00	1	1
Canada	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	1	100.00	0	
Brazil	0	0.00	0	0.00	0	0.00	1	50.00	1	50.00	0	0.00	0	0.00	1	50.00	1	50.00	2	100.00	2	100.00	0	
Total	130	18.11	18	2.51	81	11.28	282	39.28	201	27.99	117	16.30	4	0.56	56	7.80	69	9.61	473	65.88	628	88.58	81	