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RESEARCH ARTICLE

Antimicrobial resistance of *Streptococcus suis* isolated from pigs: A meta-analysis of prevalence studies

Khao Keonam[1], Chuleeporn Saksangawong[2], Patchanee Sringam[3], Piyawat Saipan[2], Saijai Kongpechr[4], Peerapol Sukon[4*]

[1] *Veterinary Science Program, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand*
[2] *Division of Public Health, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand*
[3] *Division of Physiology, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand*
[4] *Division of Anatomy, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, 40002, Thailand*
[*] ***Corresponding author*** *E-mail: sukonp@kku.ac.th*

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Abstract

Objective: *Streptococcus suis* (*S. suis*) is an important zoonotic pathogen capable of causing severe disease or even death in pigs and humans. Therefore, the antimicrobial resistance of *S. suis* is a major threat to public health. This study was conducted to determine the pooled prevalence and trend of antimicrobial resistance of *S. suis* isolated from pigs worldwide.

Materials and Methods: The relevant citations were retrieved from PubMed, Scopus, and Web of Science. The retrieved citations were screened for their eligibility based on the specified inclusion and exclusion criteria. Relevant data were extracted from the included studies. Only seven most reported antibiotics from different classes were extracted. These included ceftiofur, clindamycin, enrofloxacin, erythromycin, penicillin, tetracycline, and sulfamethoxazole/trimethoprim. A random effect meta-analysis was used to estimate the pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs. Meta-regression analysis was used to determine the trend of the pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs over time. The quality of the included studies was also evaluated.

Results: A total of 360 articles were identified from three databases, but only 26 articles met the inclusion criteria and were included for meta-analysis. The highest pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs was tetracycline (89.2%, [95% confidence interval (CI), 83.5-93.2%]), followed by clindamycin (83.8%, [95% CI, 73.7-90.5%]) and erythromycin (69.3% [95% CI, 57.8%-77.7%]). The lowest pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs was ceftiofur (4.3%, [95% CI, 2.2–8.2%]) and penicillin (7.5%, [95% CI, 4.0–13.6%]). The trend of antimicrobial resistance of *S. suis* isolated from pigs was not significantly changed over time for all seven antibiotics analyzed.

Conclusion: The trend of antimicrobial resistance of *S. suis* isolated from pigs is consistently high for tetracycline, clindamycin, and erythromycin; however, the trend is consistently low for ceftiofur and penicillin.

Keywords: *Streptococcus suis*, antimicrobial resistance, pigs, prevalence

Introduction

Streptococcus suis (S. suis), a bacterium found in the respiratory, gastrointestinal, and vaginal tracts of pigs, generally does not cause disease. Piglets become colonized with the bacteria through direct contact between their noses, either through nose-to-nose or nose-to-vagina contact, resulting in a 100% colonization rate (Uruén et al., 2022). Nevertheless, it acquires pathogenicity by penetrating mucosal barriers and gaining access to the bloodstream, joints, and central nervous system, resulting in a range of complications such as bacteremia, endocarditis, arthritis, pneumonia, and death (Segura et al., 2016). Effective invasion relies on the presence of virulent factors, including as enzymes and poisons, which assist in evading the immune system and acquiring nutrients. Respiratory viral infections, particularly caused by swine influenza and pig reproductive and respiratory syndrome viruses, additionally weaken the body's ability to fight against infections in the mucous membrane (Vötsch et al., 2018). This emphasizes the potential of *S. suis* to become a harmful microorganism. *S. suis* infection causes a significant swine disease, resulting in high mortality and economic losses, globally. Incidence varies (5-20%) across regions and farms. It's a major cause of mortality in piglets (4–12 weeks), with approximately 70% mortality when the infection reaches the nervous system (Uruén et al., 2022). Economic losses stem from mortality, pig management, infection control, and increased production costs due to reduced weight gain.

Antibiotics, such as tetracyclines, beta-lactams, and macrolides, are commonly used in pig farming to treat weaning diarrhea, intestinal infections, and respiratory illnesses (Cuong et al., 2018; Lekagul et al., 2019). Combinations such as penicillin/amoxicillin with other substances are employed, and fluoroquinolones are highly successful in treating streptococcal infections (Dechêne-Tempier et al., 2021). Although second-generation (thiamphenicol) and third-generation (florfenicol) amphenicols have been authorized for the treatment of swine respiratory illness in several countries, their usage differs worldwide (Lekagul et al., 2019). The widespread utilization of antibiotics in veterinary medicine on a global scale has resulted in a rise in resistance among *S. suis* isolates around the world.

Many individual prevalence studies on antimicrobial resistance of *S. suis* have been reported worldwide (Kataoka et al., 2000; Gurung et al., 2015; Huang et al., 2015; Hernandez-Garcia et al., 2017; Holmer et al., 2019; Hayer et al., 2020; Ichikawa et al., 2020; Guo et al., 2022). The resistance rate of *S. suis* varied greatly depending on antibiotic classes and regions of the studies. For example, the resistance rate was high for tetracyclines, macrolides, and lincosamides in Europe, Asia, and North America (Dechêne-Tempier et al., 2021; Uruén et al., 2022). Although the resistance rate was low for beta-lactams and aminoglycosides in several regions of the world, the resistance rate considerably varied in different regions. For example, the resistance rate to penicillin in *S. suis* was as low as 0.3% in Netherlands to 26% in Spain (Dutkiewicz et al., 2017; Haenni et al., 2018; O'Dea et al., 2018).

Individual prevalence studies are typically limited to specific area of study or specific point of time. To overcome these limitations, we used meta-analytic techniques to combine data from the individual relevant studies. The objectives of this study were to determine the pooled prevalence and the trend of antimicrobial resistance of *S. suis* isolated from pigs worldwide.

Materials and Methods

Search strategy

The relevant citations were retrieved from PubMed, Scopus, and Web of Science using a combination of the keywords: "*Streptococcus suis, antimicrobial resistance, swine".* The search was restricted to English language.

Inclusion and exclusion criteria

The retrieved citations from each database were exported to EndNote X6. Duplicated citations were removed. Two reviewers carefully screened titles and abstracts for initial inclusion. Then, a full-text article that passed the initial screening was assessed for final inclusion regarding the specific inclusion and exclusion criteria. The

studies were included if they reported the prevalence of antimicrobial resistance in *S. suis* isolated from pigs. The studies were excluded if they were: (1) the studies not related to the prevalence of antimicrobial resistance; (2) review articles; (3) case reports; (4) experimental studies; and (5) the studies with a sample size less than 10. Discussion between the authors helped to resolve their disagreements regarding the inclusion of the pertinent articles.

Study quality assessment

Each included study was assessed for its quality using a specific checklist (Sukon et al., 2021). The checklist had five questions: (1) Was the research objective clearly described and stated? (2) Were the period and location of the study clearly stated? (3) Was the sample categorized into different subgroups? (4) Was the sampling method described in detail? (5) Were the diagnostic techniques clearly pointed out? The scoring of each question was based on a simple scale system ("2" for yes, "0" for no, or "1" for unsure); therefore, the total of the score in each article was 10.

Data extraction

Data were carefully extracted by two authors. Discrepancies were resolved by discussion. The data extraction was stored in the Microsoft Excel file format by the first author. The extracted information contained: (1) year of publication and first author; (2) year and location of the study; (3) pig characteristics; (4) sampling organs; (5) number of isolates for drug testing; (6) number of classes for drug testing; (7) number of classes of drug resistance; (8) amount of resistance/intermedia/susceptibility of *S. suis*; (9) pigs health status; and (10) methodology for detection.

Statistics analysis

Comprehensive meta-analysis (CMA) program version 3 (Biostat, Englewood, NJ, USA) was used for meta-analysis. Because several antibiotics were tested from each included study, this resulted in difficulty for meta-analysis comparisons. Therefore, we selected seven antibiotics (from different classes) that were commonly reported for meta-analysis. These antibiotics were ceftiofur (cephalosporins), clindamycin (lincosamides), enrofloxacin (fluoroquinolones), erythromycin (macrolides), penicillin (penicillins), tetracycline (tetracyclines), and sulfamethoxazole/trimethoprim (trimethoprim-sulfamethoxazole). The pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs was determined for seven antibiotics mentioned above. A p-value less than 0.05 was considered a statistical significance for all analyses, unless otherwise stated. Before pooling the prevalence, the prevalence of each included study was stabilized using the logit transformation as follows: $\text{logit}(p) = \ln(p/[1-p])$, where "p" is the proportion and "ln" is the natural log (Sukon et al., 2021).

Overall meta-analysis

The overall pooled prevalence and its 95.0% confidence interval (CI) was estimated by a random effects model. Cochran's Q and I^2 statistics were used to assess the heterogeneity. I^2 values of 25.0, 50.0, and 75.0% was considered as low, moderate, and high heterogeneity, respectively (Higgins and Thompson, 2002). The study was used as a unit of analysis for the overall pooled prevalence.

Meta-regression

Meta-regression was used to determine a trend of the prevalence of antimicrobial resistance of *S. suis* isolated from pigs over the publication year. Seven antibiotics with different classes were separately analyzed for meta-regression.

Sensitivity analysis

Sensitivity analysis was conducted to assess robustness of results in estimating the prevalence antimicrobial resistance of *S. suis* isolated from pigs. First, results of fixed effect model were compared with results of random effect model. Second, a leave-one-out meta-analysis was conducted to evaluate whether each individual study influenced the results. Seven antibiotics from different classes were separately analyzed for sensitivity analysis.

Assessments of publication bias

Egger's test, and Begg's test were used with a p-value <0.1 indicating the presence of publication bias (Begg and Mazumdar, 1994; Egger et al., 1997). The funnel plot was also used for visualization of publication bias. In case of an asymmetrical funnel plot, Duval and Tweedie's trim-and-fill method (Duval and Tweedie, 2000) was used to impute possibly missing studies and to estimate the adjusted prevalence antimicrobial resistance of *S. suis* isolated from pigs.

Results

Identification and selection of studies

A total of 360 articles were identified from three databases (Scopus 121 articles, PubMed 154 articles, Web of science 85 articles). After 153 duplications were removed, 202 articles were assessed for their eligibility. Of these, 151 articles were removed after screening of titles and abstracts. Therefore, 56 articles were retained for full-text assessment. Regarding the inclusion and exclusion criteria, 30 full-text articles were excluded. Eventually, 26 studies were included in the meta-analysis (Prieto et al., 1994; Kataoka et al., 2000; Martel et al., 2001; Vela et al., 2005; Ruzauskas et al., 2006; Zhang et al., 2008, 2020; Lakkitjaroen et al., 2011; X.-T. Li et al., 2012; L.-L. Li et al., 2012; Soares et al., 2014; Gurung et al., 2015; Huang et al., 2015; van Hout et al., 2016; Oh et al., 2017; Hernandez-Garcia et al., 2017; Matajira et al., 2019; Yongkiettrakul et al., 2019; Holmer et al., 2019; Renzhammer et al., 2020; Serpa et al., 2020; Hayer et al., 2020; Ichikawa et al., 2020; Petrocchi-Rilo et al., 2021; Tan et al., 2021; Guo et al., 2022). The process of studies selection is shown in the flow chart (Figure 1)

Characteristics of the included studies

The included studies were published between 1994 and 2022 (with the study year between 1987 and 2020). A total of 14,068 isolates (10,068 from diseased pigs, 2,374 from healthy pigs, and 1,626 from unspecified health status of pigs) were reported. The studies were conducted from 11 countries in 4 continents (Table 1) with the median sample size of 219 (ranging from 22-6746 isolates). The included studies were from Asia (13 studies), Europe (6 studies) and other continents (7 studies).

Of 26 articles, a total of 63 antibiotics from different classes were tested. According to the antibiotic class investigated, ceftiofur (belonging to cephalosporines) was commonly used for the study of antimicrobial resistance of *S. suis* isolated from pigs (N=21/26 studies). The most common diagnostic techniques used for antibiotics resistance were broth microdilution (N= 15/26 included studies) and disk diffusion (N=10/26).

Study quality assessment

Of the 26 studies, mean ± standard deviation of the overall quality scores was 9.08 ± 1.16, ranging from 6 to 10 with the median of 9.5. A detail of study quality assessment is present in Table 2.

Overall meta-analysis

Table 3 summarized the pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs for seven antibiotics of different classes. Of seven antibiotics, the highest pooled prevalence of antimicrobial resistance was tetracycline (89.2%, [95% CI, 83.5–93.2%]), followed by Clindamycin (83.8%, [95% CI, 73.7–90.5%]). The lowest pooled prevalence of the antimicrobial resistance was ceftiofur (4.3% [95% CI, 2.2–8.2%]), and penicillin (7.5% [95% CI, 4.0–13.6%]).

Meta-regression

Results of the meta-regression analysis of the prevalence of antimicrobial resistance for seven antibiotics are present in Table 4. No significant change of the trend was observed for all seven antimicrobials (p-value >0.05).

Sensitivity analysis

The results of the fixed effect and random effect analyses of the overall pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs to seven antibiotics were compared. The results of the random effect model were considerably higher than those of the fixed effect

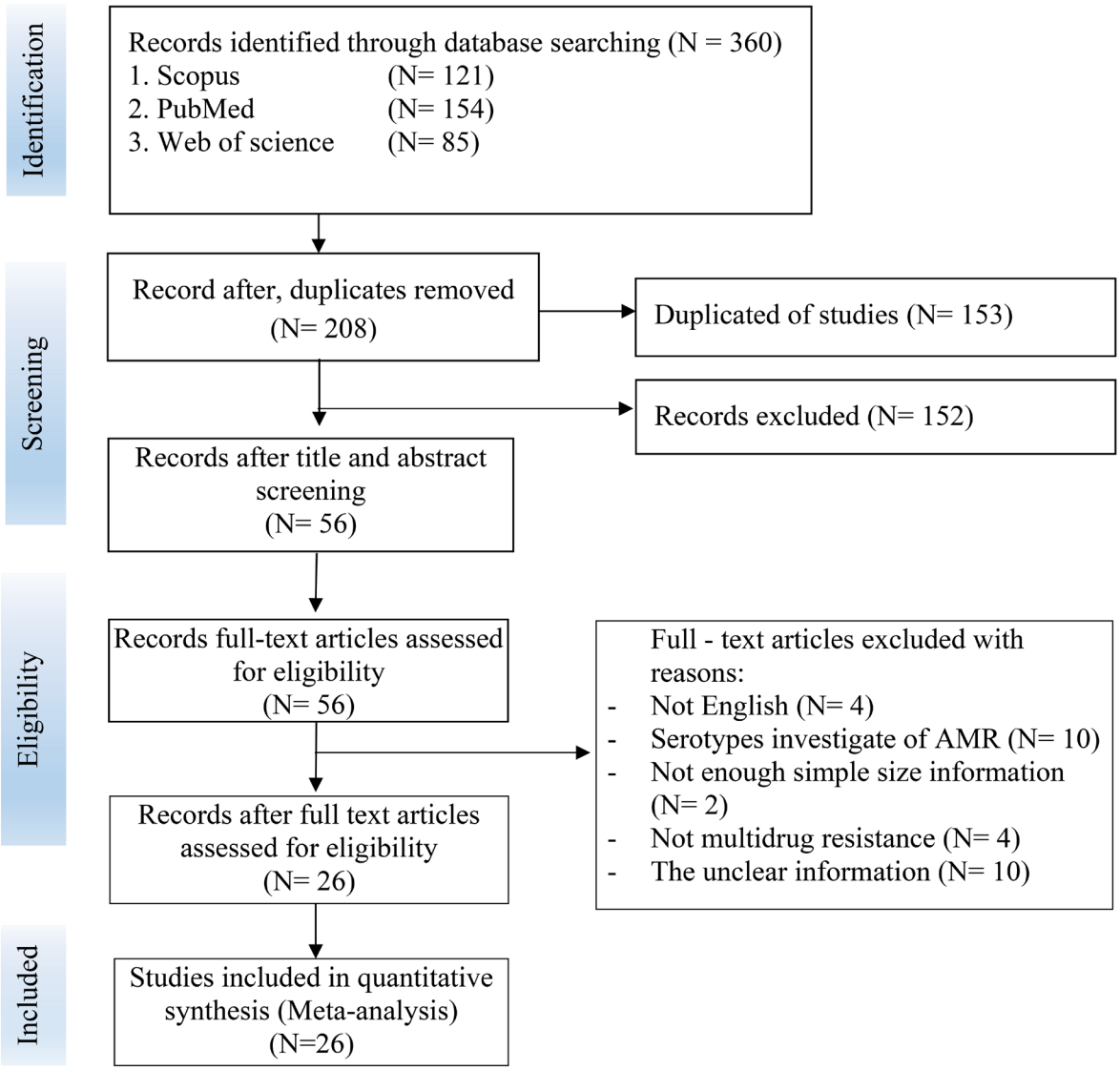


Figure 1. PRISMA flow diagram for the study selection

model for clindamycin (83.8% [95% CI, 73.7–90.5%] versus 58.8% [95% CI, 56.9–60.7%], respectively), erythromycin (69.3% [58.8–68.1%] versus 52.8% [95% CI, 51.5–54.1%], respectively), and tetracycline (89.2% [95% CI, 83.5–93.2%] versus 79.2% [95% CI, 78.1–80.4%], respectively). The results of the random effect model were considerably lower than those of the fixed effect model for ceftiofur (4.3% [95% CI, 2.2–8.2%] versus 12.7% [95% CI, 12.0–13.5%], respectively) and enrofloxacin (10.6% [95% CI, 5.0–21.1%] versus 19.3% [95% CI, 17.9–20.7%], respectively).

For the leave-one-out analysis, the pooled prevalence of antimicrobial resistance of *S. suis* to six antibiotics was slightly changed. Only sulfamethoxazole/trimethoprim was clearly changed (ranging from 11.9% [95% CI, 4.3–29.1%] to 21.9% [95% CI, 8.5–46.0%]).

Assessments of publication bias

The publication bias was observed for clindamycin (p-value of Egger's test <0.001), erythromycin (p-value of Egger's test = 0.019), enrofloxacin (p-value of Begger's

Table 1. Characteristics of the included studies (N=26)

Author	Years of study	Countries	Number of *S. suis* isolates regarding pig's health status				No. of ACT
			Healthy	Disease	Unspecify	total	
Prieto., 1994	1990		522			522	6
Kataoka., 2000	1987-1996	Japan	28	661		689	7
Martel, 2001	1999-2000			87		87	6
Vela., 2005	1999-2001	Spain		151		151	10
Ruzauskas., 2006	2000-2004	Lithuania			30	30	8
Zhang., 2008	2005-2007	China	421			421	10
Lakkitjaroen., 2011	2008-2009	Thailand	52			52	6
Li., 2012 (a)	2008/2010	China		159		159	8
Li., 2012 (b)	2009-2010	China		30		30	7
Soares., 2014	2009-2010	Brazil	260			260	8
Gurung., 2015	2010-2013	Korea	171	56		227	9
Huang., 2014	2005-2010	China		46		46	6
Van Hout., 2016	2013-2015	Netherlands		1163		1,163	10
Hernandez-Garcia., 2017	2009-2011 & 2013-2014	England	195	210		405	10
Oh., 2017	2009-2010	Korea	142	98		240	7
Holmer., 2019	2004-2017				1482	1,482	11
Matajira., 2019	2001-2016	Brazil		215		215	10
Yongkiettrakul., 2019	2006-2007 & 2012-2015	Thailand	189	46		235	11
Hayer., 2020	2006-2016	USA		6746		6,746	9
Ichikawa., 2020	2004-2007 & 2014-2016	Japan			114	114	10
Serpa., 2020	2006-2007	Brazil	42			42	9
Renzhammer., 2020	2016-2020	Austria		297		297	9
Zhang., 2020	2016-2018	China	223			223	9
Petrocchi-Rilo., 2021	2019-2020	Spain		103		103	10
Fang Tan., 2021	2017-2019	China	107			107	10
Guo., 2022	2018-2019	China	22			22	10
Total			2,374	10,068	1,626	14,068	

Abbreviation: ACT = antibiotic classes tested

Table 2. Quality assessment of the included studies (N=26)

Questions	No. of included study and category		
	yes	no	unsure
Was the research objective clearly described and state?	25	0	1
Was the period and location of the study clearly state?	21	1	4
Was the sample categorized into different subgroups?	16	0	10
Was the sampling method described in detail?	20	0	6
Were the diagnostic techniques clearly pointed out?	25	0	1

Table 3. The overall pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs

Antibiotics	No. of studies	% Resistance		Heterogeneity		
		Estimate	95% CI	Q	P-value	I^2 (%)
Ceftiofur	21	4.3	2.2–8.2	790.5	<0.001	97.5
Enrofloxacin	18	10.6	5.0–21.1	1242.0	<0.001	98.6
Penicillin	19	7.5	4.0–13.6	1050.0	<0.001	98.3
Tetracycline	19	89.2	83.5–93.2	627.6	<0.001	97.2
Erythromycin	18	69.3	58.8–78.1	614.0	<0.001	97.2
Sulfa/Trim*	14	17.1	6.6–37.9	1916.9	<0.001	99.3
Clindamycin	15	83.8	73.7–90.5	597.4	<0.001	97.7

*Abbreviation: Sulfa/Trim = Sulfamethoxazole/Trimethoprim.

Table 4. The results of the meta-regression for the resistance of *S. suis* isolated from pigs to seven antibiotics over years.

Antibiotic	Intercept	Year			
		Coefficient	95% Lower	95% Upper	P-value
Ceftiofur	94.44	-0.05	-0.20	0.11	0.540
Enrofloxacin	-133.17	0.07	-0.08	0.21	0.370
Penicillin	1.60	-0.002	-0.10	0.09	0.966
Tetracycline	-8.63	-0.01	-0.08	0.09	0.896
Erythromycin	-0.59	-0.00	-0.07	0.08	0.986
Sulfa/Trim*	-35.16	0.02	-0.11	0.15	0.799
Clindamycin	87.02	-0.04	-0.17	0.08	0.501

Note: The logit event rate = Intercept + Coefficient (year), which year is the study year
*Abbreviation: Sulfa/Trim = Sulfamethoxazole/Trimethoprim.

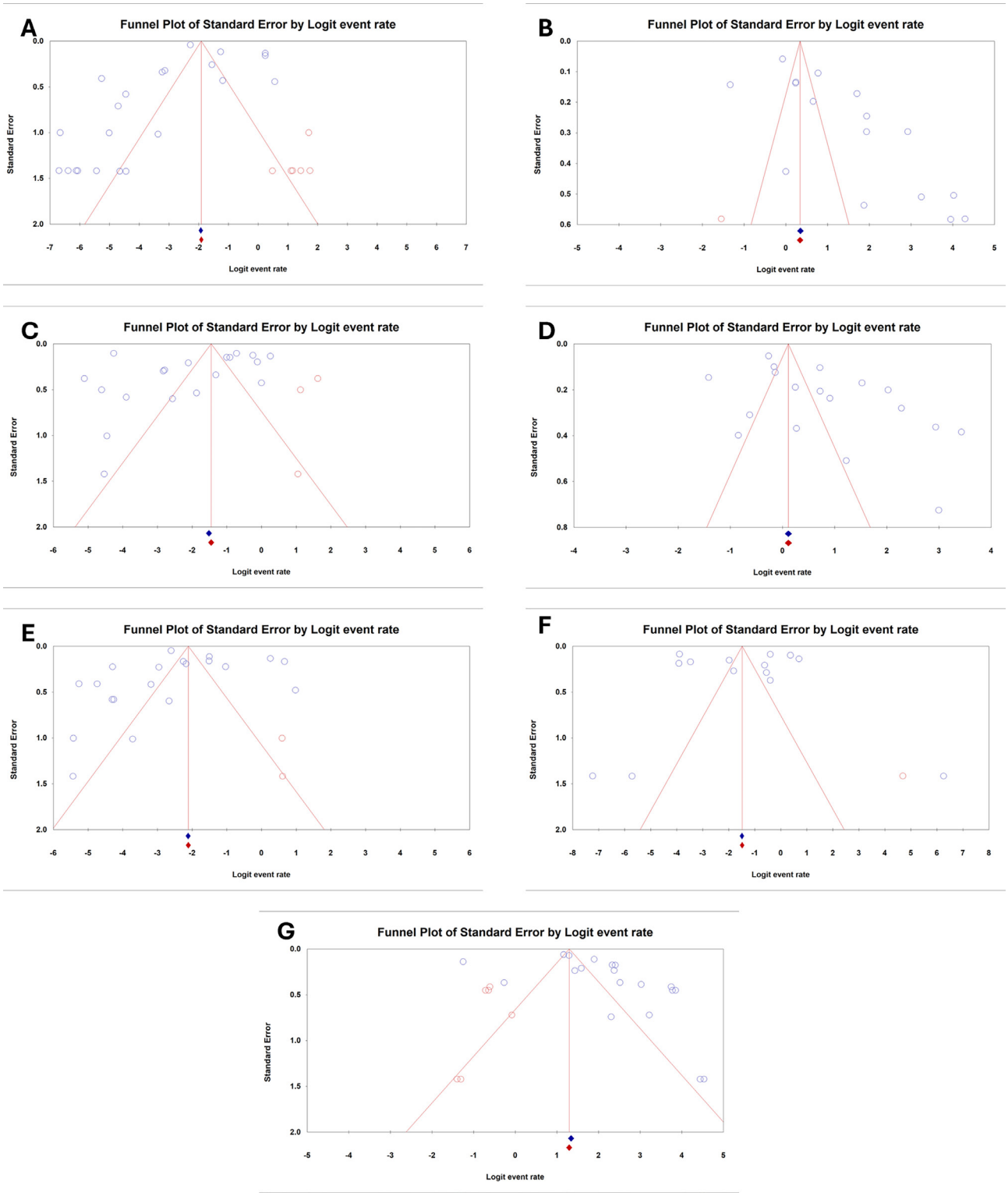


Figure 2 Funnel plots for assessing the publication bias of all seven antibiotics analyzed. A blue circle represents the included studies. A red circle represents the imputed or missing studies. Abbreviations: A for Ceftiofur, B for Clindamycin, C for Enrofloxacin, D for Erythromycin, E for Penicillin, F for Sulfamethoxazole/Trimethoprim, G for Tetracycline.

test = 0.080), and tetracycline (p-value of Egger's test = 0.094). The funnel plots are shown in Figure 2.

Discussion

In the present study, a random effects model was used for estimating the global prevalence of antimicrobial resistance of *S. suis* isolated from pigs from 26 included studies (1987–2020). This included 14,068 isolates from 11 countries on four continents. The common diagnosis technique for the prevalence of antimicrobial resistance was broth microdilution (Carson, Hammer, and Riley, 1995). For the seven antimicrobials analyzed, This can categorize the resistance rate into two groups: the high resistance (the resistance rate more than 60%) and the low to moderate resistance (the resistance less than 20%). Antibiotics with the high resistance rate were tetracycline, clindamycin, and erythromycin, respectively. Antibiotics with the low resistance rate were ceftiofur, penicillin, enrofloxacin, and sulfamethoxazole/trimethoprim, respectively. Below each resistance group was described in more details.

In the high resistance group, the highest overall pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs was tetracycline 89.2% (95% CI, 83.5–93.2%), followed by clindamycin 83.8% (95% CI, 73.7–90.5%), and erythromycin 69.3% (95% CI, 58.8–78.1%). The high level of resistance to tetracycline in *S. suis* isolated from pigs was comparable to that observed in humans. Yongkiettrakul et al. (2019) reported that 100.0% of *S. suis* human isolates were resistant to tetracycline and doxycycline (tetracyclines group), followed by azithromycin (macrolides group) (approximately 81.5%) (Yongkiettrakul et al., 2019). *S. suis* has been found to exhibit two distinct mechanisms of resistance to tetracyclines. (i) Efflux pumps, which transport the antibiotic out of the cell, are encoded by *tet(L)*, *tet(B)*, *tet(K)*, or *tet(40)* genes. (ii) Ribosome protection proteins, encoded by *tet(O)* (the most commonly reported gene in *S. suis*), tet(M), tet(S), tet(W), tet(O/W/32/O), or tet(O/32/O) genes (Dechêne-Tempier et al., 2021; Uruén et al., 2022). The high resistance of *S. suis* to tetracycline may be attributed to the widespread use of tetracycline in the swine industry. Therefore, tetracyclines were deemed unsuitable for treating *S. suis*-induced diseases in pigs.

In this study, the high resistance rate of *S. suis* to erythromycin and clindamycin were also observed. Although erythromycin and clindamycin are belonging to different drug classes (erythromycin is a macrolide antibiotic but clindamycin is a lincosamide antibiotic), macrolide, lincosamide, and streptogramin share some common mechanisms of action resulting in a classification as macrolide, lincosamide, and streptogramin (MLS) group. MLS antibiotics exhibit their antimicrobial action by binding to the 23S rRNA of the 50S subunit of the bacterial ribosome, which leads to the separation of peptidyl-tRNAs (Uruén et al., 2022). As a result, MLS block translation. For erythromycin, the resistance rate varied greatly among studies ranging from 19.5% in Austria (Renzhammer et al., 2020) to 96.5% in China (Zhang et al., 2020). This indicated the high variation of the resistance rate of *S. suis* to erythromycin between different regions. For clindamycin, except two studies from Austria and Netherlands (with the resistance rate of 20.9% and 48.1%, respectively) (van Hout et al., 2016; Renzhammer et al., 2020), most included studies had high resistance rates over 50%. Especially, several studies from Asia had the high resistance rate over 90% (Gurung et al., 2015; Yongkiettrakul et al., 2019; Zhang et al., 2020; Tan et al., 2021). These results suggest that erythromycin and clindamycin are not suitable for treating *S. suis* disease in pigs in certain Asian countries.

In the low to moderate resistance group, the lowest overall pooled prevalence of antimicrobial resistance of *S. suis* isolated from pigs was ceftiofur, 4.3% (95% CI, 2.2–8.2%), followed by penicillin, 7.5% (95% CI, 4.0–13.6%), enrofloxacin, 10.6% (5.0–21.1%), and sulfamethoxazole/trimethoprim, 17.1% (95% CI, 6.6–37.9%). These results indicated that these drugs may still be suitable for treating *S. suis* infections in pigs.

Ceftiofur is a broad spectrum of a third generation cephalosporin. Due to its rapid absorption, prolonged effective drug concentration in the lungs, slow elimination, and high bioavailability, ceftiofur is widely used for treating swine respiratory diseases including *S. suis*, *Pasteurella*

multocida, *Salmonella* Choleraesuis, *and Actinobacillus pleuropneumoniae* (Risco and Hernandez, 2003; Luo et al., 2021). This makes it superior to first- or second-generation cephalosporins. The current analysis observed no resistance (0%) to ceftiofur from many studies (Lakkitjaroen et al., 2011; Hernandez-Garcia et al., 2017; Holmer et al., 2019; Matajira et al., 2019; Ichikawa et al., 2020; Renzhammer et al., 2020; Serpa et al., 2020). In our included studies, the highest resistance rate was 6.5% from Korea (Gurung et al., 2015).

Penicillin is effective for treating *S. suis* infections in pigs in some regions because the resistance rate is still low. The current analysis found the resistance rate to penicillin lower than 1% from many studies (Kataoka et al., 2000; van Hout et al., 2016; Holmer et al., 2019; Ichikawa et al., 2020; Renzhammer et al., 2020). However, some studies reported the moderate resistance to high resistance to penicillin (Prieto et al., 1994; Soares et al., 2014; Gurung et al., 2015; Petrocchi-Rilo et al., 2021; Guo et al., 2022). The highest resistance rate to penicillin was 72.7% from China (Guo et al., 2022). Beta-lactams, such as penicillin, are a broad category of antibiotics that have been classified as "highly important antimicrobials" by the World Health Organization. Remarkably, despite the global utilization of beta-lactams in pigs for more than five decades, most of clinical *S. suis* strains still exhibit susceptibility to these antibiotics (Dechêne-Tempier et al., 2021). In *S. suis*, beta-lactam resistance can occur as a result of the alteration (changes in molecular weight and/or reduced affinity for penicillin) of various types of penicillin-binding proteins (PBP) that are crucial for the production of peptidoglycan (Haenni et al., 2018).

Enrofloxacin had approximately 10% for the overall resistance rate to *S. suis* isolated from pigs. The resistance rate varied greatly from studies to studies. The resistance rate was low from 0.6% in the study from Netherlands (van Hout et al., 2016), 1% from the study from England (Hernandez-Garcia et al., 2017) and China (Huang et al., 2015), to as high as 50% from the study from China (Guo et al., 2022) and 65% from the study from Korea (Gurung et al., 2015). This indicated that there was great variability in the resistance to enrofloxacin between regions even in the same country. Enrofloxacin is a fluoroquinolone compound extensively used in veterinary medicine as an antibacterial agent. It is not authorized for human use as a medication. It exhibits potent antibiotic activity against both Gram-positive and Gram-negative bacteria, primarily by inhibiting the enzymatic actions of bacterial gyrase and topoisomerase IV (Grabowski et al., 2022).

Sulfamethoxazole/trimethoprim belongs to sulfonamides and trimethoprim. Sulfonamides are characterized by their polarity and consist of a sulfonyl group linked to an amine group. Sulfonamides function as inhibitors of the enzyme dihydropteroate synthase. Folates are essential coenzymes necessary for the synthesis of amino acids and nucleotides. Therefore, due to its crucial role in bacterial growth, sulfonamides exhibit a wide range of effectiveness against both Gram-positive and Gram-negative microorganisms (Uruén et al., 2022). The current analysis observed that resistance rate of *S. suis* to sulfamethoxazole/trimethoprim varied greatly, ranging from less than 1% from the study in Japan (Kataoka et al., 2000) and from the study in Spain (Vela et al., 2005) to more than 70% from the study in Thailand (Yongkiettrakul et al., 2019) or even up to 99% from the study in Brazil (Soares et al., 2014). These indicated that sulfamethoxazole/trimethoprim is less effective for treating pig infections caused by *S. suis* in certain regions.

Regarding the trend of antimicrobial resistance of *S. suis* isolated from pigs over time (Table 4), the trend was not significantly changed over time for all antimicrobial drugs analyzed. This could be interpreted as follows: For the high-resistance group, including tetracycline, clindamycin, and erythromycin, the resistance rate was still high after 20 years. This indicated that tetracycline, clindamycin, and erythromycin are not suitable drugs for treating *S. suis* infections in pigs. For the low-resistance group, ceftiofur and penicillin were still effective against *S. suis* for over 20 years. Therefore, they are still suitable for treating *S. suis* infections in pigs.

Sensitivity analysis indicated the robustness of the present results in estimating the global prevalence of and

timicrobial resistance of *S. suis* isolated from pigs. However, the current estimate of each antimicrobial was influenced from possible publication bias because trim-and-fill method results showed missing publications. After added missing studies in model, point estimate of overall pooled prevalence of individual antibiotic resistance of *S. suis* infection in pigs were slightly changed. Results from trim-and-fill methods indicated that tree of seven antibiotics had increasing point estimate after adding missing studies to the model, ceftiofur (5 studies to the model, the point estimate slightly increased from 4.3% [95% CI, 2.2–8.2%] to 7.7% [95% CI, 4.2–13.7%] and Q=823.4), penicillin (2 studies to the model the point estimate increased from 7.5% [95% CI, 4.0–13.6%] to 9.2% [95% CI, 5.1–16.1%] Q=1064.7), sulfamethoxazole/trimethoprim (1 studies to the model the point estimate slightly increased from 17.2 % [95% CI, 6.6–37.9%] to 22.0% [95% CI, 8.9–44.8%] Q=1936.0). These results indicated that the global prevalence of three antimicrobial resistance of *S. suis* isolated from pigs may be higher if the publication bias was not present. The high prevalence of antimicrobial resistance in *S. suis* infection among pigs indicates a potential risk of *S. suis* infection in humans.

Conclusion

The present study used a random effect model to estimate the global prevalence of antimicrobial resistance of *S. suis* isolated from pigs from 26 included articles. The highest overall pooled prevalence of antibiotic resistance of *S. suis* isolated from pigs was tetracycline, 89.2% (95% CI, 83.5–93.2%), followed by clindamycin, 83.8% (95% CI, 73.7–90.5%), and erythromycin, 69.3% (95% CI, 58.8–78.1%). The lowest of overall pooled prevalence in seven antibiotics was ceftiofur, 4.3% (95% CI, 2.2–8.2%) and penicillin, 7.5% (95% CI, 4.0–13.6%). The trend of antimicrobial resistance of *S. suis* isolated from pigs was not significantly changed over time for all seven antibiotics analyzed.

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Conflicts of Interest

The authors declare no conflicts of interest.

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