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Prevalence of Senecavirus A in pigs from 2014 to 2020: a global systematic review and meta-analysis

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ABSTRACT

Background: Senecavirus A (SVA), a member of the family *Picornaviridae*, is newly discovered, which causes vesicular lesions, lameness in swine, and even death in neonatal piglets. SVA has rapidly spread worldwide in recent years, especially in Asia.

Objectives: We conducted a global meta-analysis and systematic review to determine the status of SVA infection in pigs.

Methods: Through PubMed, VIP Chinese Journals Database, China National Knowledge Infrastructure, and Wanfang Data search data from 2014 to July 26, 2020, a total of 34 articles were included in this analysis based on our inclusion criteria. We estimated the pooled prevalence of SVA in pigs by the random effects model. A risk of bias assessment of the studies and subgroup analysis to explain heterogeneity was undertaken.

Results: We estimated the SVA prevalence to be 15.90% (1,564/9,839; 95% confidence interval [CI], 44.75–65.89) globally. The prevalence decreased to 11.06% (945/8,542; 95% CI, 28.25–50.64) after 2016. The highest SVA prevalence with the VP1-based RT-PCR and immunohistochemistry assay was 58.52% (594/1,015; 95% CI, 59.90–83.96) and 85.54% (71/83; 95% CI, 76.68–100.00), respectively. Besides, the SVA prevalence in piglet herds was the highest at 71.69% (119/166; 95% CI, 68.61–98.43) ($p < 0.05$). Moreover, our analysis confirmed that the subgroups, including country, sampling year, sampling position, detected gene, detection method, season, age, and climate, could be the heterogeneous factors associated with SVA prevalence.

Conclusions: The results indicated that SVA widely exists in various countries currently. Therefore, more prevention and control policies should be proposed to enhance the management of pig farms and improve breeding conditions and the environment to reduce the spread of SVA.

Keywords: Geographic region; swine; incidence; seneca valley virus; feeding model

INTRODUCTION

Senecavirus A (SVA) is a single-stranded and non-enveloped RNA virus from the genus *Senecavirus* in the family *Picornaviridae* [1]. The virus was initially discovered and isolated from PER.C6 cell cultures [2]. Subsequently, SVA infection in pigs was confirmed, resulting in

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diseases and death [3]. SVA infection can cause severe clinical symptoms in pigs of all ages. Feeder pigs, finishing pigs, and reserve pigs present anorexia, lethargy, and fever in the early stages of the disease, followed by the snout and coronary band, sole and dewclaw vesicular lesions, acute ulceration, and lameness [4]. Newborn piglets have a high mortality rate [5]. Its clinical symptoms are very similar to other swine vesicular diseases, including vesicular stomatitis and foot-and-mouth disease. SVA can be identified in different tissues and organs of infected pigs by molecular techniques, immunohistochemistry (IHC) assay, and *in situ* hybridization techniques. Currently, the transmission mechanism of SVA is unclear, and the existence of recessive infection. Moreover, commercial vaccines are unavailable, although numerous inactivated and attenuated vaccines have been intensively tested [6,7]. Therefore, the prevention and control of SVA in pig farms depend on comprehensive feeding management and strict biosafety measures.

In recent years, SVA has been detected in pigs with a vesicular disease in numerous countries, including the United States, Canada, Brazil, China, Thailand, Vietnam, and Colombia [3,6,8-12]. In 2015, pigs in multiple farms of at least six States in Brazil and nine states in the United States were infected with SVA [6]. This finding indicates the rapid viral spread, distributed globally, resulting in considerable global livestock production and trade losses. SVA infection has also been confirmed in several provinces in China, with the first case of SVA infection in Guangdong Province in early 2015 [3,13]. From 2016 to 2018, SVA infection has been found in at least 14 provinces in China and showed an increasing trend annually [14]. It indicates that SVA infection is relatively widespread in China. China is the world's largest pig-raising country, with pork production accounting for about 50% of the global output [15]. However, the enormous pig population with high density, imperfect breeding models, and poor technology and management may further accelerate the spread of SVA and affect the health of the pig herd [3]. Sufficient awareness of the disease associated with SVA and corresponding measures should be enhanced to prevent and control the disease.

To date, no systematic assessment of the prevalence of SVA is available. Understanding the epidemiology and infection dynamics of SVA will help effectively prevent and control the spread of disease. Therefore, we conducted a systematic review and meta-analysis of SVA infection to assess potential risk factors, including sampling area (region and country), geographical factors (longitude and latitude), sampling time, sampling position, detected gene, detection method, sampling site, season, age, model, and climate (precipitation and temperature), which may provide a solid theoretical basis for controlling disease transmission.

MATERIALS AND METHODS

Search strategy

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses to select credible study reports [16]. We searched for articles about the prevalence of SVA in different countries from four literature databases, including the China National Knowledge Infrastructure, VIP Chinese Journals Database, Wanfang Data, and PubMed (the retrieval time was from inception to July 26, 2020). In PubMed, we used the MeSH terms "Seneca Valley virus" and "Senecavirus A" for searching. Simultaneously, we used the Boolean operator "OR" to link MeSH terms. Finally, the search formula "(Seneca Valley virus) OR (Senecavirus A)" was used during the search. The keywords "Seneca" and "Senecavirus" were used for advanced search in the other three Chinese databases, and synonym expansion or

fuzzy search was also added. Moreover, we did not contact the authors of original studies for additional information nor attempt to identify unpublished reports.

Selection and exclusion criteria

The following inclusion criteria were adopted in this analysis: 1) the goal of the study was to identify Senecavirus in pigs, 2) the study presented the number of pigs tested and SVA-positive pigs, and 3) the study design was based on a cross-sectional investigation. Moreover, the following exclusion criteria were used: 1) the study had internal data conflicts, 2) the study contained unextractable data, 3) the sample size was smaller than 6, and 4) the study included incomplete information.

Data extraction and analysis

From all the acquired studies, we extracted the following information according to the standardized data collection forms: first author, publication year, sampling time, the continent of the study, country of the study, sampling position, detected gene, detection method, geographical factors, sampling site, collection season, age, feeding model, and the number of pigs tested in the study and SVA-positive samples. The geographic data, including longitude, latitude, annual average precipitation, and annual average temperature, were collected from the NOAA National Centers for Environmental Information (https://gis.ncdc. noaa.gov/maps/ncei/cdo/monthly).

Quality assessment

The quality of the included studies was scored following a previous method derived from the Grading of Recommendations, Assessment, Development, and Evaluation [17-19]. The scoring criteria were as follows: detailed sampling site, random sampling, definite sampling time, precise detection method, and three or more risk factors. Each condition was scored one point. Articles with 4–5 scores were high quality, those with 2–3 were medium quality, and those with 1 or 0 were low quality [20].

Statistical analysis

All statistical analyses were conducted in R (version 4.0.2) [21], and the arcsine transformation (PAS) conversion (W = 0.93909; $p > 0.05$) (**Table 1**) was used to adapt the data to the normal distribution for our meta-analysis as previously reported [22]. The results of heterogeneity between studies were calculated by Cochran's Q, I^2 statistics (cutoff value was 50%), and χ^2 test ($p < 0.05$). Meanwhile, we used a random-effect model to conduct comprehensive data and subgroup analysis as the selected articles were significantly heterogeneous [23]. Forest plots were used to clarify the overall results of the meta-analysis. The studies of publication bias were explained with funnel plots and Egger's test. Finally, we used sensitivity analysis to estimate the stability of the results [24].

Table 1. Normal distribution test for the normal rate and the different conversion of the normal rate

Conversion form	Shapiro-Wilk test	p
PRAW	0.89226	0.002883
PLN	0.84213	0.0001876
PLOGIT	NaN	NA
PAS	0.93909	0.05792
PFT	0.90991	0.008468

PRAW, actual rate; PLN, logarithmic conversion; PLOGIT, logit transformation; PAS, arcsine transformation; PFT, double-arcsine transformation; NaN, meaningless number; NA, missing data.

We further found the potential sources of heterogeneity from the subgroups [25], including the geographic region (Asia vs. other regions), country (China vs. other countries), sampling year (before 2016 vs. 2016 or later), sampling position (serum vs. other positions), targeted gene for detection (3D vs. other genes), detection method (immunohistochemistry vs. other methods), sampling site (pig markets vs. other sites), season (winter vs. three other seasons), age (piglet vs. other ages), feeding model (extensive farming vs. intensive farming) and quality level (medium quality vs. high quality).

We also analyzed whether the subgroup of geographical risk factors, including latitude (north latitude 31°–35° vs. other latitude ranges), longitude (west longitude 90°–100° vs. other longitude ranges), annual average precipitation (20–50 mm vs. other records), and annual average temperature (0°C–15°C vs. other records), could influence heterogeneity [26].

RESULTS

Search results and qualification studies

Based on the inclusion criteria, we finally selected 34 studies from the four databases for meta-analysis (**Fig. 1**), including 15 publications with medium quality (1–3 points) and 19 publications with high quality (4–5 points) (**Supplementary Table 1**).

Publication bias and heterogeneity analysis

The funnel plot results were asymmetric, indicating the presence of publication bias (**Fig. 2**). In addition, the result of Egger's test further indicated a certain publication bias ($p < 0.05$) (**Supplementary Table 2**). The forest plot illustrated prevalence estimates of SVA in pigs
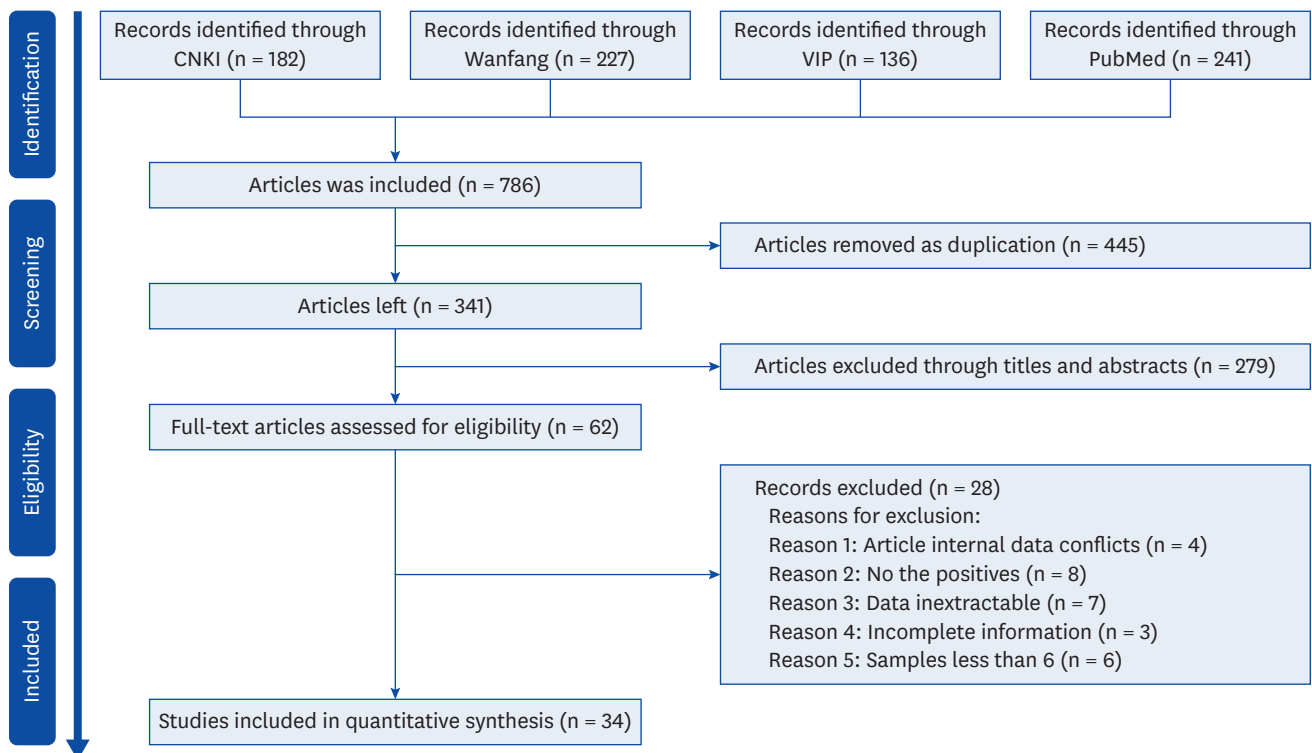

Fig. 1. Flow diagram of the screening process of inclusion and exclusion of studies.
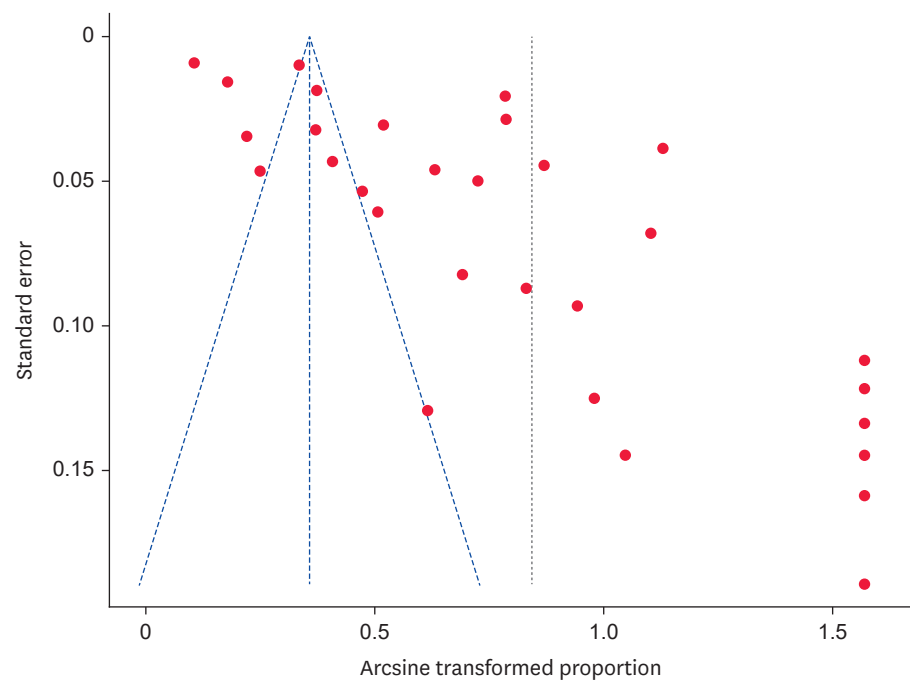
Fig. 2. Funnel plot of the analysis of publication bias of studies.

from different countries with evident heterogeneity among studies (χ^2 = 3,080.38; p = 0.00; I^2 = 98.90%; 95% confidence interval [CI], 44.75–65.89) (**Fig. 3**). Finally, sensitivity analysis explained the data reliability because the prevalence was not influenced when excluding one study (**Fig. 4**).

Results of the meta-analysis

A total of 9,839 pigs were surveyed, and the prevalence of SVA was 15.90% (95% CI, 44.75–65.89) (**Fig. 3**, **Table 2**) worldwide. The detailed SVA prevalence in pigs from varied regions ranged from 9.45% (95% CI, 35.16–59.26) to 52.27% (95% CI, 55.06–85.57; **Table 2**), and the lowest prevalence was in Asia. Thailand had the highest prevalence of 75.00% (95% CI, 47.89–94.32), whereas China had the lowest rate of 9.35% (95% CI, 33.52–57.95) (**Fig. 5**, **Table 2**).

We estimated the potential major risk factors in subgroups associated with SVA infection (p < 0.05), including sampling year, sampling position, detected gene, detection method (**Table 2**), and geographical and annual average precipitation factors (**Table 3**). The prevalence of SVA in the groups containing the cases before 2016 was higher (47.72%; 95% CI, 62.32–88.05) than in the 2016 or later group (11.06%; 95% CI, 28.25–50.64) (**Table 2**). Moreover, feces as the sample for detection had the highest rate at 78.00% (95% CI, 32.35–100.00). The VP1 target gene for detection also had the highest rate of 58.52% (95% CI, 59.90–83.96). Immunohistochemistry presented the highest prevalence at 85.54% (95% CI, 76.68–100.00) compared with other methods. Meanwhile, the prevalence of SVA in autumn was significantly higher (41.18%; 95% CI, 39.49–90.11) than in different seasons. The prevalence of SVA in piglets was the highest at 71.69% (95% CI, 68.61–98.43). The prevalence of SVA in the South latitude (range, 31°–35°) and West longitude (range, 90°–100°) was the highest at 52.60% (95% CI, 36.64–98.74) and 69.51% (95% CI, 45.76–100.00), respectively. Meanwhile, the annual average precipitation (50–80 mm) had the highest prevalence at 41.03% (95% CI, 11.65–100.00).

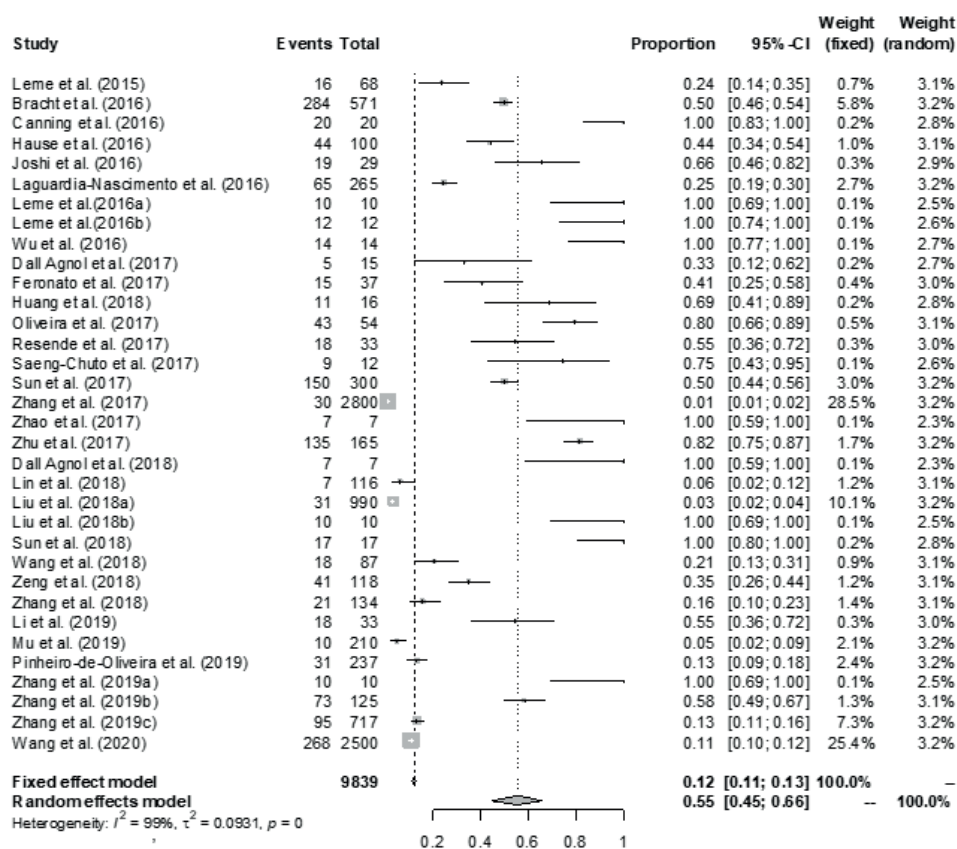| Study	Events	Total	Proportion	95%-CI	Weight (fixed)	Weight (random)
Leme et al. (2015)	16	68	0.24	[0.14; 0.35]	0.7%	3.1%
Bracht et al. (2016)	284	571	0.50	[0.46; 0.54]	5.8%	3.2%
Canning et al. (2016)	20	20	1.00	[0.83; 1.00]	0.2%	2.8%
Hause et al. (2016)	44	100	0.44	[0.34; 0.54]	1.0%	3.1%
Joshi et al. (2016)	19	29	0.66	[0.46; 0.82]	0.3%	2.9%
Laguardia-Nascimento et al. (2016)	65	265	0.25	[0.19; 0.30]	2.7%	3.2%
Leme et al. (2016a)	10	10	1.00	[0.69; 1.00]	0.1%	2.5%
Leme et al. (2016b)	12	12	1.00	[0.74; 1.00]	0.1%	2.6%
Wu et al. (2016)	14	14	1.00	[0.77; 1.00]	0.1%	2.7%
Dall Agnol et al. (2017)	5	15	0.33	[0.12; 0.62]	0.2%	2.7%
Feronato et al. (2017)	15	37	0.41	[0.25; 0.58]	0.4%	3.0%
Huang et al. (2018)	11	16	0.69	[0.41; 0.89]	0.2%	2.8%
Oliveira et al. (2017)	43	54	0.80	[0.66; 0.89]	0.5%	3.1%
Resende et al. (2017)	18	33	0.55	[0.36; 0.72]	0.3%	3.0%
Saeng-Chuto et al. (2017)	9	12	0.75	[0.43; 0.95]	0.1%	2.6%
Sun et al. (2017)	150	300	0.50	[0.44; 0.56]	3.0%	3.2%
Zhang et al. (2017)	30	2800	0.01	[0.01; 0.02]	28.5%	3.2%
Zhao et al. (2017)	7	7	1.00	[0.59; 1.00]	0.1%	2.3%
Zhu et al. (2017)	135	165	0.82	[0.75; 0.87]	1.7%	3.2%
Dall Agnol et al. (2018)	7	7	1.00	[0.59; 1.00]	0.1%	2.3%
Lin et al. (2018)	7	116	0.06	[0.02; 0.12]	1.2%	3.1%
Liu et al. (2018a)	31	990	0.03	[0.02; 0.04]	10.1%	3.2%
Liu et al. (2018b)	10	10	1.00	[0.69; 1.00]	0.1%	2.5%
Sun et al. (2018)	17	17	1.00	[0.80; 1.00]	0.2%	2.8%
Wang et al. (2018)	18	87	0.21	[0.13; 0.31]	0.9%	3.1%
Zeng et al. (2018)	41	118	0.35	[0.26; 0.44]	1.2%	3.1%
Zhang et al. (2018)	21	134	0.16	[0.10; 0.23]	1.4%	3.1%
Li et al. (2019)	18	33	0.55	[0.36; 0.72]	0.3%	3.0%
Mu et al. (2019)	10	210	0.05	[0.02; 0.09]	2.1%	3.2%
Pinheiro-de-Oliveira et al. (2019)	31	237	0.13	[0.09; 0.18]	2.4%	3.2%
Zhang et al. (2019a)	10	10	1.00	[0.69; 1.00]	0.1%	2.5%
Zhang et al. (2019b)	73	125	0.58	[0.49; 0.67]	1.3%	3.1%
Zhang et al. (2019c)	95	717	0.13	[0.11; 0.16]	7.3%	3.2%
Wang et al. (2020)	268	2500	0.11	[0.10; 0.12]	25.4%	3.2%
Fixed effect model		9839	0.12	[0.11; 0.13]	100.0%	–
Random effects model			0.55	[0.45; 0.66]	–	100.0%

Heterogeneity: $I^2 = 99\%$, $\tau^2 = 0.0931$, $p = 0$

Fig. 3. Forest plot illustrating Senecavirus A infection in pigs from different countries. CI, confidence interval.

Through the papers that satisfied the inclusion criteria, we extracted other subgroup factors including sampling location, feeding model, and annual average temperature. And we analyzed other subgroup factors ($p > 0.05$). SVA prevalence in farms was the lowest at 12.33% (95% CI, 45.88–70.80). SVA prevalence in extensive farming was higher (28.15%; 95% CI, 4.66–87.33) than in intensive farming. The prevalence of SVA in the annual average temperature (range, 15°C–20°C) was 58.38% (95% CI, 43.19–98.98), which was higher than in other records.

DISCUSSION

SVA has become prevalent in many countries in recent years and is spreading rapidly in localized areas [8]. Meanwhile, the mortality rate of piglets is also relatively high, which has caused substantial economic losses to the pig breeding industry [5]. Therefore, detailed knowledge of the epidemiology of SVA is beneficial in evaluating the infection degree in swine and preventing the transmission of the disease. To the best of our knowledge, this study is the first to conduct a systematic review and meta-analysis of global SVA infections.

Based on sampling year subgroup analysis, the SVA infection rate before 2016 was significantly higher than that after 2016 ($p < 0.05$; **Table 2**). Before 2016, SVA infections in pigs had been reported in multiple regions, including Brazil, the USA, Canada, Colombia, and Thailand [3,6,8-10,12]. However, after 2016, large-scale epidemic outbreaks of SVA
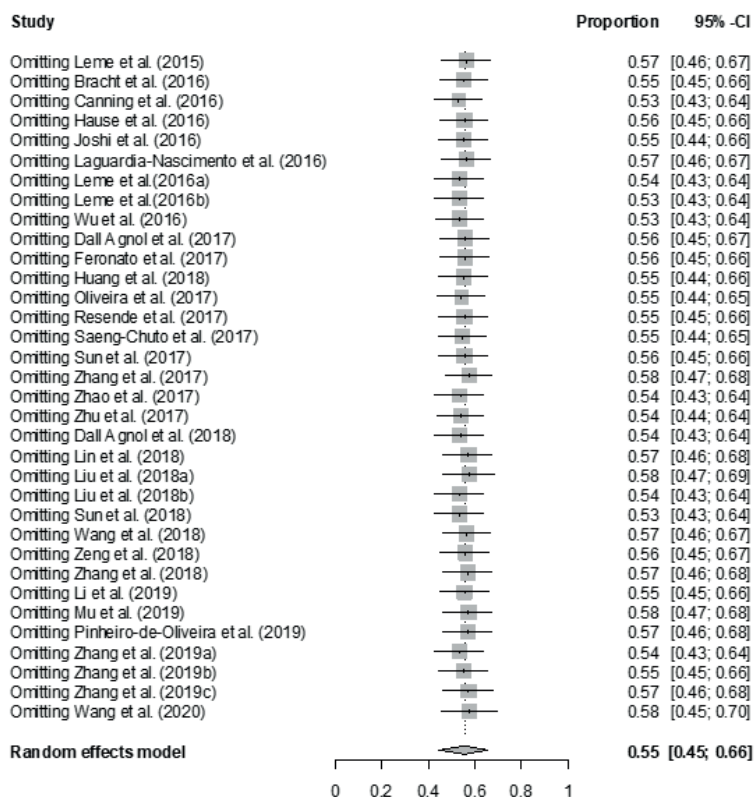
Study		Proportion	95% -CI
Omitting Leme et al. (2015)		0.57	[0.46; 0.67]
Omitting Bracht et al. (2016)		0.55	[0.45; 0.66]
Omitting Canning et al. (2016)		0.53	[0.43; 0.64]
Omitting Hause et al. (2016)		0.56	[0.45; 0.66]
Omitting Joshi et al. (2016)		0.55	[0.44; 0.66]
Omitting Laguardia-Nascimento et al. (2016)		0.57	[0.46; 0.67]
Omitting Leme et al.(2016a)		0.54	[0.43; 0.64]
Omitting Leme et al.(2016b)		0.53	[0.43; 0.64]
Omitting Wu et al. (2016)		0.53	[0.43; 0.64]
Omitting Dall Agnol et al. (2017)		0.56	[0.45; 0.67]
Omitting Feronato et al. (2017)		0.56	[0.45; 0.66]
Omitting Huang et al. (2018)		0.55	[0.44; 0.66]
Omitting Oliveira et al. (2017)		0.55	[0.44; 0.65]
Omitting Resende et al. (2017)		0.55	[0.45; 0.66]
Omitting Saeng-Chuto et al. (2017)		0.55	[0.44; 0.65]
Omitting Sun et al. (2017)		0.56	[0.45; 0.66]
Omitting Zhang et al. (2017)		0.58	[0.47; 0.68]
Omitting Zhao et al. (2017)		0.54	[0.43; 0.64]
Omitting Zhu et al. (2017)		0.54	[0.44; 0.64]
Omitting Dall Agnol et al. (2018)		0.54	[0.43; 0.64]
Omitting Lin et al. (2018)		0.57	[0.46; 0.68]
Omitting Liu et al. (2018a)		0.58	[0.47; 0.69]
Omitting Liu et al. (2018b)		0.54	[0.43; 0.64]
Omitting Sun et al. (2018)		0.53	[0.43; 0.64]
Omitting Wang et al. (2018)		0.57	[0.46; 0.67]
Omitting Zeng et al. (2018)		0.56	[0.45; 0.67]
Omitting Zhang et al. (2018)		0.57	[0.46; 0.68]
Omitting Li et al. (2019)		0.55	[0.45; 0.66]
Omitting Mu et al. (2019)		0.58	[0.47; 0.68]
Omitting Pinheiro-de-Oliveira et al. (2019)		0.57	[0.46; 0.68]
Omitting Zhang et al. (2019a)		0.54	[0.43; 0.64]
Omitting Zhang et al. (2019b)		0.55	[0.45; 0.66]
Omitting Zhang et al. (2019c)		0.57	[0.46; 0.68]
Omitting Wang et al. (2020)		0.58	[0.45; 0.70]
Random effects model		**0.55**	**[0.45; 0.66]**

0   0.2   0.4   0.6   0.8   1

Fig. 4. Sensitivity analysis of eligible studies.
CI, confidence interval.

infection have been confirmed in several regions of China, indicating the rapid evolution of SVA strains and changes in susceptibility [3,14]. Besides, according to the US Department of Agriculture's Veterinary Services Guidance Document 7406.2, pig herds with the vesicular disease should be immediately reported to ensure that it was not caused by imported animal disease (FAD; United States Department of Agriculture, 2016). Furthermore, the general office of Ministry of Agriculture of China issued the "key points of veterinary work in 2018," which pointed out that new infectious diseases such as SVA should be effectively prevented and controlled [27]. Implementing control policies may play an active role in reducing SVA infection in pigs.

The prevalence of SVA in North and South America was higher than that in Asia (**Table 2**). The prevalence also varied significantly among countries, e.g., China, with the lowest prevalence at 9.35% ($p < 0.05$; **Table 2**). The geographical subgroup analysis showed that the SVA prevalence was the highest in the latitude range 31–35°S and longitude range 90–100°W and the lowest in the latitude range 26–30°N and longitude range 111–120°E (**Table 3**). This finding was in agreement with the survey results of the continental subgroup. According to the "*National Development Plan for Live Pig Production (2016–2020)*," the standardization level of pig farms in China has dramatically improved, pig disease prevention and control have been strengthened, and the breeding environment has been significantly improved. As a result, exposure to SVA is decreasing compared with other countries [28]. The policy "key points of veterinary work in 2018" for SVA may have played a role [27]. Therefore, we recommend more effective relevant policies and legislation to control SVA infections.

Table 2. The pooled prevalence of Senecavirus A

Factor	Category	No. of studies	No. of tested	No. of positive	% (95% CI)	Heterogeneity			Univariate meta-regression	
						χ^2	p value	I^2 (%)	p value	Coefficient (95% CI)
Region	South America	11	1,024	363	58.88% (41.31–75.35)	263.10	< 0.01	96.20%	0.0633	−0.1663 (−0.3418 to 0.0092)
	North America	6	859	449	71.59% (55.06–85.57)	75.64	< 0.01	93.40%		
	Asia	18	7,956	752	47.12% (35.16–59.26)	1,485.43	< 0.01	98.90%		
Country	Brazil	10	724	213	60.63% (40.02–79.44)	224.27	< 0.01	96.00%	0.0357	−0.1869 (−0.3613 to −0.0125)
	China	17	7,944	743	45.60% (33.52–57.95)	1,456.37	< 0.01	98.90%		
	Colombia	1	300	150	50.00% (44.35–55.65)	0.00	-	-		
	Thailand	1	12	9	75.00% (47.89–94.32)	0.00	-	-		
	USA	6	859	449	71.59% (55.06–85.57)	75.64	< 0.01	93.40%		
Sampling year	Before 2016	14	1,297	619	76.43% (62.32–88.05)	1,670.81	< 0.01	95.70%	< 0.001	0.3821 (0.1958 to 0.5685)
	2016 or later	20	8,542	945	39.16% (28.25–50.64)	293.16	0	98.90%		
Sampling position	Feces	2	50	39	89.60% (32.35–100.00)	20.31	< 0.01	95.10%	0.0322	−0.3123 (−0.5982 to −0.0265)
	Serum	8	584	96	29.90% (14.85–47.60)	120.75	< 0.01	94.20%		
	Tissue	20	2,399	660	52.18% (36.04–68.09)	1,081.25	< 0.01	98.20%		
	Vesicular fluid	11	679	122	75.42% (45.98–95.58)	357.85	< 0.01	97.20%		
Detected gene	VP1	11	1,015	594	72.77% (59.90–83.96)	120.30	< 0.01	91.70%	0.0086	−0.4095 (−0.7149 to −0.1040)
	VP2	2	132	55	78.79% (2.89–100.00)	44.27	< 0.01	97.70%		
	VP1/VP3	5	2,624	318	60.73% (27.30–89.29)	139.71	< 0.01	97.10%		
	3D	7	939	234	30.80% (16.45–47.38)	156.00	< 0.01	96.20%		
Detection method	Others[a]	8	833	279	39.49% (20.30–60.53)	254.16	< 0.01	97.20%	0.0034	0.5245 (0.1741 to 0.8748)
	IHC	4	83	71	95.00% (76.68–100.00)	13.79	< 0.01	78.20%		
	RT-PCR	21	7,384	799	57.31% (44.82–69.35)	1,630.22	0	98.80%		
	qRT-PCR	16	2,588	848	56.33% (39.94–72.03)	935.98	< 0.01	98.40%		
Sampling site	Farms	24	7,868	970	58.62% (45.88–70.80)	2,211.59	0	99.00%	0.6325	−0.1449 (−0.7390 to 0.4491)
	Pig markets	1	100	44	44.00% (34.45–53.78)	0.00	-	-		
	Slaughter houses	2	563	72	65.80% (0.00–100.00)	59.38	< 0.01	98.30%		
Season	Spring	7	206	70	83.84% (40.17–100.00)	206.85	< 0.01	97.10%	0.0109	−0.3856 (−0.6824 to −0.0888)
	Summer	9	3,954	169	78.51% (58.23–93.32)	674.06	< 0.01	98.80%		
	Autumn	5	153	63	67.60% (39.49–90.11)	20.46	< 0.01	80.50%		
	Winter	9	3,350	607	41.55% (20.30–64.60)	633.09	< 0.01	98.70%		
Age	Adult pigs	7	1,438	246	61.19% (28.67–88.93)	528.60	< 0.01	98.90%	0.0022	0.3935 (0.1421 to 0.6450)
	Growing finishing pigs	5	2,832	341	43.09% (21.50–66.15)	156.02	< 0.01	97.40%		
	Piglets	10	166	119	87.57% (68.61–98.43)	67.54	< 0.01	86.70%		
Model	Extensive	2	103	29	42.72% (4.66–87.33)	13.81	< 0.01	92.80%	0.8211	0.0672 (−0.5151 to 0.6494)
	Intensive	7	3,741	305	36.25% (13.38–63.08)	826.65	< 0.01	99.30%		
Quality level	Medium	15	4,980	1,083	46.65% (33.60–59.93)	919.31	< 0.01	98.50%	0.4314	0.0922 (−0.1375 to 0.3218)
	High	19	4,859	481	63.10% (45.85–78.78)	1,683.23	0	98.90%		
Total		34	9,839	1,564	55.45% (44.75–65.89)	3,080.38	0	98.90%		

CI, confidence interval; IHC, immunohistochemistry; RT-PCR, reverse-transcription polymerase chain reaction; qRT-PCR, quantitative RT-PCR.
[a]Others: nested RT-PCR (n = 1), reverse transcription-recombinase polymerase amplification (RT-RPA; n = 1), reverse transcription droplet digital PCR (RT-ddPCR; n = 2), reverse transcription-insulated isothermal PCR (RT-iiPCR; n = 1), real-time reverse-transcription loop-mediated isothermal amplification (rRT-LAMP; n = 2), RNA *in situ* hybridization (ISH-RNA; n = 1).

In terms of seasonal subgroups, the SVA infection rate of pigs in autumn was significantly higher than that in other seasons (*p* < 0.05; **Table 2**). SVA infections are more frequent in spring and autumn, and incubation is usually 4–5 days [29]. At the same time, the combination of climatic factors revealed that areas with a temperature of 15°C–20°C and annual precipitation of 50–80 mm have the highest SVA prevalence (**Table 3**). Therefore, SVA may prefer to survive in a warm, low-humidity environment. This finding was generally consistent with the results of continental subgroups. We suggest that pig farms in the above climate environment strengthen protection management to prevent disease epidemics and outbreaks.

The diagnostic methods applicable to SVA include pathogenic diagnostic and serological methods [29]. In 34 studies, IHC had the highest positive detection rate (*p* < 0.05; **Table 2**). The IHC method can localize SVA-infected tissues accurately but requires specific monoclonal antibodies [30]. However, reverse-transcription polymerase chain reaction
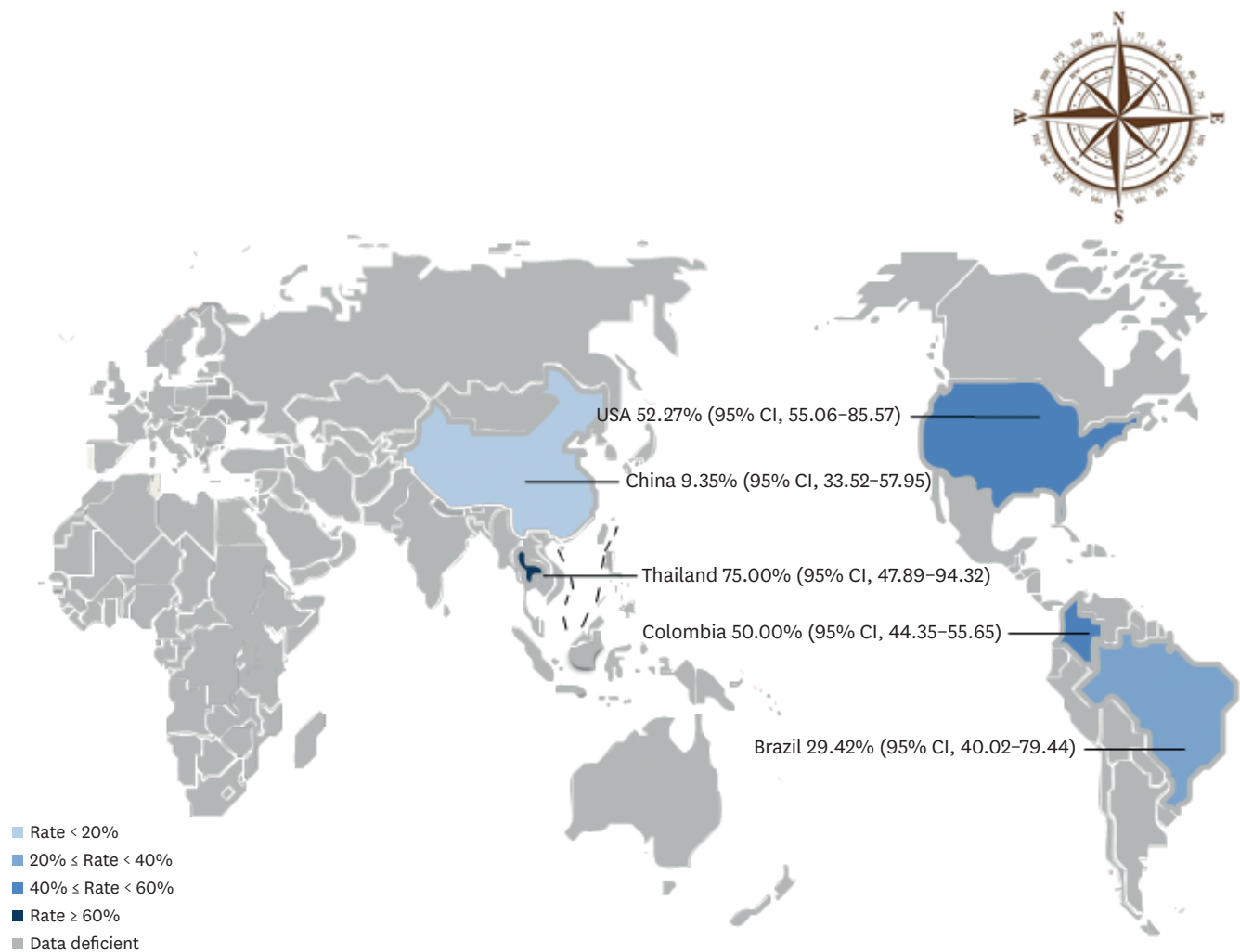
Fig. 5. Map of the prevalence of Senecavirus A in pigs from other countries.
CI, confidence interval.

(RT-PCR) assay and quantitative RT-PCR (qRT-PCR) are the most commonly used detection assays [29]. qRT-PCR appears to be of higher sensitivity than RT-PCR and IHC, which thus should be the preferred screening method for SVA [30]. Several amplification technologies have been rapidly developed in recent years, such as nested RT-PCR [31] and real-time reverse-transcription loop-mediated isothermal amplification [32]. They are more sensitive than RT-PCR but more prone to contamination [33]. The reverse-transcription droplet digital PCR (RT-ddPCR) and reverse-transcription insulated isothermal PCR (RT-iiPCR) are emerging detection technology, which has been developed and validated for the detection of SVA [34]. The main advantages of RT-ddPCR are accurate detection of low viral load samples and RT-iiPCR can help on-site diagnosis of SVA in swine [35]. Most importantly, the sensitivity and specificity of these two assays are similar to the qRT-PCR method [34]. At the same time, real-time recombinase polymerase amplification [27] and *in situ* hybridization [36] have rapidly been used to diagnose SVA infection. These two methods have short reaction times and high specificity, but their sensitivity is lower than that of qRT-PCR [36]. We conducted subgroup analysis for sampling different genes in the diagnostic method, and the results demonstrated that the assay had the highest detection rate for structural

Table 3. The pooled estimates Prevalence of Senecavirus A in pigs by geographical factors with meta-analysis

Factor	Category	No. of studies	No. of tested	No. of positive	% (95% CI)	Heterogeneity			Univariate meta-regression	
						χ^2	p value	I^2 (%)	p value	Coefficient (95% CI)
Latitude	0–20°N	2	312	159	59.22% (34.97–81.29)	3.16	0.08	68.40%	0.0497	−0.3576 (−0.7147 to 0.0005)
	21–25°N	12	4,027	450	52.13% (37.76–66.33)	506.77	< 0.01	97.80%		
	26–30°N	4	3,147	192	48.01% (5.13–92.97)	751.59	< 0.01	99.60%		
	31–35°N	3	294	71	22.74% (5.90–46.34)	38.63	< 0.01	94.80%		
	36–45°N	6	688	143	53.52% (27.32–78.71)	214.79	< 0.01	97.70%		
	31–35°S	5	154	81	75.61% (36.64–98.74)	84.48	< 0.01	95.30%		
	40–45°S	3	314	92	61.65% (19.16–95.32)	52.97	< 0.01	96.20%		
Longitude	85–110°E	5	2,803	318	34.69% (18.40–53.08)	87.76	< 0.01	95.40%	0.0238	0.3729 (0.0496 to 0.6961)
	111–120°E	12	4,708	375	48.78% (30.15–67.60)	1,220.37	< 0.01	99.10%		
	121–130°E	2	304	31	11.98% (0.75–33.78)	19.26	< 0.01	94.80%		
	36–40°W	3	314	92	61.65% (19.16–95.32)	52.97	< 0.01	96.20%		
	56–60°W	6	161	88	82.23% (46.70–99.73)	98.65	< 0.01	94.90%		
	76–80°W	2	400	194	48.38% (43.17–53.61)	1.09	0.30	7.90%		
	90–100°W	4	82	57	85.13% (45.76–100.00)	44.92	< 0.01	93.30%		
Precipitation	20–50 mm	2	229	19	21.20% (0.00–71.38)	20.25	< 0.01	95.10%	0.0194	−0.5118 (−0.9410 to −0.0827)
	50–80 mm	3	117	48	86.71% (11.65–100.00)	107.69	< 0.01	98.10%		
	80–110 mm	4	2,622	331	60.44% (22.95–91.86)	141.53	< 0.01	97.90%		
	110–140 mm	2	2,810	40	54.33% (0.00–100.00)	85.79	< 0.01	98.80%		
	140–170 mm	6	1,344	230	78.76% (38.15–99.72)	595.70	< 0.01	99.20%		
Temperature	10–15℃	3	307	38	42.86% (7.58–83.20)	78.75	< 0.01	97.50%	0.0907	−0.2959 (−0.6387 to 0.0470)
	15–20℃	3	161	94	78.88% (43.19–98.98)	33.59	< 0.01	94.00%		
	20–25℃	10	6,383	407	62.93% (47.91–76.77)	769.44	< 0.01	98.80%		

CI, confidence interval.

protein VP1 ($p < 0.05$; **Table 2**). Moreover, in this subgroup of sampling positions, we found the highest prevalence of SVA when fecal samples were collected (**Table 2**), but due to fewer studies (n = 2) and sourced from North America, where the prevalence is highest (**Table 2**). SVA infection affects several tissues and organs of piglets, with the highest viral loads in the lymphoid organs, followed by the lungs and liver [30]. Therefore, we suggest adopting appropriate biological samples, detection methods, and genes to obtain more accurate test data and effectively diagnose SVA infection.

In the subgroup analysis of sampling sites, the point estimate of pig markets was higher than that of farms and slaughterhouses, but the difference was insignificant ($p = 0.6325$; **Table 2**). It may result from farms selling pigs with the disease to the market at a lower price [37]. When we analyzed the subgroups of farm models, this extensive farming model had a higher infection rate (**Table 2**). We infer that intensive farming has complete biosecurity measures, well-equipped veterinarians, and a good sanitary environment [38]. Management should be strengthened, the feeding conditions should be improved to control SVA infection, and the environment of pig farms should be disinfected.

The age factor also has an important impact on the SVA infection rate in pigs [5]. Moreover, the infection rate in piglets was significantly higher than that in elder herds ($p < 0.05$; **Table 2**). Infected piglets have severe clinical symptoms and even sudden death [6]. Additionally, previous studies indicated that SVA could be transmitted to other pigs through piglets before vesicular lesions were observed [39]. Post-weaning piglet polyculture is a common phenomenon in the US swine industry. Therefore, weaned piglets should be moved cautiously to avoid commingling piglets from different sows, otherwise accelerating the spread of SVA infection [39].

In our research, 15 medium-quality articles were obtained, and the detection rate of medium-quality articles was higher than that of high-quality articles (**Table 2**). There was no defined

sampling time, location, or definite detection method (**Supplementary Table 1**). The data analysis was not detailed enough to accurately find the potential risk factors for SVA infection, resulting in biased results. Thus, researchers should determine the influencing factors of SVA infection in pigs to effectively prevent the epidemic disease outbreak and provide reliable data for future studies.

Of note, our meta-analysis has several limitations. First, some subgroups had a small number of studies, which might affect the stability of the results (e.g., country and sampling position). Second, as SVA disease has affected the pig industry in recent years, most of the data were from 2015 to 2017, which is a short period. We should continue to pay attention to the epidemic situation of the disease. Third, given that the included studies did not provide enough information, pig gender and health status would also affect the analysis results. However, our study utilized a wide range of research areas, a detailed analysis approach, and a systematic assessment of risk factors, which could effectively clarify the potential prevalence of SVA infection globally. It provides a theoretical basis for effectively controlling the spread of diseases.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Characteristics and quality scores of eligible studies

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Supplementary Table 2

Egger's test for publication bias

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