Epidemiology, Clinical Manifestations, and Outcomes of *Streptococcus suis* Infection in Humans

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Streptococcus suis, a bacterium that affects pigs, is a neglected pathogen that causes systemic disease in humans. We conducted a systematic review and meta-analysis to summarize global estimates of the epidemiology, clinical characteristics, and outcomes of this zoonosis. We searched main literature databases for all studies through December 2012 using the search term "streptococcus suis." The prevalence of *S. suis* infection is highest in Asia; the primary risk factors are occupational exposure and eating of contaminated food. The pooled proportions of case-patients with pig-related occupations and history of eating high-risk food were 38.1% and 37.3%, respectively. The main clinical syndrome was meningitis (pooled rate 68.0%), followed by sepsis, arthritis, endocarditis, and endophthalmitis. The pooled case-fatality rate was 12.8%. Sequelae included hearing loss (39.1%) and vestibular dysfunction (22.7%). Our analysis identified gaps in the literature, particularly in assessing risk factors and sequelae of this infection.

Streptococcus suis is a neglected zoonotic pathogen that has caused large outbreaks of sepsis in China (*1*,*2*) and has been identified as the most common and the third leading cause of bacterial meningitis in adults in Vietnam and Hong Kong, respectively (*3–5*). *S. suis* infection is acquired from pigs, either during slaughtering or by handling and eating undercooked pork products. It is potentially preventable (*3*,*6*). Epidemiology of the infection differs between Western and Asian regions (*7*), and the role of high-risk eating habits (i.e., ingesting raw or undercooked pig parts, including pig blood, organs, and meat) in some Asian communities recently has been recognized (*6*,*8*,*9*). Rates of *S. suis* infection are low in the general populations of Europe and North America, and cases are concentrated among occupationally exposed groups, including abattoir workers, butchers, and pig breeders (*10*,*11*).

In a 2009 review, ≈700 *S. suis* infections were reported worldwide by 2009, mostly from China and Vietnam (*12*). Clinical characteristics of this infection have been reviewed (*12*,*13*) and include meningitis, sepsis, endocarditis, arthritis, hearing loss, and skin lesions. Treatment of *S. suis* infection requires ≈2 weeks of intravenous antimicrobial drugs (*12*). The death rate varies, and deafness is a common sequela in survivors.

Although substantial new data on the incidence, clinical and microbiological characteristics, and risk factors for *S. suis* infection have accumulated during recent years, the prevalence of this infection has not measurably decreased. We conducted a systematic review and meta-analysis to update the evidence and summarize the estimates of epidemiologic and clinical parameters to support practitioners' and policy makers' efforts to prevent and control this infection.

Methods

We conducted the review in accordance with recommendations of the PRISMA statement (*14*). The protocol

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Search Strategy and Selection Criteria

We systematically and inclusively searched 5 main electronic databases (PubMed, Scopus, ISI Web of Science, Science Direct, and Google Scholar) for all studies published until the end of December 2012 (Figure 1). The following search term was used as a text word in each database, as follows: PubMed—"streptococcus suis" in all fields, limited to humans; Scopus—"streptococcus suis" in all fields, excluding veterinary medicine articles; ISI Web of Science—"streptococcus suis" in topic with exclusion of veterinary science areas; Science Direct—"streptococcus suis" in all fields, with articles in veterinary medicine journals excluded; and Google Scholar—"all in title: 'streptococcus suis.'"

We also searched using the same search term "streptococcus suis" in other databases, including Virtual Health Library, SIGLE, WHOLIS, LILACS, IMSEAR-HELLIS, and China Academic Journals Full-text Database and checked the reference lists of retrieved articles. We did not restrict the types of studies and publication languages, and non-English papers were translated for review. Publications were excluded if they did not report any human cases of *S. suis* infection, reported data that overlapped with already included articles and provided no additional information, reported cases without information indicating the location of the patients, or reported data that could not be reliably extracted.

Figure 1. Flow diagram of the search and review process for this review of *Streptococcus suis* infection.

Data Extraction

Two reviewers (N.H. and V.T.L.H.) independently screened the titles and abstracts, and examined the full-text publications by using identical selection criteria and data abstraction forms. The results of data extraction showed a high degree of agreement between the reviewers (κ>0.90 for the main variables). Any disagreements were resolved by discussion and consensus between the reviewers and other authors (N.T. Huy, H.W., P.H., K.H.). We emailed the original authors of the articles that contained ambiguous data (1 email attempt per author) for clarification, and the ambiguous data were excluded from analyses if we did not receive a response.

Data extracted included year of publication, year of data collection, study design, data collection approach, country of origin, hospital where the patients were recruited, patient characteristics, clinical manifestations, methods of diagnosis, clinical and laboratory parameters, outcomes, and histories.

Analyses

We described the relevant epidemiologic and clinical factors using count for number of cases, proportions with 95% CIs for categorical factors (sex, occupation, exposure, history), and mean with SD for continuous factors (age, duration, and laboratory parameters). Event rates are presented as proportions with 95% CIs for signs, symptoms, and outcomes. We defined an event rate as the ratio of number of events to the number of all patients assessed in each study.

We pooled all single cases from the publications that reported <5 cases into 1 dataset and produced summary outputs, which were then meta-analyzed with other large studies (reporting ≥5 cases). We report the values of reviewed factors in 3 sets: summary values from the single-case dataset, median values (range) of the large studies, and pooled values from the meta-analysis as appropriate.

Meta-analysis was conducted by using Comprehensive Meta-analysis software version 2 (Biostat, Englewood, NJ, USA; http://www.Meta-Analysis.com) when >2 studies reported the reviewed factor. We tested heterogeneity using the Q statistic and I^2 test (*15*). Pooled values and 95% CIs were generated from a fixed-effects model or from a random-effects model, and each was study weighted by the inverse of that study's variance. We used the fix-effects model when heterogeneity was not significant and a random-effects model when heterogeneity was evident (*16*). Median (range) was converted to mean (SD) by using proposed formulas (*17*), and interquartile ranges to SDs and subgroup values to total values by Cochrane suggested methods (*18*).

We assessed publication bias using funnel plots and the Egger's regression test (if ≥10 studies were included in the meta-analysis). If publication bias was found, the Duvall and Tweedie trim and fill method was performed to add possible missing studies to improve the symmetry and calculate the adjusted pooled values (*19*). We used subgroup analyses (when >10 studies were included) and bivariate meta-regression (when >20 studies were included) to examine the effect of study-level variables, including year of publication (2005 and earlier vs. after 2005 [because the Sichuan outbreak occurred in 2005]), study design (case series, outbreak investigation, cross-sectional), location (China mainland, Hong Kong, Thailand, Vietnam, and others), data collection (retrospective vs. prospective) and meningitis rate (<50%, 50%–90%, and >90%) on the main outcomes. The general linear model was used for meta-regression, with adjustment for multiple comparisons by using the Bonferroni method and weighting by study sample size.

Results

Systematic Review

We used 177 publications that met inclusion and exclusion criteria for data extraction and final analyses (Figure 1; online Technical Appendix Table 1, http://wwwnc.cdc.gov/EID/article/20/7/13-1594-Techapp1.pdf). The studies were diverse in terms of design, data collection, and reporting approaches. We identified 20 case series (8 from South-East Asia region, 8 from the Western Pacific region, and 4 from Europe) and 21 cross-sectional studies (9 SouthEast Asia, 8 Western Pacific, and 4 Europe). Five articles about 3 outbreaks (in Sichuan and Jiangsu, China; and Phayao, Thailand) were classified as outbreak investigation reports. The only prospective case–control study was conducted in Vietnam (Table 1).

Epidemiology

By the end of 2012, a total of 1,584 cases had been reported in the literature (including 189 probable cases identified in 3 outbreaks), mainly from Thailand (36%), Vietnam (30%), and China (22%). More than half (53%) were in the Western Pacific region; 36% were in the South East Asia region, 10.5% in the European region, and 0.5% in the Americas. The highest cumulative prevalence rate was in Thailand (8.21 cases/million population), followed by Vietnam (5.40) and the Netherlands (2.52) (country population data for 2008–2012 by World Bank [*20*]) (Figure 2).

The pooled mean age of the patients was 51.4 years, and 76.6% were men (Table 2). All case-patients were adults, except 1 female infant reported in Thailand (*21*). The pooled proportion of case-patients with occupational exposure was 38.1% (95% CI 24.4%–53.9%); this proportion was higher for industrialized countries than for other countries (83.8% [95% CI 73.4%–90.7%] for the United Kingdom, Netherlands, and Japan together). Recent

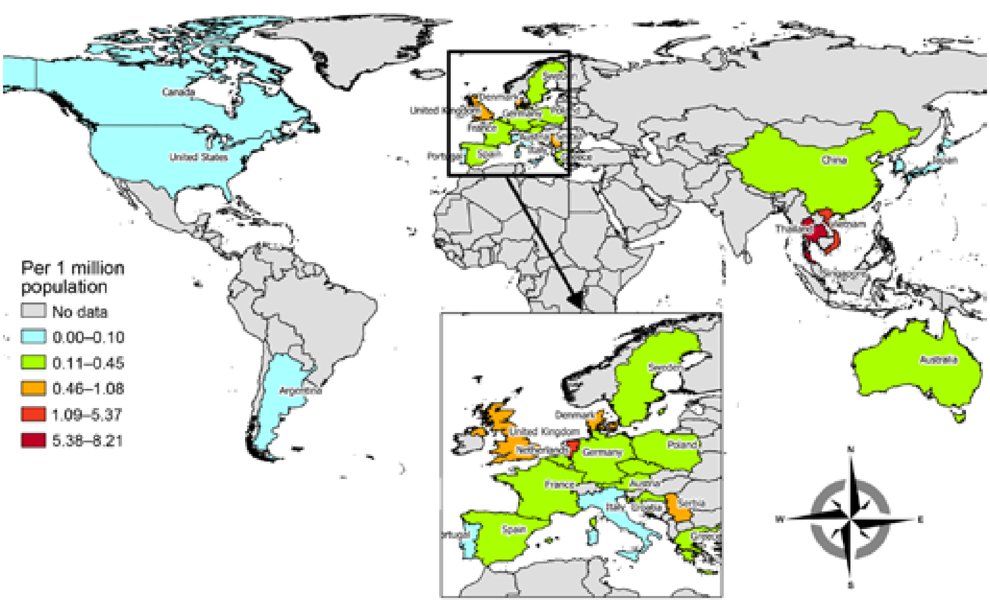

Figure 2. Global cumulative prevalence of *Streptococcus suis* infection through 2012.

Table 1. Characteristics of 177 articles in a systematic review of *Streptococcus suis* infection		
Characteristic	Articles, no. (%)	Cases reported, no. (%)*
Geographic region†		
Europe	98 (55)	168 (11)
Western Pacific	47 (27)	836 (53)
SouthEast Asia	24 (14)	572 (36)
Americas	8 (5)	8 (0.5)
Type of study design		
Case report	130 (73)	151 (7)
Case series	20 (11)	511 (25)
Cross-sectional	21 (12)	761 (37)
Outbreak investigation	5 (3)‡	532 (26)
Case–control	1 (1)	101 (5)
Data collection approach		
Retrospective	159 (90)	1299 (63)
Prospective	15 (9)	697 (34)
Both§	3 (1)	60 (3)
Language of publication¶		
English	130 (74)	1947 (95)
Spanish	13 (7)	15 (1)
French	12 (7)	13 (1)
Other#	22 (12)	81 (4)
Year of publication		
1968–1980	13 (7.5)	18 (1)
1981–1990	27 (15)	95 (5)
1991–2000	32 (18)	119 (6)
2001–2005	28 (16)	115 (6)
2006–2010	55 (31)	1052 (51)
2011–2012	22 (12.5)	659 (32)

*Case duplicates were removed in the counts for the geographic region subheading (totaling 1,584 cases, no duplicates). Duplicates were not removed in the counts for other subheadings (totaling 2,056 cases, with duplicates).
†Geographic regions as defined by the World Health Organization.
‡Includes 3 articles reporting about the patients in the Sichuan outbreak in China; each was included for analysis of different factors.
§Included in the prospective groups in subsequent analyses.
¶Almost all large studies were published in English. Most reports in languages other than English were case reports.
#German (7 articles); Dutch (4); Czech, Italian, and Japanese (2 each); Chinese, Polish, Serbian, Swedish, and Thai (1 each).

contact with pigs or pork was reported for 15.5% of single cases but for 33.9% (95% CI 21.1%–49.5%) in the meta-analysis. History of eating meals containing pork was reported mainly in Asia (Thailand and Vietnam); the pooled estimate was 37.3% (95% CI 20.2%–58.3%). For Thailand only, the proportion was 55.8% (95% CI 33.7%–75.9%). In other countries, only 1 patient in France was reported eating artisanal dry sausage (*22*), and 1 patient in the United States ate raw pork while traveling in the Philippines (*23*) before the infection.

Skin injury was shown for one fourth of case-patients, and alcohol use was evident in approximately one third of case-patients. However, a case–control study in Vietnam did not identify alcohol use as an independent risk factor after adjustment for other risk factors and confounders (*6*). The most commonly reported preexisting condition was diabetes. Other conditions included underlying heart disease, hypertension, cirrhosis, and cancer (online Technical Appendix Table 3). Smoking was mentioned in 5.2% of patients in the single-case dataset.

Microbiological Diagnosis

Blood and/or cerebrospinal fluid culture were the most common reported diagnostic methods among the case reports (online Technical Appendix Table 4). Molecular diagnosis was more common in the large studies (11 studies) than in case reports. The most prevalent strain was serotype 2 (86.5%), followed by serotype 14 (2.3%), and serotype 1 (0.6%) of all 1,156 patients with serotype information mentioned in the articles. Serotypes 4, 5, 16, and 24 also were reported (1 patient per serotype).

Misdiagnosis of *S. suis* infection was not uncommon, either by conventional biochemical tests or commercial identification systems. The bacteria were often reported as viridans streptococci in initial cultures. In fact, up to 70% of all viridans streptococci cases in Thailand were confirmed as *S. suis* infections in the follow-up investigations (*24*). A total of 62.5% of *S. suis*–infected patients in another study in Thailand (*25*) and 20% in a study inthe Netherlands (*10*) were initially reported to be infected with viridans streptococci. Misidentification of the infectious agent as *S. bovis* (2 patients), *S. pneumoniae* (1 patient), and *S. faecalis* (1 patient) also was reported in the Netherlands series. Tsai et al. (*26*) showed large variations between the 2 commercial systems (Phoenix Identification System, Beckon Dickinson, Sparks, MD, USA; and Vitek II GPI Card, bioMérieux Vitek, Hazelwood, MO, USA), and misidentification of *S. suis* as *S. acidominimus* was common when the Phoenix system was used.

Table 2. Epidemiologic factors of patients with *Streptococcus suis* infection included in a systematic review				
Variable	Single-case dataset, %*	Large studies, median (range), %	Meta-analysis, pooled mean (95% CI), %†	No. studies meta-analyzed, %‡
Mean age, y, n = 156	49.4	50.5 (37.0–61.2)	51.4 (49.5–53.2)	25
Male sex, n = 155	83.2	77.5 (37.5–100)	76.6 (72.2–80.6)	26
Pig-related occupation	58.6	25.0 (0–100)	38.1 (24.4–53.9)	21
Contact with pig/pork	15.5	33.3 (2.4–100)	33.9 (21.1–49.5)	14
Eating of high-risk food	4.0	53.3 (5.9–88.7)	37.3 (20.2–58.3)	9
Skin injury	19.5	16.0 (9.5–71.4)	25.1 (15.1–38.7)	8
Drinking of alcohol	8.6	23.0 (4.8–83.9)	29.7 (17.2–46.3)	13
Concurrent diabetes§	2.9	7.2 (3.2–25.0)	8.0 (4.6–13.7)	9

*N = 174 unless otherwise indicated.
†Random-effects model unless otherwise specified.
‡Include the single-case dataset and the large studies (online Technical Appendix Table 2, http://wwwnc.cdc.gov/EID/article/20/7/13-1594-Techapp1.pdf).
§Other less common underlying conditions are listed in online Technical Appendix Table 3.

S. suis is mostly sensitive to penicillin; resistance was reported in only 2 patients (*21*,*27*). After cessation of antimicrobial drug treatment, infection relapsed in a small proportion of patients, including those for whom the organism tested highly sensitive to penicillin (*28*,*29*). The pooled relapse rate was 4.4% (Table 3).

Clinical Syndromes

Meningitis was the most common clinical syndrome (pooled rate 68.0% [95% CI 58.9%–75.8%]), followed by sepsis (25.0% [95% CI 20.5%–30.2%]), arthritis (12.9% [95% CI 6.0%–25.6%]), endocarditis (12.4% [95% CI 6.7%–21.9%]), and endophthalmitis (4.6% [95% CI 2.8%–7.4%]) (Table 3). Toxic shock syndrome also was reported as a distinct severe clinical feature at high rates in 2 outbreaks in China (64.0% and 28.9% of patients) (*2*,*30*) and in Thailand (37.7%) (*24*) but at a rate of only 2.9% among the case reports.

We found evidence of publication bias in the meta-analysis of meningitis rates (Figure 3) (significant Egger's test result). The adjusted rate, based on the Duvall and Tweedie trim and fill method, was 56.0% (95% CI 45.2%–66.2%). Our meta-regression analysis showed that meningitis rate was significantly associated with country of publication, study design, and data collection approach (online Technical Appendix Table 5), although only country of publication remained significant in a multivariable model. All patients in the 4 studies conducted in Vietnam had meningitis. When we excluded these studies, the pooled rate of meningitis was reduced to 59.4% (95% CI 51.1%–67.1%), and the adjusted value after we used the trim and fill method was 54.8% (95% CI 46.0%–63.4%). In contrast, if we excluded the 2 outbreak investigations in China, because sepsis dominated these outbreaks, the pooled meningitis rate increased slightly to 72.2% (95% CI 62.4%–80.2%).

Table 3. Main clinical and laboratory parameters at admission of the patients with *Streptococcussuis* infection in a systematic review*

Variable	Single-case dataset	Large studies, median value (range)	Meta-analysis, pooled mean (95% CI)†	No. studies meta-analyzed‡
Clinical syndrome, %§				
Meningitis	69.5	64.5 (30.2–100)	68.0 (58.9–75.8)	26
Sepsis¶	19.5	23.8 (11.8–39.4)	25.0 (20.5–30.2)	12
Arthritis	2.87	16.7 (1.5–50.0)	12.9 (6.0–25.6)	12
Endocarditis	8.6	14.3 (1.9–39.0)	12.4 (6.7–21.9)	10
Endophthamiltis	2.9	4.5(1.5–28.6)	4.6 (2.8–7.4)#	9
Spondylodiscitis	4.6	1.9 (1.5-2.4)	3.7 (2.1-6.6)	4
Toxic shock syndrome	2.9**	37.7 (28.9–64.0)	25.7 (9.8-52.6)	4††
Mean duration, d				
Onset to admission, n = 90	7.3	3.5 (2.0–11.4)	4.1 (2.7–5.4)	7
Hospitalization, n = 68	20.5	17.4 (13.0–19.2)	17.2 (15.6–18.9)#	5
Symptoms, %				
Meningeal sign‡‡	49.4	66.7 (12.5–95.1)	67.1 (54.9–77.4)	18
Skin rash	10.9	12.5 (0–52.0)	15.4 (8.6–25.9)	10
Shock	8.6	11.8 (1.3–64.0)	11.9 (6.3–21.5)	12
Respiratory failure	5.2	20.0 (8.3–35.8)	16.7 (8.6–29.9)	6
Acute renal failure	5.2	8.3 (1.3–28.0)	7.1 (2.2–20.5)	5
Disseminated intravascular coagulation	10.3	6.0 (2.4–57.1)	10.3 (5.4–18.8)	9
Relapse	2.9	7.3 (2.9–8.3)	4.4 (2.4–7.8)#	5
Laboratory values (mean)§§				
Leukocytes, 10^9 cells/L, n = 98	17.4	15.1 (13.9–18.2)	15.8 (14.6–16.9)	9
Hemoglobin, g/L, n = 22	106.7	–	–	–
Platelets, 10^9/L, n = 41	121.0	182.4 (115–241.5)	164.9 (132.9–197)	7
Blood glucose, mg/dL, n = 32	147.8	–	–	–
C-reactive protein, mg/L, n = 36	349.7	–	–	–
Cerebrospinal fluid				
Leukocytes, cells/mm^3, n = 88	3,166	2029 (450–3253)	2330 (1721–2939)#	7
Protein, g/L, n = 74	3.20	2.35 (1.7–4.18)	2.45 (1.91–2.99)	7
Glucose, mg/dL, n = 70	20.9	8.60 (1.7–25.6)	12.6 (3.5–21.7)	6

*N = 174 unless otherwise indicated. –, not applicable because no large study reported these data.
†Random-effects model unless otherwise indicated.
‡Includes the single-case dataset and the large studies (online Technical Appendix Table 2, http://wwwnc.cdc.gov/EID/article/20/7/13-1594-Techapp1.pdf).
§Other less common syndromes included peritonitis, myositis, pneumonia, sacroiliitis, abdominal aortic aneurysm, hemorrhagic labyrinthitis, gastroenteritis, vertebral osteomyelitis, lymphadenopathy, cellulitis, and vertigo.
¶Case-patients with toxic shock syndrome in China and in Thailand not included in this sepsis category.
#Mixed-effects model.
**Counted if the author described the case as toxic shock syndrome.
††Include 3 large studies reporting toxic shock syndrome, including 2 outbreaks in China (*2*,*30*) and 1 prospective study in Thailand (*24*).
‡‡Mainly reported with neck stiffness.
§§Reference values may differ among laboratories. Commonly used reference values for presented laboratory blood tests are as follows: leukocytes 4.0–10 × 10^9 cells/L; hemoglobin 140–170 g/L (for male patients) and 120–160 g/L (for female patients); platelets 150–350 × 10^9/L; blood glucose (fasting) 70–100 mg/dL; C-reactive protein 0–8.0 mg/L. Reference ranges for cerebrospinal fluid are as follows: leucocytes 0–5 cells/mm^3; protein 0.15–0.60 g/L; glucose 40–80 mg/dL. (Source: http://im2014.acponline.org/for-meeting-attendees/normal-lab-values-reference-table/)

Table 4. Summary rates of the main clinical outcomes among patients with *Streptococcus suis* infection included in a systematic review

Variable	Single-case dataset, n = 174	Large studies, median (range)	Meta-analysis, pooled mean (95% CI)	No. studies meta-analyzed*
Death	10.3	8.9 (0.0–56.0)	12.8 (9.0–18.0)	25
Hearing loss†	44.8	38.7 (6.0–100)	39.1 (31.0–47.8)	26
Recovery from hearing loss	‡	5.0 (0.0–52.3)	15.4 (5.3–37.3)	8
Vestibular dysfunction§	16.7	25.0 (3.3–60.0)	22.7 (15.6–32.0)	13
Visual impairment	4.0	–	–¶	–

*Includes the single-case dataset and the large studies (online Technical Appendix Table 2,http://wwwnc.cdc.gov/EID/article/20/7/13-1594-Techapp1.pdf).
†Studies included if case-patients were reported to have any degree of hearing impairment (unilateral or bilateral, temporary or permanent).
‡Reliable data could not be extracted for the majority of the case reports.
§Studies included if case-patients were reported to have ataxia, vertigo, loss of balance, or vestibular dysfunction.
¶Dashes indicate not applicable because no large study reported these data.

Case-Fatality Rates

The pooled case-fatality rate (CFR) for *S. suis*–infected patients was 12.8% (95% CI 9.0%–18.0%) (Table 4). This rate varied by country; reported rates were lowest in Vietnam (Figure 4). However, country of publication was not significant in the bivariate meta-regression after adjustment for multiple comparisons (online Technical Appendix Table 5). Instead, only meningitis rates remained significant in explaining between-study variations in CFR. Meningitis rates correlated negatively with CFRs among the included studies (Figure 5). Studies with meningitis rates <50% had significantly higher CFRs than did studies with meningitis rates >90% (mean CFR difference 20.3%, p = 0.001). The pooled CFR was 4.0% (95% CI 2.2%–7.0%), estimated for the studies in which all patients had meningitis (*3*,*4*,*9*,*10*,*31*–*33*), whereas the pooled rate for the other studies was 17.1% (95% CI 12.3%–23.4%). CFRs were higher for outbreaks than for nonoutbreaks (21.6% [95% CI 6.4%–52.5%] vs. 11.5% [95% CI 7.9%–16.7%]).

Clinical Outcomes

Among the survivors, hearing loss (pooled rate 39.1% [95% CI 31.0%–47.8%]) and vestibular dysfunction (22.7% [95% CI 15.6%–32.0%]) were the most common sequelae (Table 4). Reported rates for both sequelae varied widely, even within a country such as Thailand, (online Technical Appendix Figures 1–4). Similar to CFRs, there was a marginally positive correlation between hearing loss and meningitis rates (p = 0.05) (online Technical Appendix Table 5). The pooled hearing loss rate for studies in which all patients had meningitis was 55.3% (95% CI 36.2%–72.9%), compared with 34.0% (95% CI 26.0%–43.1%) for the remaining studies. For the vestibular dysfunction, none of the investigated study-level factors were significant. Among the Asian countries, the reported rate of vestibular sequelae was lowest in Vietnam (4.0%).

Limited information described how hearing loss and vestibular dysfunction were evaluated during and after infection. Eight of 25 large studies reporting hearing loss indicated whether hearing loss was permanent after hospital discharge. Only 4 described their follow-up processes; follow-up time ranged from 2 months to 30 months (*4*,*8*,*28*,*31*). On the basis of these limited data, we estimated a comparatively low median rate of recovery from hearing loss of 5.0% (range 0%–52.3%) and the pooled rate of 15.4% (95% CI 5.3%–37.3% (Table 4). Hearing loss might be mediated by adjunctive corticosteroid treatments, as was shown in a trial in Vietnam (*34*). Of the *S. suis* patients, 12.3% had deafness in at least 1 ear in the dexamethasone treatment group (n = 57), compared with 37.7% in the placebo group (n = 53).

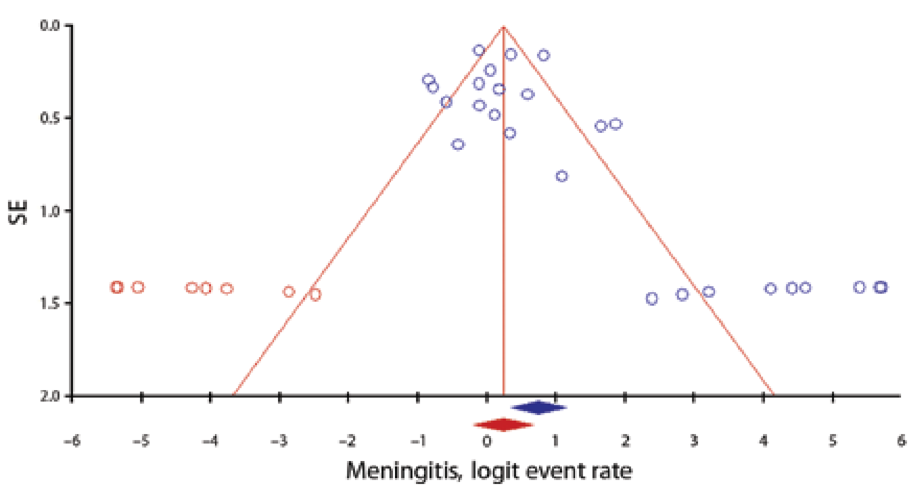

Figure 3. Funnel plot showing evidence of publication bias among 26 studies in a meta-analysis of meningitis rates in *Streptococcus suis* infection. Each blue circle represents each study in the meta-analysis, forming an asymmetric funnel plot with a pooled log event rate (gray rhombus). Eight missing studies (red circles) added in the left side through the trim and fill method to make the plot more symmetric and gave an adjusted log event rate (red rhombus), which was lower than the original one.

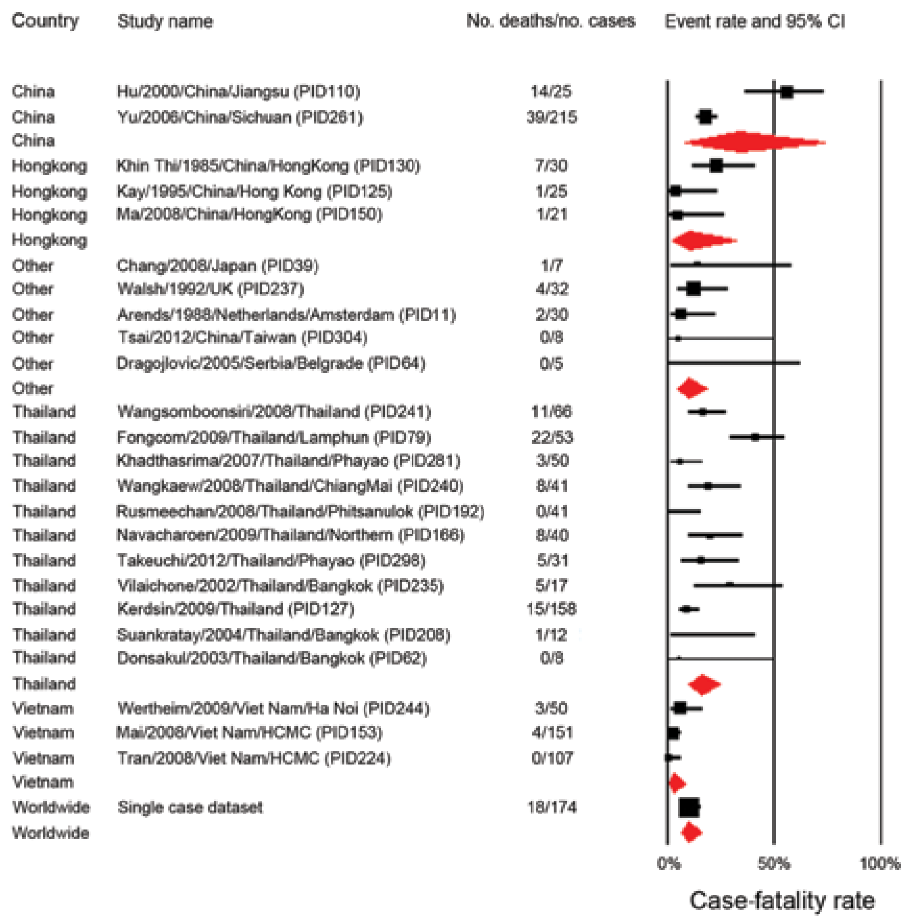

Figure 4. Forest plot of subgroup meta-analysis (random effects) for the case-fatality rates by country reported in the 25 studies included in a review of *Streptococcus suis* infection. For each study, the event rate of the death outcome and 95% CI are presented, with size proportional to study weight. The red rhombus indicates the pooled event rate for each country group.

Discussion

We have updated estimates of the global prevalence, epidemiology, and clinical characteristics of *S. suis* infections in humans. After possible duplicates were removed, the total number of *S. suis* infections by 2012 was close to 1,600 cases, doubling the figure published in 2009 (*12*). Most of the increase comprised cases from Thailand and Vietnam, placing both countries in the highest disease prevalence stratum in the world. In contrast, only a few cases have been reported from the Americas, particularly the United States, the second largest producer of pigs worldwide (*35*). This low number might be attributable to the high industrialization of pig farming systems in the region. Nevertheless, we saw far more cases in Europe, a region where modern farming operations are presumably similarto those in the Americas. Other plausible explanations include the lower virulence of North American bacterial strains (*36*) or different slaughtering practices.

We counted only published cases; the actual number of cases would be considerably higher, particularly in areas to which *S. suis* is endemic, such as Asian countries with extensive pig rearing. The problem of underestimation is further exacerbated by the fact that *S. suis* infection is not a notifiable disease in many countries. In addition, lack of diagnostic capacities or limited disease awareness in local laboratories can result in undiagnosed or misdiagnosed cases.

Meningitis is the main syndrome in approximately two thirds of *S. suis*–infected patients, although this finding varied by country. The syndromic distribution of the reported cases may depend on study design and case ascertainment methods. All major studies in Vietnam ascertained *S. suis* cases from the population of patients with central nervous system diseases, which could lead to underrepresentation of *S. suis* patients with clinical syndromes other than meningitis. Only 1 patient without meningitis (diagnosed as spontaneous bacterial peritonitis with serotype 16 infection) has been reported in this country (*37*). Nevertheless, whether the existing strains infecting humans in Vietnam mainly cause meningitis remains unclear. In fact, lumbar puncture is performed regularly for all *S. suis*–infected patients, including those with severe sepsis, at a hospital for tropical diseases in Vietnam, and almost all had exhibited typical characteristics of bacterial meningitis in cerebrospinal fluid. On the other hand, meningitis might not be diagnosed or reported from other countries, therefore reducing the global *S. suis* meningitis estimate.

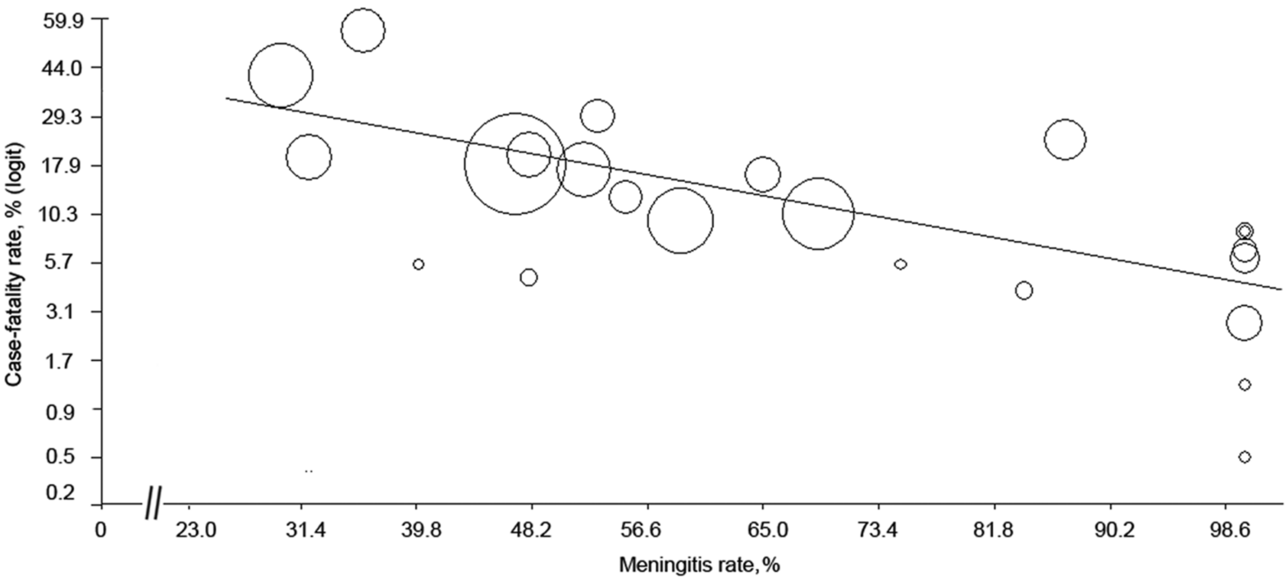

Figure 5. Meta-regression scatter plot showing the correlation between case-fatality rate and meningitis rate in a review of *Streptococcus suis* infection. The logit event rate was calculated for case-fatality rate as follows: logit event rate = ln[event rate/(1 – event rate)]. Each circle represents a study in the meta-analysis, and the size of the circle is proportional to study weighting. Studies with higher meningitis rates tended to report lower death rates.

The difference in CFR between case-patients with meningitis and case-patients with severe sepsis has been documented in both outbreak and nonoutbreak situations in China and Thailand (*1*,*2*,*24*). Significantly more deaths were reported among *S. suis* patients with systemic infection, including hypotension, septic shock, multiorgan failure, and disseminated intravascular coagulation in these studies. In the Sichuan outbreak in 2005, the CFR reached 62% for patients classified as having streptococcal toxic shock syndrome (*1*). Several hypotheses have been suggested; however, the pathologic mechanisms underlying this high CFR remain to be elucidated (*7*,*12*). Regarding meningitis cases, the pooled CFR is lower than that for other common causes of adult bacterial meningitis, such as *S. pneumoniae* (19%–37%) (*38*) and *Neisseria meningitidis* (10%) (*39*). However, the rates of sequelae caused by *S. suis* tend to be higher than those caused by other agents reported in a recent meta-analysis (*40*).

We were unable to establish pooled risk estimates for different risk factors because of a lack of studies with appropriate designs. In the Netherlands, the annual risk for *S. suis* meningitis among abattoir workers and pig breeders was 1,500 times higher than that in the general population (*10*). In Vietnam, *S. suis*–infected patients were more likely to have eaten high-risk foods (odds ratio [OR] 4.38), to have pig-related occupations (OR 5.52), and to have pig exposure while having skin injuries (OR 15.96) than community controls (*6*). The lower proportions of patients with occupational exposure in Thailand and Vietnam than in Europe shown in our meta-analysis supports the hypothesis that other risk factors, including food consumption practices, may play a major role in the epidemiology of *S. suis* infection in Asia.

This review is not without limitations. The included studies were highly heterogeneous in quality and in the factors reported, which reduced the number of studies included in each meta-analysis. The summary values of the single-case dataset should be interpreted with caution because the patients in this merged "sample" were heterogeneously "recruited" from different populations, with different assessment protocols. In addition, the studies were mainly retrospective; data could have been easily missed on recall or by re-collecting from the existing data records. We were unable to assess the extent to which this misinformation could affect the overall estimates. However, data collection approach was not significantly associated with the main outcomes examined under this review in our meta-regression analyses.

This review helps to highlight areas in which additional research is needed. Geographic gaps obviously exist in the data on *S. suis* cases, especially in the pig rearing countries in the Americas, Eastern Europe, and Asia, such as Mexico and Brazil, Russia, and the Philippines, respectively. Second, much uncertainty remains in understanding sequelae of *S. suis* infection and recovery from these conditions over time. Careful prospective assessments of these debilitating outcomes and associated social and economic impacts are essential for understanding and reducing the effects of *S. suis* infection. More studies also are needed to assess the treatment effects of adjunctive corticosteroid on hearing loss or other neurologic sequelae.

The effects of *S. suis* infection are mainly in Asia; occupational exposure and eating possibly contaminated foods containing undercooked pig tissues are prime risk factors. Further research in Asia should focus on the factors pertinent to local risk for infection, including the practices of unsafe handling and consumption of pork. Prevention of human infections needs to be tailored for different risk groups, and studies are needed to assess the feasibility and effectiveness of those tailored programs. Additional work is needed to assess the fraction of *S. suis* cases that can be attributed to different risk factors (the population-attributable fraction) and the proportion of *S. suis* cases that might be preventable if specific risk factors were reduced.

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Epidemiology, Clinical Manifestations, and Outcome of *Streptococcus suis* Infection

Technical Appendix

Technical Appendix Table 1. Details of 177 included publications in review of the epidemiology, clinical manifestations, and outcome of *Streptococcus suis* infection in humans

PID	Author/year/country/city	Study design	Data collection	Study population	Age group	Recruitment period	*S. suis* diagnosis method	No. *S. suis* cases	Included
7	Agass/1977/England/Oxford	Case report	Retrospective		A	ND	Culture	1	In single dataset
8	Alonso-Socas/2006/Spain/Tenerife	Case report	Retrospective		A		Culture	1	In single dataset
9	Arends/1995/Netherlands/Leiden	Case report	Retrospective		A	1994	Culture	1	In single dataset
11	Arends/1988/Netherlands/Amsterdam	Case series	Retrospective	We only included the Netherlands' cases	A	1968–1984	Culture (CSF)	30	As a large study
12	Asensi/2001/Spain/Oviedo	Case report	Retrospective		A	1998	Culture (blood + CSF)	2	In single dataset
13	Aspiroz/2009/Spain/zaragoza	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
14	Atterholm/1985/Sweden/Lund	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
15	Baddeley/1995/UK/Gloucestershire	Case report	Retrospective		A	ND	ND	1	In single dataset
16	Bahloul/2008/France/Salon de Provence	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
24	Berlit/1989/Gemany/Mannheim	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
25	Bezian/1996/France/Bordeaux	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
28	Bouchaud/1997/France/Elbeuf	Case report	Retrospective		A	Feb 1995	Culture (CSF + blood)	1	In single dataset
29	Busova/2010/Czech Republic/	Case report	Retrospective		A	Jul 2005	Culture (CSF)	1	In single dataset
31	Braun/2007/Germany/Augsburg	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
34	Bungener/1989/Federal Republic of Germany	Case report	Retrospective		A	1984	Culture (blood)	1	In single dataset
35	Cammaert/1990/Belgium/	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
36	Camporese/2007/Italy/Pordenone	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
37	Caumont/1996/France/Reims	Case report	Retrospective		A	ND	Culture (disco-vertebral biopsy)	1	In single dataset
38	Chan/2002/Singapore	Cross section	Retrospective	Bacterial meningitis	A	1993–Jun 2000	Culture (blood)	1	In single dataset
39	Chang/2006/Japan	Case series	Retrospective		A	1994–2006	Culture	7	As a large study
41	Chattopadhyay/1980/England/London	Cross section	Combinaton	Meningitis	A	1971–1978	Culture	1	In single dataset
42	Chau/1983/China/Hong Kong	Case series	Retrospective		A	1978–1981	Culture (blood or CSF)	8	As a large study
43	Cheng/1987/China/Hong Kong	Case report	Retrospective		A	ND	Culture (blood + knee aspirate)	1	In single dataset

PID	Author/year/country/city	Study design	Data collection	Study population	Age group	Recruitment period	*S. suis* diagnosis method	No. *S. suis* cases	Included
44	Chotmongkol/1999/Thailand	Case report	Retrospective		A	1997		1	In single dataset
							Culture (blood + CSF)		
47	Clarke/1991/UK/London	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
48	Clements/1982/UK/Cambridge	Case report	Retrospective		A	ND	Culture (1st pt: blood + CSF, 2nd pt: blood)	2	In single dataset
52	Colaert/1985/Belgium	Case report	Retrospective		A	1984	Culture	1	In single dataset
55	Coolen/1989/Belgium	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
56	D'Agostino/2009/Italia/Rome	Cross section	Prospective	Vertebral osteomyelitis		ND	Culture	1	In single dataset
58	De La Hoz/2005/Spain/Cadiz	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
60	Desjars/1987/France/Nantes	Case report	Retrospective		A	Nov 1986	Culture (blood + CSF)	1	In single dataset
61	Dickie/1987/New Zealand	Case report	Retrospective		A	Nov 1986	Culture (blood)	1	In single dataset
62	Donsakul/2003/Thailand/Bangkok	Cross section	Retrospective	Bacterial meningitis	A	1993–1999	Culture	8	As a large study
63	Doube/1988/England/Bath	Case report	Retrospective		A	ND	Culture (synovial pus + blood)	1	In single dataset
64	Dragojlovic/2005/Serbia/Belgrade	Case series	Retrospective		A	2003	Culture (CSF + blood)	5	As a large study
65	Duong/2004/VietNam/HoChiMinh city	Case report	Retrospective		A		Culture (blood, CSF, + lesions fluid)	1	In single dataset
66	Dupas/1992/France/Nantes	Case report	Retrospective		A	Apr 1991	CSF (not specified diagnostic method)	1	In single dataset
67	Durand/2001/France/Grenoble	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
69	Faucqueur/1983/France/Chateaudun	Case report	Retrospective		A	Oct 1981	Culture (CSF, blood)	1	In single dataset
70	Fauveau/2007/France/Blois	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
73	Feng/2009/China/Shenzhen City and Sichuan	Case report	Retrospective		A	Jul–Aug 2007	Culture	3	In single dataset
75	Fernandez/2011/Spain/A Coruna	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
76	Fittipaldi/2009/US/Hawaii	Case report	Retrospective		A		Culture	1	In single dataset
78	Fongcom/2009/Thailand/Lamphun	Case series	Retrospective		A	1999–2000	Culture (blood)	10	As a large study
79	Fongcom/2009/Thailand/Lamphun	Case series	Combine		A	Apr 2001–Apr 2002: Jul 2005–Jul 2007	Culture (blood + CSF)	53	As a large study
80	Francois/1998/France/Limoges	Case report	Retrospective		A	1996	Culture (blood + CSF)	1	In single dataset
81	Galbarro/2009/Spain/Huelva	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
84	Garau/1995/Itali/Cagliari	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
85	Geffner/2001/Spain/Castellon	Case report	Retrospective		A	ND	Culture (blood + CSF)	2	In single dataset
95	Grebe/1997/Germany/Heidelberg	Case report	Retrospective		A	ND	Culture (CSF, blood)	1	In single dataset
97	Halaby/2000/Netherlands/Maastricht	Case report	Retrospective		A	ND	Culture (blood, CSF)	1	In single dataset
98	Haleis/2009/Canada/Manitoba	Case report	Retrospective		A	Oct 2007	Culture (CSF)	1	In single dataset
99	Hantson/1991/Belgium/Brussels	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
100	Hay/1989/UK/Edinnburgh	Case report	Retrospective		A	Apr–1987	Culture (CSF)	2	In single dataset
102	Heidt/2005/Germany/Giessen	Case report	Retrospective		A		Culture (blood + aortic valve)	1	In single dataset
103	Helbok/2006/Thailand/Bangkok	Cross section	Retrospective	Chronic meningitis		1993–1999	Culture	2	In single dataset
105	Hidalgo/2007/Spain/Malaga	Case report	Retrospective		A		Culture (CSF + blood)	1	In single dataset

PID	Author/year/country/city	Study design	Data collection	Study population	Age group	Recruitment period	*S. suis* diagnosis method	No. *S. suis* cases	Included
106	Ho/1990/China/Hong Kong	Case report	Retrospective		A	Aug 1989	Culture (blood)	1	In single dataset
108	Hoa/1998/Vietnam/Ho Chi Minh	Cross section	Prospective	Community acquired septicemia		1 Jun 1993–30 May 1994	Culture (blood)	4	In single dataset
110	Hu/2000/China/Jiangsu	Outbreak investigation	Retrospective			Jul 1998	Culture (CSF or blood)	25	As a large study
112	Huang/2005/China/Taiwan/Taipei	Case report	Retrospective		A	Mar 2000, Sep 2002	Culture (CSF, blood)	2	In single dataset
113	Huh/2011/Korea/Seoul	Case report	Retrospective		A		Culture (CSF + blood)	1	In single dataset
114	Hui/2005/China/Hongkong	Cross section	Combine	Bacterial meningitis	A	1992–2001	Culture	6	As a large study
115	Ibaraki/2003/Japan/Nagaoka	Case report	Retrospective		A	Aug 2002	Culture (CSF)	1	In single dataset
116	Ip/2007/Hongkong	Case series	Retrospective		8A, 2ND	1995–2005	Culture (CSF or blood)	10	As a large study
121	Juncal/1997/Spain/La Coruna	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
122	Kaufhold/1988/Germany/Koln	Case report	Retrospective		A	Sep 1987	Culture (CSF + blood)	1	In single dataset
125	Kay/1995/China/Hong Kong	Case series	Retrospective		A	1984–1993	Culture (blood and/or CSF)	25	As a large study
126	Kennedy/2008/Australia/New South Wales	Case report	Retrospective		A	Oct 2006, Jan 2008	Culture (blood)	2	In single dataset
127	Kerdsin/2009/Thailand	Cross section	Retrospective	Unidentified streptoccocal isolates	A	Jan 2006–Sep 2008	Culture (blood or CFS)	165	As a large study
128	Kerdsin/2011/Thailand/Uttaradit	Case report	Retrospective		A	Jun and May 2007	Culture (1 case acitic fluid, 1 case blood)	2	In single dataset
129	Kerdsin/2009/Thailand	Cross section	Retrospective	Confirmed *S. suis*	A	Jan 2006–Sep 2008	Culture (blood + CSF)	12	As a large study
130	Khin Thi/1985/China/HongKong	Case series	Prospective		A	1982–1984	Culture (CSF, blood)	30	As a large study
131	Kim/2011/Korea/Chungcheong	Case report	Retrospective		A	ND	Culture (blood, joint fluid)	1	In single dataset
134	Kohler/1989/Germany/	Case report	Retrospective		A	Jun 1987	Culture (CSF+ blood)	1	In single dataset
135	Kopic/2002/Croatia/Slavonski Broad	Case report	Retrospective		A	Nov 2000	Culture (1 blood, 1 CFS)	2	In single dataset
137	Kowalik/2007/Poland/Gdansk	Cross section	Prospective	Community acquired bacterial meningitis	A	Jan 1999–Dec 2001	Culture (CSF)	3	In single dataset
138	Laohapensang/2010/Thailand/Chiang Mai	Case report	Retrospective		A	ND	Culture (blood, aspirated synovial fluid)	1	In single dataset
139	Lecuyer/2004/France/Saint Quentin	Case report	Retrospective		A	ND	ND	1	In single dataset
140	Lee/2008/US/San Francisco	Case report	Retrospective		A	2003	Culture (blood)	1	In single dataset
141	Leelarasamee/1997/Thailand/bangkok	Case report	Retrospective		A	ND	Culture (blood + CSF)	3	In single dataset
145	Lopreto/2005/Agentina/La Plata	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
146	Luengo/2006/Spain/Caceres	Case report	Retrospective		A	2004	Culture (CSF+ blood)	1	In single dataset
149	Lutticken/1986/Germany/Munich	Case report	Retrospective		A	1985	Culture (CSF, blood)	1	In single dataset
150	Ma/2008/China/HongKong	Case series	Retrospective		A	1 Jan 2003–31 Jul 2005	Culture (CSF, blood)	21	As a large study
152	Maher/1991/UK/Leeds	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
153	Mai/2008/VietNam/HCMC	Cross section	Prospective	Bacterial meningitis	A	Nov 1996–Jun 2005	Culture + PCR	151	As a large study

PID	Author/year/country/city	Study design	Data collection	Study population	Age group	Recruitment period	*S. suis* diagnosis method	No. *S. suis* cases	Included
155	Manzin/2008/Italy/Sardinia	Case report	Retrospective		A	Nov 2007	Culture (CSF)	1	In single dataset
156	Martimez Aviles/1994/Spain/Madrid	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
157	Matano/1984/Italy/Caserta	Case report	Retrospective		A	Jan 1983	Culture (CSF)	1	In single dataset
158	Matsuo/2003/Japan/Nagasaki	Case report	Retrospective		A	Feb 2002	Culture (CSF)	1	In single dataset
159	Mazokopakis/2005/Greece/Crete	Case report	Retrospective		A	ND	Culture (blood, CSF)	1	In single dataset
160	McLedon/1978/Leicester/UK	Case report	Retrospective		A	1976	Culture (CSF, blood)	1	In single dataset
161	McNeil/1986/London/UK	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
162	Meecham/1992/England/Chester	Case report	Retrospective		A	ND	Culture (blood, CSF)	1	In single dataset
163	Michaud/1996/Canada/Quebec	Case report	Retrospective		A	1994	Culture (CSF)	1	In single dataset
165	Nagel/2008/Agentina/Santa Fe	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
166	Navacharoen/2009/Thailand/Northern	Case series	Retrospective		A	Jan 2003–Jan 2007	Culture	40	As a large study
167	Nghia/2008/VietNam/Long An	Case report	Retrospective		A	2001	Culture (blood)	1	In single dataset
168	Nghia/2011/VietNam/Ho Chi Minh city	Case control	Prospective	Hospital cases and controls, community controls	A	May 2006–Jun 2009	Culture (blood, CSF)	101	As a large study
172	Pedroli/2003/France/Montbrison	Case report	Retrospective		A	Nov 2000	Culture (blood)	1	In single dataset
173	Peetermans/1989/Netherlands/Leiden	Case report	Retrospective		A	1988	Culture (blood)	1	In single dataset
174	Perseghin/1995/Italy/Sondalo	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
175	Piech/2009/France/Clermont-Ferrand	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
177	Poggenborg/2008/Denmark/Copenhagen	Case report	Retrospective		A	2006	Culture (CSF, blood)	1	In single dataset
179	Pychova./2011Czech/Brno	Case report	Retrospective		A	2008; 2009	CSF culture and PCR	2	In single dataset
180	Plotek/2007/Poland/Kalisz	Case report	Retrospective		A		Culture (blood + CSF)	1	In single dataset
183	Rao/2008/UK/Kent	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
186	Riquelme/2008/Spain/Santander	Case report	Retrospective		A		Culture (CSF + blood)	1	In single dataset
190	Rosenkranz/2003/Germany	Case report	Retrospective		A	ND	Culture (blood, CSF)	1	In single dataset
191	Rosenstingl/2008/France/Coulommiers	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
192	Rusmeechan/2008/Thailand/Phitsanulok	Case series	Retrospective		A	2001–2006	Culture (blood, CSF)	41	As a large study
197	Seidel/1995/Germany/Munster	Case report	Retrospective		A	Jan 1994	Culture (CSF)	1	In single dataset
198	Shneerson/1980/UK/London	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
199	Sia/2006/China/Hong Kong	Case report	Retrospective		A	2004	Culture (blood, CSF)	1	In single dataset
202	Soemirien/2010/Netherlands/Amsterdam	Case series	Prospective	Adult community-acquired bacterial meningitis	A	Mar 2006–Jan 2009	Culture (CSF)	2	In single dataset
204	Spiss/1999/Austria/Innsbruck	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
206	Strangmann/2002/Germany/Oldenberg	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
208	Suankratay/2004/Thailand/Bangkok	Case series	Retrospective		A	Jan 1997–May 2002	Culture (blood + CSF)	12	As a large study
209	Taipa/2008/Portugal?Porto	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset

PID	Author/year/country/city	Study design	Data collection	Study population	Age group	Recruitment period	*S. suis* diagnosis method	No. *S. suis* cases	Included
212	Tambyah/1997/Singapore	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
213	Tan/2010/Singapore/	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
214	Tang/2006/China/Sichuan	Outbreak investigation	Retrospective		A	Jun 2005	Culture + PCR	204	As a large study
216	Taradas/2001/Spain/Castellon	Case report	Retrospective		A	ND	culture (CSF)	2	In single dataset
217	Tayoro/1996/France/Tours	Case report	Retrospective		A	1994	Culture (blood)	1	In single dataset
219	Thwaites/2002/Viet Nam/Ho Chi Minh city	Cross section	Prospective	Bacterial meningitis of tuberculous meningitis	A	1997–2000	Culture (CSF)	31	As a large study
222	Tramontana/2008/Australia/Melbourne	Case report	Retrospective		A	2007	Culture (blood)	1	In single dataset
224	Tran/2011/Viet Nam/HCMC	Cross section	Prospective	Baterial meningitis	A	May 2006–Jun 2009	Culture (blood, CSF)	110	As a large study
225	Trottier/1991/Canada/Quebec	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
226	Tsai/2005/China/Taiwan	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
227	Twort/1981/England/Chichester	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
230	van de Beek/2008/Netherlands/nationwide	Cross section	Prospective	Community-acquired bacterial meningitis	A	Oct 1998–Apr 2002	Culture (CSF)	4	In single dataset
231	van Jaarsveld/1990/Netherlands/Nijimegen	Case report	Retrospective		A	April 1989	Culture (blood)	1	In single dataset
232	Van Ooteghem/1988/Belgium/Gent	Case report	Retrospective		A	Mar1986	Culture (blood + CSF)	1	In single dataset
235	Vilaichone/2002/Thailand/Bangkok	Case series	Retrospective			1994–2001	Culture (blood or CSF or peritoneal fluid)	17	As a large study
236	Voutsadakis/2006/Greece/Larissa	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
237	Walsh/1992/UK/	Case series	Retrospective		A	1975–1990	Culture (blood or CSF)	35	As a large study
240	Wangkaew/2006/Thailand/ChiangMai	Case series	Retrospective		A	May 2000–Dec 2002	Culture	41	As a large study
241	Wangsomboonsiri/2008/Thailand/Nokornsawan	Case series	Retrospective		A	Jan 2005–Oct 2007	Culture	66	As a large study
242	Watkins/2001/UK/Leeds	Case report	Retrospective		A	Aug 1999	Culture (blood)	1	In single dataset
244	Wertheim/2009/Viet Nam/Ha Noi	Case series	Retrospective		A	Jan–Dec 2007	Culture, PCR	50	As a large study
245	Wilenburg/2006/US/	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
248	Woo/1987/China/Hongkong	Case report	Retrospective		A	ND	Culture (blood + CSF)	2	In single dataset
252	Yamaguchi/1994/Japan	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
253	Yang/2005/China/Taiwan	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
254	Yang/2009/China	Case report	Retrospective		A	Jul 2005		4	In single dataset
257	Ye/2009/China/	Outbreak investigation	Retrospective		A	2005	Culture	38	As a large study
259	Yen/1994/China/Taiwan/Kaohsiung	Case report	Retrospective		A	Apr1991	Culture (CSF)	1	In single dataset
261	Yu/2006/China/Sichuan	Outbreak investigation	Retrospective		A	Jun–Aug 2005	Culture	215	As a large study
269	Chau/1983/China/Hong Kong	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
270	Koldkjaer/1972/Danmark/Odense	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
271	Perch/1968/Denmrk/Hillerød	Case report	Retrospective		A	1960–1966	Culture (blood + CSF)	3	In single dataset

PID	Author/year/country/city	Study design	Data collection	Study population	Age group	Recruitment period	*S. suis* diagnosis method	No. *S. suis* cases	Included
272	Hickling/1976/England/London	Case report	Retrospective		A	ND	Culture (CSF + blood)	1	In single dataset
273	Kloppenburg/1975/Netherlands/Groningen	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
281	Khadthasrima/2008/Thailand/Phayao	Outbreak investigation	Retrospective		A	12 April–11 May/2007	Culture (CSF + blood)	50	As a large study
282	Joynson/1980/Wales/West Glamorgan	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
283	Peel/1979/UK/York	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset
290	Damodaram/2011/India/Andhra Pradesh	Cross section	Retrospective	Myositis		2006–2011		1	In single dataset
295	Isaradisaikul/2010/Thailand	Cross section	Retrospective	Vertigo	A	April 2005–December 2007	ND	1	In single dataset
296	Bronstein/1995/UK/London	Case report	Retrospective			ND	ND	1	In single dataset
297	Pachirat/2012/Thailand	Cross section	Prospective	Infective endocarditis	A	January 2010–December 2011	PCR, culture (blood)	3	In single dataset
298	Takeuchi/2012/Thailand/Phayao	Cross section	Prospective		A	2010	Culture (blood or CSF)	31	As a large study
299	Moon/2011/Korea	Case report	Retrospective		A		Culture (blood, joint fluid)	1	In single dataset
300	Nghia/2012/Vietnam	Cross section	Prospective	CNS infections	A	August 2007–April 2010	Culture (blood, CSF) + PCR	147	As a large study
302	Boonyagars/2010/Thailand/	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
303	Choi/2012/Korea/Gwangju	Case report	Retrospective		A	ND	Culture (CSF)	1	In single dataset
304	Tsai/2012/China/Taiwan/	Case series	Retrospective		A	2000, 2002, 2005, 2007, 2009, 2010, 2010, 2011	PCR	8	As a large study
305	Thayawiwat/2012/Thailand/Phayao	Cross section	Prospective	Sepsis, meningitis, IE, pneumonia, arthritis	A	January 2009–December 2011	Culture (blood or CSF)	31	As a large study
307	Taylor/2012/Vietnam/Hanoi	Cross section	Prospective	CNS infections	A	May 2007–December 2008	Culture (blood or CSF) + PCR	48	As a large study
308	Hanterdsith/2012/Thailand/	Case report	Retrospective		A		Culture (blood_	1	In single dataset
309	Paul/1977/France/	Case report	Retrospective		A		ND	1	In single dataset
310	Avril/1977/France/Paris	Case report	Retrospective		A		Culture (blood + CSF)	2	In single dataset
311	Perch/1971/Denmark/Copenhagen	Case report	Retrospective		A		Culture (CSF)	1	In single dataset
312	Yoon/2012/Korea/Jeju	Case report	Retrospective		A	ND	Culture (blood + pleural fluid)	1	In single dataset
313	de Ceuster/2012/Netherlands	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
314	Zalas-Wiêcek/2012/Poland/Bydgoszcz	Case report	Retrospective		A	ND	Culture (blood + CSF)	1	In single dataset
315	Vela/2012/Spain/	Case report	Retrospective		A	ND	Culture (blood)	1	In single dataset

*PID, publication identification ; A, adult; ND, not determined

Technical Appendix Table 2. Articles included in the meta-analysis of each variable

Variable	No. studies included	PID of papers included
Mean age, y	25	Pooled single-case dataset, and papers PID 261, 127, 153, 224, 241, 79, 244, 281, 192, 240, 166, 237, 298, 11, 130, 125, 235, 129, 208, 116, 42, 62, 304, 39.
Male sex	26	Pooled single-case dataset, and papers PID 261, 127, 153, 224, 241, 79, 244, 281, 192, 240, 166, 237, 298, 305, 11, 130, 125, 150, 235, 208, 42, 62, 304, 39, 64.
Pig-related occupation	21	Pooled single-case dataset, and papers PID 153, 168, 241, 240, 166, 237, 298, 11, 261, 42, 150, 114, 208, 235, 62, 125, 304, 129, 110, 39.
History of contact with pig/pork	14	Pooled single-case dataset, and papers PID 168, 240, 261, 150, 208, 235, 127, 224, 244, 130, 110, 39, 64.
History of eating high-risk pork food	9	Pooled single-case dataset, and papers PID 168, 241, 166, 298, 235, 127, 79, 244.
Skin injury	8	Pooled single-case dataset, and papers PID 168, 237, 261, 150, 235, 125, 39.
Drinking history	13	Pooled single-case dataset, and papers PID 127, 168, 241, 79, 244, 240, 166, 305, 125, 150, 235, 208.
Concurrent diabetes	9	Pooled single-case dataset, and papers PID 224, 241, 240, 192, 166, 298, 125, 150.
Meningitis	26	Pooled single-case dataset, and papers PID 261, 127, 153, 300, 224, 241, 79, 244, 192, 240, 166, 237, 298, 130, 11, 125, 110, 150, 235, 129, 208, 304, 42, 62, 64.
Sepsis	12	Pooled single-case dataset, and papers PID 261, 127, 241, 79, 240, 166, 298, 130, 150, 235, 129.
Endocarditis	10	Pooled single-case dataset, and papers PID 127, 241, 79, 240, 166, 125, 150, 235, 62.
Endophthalmitis	9	Pooled single-case dataset, and papers PID 241, 244, 240, 166, 237, 130, 39, 64.
Arthritis	12	Pooled single-case dataset, and papers PID 127, 241, 237, 298, 130, 125, 150, 208, 42, 62, 39.
Spondylodiscitis	3	Pooled single-case dataset, and papers PID 241, 79, 240
Toxic shock syndrome	4	Pooled single-case dataset, and papers PID 110, 79, 214
Mean onset–admission duration	7	Pooled-single case dataset, and papers PID 241, 244, 240, 298, 208, 150.
Mean hospitalization duration	5	Pooled single-case dataset, and papers PID 241, 244, 208, 129.
Meningeal sign	18	Pooled single-case dataset, and papers PID 127, 153, 224, 79, 244, 240, 192, 166, 257, 237, 125, 150, 235, 208, 62, 304, 39.
Skin rash	10	Pooled single-case dataset, and papers PID 214, 153, 79, 244, 192, 11, 130, 110, 62.
Shock	12	Pooled single-case dataset, and papers PID 127, 153, 241, 79, 244, 240, 11, 125, 110, 150, 235.
Respiratory failure	6	Pooled single-case dataset, and papers PID 214, 79, 244, 129, 64.
Acute renal failure	5	Pooled single case dataset, and papers PID 153, 244, 240, 235.
Disseminated intravascular coagulation	9	Pooled single case dataset, and papers PID 214, 241, 240, 130, 125, 150, 235, 39.
Relapse	5	Pooled single-case dataset, and papers PID 11, 237, 125, 208.
Death	25	Pooled single-case dataset, and papers PID 39, 241, 79, 281, 244, 240, 192, 166, 237, 298, 130, 11, 125, 110, 261, 150, 235, 127, 153, 208, 224, 62, 304, 64.
Hearing loss	26	Pooled single-case dataset, and papers PID 39, 241, 79, 281, 244, 240, 192, 166, 237, 298, 130, 11, 125, 150, 235, 127, 153, 208, 224, 42, 62, 257, 305, 304, 64.
Recovery from hearing loss	8	Papers PID 79, 192, 166, 237, 125, 235, 153, 62.
Vestibular dysfunction	13	Pooled single-case dataset, and papers PID 79, 244, 192, 166, 237, 11, 125, 208, 42, 62, 304, 64.
Blood leukocytes, 109/L	9	Pooled single-case dataset, and papers PID 261, 153, 241, 244, 240, 125, 235, 208.
Blood platelet, 109/L	7	Pooled single-case dataset, and papers PID 261, 153, 241, 244, 240, 208.
CSF leukocytes/mm3	7	Pooled single-case dataset, and papers PID 153, 241, 244, 125, 208, 42.
CSF protein, g/L	7	Pooled single-case dataset, and papers PID 153, 241, 244, 125, 208, 42.
CSF glucose, mg/dL	6	Pooled single-case dataset, and papers PID 241, 244, 125, 208, 42.

*PID, Publication Identification; CSF, cerebrospinal fluid.

Technical Appendix Table 3. Summary of preexisting conditions (other than diabetes) of human *Streptococcus suis* cases worldwide

Preexisting condition	No. cases	Publication ID
Heart disease	14 (10 had infective endocarditis as the main syndrome)	240, 62, 208, 235, 106, 213, 217
Hypertension	13	213, 166, 298, 302, 159, 121, 8, 113, 179, 195
Cirrhosis	10	166, 298, 128, 167, 150
Cancer	5	240, 208, 150, 236, 155
Dyslipidemia/hyperlipidemia	2	166, 302
Tuberculosis	2	150, 125
Psoriasis	2	150
Chronic liver disease	1	79
Aplastic anemia	1	298
Spinal canal stenosis	1	298
Rheumatoid arthritis	1	298
Chronic pancreatitis	1	84
Pelger-Huet anomaly	1	135
Splenectomy	9	168, 135, 15, 180, 242, 58, 80, 145, 237
History of corticoid use	2	208
Past *S. suis* infection	1	80

Technical Appendix Table 4. Microbiological characteristics of the merged single-case dataset in a systematic review of *Streptococcus suis* infection*

Characteristic	No. (%)
Microbiological diagnosis, n = 141	
Blood culture only	33 (23.4)
CSF culture only	34 (24.1)
Both CSF and blood culture, no PCR	53 (37.6)
PCR and culture (blood and/or CSF)	18 (12.8)
PCR only	3 (2.1)
Initial misdiagnosis, n = 174 (9 viridans streptococci, 2 *S. faecalis*, 1 *S. acidominimus* and 1 *S. bovis*)	13 (7.5)
Serotype 2, n = 174	94 (54)
Penicillin sensitivity, n = 92	90 (97.8)
Penicillin resistance, n = 92	1 (1.1)

*CSF, cerebrospinal fluid.

Technical Appendix Table 5. Bivariate meta-regression for meningitis, death, and hearing loss among included studies in the systematic review of *Streptococcus suis* infection*

			Meta-regression†	
Study-level factor	No. studies	Pooled group event rate (95% CI)	Rate difference	p value
Meningitis				
Country of publication				
Other‡[†]	4	0.731 (0.381–0.923)	–0.258	0.773
China mainland	2	0.456 (0.375–0.540)	–0.538	<0.001
Hong Kong	4	0.789 (0.526–0.927)	–0.226	1.000
Thailand	11	0.545 (0.434–0.651)	–0.436	<0.001
Vietnam	4	0.995 (0.981–0.999)	reference	
Year of publication				
2005 and earlier	10	0.771 (0.599–0.884)	0.034	0.824
After 2005	15	0.633 (0.513–0.738)	reference	
Study design				
Case series	17	0.670 (0.539–0.779)	–0.234	0.054
Outbreak	2	0.456 (0.375–0.540)	–0.404	0.004
Cross-sectional	6	0.920 (0.744–0.978)	reference	
Data collection				
Retrospective	19	0.595 (0.504–0.680)	–0.298	0.003
Prospective	6	0.931 (0.6960.988)	reference	
Death				
Country of publication				
Other‡	5	0.100 (0.051–0.188)	0.063	1.000
China mainland	2	0.338 (0.085–0.739)	0.198	0.060
Hong Kong	3	0.099 (0.025–0.320)	0.096	1.000
Thailand	11	0.158 (0.098–0.244)	0.129	0.264
Vietnam	3	0.030 (0.011–0.080)	reference	
Year of publication				
2005 and earlier	9	0.163 (0.079–0.306)	0.069	0.316
After 2005	15	0.112 (0.071–0.173)	reference	
Study design				
Case series	16	0.147 (0.097–0.216)	0.103	0.159
Outbreak	3	0.216 (0.064–0.525)	0.140	0.070
Cross-sectional	5	0.059 (0.024–0.140)	reference	
Data collection				

Retrospective	19	0.135 (0.093–0.190)	0.035	0.522
Prospective	5	0.108 (0.030–0.322)	Reference	
Meningitis rate				
<0.5	7	0.244 (0.143–0.384)	0.203	0.001
0.5– 0.9	8	0.149 (0.104–0.210)	0.106	0.106
>0.9	7	0.040 (0.022–0.070)	Reference	
Hearing loss				
Country of publication				
Other‡	5	0.479 (0.344–0.619)	–0.014	1.000
China mainland	1	0.237 (0.128–0.396)	–0.245	1.000
Hong Kong	4	0.520 (0.278–0.753)	0.018	1.000
Thailand	12	0.313 (0.208–0.442)	–0.170	1.000
Vietnam	3	0.437 (0.205–0.699)	Reference	
Year of publication				
2005 and earlier	9	0.508 (0.388–0.627)	0.128	0.327
After 2005	16	0.331 (0.231–0.450)	Reference	
Study design				
Case series	17	0.419 (0.311–0.536)	0.012	1.000
Outbreak	2	0.131 (0.031–0.413)	–0.266	0.420
Cross-sectional	6	0.422 (0.248–0.617)	Reference	
Data collection				
Retrospective	19	0.385 (0.285–0.497)	–0.096	0.327
Prospective	6	0.399 (0.238–0.586)	Reference	
Meningitis rate				
<0.5	5	0.236 (0.113–0.428)	–0.303	0.066
0.5–0.9	9	0.356 (0.259–0.466)	–0.241	0.051
>0.9	8	0.586 (0.400–0.751)	Reference	

*Boldface indicates dependent variable being analyzed in meta-regression.
†General linear model, weighted by sample size, study-level factors were included as random factors, with adjustment for multiple comparisons by the Bonferroni method.
‡Includes the United Kingdom, the Netherlands, Serbia, Taiwan, and Japan.

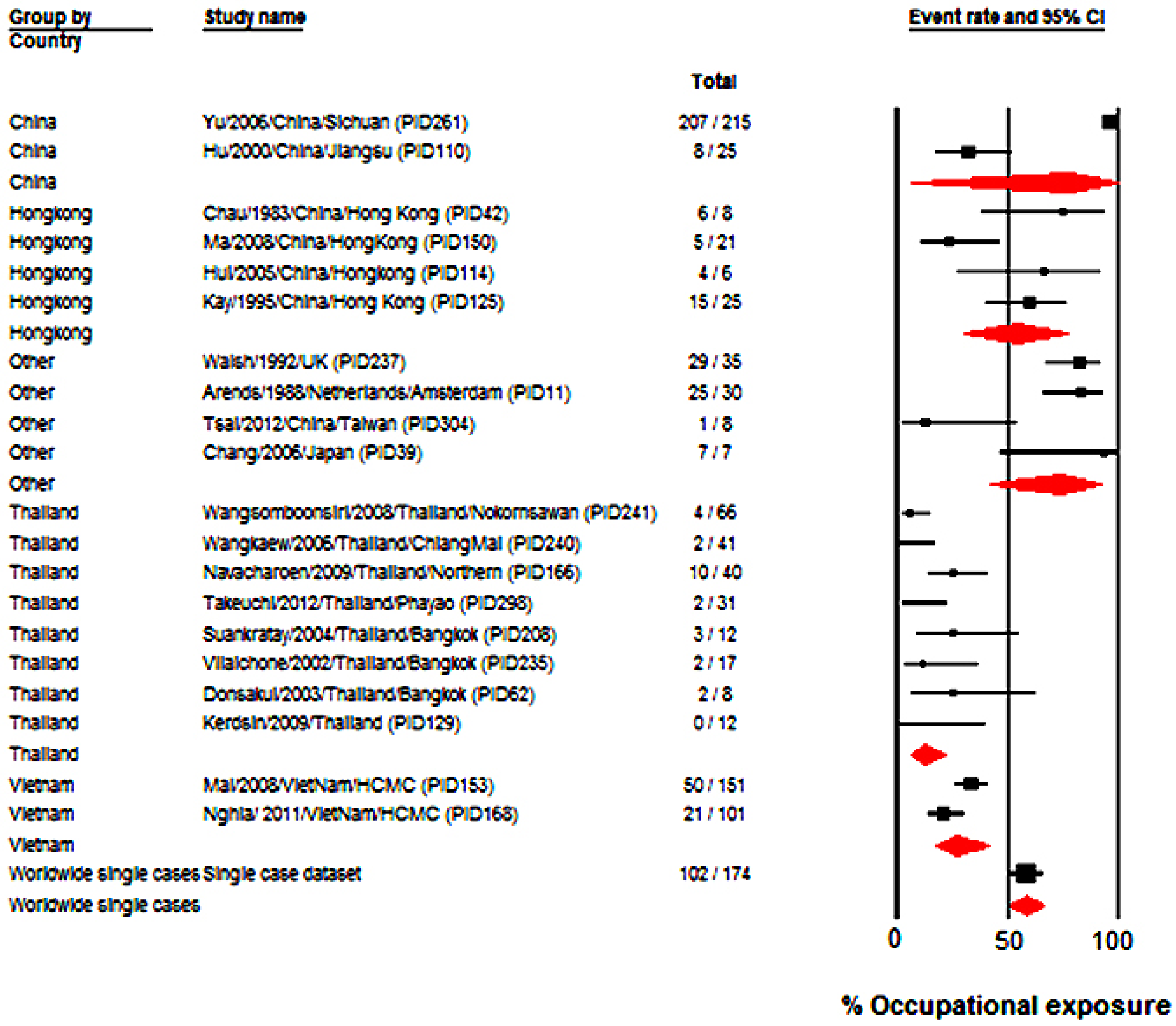

Figure 1. Forest plot of subgroup meta-analysis (random-effects) for proportions of *S. suis* patients with pig-related occupation by country reported in the 21 included studies. For each study, proportion and 95% CI is presented, with the size proportional to the study weight. The red rhombus presents the pooled proportion for each country group.

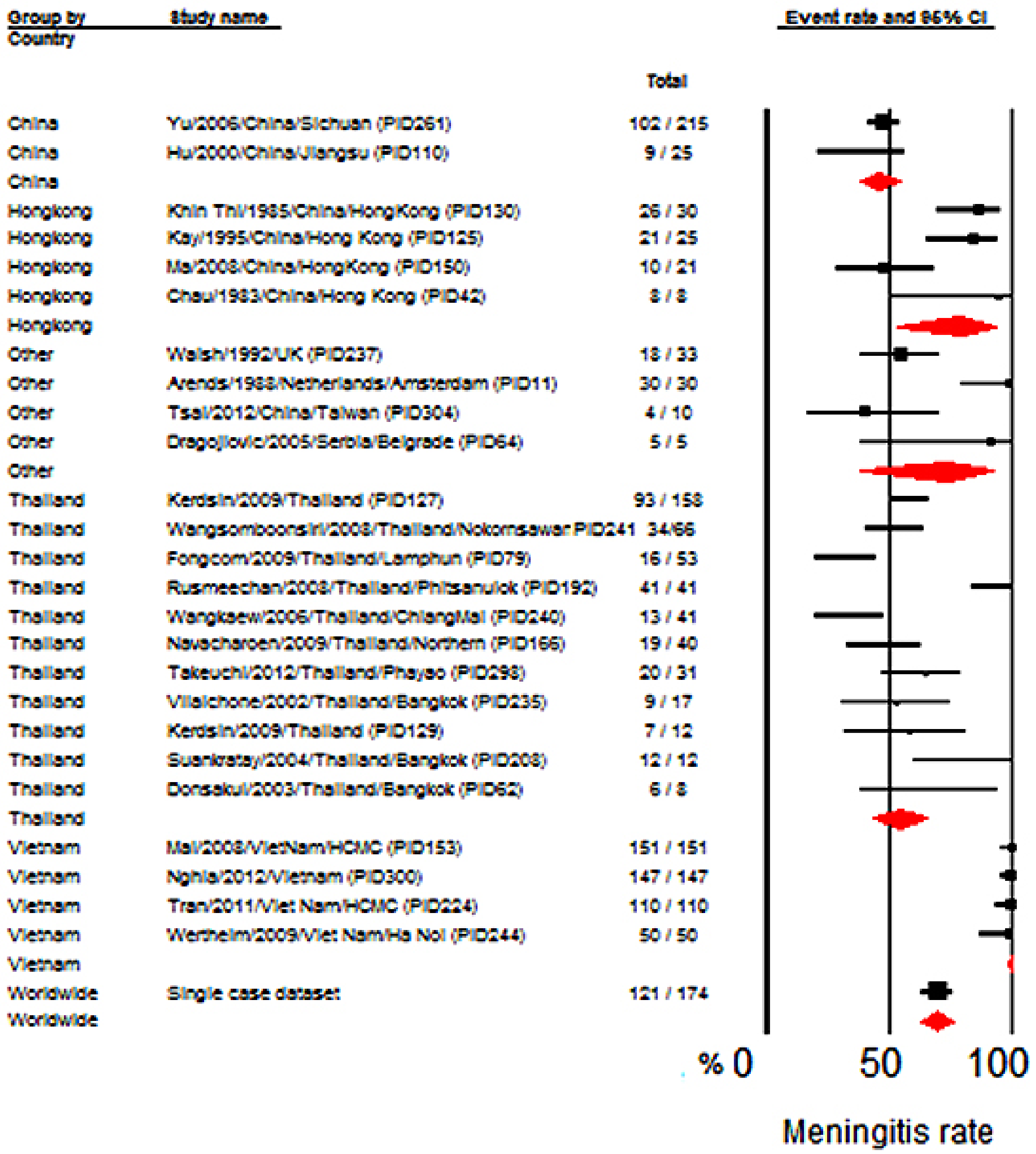

Figure 2. Forest plot of subgroup meta-analysis (random-effects) for the rates of meningitis by country reported in the 26 included studies. For each study, the event rate of meningitis and 95% CI is presented; size is proportional to study weight. The red rhombus presents the pooled event rate for each country group.

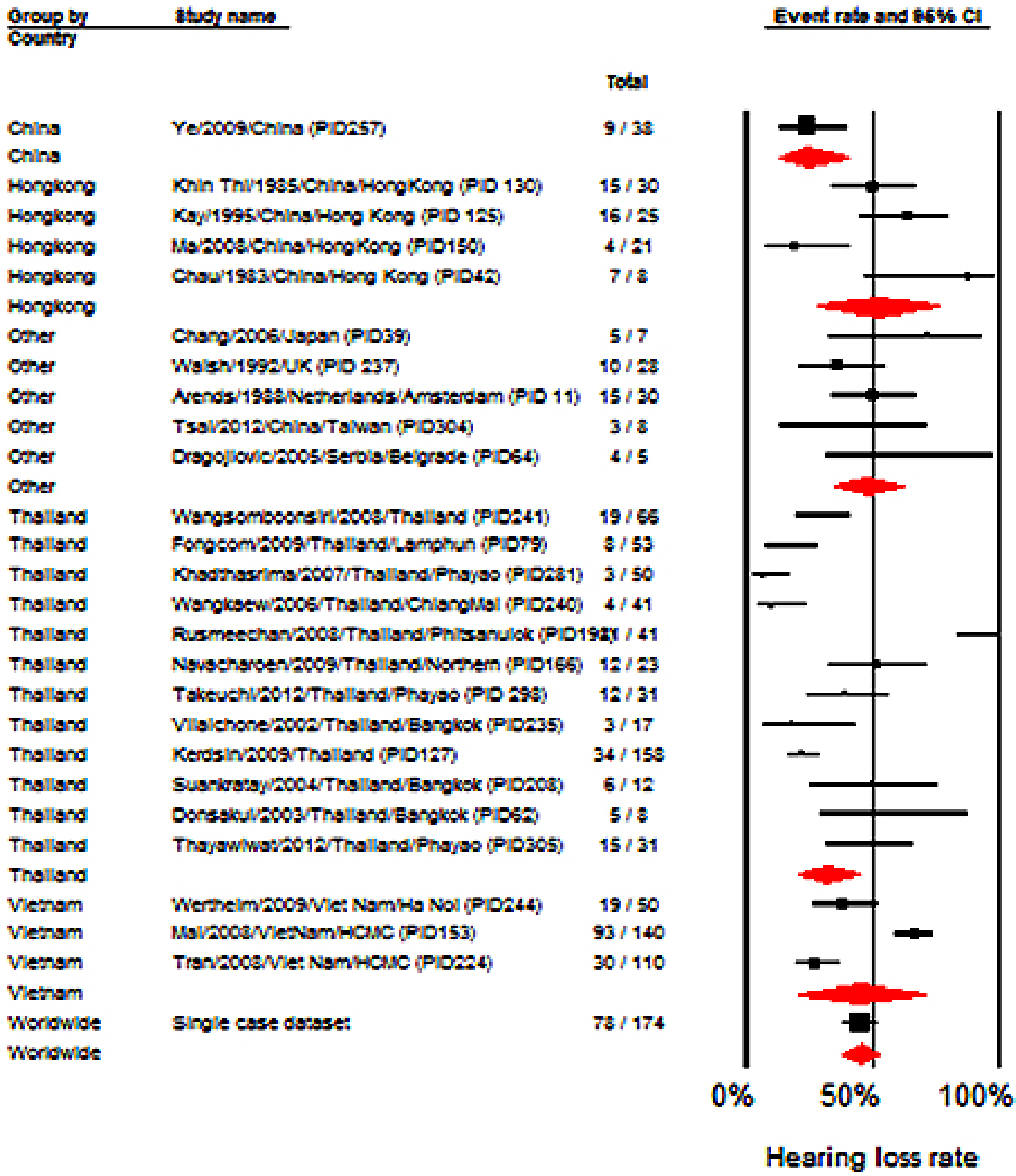

Figure 3. Forest plot of subgroup meta-analysis (random-effects) for the rates of hearing loss reported in the 26 included studies by country. For each study, the event rate and 95%CI is presented; size proportional to study weight. The red rhombus presents the pooled event rate for each country group.

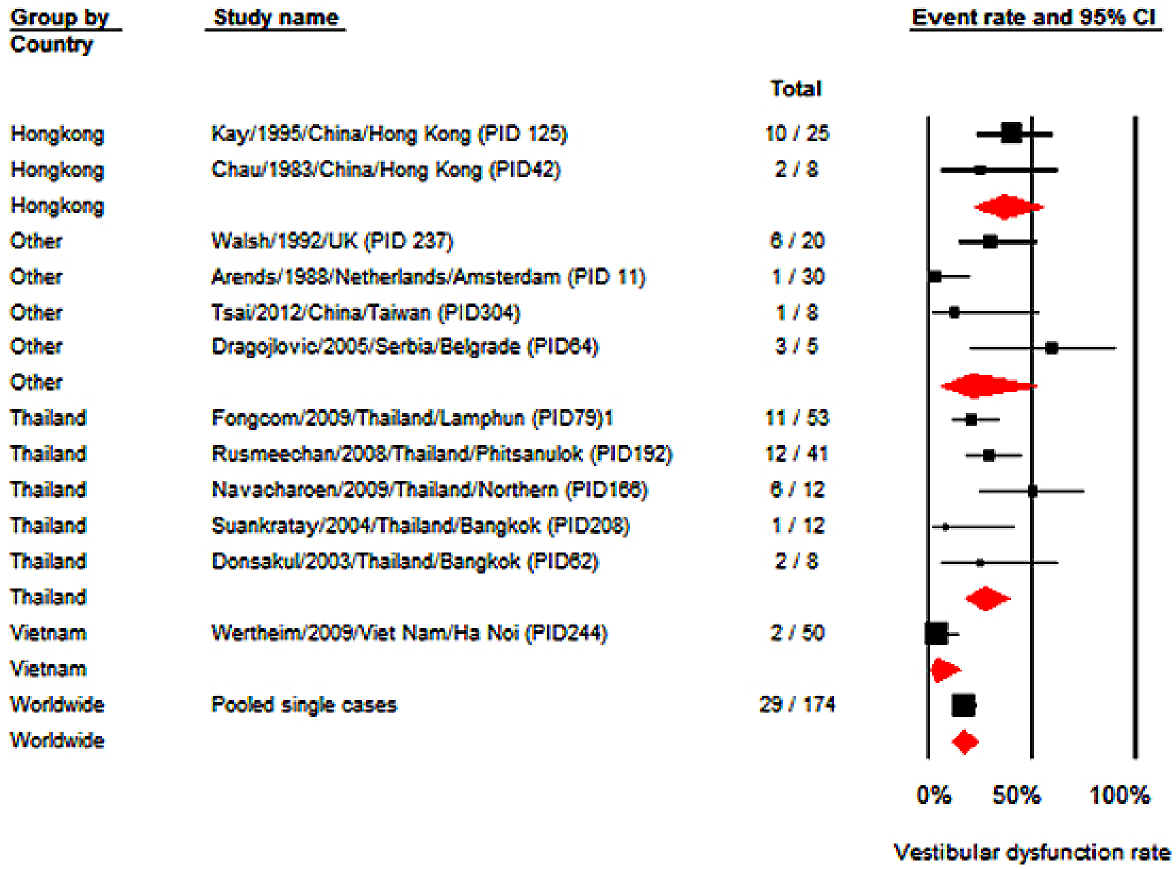

Figure 4. Forest plot of subgroup meta-analysis (random-effects) for the rates of vestibular dysfunction by country reported in the 13 included studies. For each study, the event rate and 95% CI is presented; size is proportional to study weight. The red rhombus presents the pooled event rate for each country group.