Charting the global footprint of borderline oxacillin-resistant Staphylococcus aureus (BORSA): The first systematic review and meta-analysis (#105033)

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Charting the global footprint of borderline oxacillin-resistant Staphylococcus aureus (BORSA): The first systematic review and meta-analysis

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Borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) has been a persistent yet under-researched concern in the realm of antibiotic resistance, characterized by its unique resistance mechanisms and potential for severe infections. This systematic review and meta-analysis consolidates data from 29 studies encompassing 18,781 samples, revealing a global BORSA prevalence of 6.6% (95% CI, 4.0 – 10.7). Notably, regional disparities were observed, with Brazil exhibiting the highest prevalence at 70.0%, while The Netherlands reported a mere 0.5%. These findings underscore the multifaceted nature of BORSA epidemiology, influenced by local antibiotic usage practices and healthcare infrastructures.

The analysis also highlights substantial heterogeneity (I^2 = 96.802%), emphasizing the need for standardized surveillance and reporting protocols. As antibiotic resistance continues to escalate, understanding BORSA's global footprint is crucial for informing targeted interventions and optimizing antibiotic stewardship programs. This study not only fills critical gaps in current knowledge of BORSA but also calls for enhanced collaboration among researchers, healthcare providers, and policymakers to effectively combat the rising threat of antibiotic-resistant pathogen like BORSA.

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Abstract

Borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) has been a persistent yet under-researched concern in the realm of antibiotic resistance, characterized by its unique resistance mechanisms and potential for severe infections. This systematic review and meta-analysis consolidates data from 29 studies encompassing 18,781 samples, revealing a global BORSA prevalence of 6.6% (95% CI, 4.0 – 10.7). Notably, regional disparities were observed, with Brazil exhibiting the highest prevalence at 70.0%, while The Netherlands reported a mere 0.5%. These findings underscore the multifaceted nature of BORSA epidemiology, influenced by local antibiotic usage practices and healthcare infrastructures. The analysis also highlights substantial heterogeneity (I^2 = 96.802%), emphasizing the need for standardized surveillance and reporting protocols. As antibiotic resistance continues to escalate, understanding BORSA's global

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Introduction

Over the past few decades, the rise and dissemination of antibiotic resistance in bacterial pathogens have presented major public health challenges globally. Among these resistant organisms, *Staphylococcus aureus*, a versatile and resilient bacterium, has garnered particular attention. Within the spectrum of antibiotic-resistant *S. aureus* strains, borderline oxacillin-resistant *S. aureus* (BORSA) presents a unique clinical and epidemiological profile.

BORSA strains, characterized by their marginal resistance to penicillinase-resistant penicillin (PRPs), typically with oxacillin minimum inhibitory concentrations (MICs) spanning from 1 – 8 µg/ml, represent a critical subset within the broader landscape of antimicrobial resistance (Hryniewicz & Garbacz, 2017). In contrast to methicillin-resistant *S. aureus* (MRSA), BORSA do not possess the altered penicillin-binding protein (PBP2a) that is encoded by the *mecA* or *mecC* genes (García-Álvarez et al., 2011). Instead, their resistance often stems from heightened beta-lactamase production or occasional mutations in PBP genes. This resistance can be effectively managed with enzyme inhibitors such as clavulanic acid or sulbactam. This differentiates BORSA from MRSA strains, where beta-lactamase inhibitors may lower the MIC of penicillin but do not impact the MIC of penicillin-resistant phenotypes (PRPs), even at higher concentrations (McDougal & Thornsberry, 1986).

BORSA strains defy easy classification as either fully methicillin-resistant or methicillin-susceptible. However, they are frequently misidentified, presenting significant challenges in epidemiology and treatment. BORSA strains are commonly isolated from both human and animal sources, prevalent in hospital and community settings alike (Hryniewicz & Garbacz, 2017). The epidemiology and clinical manifestations of BORSA infections closely resemble those of MRSA, often resulting in more severe results in comparison to infections caused by methicillin-sensitive *S. aureus* (MSSA) (Konstantinovski et al., 2021). Another characteristic of BORSA strains that complicates their identification and subsequent treatment is the absence of species-specific proteins like thermonuclease or coagulase. Skinner et al., (2009) reported an infection caused by a strain exhibiting borderline resistance to oxacillin and lacking both thermonuclease and coagulase – two fundamental taxonomic markers of *S. aureus* (Skinner et al., 2009). Beyond the challenge of selecting effective antibiotic therapy, accurately identifying the isolate at a species level also present difficulties (Skinner et al., 2009).

Determining the exact prevalence of BORSA strains has proven challenging and remains uncertain to date. Only a few prior studies have investigated the carriage rates of these strains. However, these microorganisms appear to inhabit the nasal passages of asymptomatic individuals. For instance, in a study involving 500 healthy children, over 5% of them were found to harbour staphylococcal strains exhibiting the BORSA phenotype (Suggs et al., 1999).

Treatment of severe BORSA infections may prove challenging, even with higher doses of oxacillin. Identifying *S. aureus* strains exhibiting borderline resistance to oxacillin in clinical samples can complicate the selection of appropriate antibiotic therapies (Skinner et al., 2009).

At first, infections caused by BORSA strains with oxacillin MICs ≤ 2 µg/ml were commonly addressed with penicillin-resistant antibiotics. Despite these strains synthesizing significant quantities of beta-lactamase that gradually hydrolyse these antibiotics in laboratory settings, this hydrolysis was initially believed to be too slow to pose significant clinical implications such as treatment failure (Montanari et al., 1990; Massidda, Montanari & Varaldo, 1992). Thus, understanding the nuances of BORSA infections underscores the evolving challenges in antibiotic therapy. While BORSA strains may exhibit resistance levels below conventional thresholds, their ability to produce enzymes that slowly degrade oxacillin suggests a need for vigilant monitoring and potentially tailored treatment strategies to mitigate risks of treatment failure.

This systematic review and meta-analysis seek to aggregate the current global data on BORSA prevalence in diverse environments. By synthesizing data from a diverse array of studies, encompassing clinical, food-related, and animal sources, this review seeks to elucidate the geographic variability and prevalence trends over time. Through this comprehensive synthesis of available data, this review not only aims to provide a current snapshot of BORSA prevalence but also to identify gaps in knowledge and areas requiring further research. Such insights are essential as we strive to mitigate the growing threat of antibiotic resistance and ensure effective treatment of staphylococcal infections worldwide.

Materials & Methods

Standards and study framework

Utilising the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009; Engku Abd Rahman et al., 2022), a meta-analysis of documented cases of BORSA infection across the globe was conducted. The study protocol underwent submission to PROSPERO and obtained registration number CRD42024551780.

Eligibility criteria for included studies

The study encompassed the following categories of literature: (1) investigations detailing the prevalence of BORSA; (2) recent studies within the past decade were incorporated to capture contemporary trends; (3) primary research, such as cross-sectional, cohort, and case-control studies conducted across diverse settings. Conversely, the following types of literature were excluded: (1) subjective pieces such as opinions, editorials, perspectives, book chapters, reviews, case reports, and data from websites; (2) studies where full texts were inaccessible; (3) investigations lacking clear or comprehensive data on BORSA prevalence; (4) studies reliant on self-reported cases rather than laboratory-confirmed diagnoses; (5) reports concerning oxacillin-sensitive *S. aureus* (OSSA) or oxacillin-resistant *S. aureus* (ORSA) other than BORSA.

Literature search

To prevent duplication, a meticulous examination of records in the PROSPERO database and other electronic databases was conducted to ascertain the absence of ongoing or completed meta-analyses on the global prevalence of BORSA. Two authors (ENSEAR and AAI) performed search strategy throughout five electronic databases–PubMed, Google Scholar, Scopus, ScienceDirect, and Web of Science (Core Collection)–without restrictions on the timeframe of studies, language, or study design. Disagreements about the search strategy were resolved by discussing the issues and consulting with two other authors DY and AHE). A preliminary search was conducted on May 16th, 2024, followed by a final update search completed on July 2nd, 2024, yielding a total of 3,765 articles (**Figure 1**).

The search approach employed a blend of relevant terms to examine the worldwide effect of BORSA infections. Boolean operators 'AND' and 'OR' were employed with predefined search terms including "borderline oxacillin-resistant Staphylococcus aureus", "oxacillin-resistant", and "BORSA" to ensure comprehensive coverage. Moreover, references and titles from the studies included were employed as additional search techniques. Comprehensive search strategies for each of the five data repositories are outlined in **Table S1**.

Duplicate studies were identified and excluded using Mendeley Desktop version 1.19.8 software (London, England, UK). Two authors meticulously reviewed the relevant articles, first by screening titles and abstracts, then by conducting a detailed assessment of the full-text articles. Discrepancies concerning article inclusion were addressed through discussion and consultation with two additional authors.

Figure. 1. Summary of PRISMA flow diagram of study selection

Data retrieval

The assessment of included studies involved scrutiny of their titles, abstracts, and full-texts. Data extraction was conducted using an Excel spreadsheet (Microsoft® Office, WA) with predefined fields. Authors independently gathered the following details from qualifying studies: the surname of the lead author and publication year, the countries of origin for the samples (clinical, food, or animal), laboratory methods used for diagnosing BORSA, reported instances of BORSA infections and the total number of isolates tested, along with their respective proportions.

Quality assessment

Two authors individually evaluated the quality of selected studies using the Joanna Briggs Institute (JBI) assessment tool, which is specifically crafted for prevalence research (**File S1**) (Munn et al., 2015). This checklist assesses nine elements, including the suitability of the sampling frame, sampling method, sample size sufficiency, description of study participants and settings, adequacy of data analysis, use of reliable methods for the identified conditions, valid measurements for all participants, appropriate statistical methods, and a sufficient response rate.

Each element was rated as "Yes", "No", "Unclear", or "Not applicable". A score of 1 was awarded for "Yes", whereas "No" and "Unclear" were given a score of 0. The average score for each included study was then computed. The quality of the 29 studies was evaluated on a scale from one to nine (**Table S2**) and classified according to their overall score as "low quality" (< 50%), "moderate quality" (50 – 70%), and "high quality" (> 70%) (Ahmed et al., 2024).

Data integration and quantitative analysis

The DerSimonian-Laird approach was utilised to determine the global prevalence of BORSA, with subgroup analyses performed according to country and sample origins. Anticipating variability from the diverse locations and contexts of the studies, a random-effects model was applied.

Variation among studies was evaluated using the I^2 statistics, with a value exceeding 75% indicating significant heterogeneity (Higgins & Thompson, 2002). Subgroup analysis by country and sample type (human, food, and animal) was carried out to derive regional prevalence estimates and assess factors contributing to variation. Publication bias was examined using a funnel plot, which displayed prevalence estimates against their respective standard errors. Egger's test was used to evaluate asymmetry in the funnel plot, with a significance threshold set at < 0.05. Sensitivity analysis was conducted to explore the influence of each study on the overall estimate. Data analysis and visualizations were performed using OpenMeta[Analyst] (version 10.12) and Comprehensive Meta-Analysis (CMA) (version 2.2.027) software (Irekeola et al., 2022; Engku Abd Rahman et al., 2022).

Results

Selection of the relevant studies

A comprehensive search across multiple databases initially identified 3,765 unique records. Following automatic deduplication, 2,033 articles were left for further screening based on predefined inclusion and exclusion criteria using their titles and abstracts. Of these, 2,004 articles were found irrelevant to the research objectives and were subsequently excluded. Ultimately, 29 articles met the criteria for inclusion in the systematic review and meta-analysis. The detailed selection process is illustrated in **Figure 1**.

Features of the qualified studies

Among the 29 studies incorporated into the meta-analysis, which encompassed a total sample size of 18,781 samples, there were 576 documented cases of BORSA infection. Approximately 20.6% of these studies originated from the United States of America (USA), with data collected from a total of 19 countries worldwide. Samples were sourced from human (clinical), food, and animal. Various detection techniques were utilised, including antibiotic sensitivity testing (AST) methods such as disk diffusion, broth dilution, agar dilution, E-test, antibiogram, automated systems (e.g., VITEK, MicroScan). Additionally, other approaches such as polymerase chain reaction (PCR), pulse field gel electrophoresis (PFGE), whole genome

sequencing (WGS), multi-locus sequence typing (MLST), amplified fragment length polymorphism (AFLP), multiple locus variable number tandem repeat analysis (MLVA), surface plasmon resonance (SPR) were also employed for BORSA detection. **Table 1** offers a comprehensive summary of the principal characteristics of the studies included in the analysis.

Table 1. Major characteristics of the qualified studies.

Major outcomes of BORSA infection worldwide

Employing the random-effect model to derive the summary assessments, the combined prevalence estimate for BORSA infections globally was 6.6% (95% CI, 4.0 – 10.7) (**Figure 2**). The findings indicated a high degree of variability (I^2 = 96.802%, Q = 875.460; $p < 0.001$).

A subgroup meta-analysis was conducted to assess the prevalence of BORSA detection across various countries globally (**Figure 3**). Data were available from 28 studies worlwide, with the USA (n = 6) representing the majority of these studies (**Figure 4; Table 2**). Brazil exhibited the highest pooled prevalence estimate of 70.0% (95% CI, 47.3 – 85.9), whereas The Netherlands had the lowest estimate of 0.5% (95% CI, 0.0 – 10.6) (**Figure 4; Table 2**). The Netherlands had the highest heterogeneity (I^2 = 96.90%; $p < 0.001$), which may have influences the overall variability.

Another sub-group meta-analysis stratified according to sample sources for BORSA detection was also performed. The data was available for 28 studies around the world, with human (clinical) source (n = 22) representing the majority of the studies (**Figure 5; Table 3**). Sources from animal exhibited the highest aggregated prevalence estimate of 46.3% (95% CI, 11.7 – 84.8), whereas sources from human (clinical) reported the lowest estimate of 5.1% (95% CI, 2.7 – 9.4) (**Figure 5; Table 3**). However, sources from human (clinical) had the most heterogeneity (I^2 = 97.32%; $p < 0.001$), which might have contributed to the overall variability in this study.

Figure 2. Forest plot of aggregated prevalence of BORSA detection worldwide (n = 29)

Figure 3. Global distribution of BORSA cases reported

Figure 4. Forest plot of sub-group analysis on prevalence of BORSA detection worldwide stratified by country

Table 2. Subgroup analysis of global BORSA detection prevalence, categorised by country

Figure 5. Forest plot of sub-group analysis on prevalence of BORSA detection worldwide stratified by source

Table 3. Subgroup analysis of global BORSA detection prevalence, categorised by sample source

Analyses of publication bias, quality assessment, and sensitivity

A funnel plot of all qualified studies was created to investigate publication bias. Visual inspection of the plot revealed asymmetry, indicating possible publication bias (**Figure 6**). Nevertheless, Egger's regression test for funnel plot asymmetry yielded a non-significant *p*-value of 0.75899.

Figure 6. Funnel plot illustrating publication bias in studies reporting the global prevalence of BORSA detection (Egger's test: $p = 0.75899$). The plot shows fewer studies on the right side compared to the left, resulting in observed asymmetry.

Notably, the studies included in the analysis exhibited high methodological quality (**Table S2**). By adhering to rigorous methodological standards, the risk of bias and inaccuracies in the analysis is minimised, ensuring that the findings accurately reflect the true prevalence of BORSA detection.

To evaluate the robustness of the prevalence estimates for BORSA detection, a sensitivity analysis was conducted to assess the effect of each qualified studies on the total prevalence aggregated. Excluding the Liu et al., (1990) study resulted a prevalence value of 5.9% (95% CI, 3.7 – 9.2) was obtained. A similar result was observed when Santos et al., (2021) study was excluded, yielding a prevalence estimate of 5.9% (95% CI, 3.6 –9.6). These were the lowest value found (**Figure 7**). Excluding the Konstantinovski_a et al., (2021) study resulted in the highest prevalence value of 7.7% (95% CI, 4.9 – 12.0). Despite these variations in individual values, the overall prevalence estimates of BORSA detection worldwide remained stable across scenarios (**Figure 7**).

Figure 7. Forest plot of sensitivity analysis on global prevalence of BORSA detection

Discussion

This meta-analysis provides novel insights into the global epidemiology of BORSA infections, highlighting a significant prevalence across diverse geographical regions which reflect the multifaceted nature of BORSA epidemiology and highlight the global relevance of this persistent yet under-researched concern public health issue. Furthermore, the diversity in detection methodologies employed—from traditional culture-based techniques to advanced molecular methods—underscores the complexity in accurately identifying and characterizing BORSA strains in different epidemiological contexts.

The meta-analysis synthesized data from 29 studies involving 18,781 samples, identifying 576 cases of BORSA infection. The aggregated prevalence estimate of BORSA worldwide was 6.6% (95% CI, 4.0 – 10.7), indicating a noteworthy presence of this antibiotic-resistant strain in

various settings. The distribution of studies revealed significant regional variation, with Brazil showing the highest prevalence estimate (70.0%) and The Netherlands the lowest (0.5%). This suggest the influence of regional antimicrobial usage practices, healthcare infrastructure, and socio-economic factors. Study from Dutra et al., (2021) reported that Brazil is facing significant issues with antimicrobial use in pig farming, which can lead to health risks, including antibiotic resistance. Initial findings from 2016 revealed high antimicrobial consumption (an average of 358.4 mg/ kg per pig and a median lifetime exposure of 73.7%), often without justifiable medical need (Dutra et al., 2021). However, by 2020, following the implementation of good practices, there was a notable 30% reduction in antimicrobial use and 44.3% decrease in lifetime exposure, suggesting progress toward more responsible usage. These disparities emphasize the need for targeted interventions tailored to local contexts to mitigate the spread of antibiotic-resistant bacteria. Detection methods varied widely across studies, including conventional techniques such as AST and more advanced molecular methods such as PCR, WGS, and MLST. This diversity underscores the complexity and adaptability required in surveillance and diagnostic practices to accurately capture and monitor BORSA prevalence.

The analysis detected substantial heterogeneity (I^2 = 96.802%), attributed partly to differences in study locations, methodologies, and possibly variations in local antimicrobial resistance patterns. Subgroup analyses by country and sample source (human, food, animal) further highlighted varying prevalence rates and heterogeneity levels across different contexts. Notably, studies originating from The Netherlands exhibited particularly high heterogeneity, suggesting diverse local epidemiological factors influencing BORSA prevalence. The significant heterogeneity observed across studies underscores the importance of standardized reporting and surveillance protocols in antimicrobial resistance research. The high prevalence of BORSA in animals compared to humans and food can be attributed to several factors. Antibiotic use in veterinary medicine, particularly in agricultural settings, contributes to increased selective pressure for resistant strains (Van Boeckel et al., 2015). Furthermore, the close contact between humans and animals in farming and veterinary environments can facilitate the transmission of resistant bacteria (Pandey et al., 2024). Additionally, farms and animal habitats may harbour higher concentrations of resistant bacteria due to waste management practices and the unique microbiomes present in these environments (Larsson & Flach, 2022).

These findings call for enhanced collaboration between researchers, healthcare providers, and policymakers to implement effective infection control measures, optimize antibiotic stewardship programs, and strengthen global health responses to combat BORSA and other resistant pathogens. The funnel plot and Egger's regression test suggested potential publication bias, but it was not statistically significant. Sensitivity analysis demonstrated that while excluding specific studies could influence individual prevalence estimates, the overall global prevalence of BORSA remained relatively stable across scenarios, affirming the robustness of the findings.

Conclusions

In conclusion, this meta-analysis provides a comprehensive assessment of BORSA prevalence worldwide, highlighting regional disparities, and implications for public health policy and practice. This systematic review and meta-analysis findings benefit the researchers, healthcare professionals, and policymakers as continued monitoring and research are essential to mitigate the impact of antibiotic-resistant pathogens like BORSA on global health systems. Additionally, exploring the genetic and phenotypic characteristics of BORSA strains using advanced genomic techniques could provide deeper insights into resistance mechanisms and inform targeted therapeutic strategies.

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Not applicable.

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Figure 1

Summary of PRISMA flow diagram of study selection

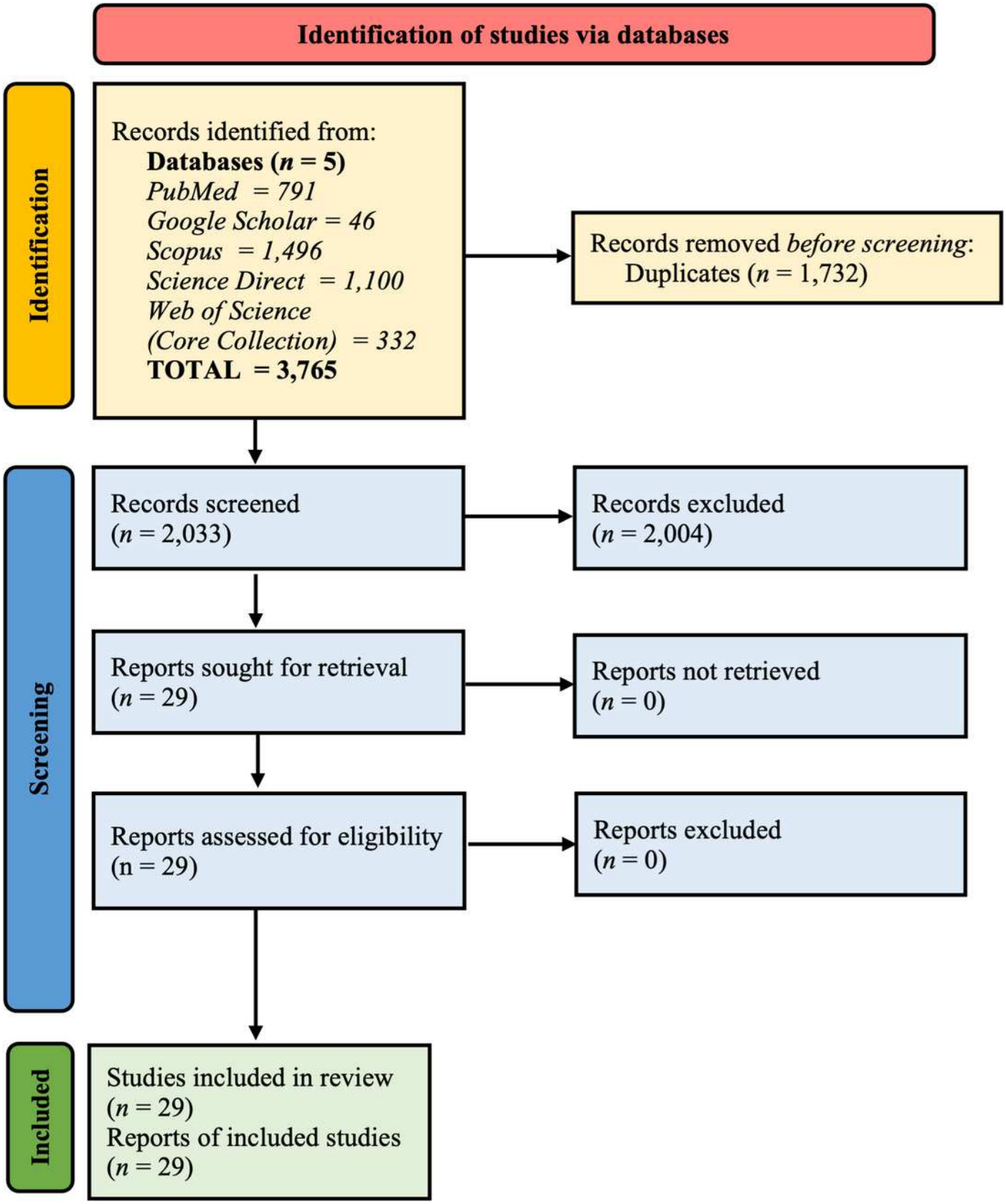
Identification of studies via databases
Identification
Records identified from:
Databases (n = 5)
PubMed = 791
Google Scholar = 46
Scopus = 1,496
Science Direct = 1,100
Web of Science
(Core Collection) = 332
TOTAL = 3,765
Records removed before screening:
Duplicates (n = 1,732)
Screening
Records screened
(n = 2,033)
Records excluded
(n = 2,004)
Reports sought for retrieval
(n = 29)
Reports not retrieved
(n = 0)
Reports assessed for eligibility
(n = 29)
Reports excluded
(n = 0)
Included
Studies included in review
(n = 29)
Reports of included studies
(n = 29)

Figure 2

Forest plot of aggregated prevalence of BORSA detection worldwide (*n* = 29)

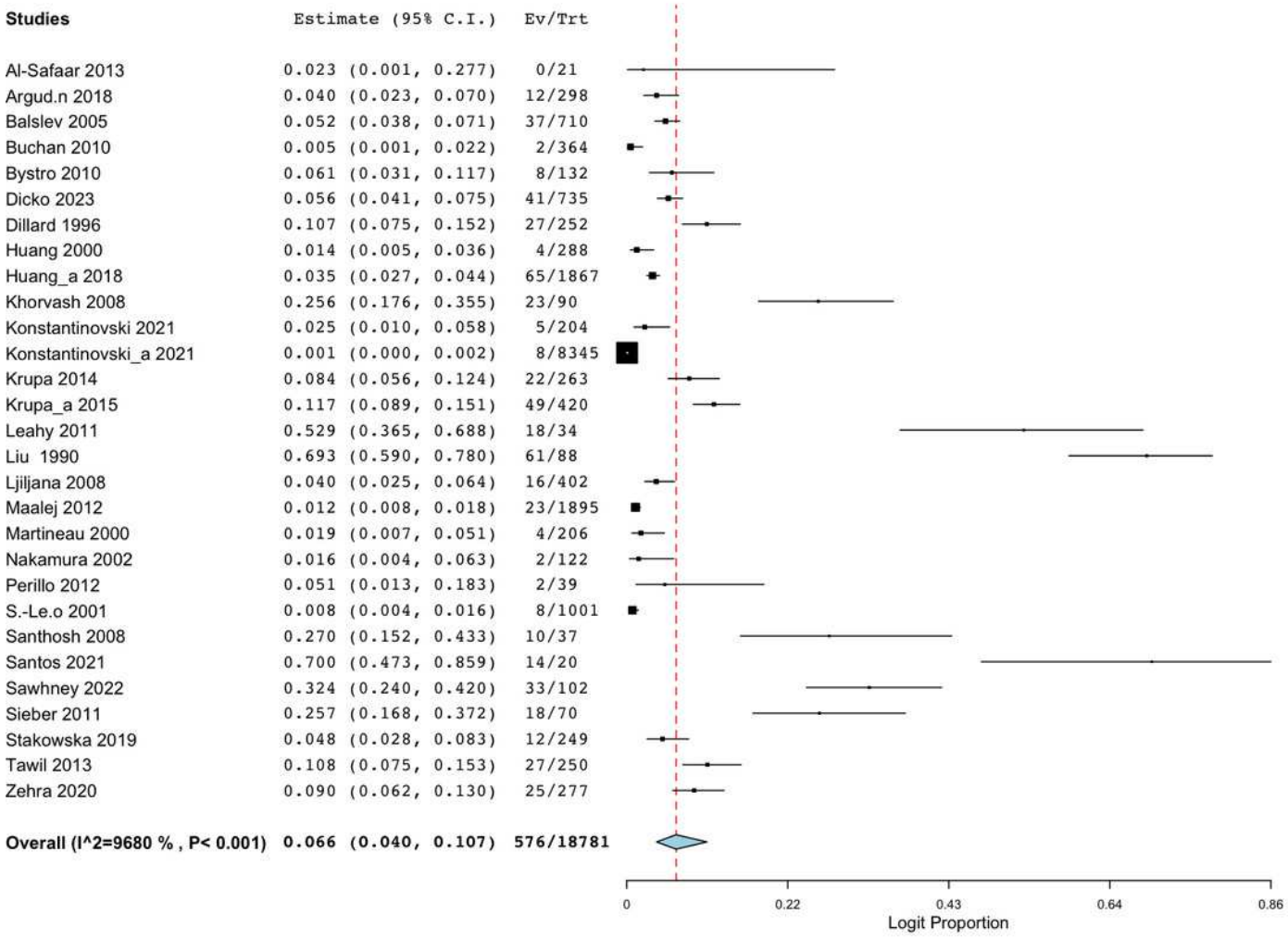

Figure 3

Global distribution of BORSA cases reported

Figure 4

Forest plot of sub-group analysis on prevalence of BORSA detection worldwide stratified by country

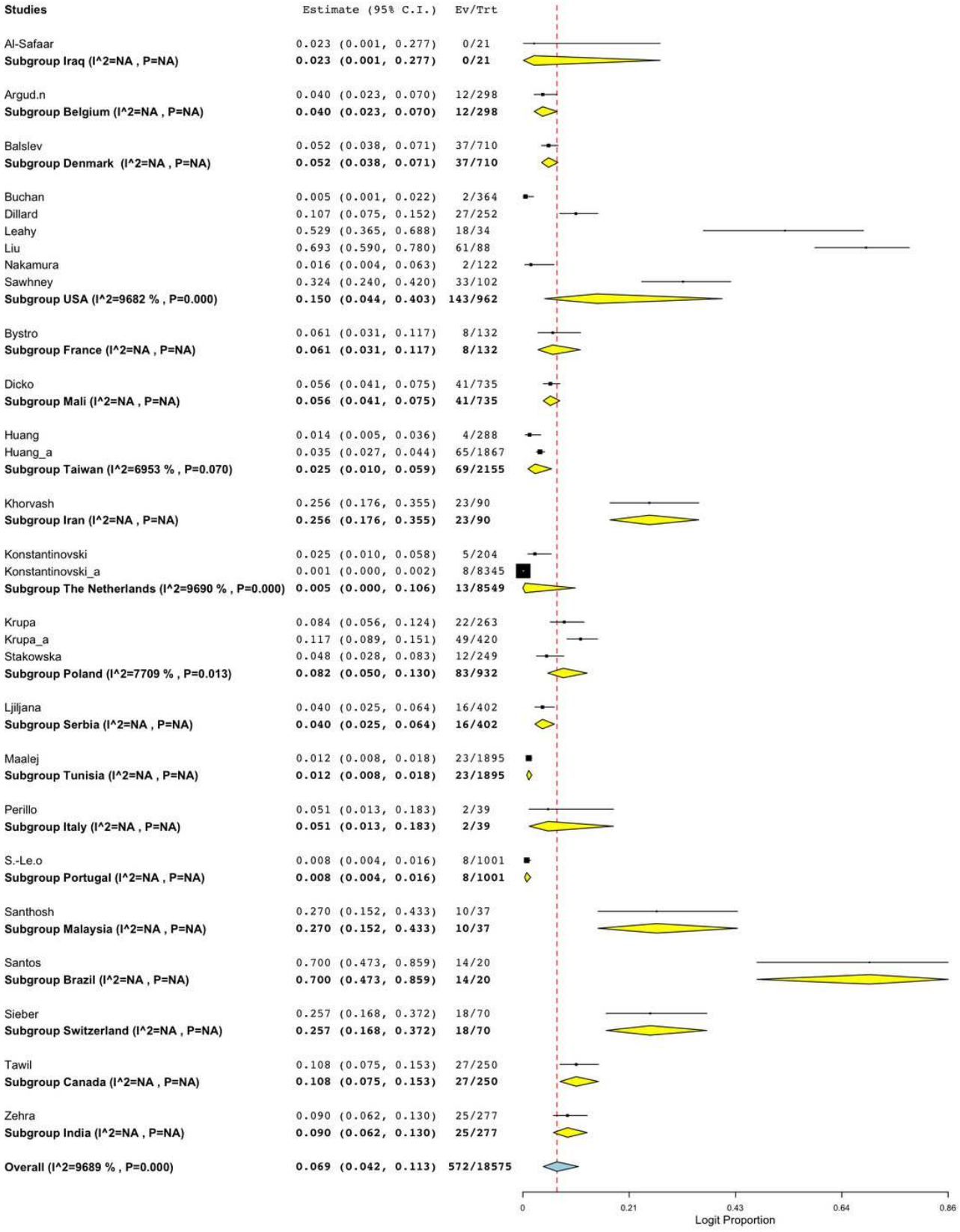
Studies
Estimate (95% C.I.)
Ev/Trt
Al-Safaar 0.023 (0.001, 0.277) 0/21
Subgroup Iraq (I^2=NA , P=NA) 0.023 (0.001, 0.277) 0/21
Argud.n 0.040 (0.023, 0.070) 12/298
Subgroup Belgium (I^2=NA , P=NA) 0.040 (0.023, 0.070) 12/298
Balslev 0.052 (0.038, 0.071) 37/710
Subgroup Denmark (I^2=NA , P=NA) 0.052 (0.038, 0.071) 37/710
Buchan 0.005 (0.001, 0.022) 2/364
Dillard 0.107 (0.075, 0.152) 27/252
Leahy 0.529 (0.365, 0.688) 18/34
Liu 0.693 (0.590, 0.780) 61/88
Nakamura 0.016 (0.004, 0.063) 2/122
Sawhney 0.324 (0.240, 0.420) 33/102
Subgroup USA (I^2=9682 % , P=0.000) 0.150 (0.044, 0.403) 143/962
Bystro 0.061 (0.031, 0.117) 8/132
Subgroup France (I^2=NA , P=NA) 0.061 (0.031, 0.117) 8/132
Dicko 0.056 (0.041, 0.075) 41/735
Subgroup Mali (I^2=NA , P=NA) 0.056 (0.041, 0.075) 41/735
Huang 0.014 (0.005, 0.036) 4/288
Huang_a 0.035 (0.027, 0.044) 65/1867
Subgroup Taiwan (I^2=6953 % , P=0.070) 0.025 (0.010, 0.059) 69/2155
Khorvash 0.256 (0.176, 0.355) 23/90
Subgroup Iran (I^2=NA , P=NA) 0.256 (0.176, 0.355) 23/90
Konstantinovski 0.025 (0.010, 0.058) 5/204
Konstantinovski_a 0.001 (0.000, 0.002) 8/8345
Subgroup The Netherlands (I^2=9690 % , P=0.000) 0.005 (0.000, 0.106) 13/8549
Krupa 0.084 (0.056, 0.124) 22/263
Krupa_a 0.117 (0.089, 0.151) 49/420
Stakowska 0.048 (0.028, 0.083) 12/249
Subgroup Poland (I^2=7709 % , P=0.013) 0.082 (0.050, 0.130) 83/932
Ljiljana 0.040 (0.025, 0.064) 16/402
Subgroup Serbia (I^2=NA , P=NA) 0.040 (0.025, 0.064) 16/402
Maalej 0.012 (0.008, 0.018) 23/1895
Subgroup Tunisia (I^2=NA , P=NA) 0.012 (0.008, 0.018) 23/1895
Perillo 0.051 (0.013, 0.183) 2/39
Subgroup Italy (I^2=NA , P=NA) 0.051 (0.013, 0.183) 2/39
S.-Le.o 0.008 (0.004, 0.016) 8/1001
Subgroup Portugal (I^2=NA , P=NA) 0.008 (0.004, 0.016) 8/1001
Santhosh 0.270 (0.152, 0.433) 10/37
Subgroup Malaysia (I^2=NA , P=NA) 0.270 (0.152, 0.433) 10/37
Santos 0.700 (0.473, 0.859) 14/20
Subgroup Brazil (I^2=NA , P=NA) 0.700 (0.473, 0.859) 14/20
Sieber 0.257 (0.168, 0.372) 18/70
Subgroup Switzerland (I^2=NA , P=NA) 0.257 (0.168, 0.372) 18/70
Tawil 0.108 (0.075, 0.153) 27/250
Subgroup Canada (I^2=NA , P=NA) 0.108 (0.075, 0.153) 27/250
Zehra 0.090 (0.062, 0.130) 25/277
Subgroup India (I^2=NA , P=NA) 0.090 (0.062, 0.130) 25/277
Overall (I^2=9689 % , P=0.000) 0.069 (0.042, 0.113) 572/18575
0
0.21
0.43
0.64
0.86
Logit Proportion

Figure 5

Forest plot of sub-group analysis on prevalence of BORSA detection worldwide stratified by source

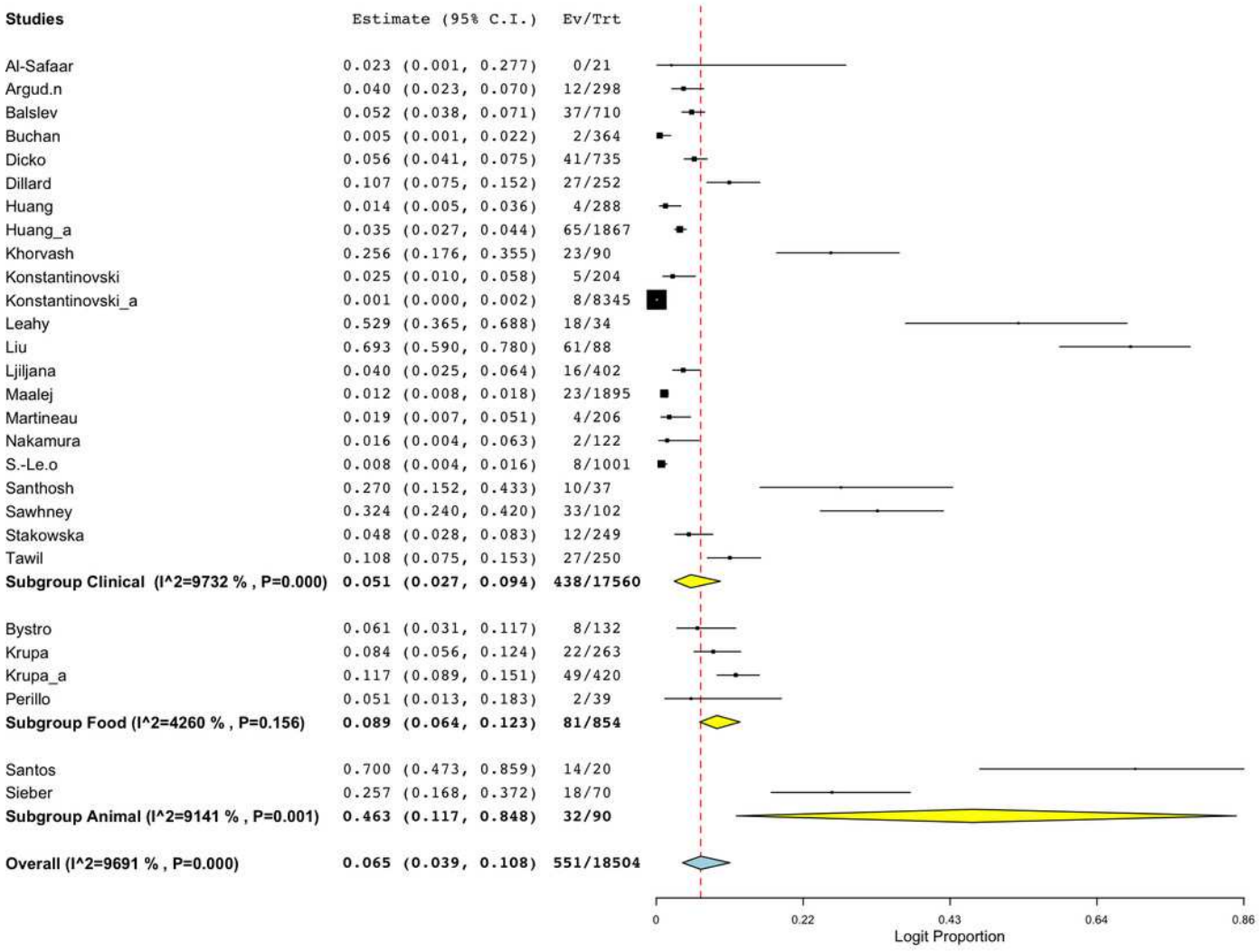

Figure 6

Funnel plot illustrating publication bias in studies reporting the global prevalence of BORSA detection (Egger's test: $p = 0.75899$). The plot shows fewer studies on the right side compared to the left, resulting in observed asymmetry.

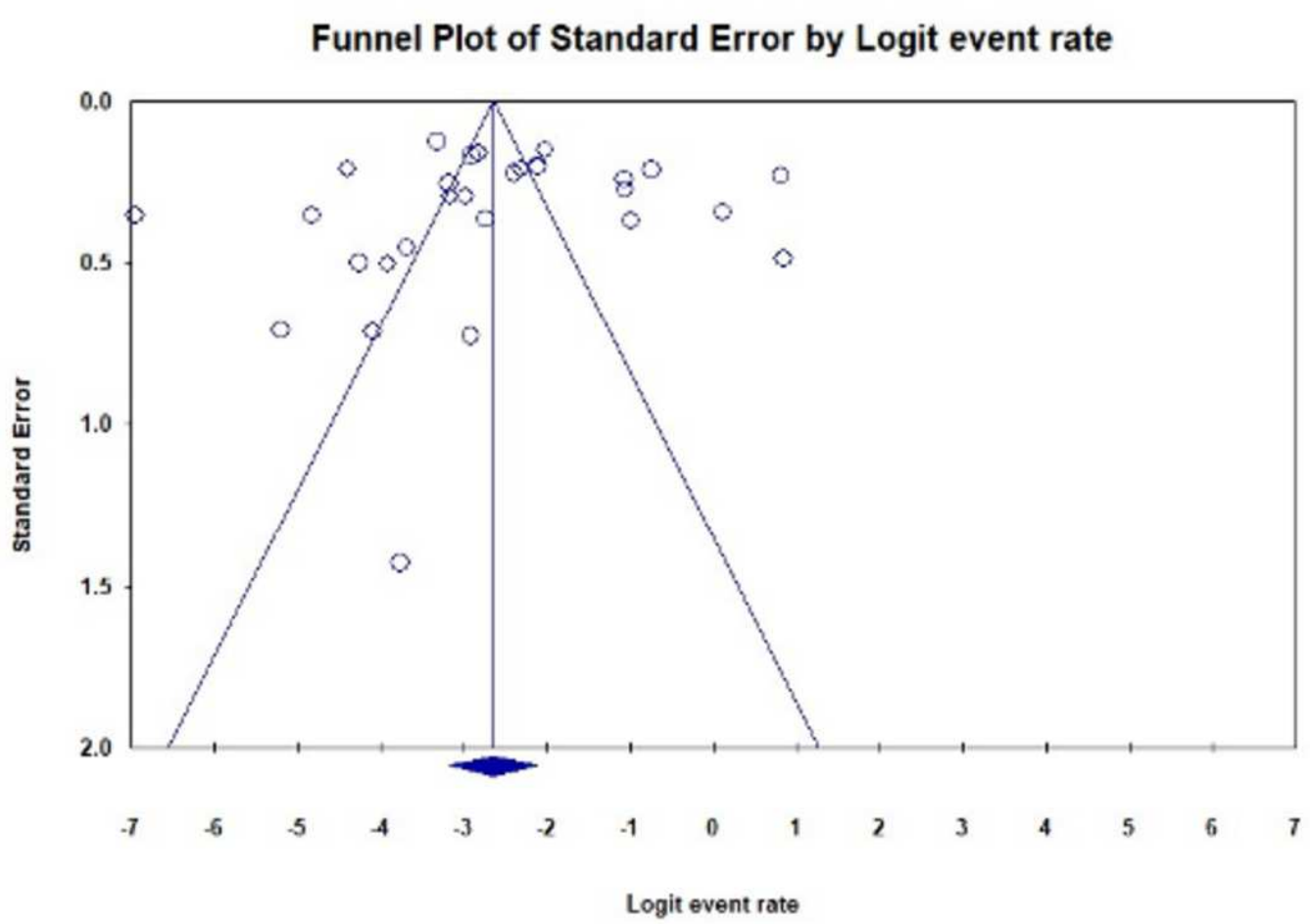

Figure 7

Forest plot of sensitivity analysis on global prevalence of BORSA detection

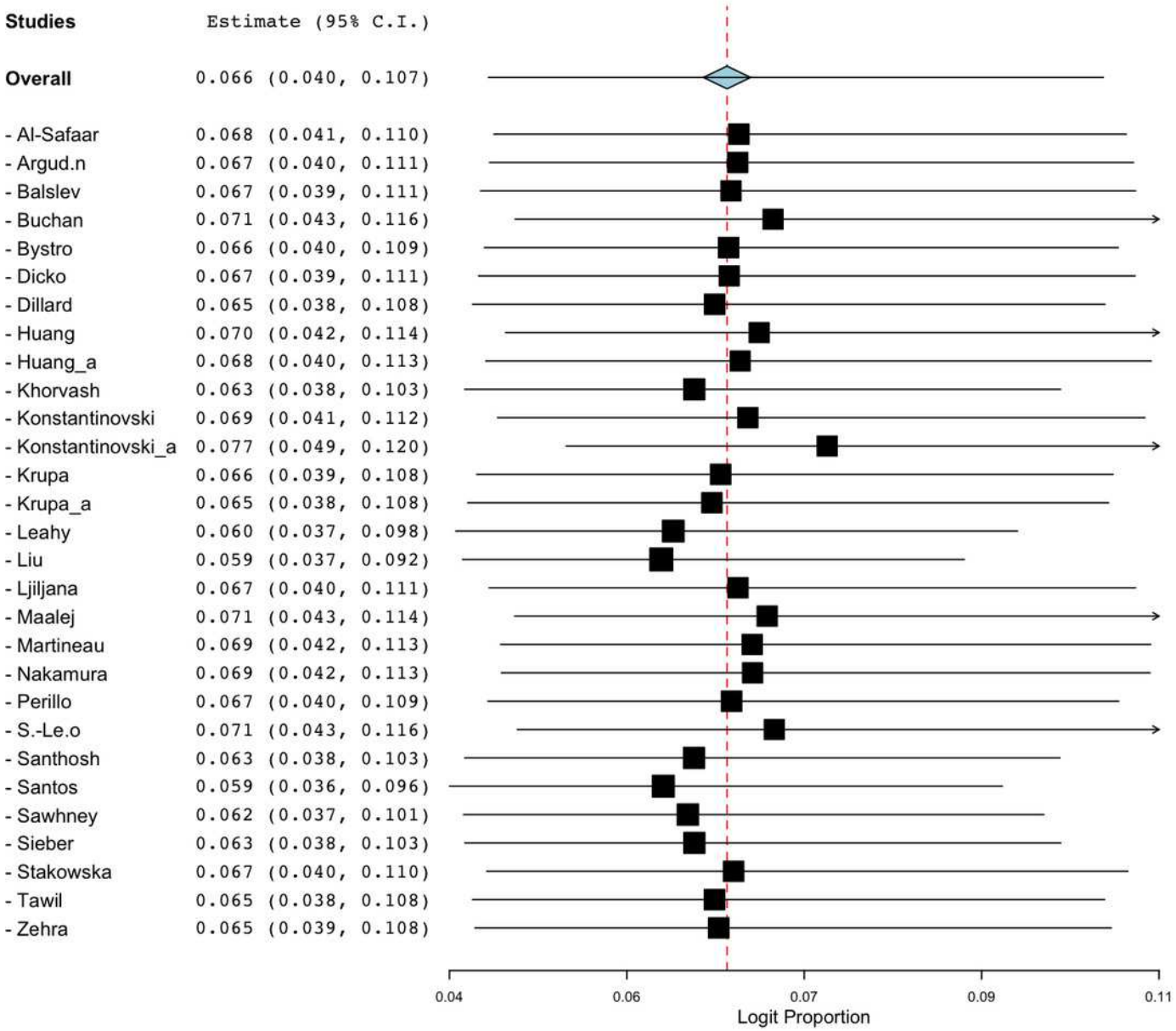

Table 1(on next page)

Major characteristics of the qualified studies

Table 1. Major characteristics of the qualified studies.

S/N	Author (year)	Study period	Location	Study design	Sample source	Detection method	Total (samples/ isolates)	Positive cases (samples/ isolates)	Proportion (%)	Reference
1	Al-Safaar (2013)	2010 – 2013	Iraq	Cross-sectional	Clinical	AST	21	0	0	[15]
2	Argudin (2018)	2013 – 2015	Belgium	Retrospective	Clinical	AST	298	12	4	[16]
3	Balslev (2005)	2000	Denmark	Case-control	Clinical	AST, phage type, PFGE & genotyping	710	37	5.2	[17]
4	Buchan (2010)	NR	USA	NR	Clinical	AST	364	2	0.5	[18]
5	Bystroń (2010)	NR	France	NR	Food	AST, genotyping & MLST	132	8	6	[19]
6	Dicko (2023)	2014 – 2020	Mali	Retrospective	Clinical	AST	735	41	5.6	[20]
7	Dillard (1996)	1994	USA	Cross-sectional	Clinical	AST	252	27	10.7	[21]
8	Huang (2000)	1990 – 1998	Taiwan	Cross-sectional	Clinical	AST	288	4	1.4	[22]
9	Huang_a (2018)	2001 – 2015	Taiwan	Retrospective cohort	Clinical	AST, MLST & PFGE	1867	65	3.5	[23]
10	Khorvash (2008)	2005 – 2006	Iran	Cross-sectional	Clinical	AST	90	23	25.5	[24]
11	Konstantinovski (2021)	2018 – 2019	The Netherlands	NR	Clinical	AST, AFLP, cgMLST & WGS	204	5	2.5	[25]
12	Konstantinovski_a (2021)	2014 – 2016	The Netherlands	Cross-sectional	Clinical	AFLP, MLST, MLVA, cgMLST, & wgSNP	8345	8	0.1	[4]
13	Krupa (2014)	2013	Poland	NR	Food	AST & genotyping	263	22	8.4	[26]
14	Krupa_a (2015)	2011 – 2012	Poland	Cross-sectional	Food	AST	420	49	11.7	[27]

15	Leahy (2011)	1992 – 2007	USA	Retrospective	Clinical	AST	34	18	53	[28]
16	Liu (1990)	1985 – 1987	USA	Cross-sectional	Clinical	AST	88	61	69	[29]
17	Ljiljana (2008)	NR	Serbia	NR	Clinical	AST	402	16	4	[30]
18	Maalej (2012)	2006 – 2011	Tunisia	Cross-sectional	Clinical	AST & latex agglutination test	1895	23	1.2	[31]
19	Martineau (2000)	NR	-	NR	Clinical	AST & Nitrofecin test	206	4	1.9	[32]
20	Nakamura (2002)	2001	USA	Cross-sectional	Clinical	AST & PFGE	122	2	1.6	[33]
21	Perillo (2012)	NR	Italy	NR	Food	AST & Nitrofecin test	39	2	5.1	[34]
22	Sá-Leão (2001)	1993 – 2000	Portugal	Cross-sectional	Clinical	AST, dot-blot hybridization, & MLST	1001	8	0.8	[35]
23	Santhosh (2008)	NR	Malaysia	Cohort	Clinical	AST	37	10	27.02	[36]
24	Santos (2021)	NR	Brazil	Cross-sectional	Animal	MALDI-TOF, AST, PFGE & Rep-PCR	20	14	70	[37]
25	Sawhney (2022)	NR	USA	NR	Clinical	AST, MALDI-TOF, WGS, Beta lactamase activity, PBP2 LFD	102	33	32.4	[38]
26	Sieber (2011)	2005 – 2011	Switzerland	Cross-sectional	Animal	AST & genotyping	70	18	25.7	[39]
27	Stańkowska (2019)	NR	Poland	Retrospective	Clinical	AST & genotyping	249	12	4.8	[40]
28	Tawil (2013)	NR	Canada	NR	Clinical	SPR, PCR, DNA sequence analysis	250	27	10.8	[41]
29	Zehra (2020)	NR	India	NR	Food & Community	AST	277	25	9	[42]

3

Table 2(on next page)

Subgroup analysis of global BORSA detection prevalence, categorised by country

Table 2. Subgroup analysis of global BORSA detection prevalence, categorised by country

Subgroup	No of studies	Prevalence (%)	95% CI	I^2 (%)	Q	Heterogeneity test	
						DF	*p*
Iraq	1	2.3	0.1 – 27.7	NA	NA	NA	NA
Belgium	1	4.0	2.3 – 7.0	NA	NA	NA	NA
Denmark	1	5.2	3.8 – 7.1	NA	NA	NA	NA
USA	6	15.0	4.4 – 40.3	9682	157.134	5	< 0.001
France	1	6.1	3.1 – 11.7	NA	NA	NA	NA
Mali	1	5.6	4.1 – 7.5	NA	NA	NA	NA
Taiwan	2	2.5	1.0 – 5.9	6953	3.282	1	0.070
Iran	1	25.6	17.6 – 35.5	NA	NA	NA	NA
The Netherlands	2	0.5	0.0 – 10.6	9690	32.292	1	< 0.001
Poland	3	8.2	5.0 – 13.0	7709	8.729	2	0.013
Serbia	1	4.0	2.5 – 6.4	NA	NA	NA	NA
Tunisia	1	1.2	0.8 – 1.8	NA	NA	NA	NA
Italy	1	5.1	1.3 – 18.3	NA	NA	NA	NA
Portugal	1	0.8	0.4 – 1.6	NA	NA	NA	NA
Malaysia	1	27.0	15.2 – 43.3	NA	NA	NA	NA
Brazil	1	70.0	47.3 – 85.9	NA	NA	NA	NA
Switzerland	1	25.7	16.8 – 37.2	NA	NA	NA	NA
Canada	1	10.8	7.5 – 15.3	NA	NA	NA	NA
India	1	9.0	6.2 – 13.0	NA	NA	NA	NA
Overall	**28**	**6.9**	**4.2 – 11.3**	**9689**	**867.252**	**27**	**< 0.001**

CI: Confidence interval, I^2: Heterogeneity, Q: Heterogeneity chi-square, df: Degree of freedom, *p*: *p*-value

The total number of studies are as stated (*n* = 28/ 29) because one study collected samples from unknown country, and were thus, excluded. Analysis was conducted on data from a distinct source.

Table 3 (on next page)

Subgroup analysis of global BORSA detection prevalence, categorised by sample source

CI: Confidence interval, I^2: Heterogeneity, Q: Heterogeneity chi-square, df: Degree of freedom, *p*: *p*-value The overall number of studies are as stated (n = 27/ 28) because one study collected samples from a combination of food and community, and were thus, excluded. Analysis was conducted on data from a distinct source.

Table 3. Subgroup analysis of global BORSA detection prevalence, categorised by sample source

Subgroup	No of studies	Prevalence (%)	95% CI	I^2 (%)	Q	Heterogeneity test	
						DF	*p*
Clinical	22	5.1	2.7 – 9.4	9732	782.430	21	< 0.001
Food	4	8.9	6.4 – 12.3	4260	5.226	3	0.156
Animal	2	46.3	11.7 – 84.8	9141	11.637	1	< 0.001
Overall	**28**	**6.5**	**3.9 – 10.8**	**9691**	**874.762**	**27**	**< 0.001**

CI: Confidence interval, I^2: Heterogeneity, Q: Heterogeneity chi-square, df: Degree of freedom, *p*: *p*-value

The overall number of studies are as stated (n = 27/ 28) because one study collected samples from a combination of food and community, and were thus, excluded. Analysis was conducted on data from a distinct source.