Title

Revisiting the role of swine on the risk of Japanese Encephalitis Virus (JEV) transmission in the United States: a rapid systematic review of the literature

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Contributions of the authors

Natalia Cernicchiaro is the guarantor. Study protocol was initially drafted by Vanessa Veloso (VV), Andrea Dixon (AD), and Natalia Cernicchiaro (NC), and all authors provided feedback. Vanessa Veloso will conduct the search and deduplication of reference list obtained with the primary search strategy. Vanessa Veloso and Christy Hanthorn (CH) will perform the primary relevance screening, where VV will independently perform the relevance screening of primary database and Madison Evje (ME) will independently perform the relevance screening of grey literature, and CH will serve as second reviewers for VV, and VV will serve as second reviewer for ME (resolving conflicts, and checking excluded and unclear references). Note that VV and ME will not perform the relevance screening in duplicate, but concurrently (VV will screen the primary database, and ME will perform hand search and grey literature search and screening). Vanessa Veloso and CH will independently, and concurrently, conduct the data extraction (i.e., data extraction will be performed in duplicate). Natalia Cernicchiaro will conduct the risk of bias assessment. Vanessa Veloso will conduct identification and characterization of knowledge gaps, data synthesis, and manuscript preparation. Vanessa Veloso, CH, NC, and AD will identify, develop and/or modify all necessary tools for this rapid review (i.e., relevance screening tool, data extraction tool, risk of bias tool, and knowledge gap identification tool). All authors will read and provide feedback on the original and subsequent versions of the

manuscript. A final version of the manuscript will be submitted for publication after approval of all study contributors.

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Background

Japanese Encephalitis (JE) is an emerging, zoonotic disease transmitted primarily by *Culex* species mosquitoes (particularly *Culex tritaeniorhynchus*) carrying the flavivirus Japanese encephalitis virus (JEV). Japanese encephalitis virus maintains its life cycle between mosquitoes and vertebrate hosts, primarily pigs and wading birds (Le Flohic et al., 2013). In humans, JEV infection causes inflammation of the brain (encephalitis) that can cause fever, headache, respiratory distress, gastrointestinal pain, confusion, seizures, and, in some cases, death (Fischer et al., 2012; Hills et al., 2014). The global incidence of JE is uncertain. Effectivity and quality of JE surveillance in endemic countries vary (Jayatilleke et al. 2020), as does availability of diagnostic testing throughout the world. In 2006, the WHO published a position paper on JE vaccines reporting an annual estimation of at least 50,000 new JE cases among those living in countries considered endemic. Campbell et al. (2011) updated prior estimations and predicted a global incidence of JE cases to be nearly 67,900 per year. Most recently, Quan et al. (2020)

reported a global estimation of JE incidence of approximately 100,000 per year. Among all clinical cases, children under the age of 10 comprise the majority affected (WHO, 2006). Whereas less than 1% of the cases are accompanied by symptoms, 30% of the symptomatic cases are fatal (Campbell et al., 2011). Furthermore, JE is an untreatable and incurable disease that, once introduced in a community, can lead to devastating economic and health impacts.

The United States (US) is considered a susceptible region with great potential for JEV introduction. The availability of competent vectors, susceptible maintenance hosts (avian), intensive travel and trade activities to and from JEV-affected countries, areas with similar climatic and environmental conditions to countries where the virus is epidemic, and large populations of susceptible, amplifying hosts (domestic and feral pigs), makes the US the perfect next-stop in the JEV travel itinerary. In fact, the US is the world's third-largest producer and consumer of pork and pork products (USDA - ERS). The size of the swine industry in the US can not only be positively correlated with the ability of this virus to invade and establish itself, but also to the impact that an incursion would cause to the economy and the populations' health. As pigs are considered the main amplifying host of JEV, an extensive review of the literature and identification of knowledge gaps may guide researchers, stakeholders, and policy makers on effort prioritization, development of precautionary intervention measures (to prevent JEV introduction), and evaluation of disease control measures (in case of JEV incursion). Although current conditions have not been favorable for JEV to establish in the US, increases in international trade and globalization, as well as changes in climate and land use, and reductions in pesticide use, can contribute to its rapid and wide geographical spread (Oliveira et al., 2018). A good understanding of the role of swine as an amplifying host for this virus is critical to public health authorities when planning and executing interventions to control the spread of JEV.

Therefore, our objectives are 1) to investigate the role of swine on the risk of JEV transmission in the US as an effort for preparedness in the case of an introduction, and 2) to identify knowledge gaps that may serve as a guide to future research efforts.

Objectives

The objectives of this review are: 1) to gather and summarize available scientific literature on the role of swine (with emphasis on the role of feral swine) in the transmission of the JEV and 2) to identify knowledge gaps and potential areas amenable for future research, focusing on the role of swine (domestic and feral) in the transmission of the JEV.

Therefore, this rapid review will address the following questions as they are related to both domestic and feral pigs: 1) What is the role of swine in the transmission of JEV?; 2) What is the JEV seroprevalence in pigs (domestic and feral)?; 3) Are there differences in JEV transmission depending on the type of swine operations (confined commercial or research vs. opened commercial or research vs. semi-opened commercial or research vs. subsistence farming)?; 4) Are there differences in JEV transmission depending on the size of the swine operations?; 5) Are there differences in JEV transmission depending on the location of the swine operations (urban vs peri-urban vs rural; proximity to bodies of water)?; 6) What are the most important routes of infection/transmission in swine?; 7) Are there differences in swine transmission and/or pathophysiology among JEV genotypes (including differences in infectiousness, lesions, clinical signs)?; 8) Are there management or biosecurity/hygiene procedures that are associated with susceptibility of JEV introduction/transmission (e.g., quarantine, segregation, personnel standard procedures, animal-sourcing, truck trafficking procedures, testing, mosquito trapping, in-house surveillance/testing)?; 9) What surveillance

efforts have been put in place worldwide (e.g., use of bird or pig sentinels, mosquito trapping)?; 10) What is the speed by which JEV spreads within a population (reproductive number/ratio (R_0) for JEV); 11) What have been the most successful preparedness response strategies (vaccine banks, diagnostic tests, trained veterinarians, other strategic measures that allow a quick response) deployed in other countries for reducing JEV prevalence/transmission?; 12) Are there differences among pig breeds/genetic makeup that are known to influence swine herd susceptibility to JEV transmission?; 13) Is there a difference in JEV susceptibility based on the sex and/or age category of pigs?; 14) Regarding immunization status (to other viruses besides JEV), is there any cross-protection with other viruses?; 15) Which JEV vaccines are available for use in swine?; 16) What vaccines are the most effective for swine?; 17) What is the sensitivity/specificity of diagnostic tests available for detection of JEV in swine?; 18) Can JEV be found/transmitted/introduced via pork products?

Registration and amendments

This protocol has been drafted, using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P). This protocol will be made publicly available within the K-Rex database (K-Rex/CORE collection). *Post hoc* changes made to the protocol will be recorded and posted as an updated version in the same database. Any changes in the original protocol will be accompanied by a footnote indicating the date of change, and the rationale. Added content will be displayed with an underline and deleted text will be shown with a strike through.

Eligibility criteria

For the "primary" search, the sources of evidence must include peer-reviewed papers, written in English, and containing information regarding the role of domestic and feral swine in the transmission of JEV. For the "grey literature" search, the sources of evidence may or may not be peer-reviewed, but must be in English, and include information regarding the role of feral swine in the transmission of JEV. We will use a POS (Population Outcome Study design) framework for both primary and grey literature searches with no time restrictions, as depicted in Table 1 and Table 2, respectively.

Table 1. Eligibility criteria for the **primary database search** (does not include grey literature search)

Population (P)	Swine (domestic (*Sus domesticus)* and feral (*Sus scrofa*)) of all ages, sexes, and breeds
Outcome (O)	Transmission efficiency, infectiousness, susceptibility to infection, incubation time, duration of viremia, routes of transmission, physiopathology, economic/productivity (reproductive) impacts, vaccine efficacy, diagnostic test performance, pathogen/genotype characteristics (pathogenicity, virulence, infectivity, etc.), among others.
Study design (S)	No restriction.
Language	English
Location	No restriction
Time period	No restriction
Type of evidence	Peer-reviewed articles, and government reports

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Table 2. Eligibility criteria for the **grey literature** search

Population (P)	Feral swine (*Sus scrofa*) of all ages, sexes, and breeds
Outcome (O)	Transmission efficiency, infectiousness, susceptibility to infection, incubation time, duration of viremia, routes of transmission, physiopathology, economic/productivity (reproductive) impacts, vaccine efficacy, diagnostic test performance, pathogen/genotype characteristics (pathogenicity, virulence, infectivity, etc.), among others.
Study design (S)	No restriction.
Language	English
Location	No restriction
Time period	No restriction
Type of evidence[£]	Theses, technical reports, APHIS reports

148 [£]Include articles by Vienna Brown, USDA National Wildlife Research Center
149 (https://www.aphis.usda.gov/aphis/ourfocus/wildlifedamage/programs/nwrc), and USDA
150 Current Research Information System (CRIS; https://cris.nifa.usda.gov/).

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152 The following rapid review (RR) approaches will be incorporated to expedite the
153 eligibility assessment of the studies: 1) Limit the number of outcomes focusing on those most
154 important for decision-making (outcomes of interest will be defined based on stakeholder group
155 interests) (Garrity et al., 2021), 2) Limit inclusion criteria to English language only publications
156 (Nussbaumer-Streit et al., 2020). Nussbaumer-Streit et al. (2020) reported that this approach had

minimal effect on overall conclusions when applied on clinical interventions; however, the authors advise to consider the subject carefully (i.e., topics that are expected to have relevant literature in other languages beside the chosen one).

Information sources

Identification of potentially relevant literature will be performed using the databases described in Table 3.

Table 3. Databases, interface used, and dates encompassed for the rapid review

Database	Interface	Dates included
Web of Science Core Collection; KCI-Korean Journal Database; MEDLINE; SciELo Citation Index	Web of Science	1950 - 2022
Scopus	Scopus, Elsevier	1920 - 2022

The following RR approaches will be incorporated to expedite the identification of relevant literature: 1) Limit the number of electronic databases searched (Garrity et al., 2021). Nussbaumer-Streit et al. (2020) evaluated the effect of various abbreviated search approaches on the overall conclusions of evidence synthesis and concluded that combining at least one electronic database with a search of reference lists or a second database provides a solid base for decision-making in most cases. MEDLINE was the only exception where the combination with reference lists was not sufficient. 2) Hand searching only reference lists that were deemed relevant by reviewers and after consultation with experts (Royle and Waugh, 2003). Royle and Waugh (2003) concluded that a more selective approach to database searching is a viable approach to expedite reviews and save resources.

Before defining the primary databases and based on recommendations from Garrity et al. (2021), we performed a pilot search using WOS, Scopus, and CAB to evaluate the total number of references yielded with the proposed search strategy (described in the Search strategy section) in each database, the overlapping of results among those 3 databases (WOS, Scopus, and CAB), and the relevance of results. The two selected databases were the ones with less overlap, that yielded a great number of relevant references.

Search strategy

Primary databases (Table 4) searches will be performed by one reviewer (VV), using the following search terms: “Japanese encephalitis”, “Japanese B encephalitis”, “viral encephalitis”, “JE”, “JEV”, “summer encephalitis”, “viral meningitis”, “Russian autumnal encephalitis”, “swine”, “pork”, “sow”, “gilt”, “piglet”, “barrow”, “hog”, “pig”, “boar”, “*Sus domesticus*”, and “*Sus scrofa*”.

A grey literature search will be conducted based on expert guidance to address the role of swine, but specifically feral swine, in the transmission of JEV. The grey literature search will be specified based on the filtering allowances of each database, but guided by the following search terms: “Japanese encephalitis”, “Japanese b encephalitis”, “JEV”, “JE”, “summer encephalitis”, “viral encephalitis”, “viral meningitis”, “Russian autumnal encephalitis”, “swine”, “boar”, “hog”, “pig”, “pork”, “sow”, “gilt”, “piglet”, “barrow”, “wild”, “feral”, “game”, “free range”, “ranging”, “free-roaming”, “sus scrofa”, “undomesticated”, and “non-domesticated”. Tables 4 and 5 describe results obtained from specific search strategies implemented in Web of Science (WOS) and Scopus, and when searching grey literature (respectively).

Table 4. Results obtained from Web of Science (WOS) and Scopus using the search strategy, and different combinations, on August 09, 2022

Database [§]	Keyword search	Results
WOS	3: #1 AND #2	618
	2: ((((((((((((TS=(swine)) OR TS=(pig)) OR TS=(hog)) OR TS=(boar)) OR TS=(pork)) OR TS=("sus scrofa")) OR TS=("sus domesticus")) OR TS=(barrow)) OR TS=(gilt))) OR TS=(piglet)) OR TS=(sow))	
	1: (((((((TS= ("Japanese encephalitis")) OR TS= ("Japanese b encephalitis")) OR TS=(JEV)) OR TS=(JE)) OR TS= ("summer encephalitis")) OR TS= ("viral encephalitis")) OR TS= ("viral meningitis")) OR TS= ("Russian autumnal encephalitis")	
Scopus	TITLE-ABS-KEY ("Japanese encephalitis" OR "Japanese b encephalitis" OR "JEV" OR "je" OR "summer encephalitis" OR "viral encephalitis" OR "viral meningitis" OR "Russian autumnal encephalitis" OR "viral encephalitis") AND (swine OR boar OR hog OR pig OR pork OR "sus scrofa" OR "sus domesticus" OR sow OR piglet OR gilt OR barrow)	2,545

[§] TS = Search for topic terms in the following fields within a record. Search in title, abstract, author keywords, and keywords Plus®. TITLE-ABS-KEY = Search for topic terms in the title, abstract, and keywords.

Table 5. Results obtained from grey literature and hand search, in August 2022.

Database	Keyword search	Results[0]
USDA Animal and Plant Health Inspection Service (APHIS)[1]	"Feral swine" "Japanese encephalitis"	1881
Center for Disease Control and Prevention (CDC)[2]	ALL THIS WORD: Japanese encephalitis ANY OF THESE WORDS: feral wild undomesticated free-range ranging roaming swine pig hog boar pork	7266
USDA National Wildlife Research Center[3]	6: “japanese encephalitis” AND feral AND boar (n = 2) 5: “japanese encephalitis” AND wild AND boar (n = 2) 4: “japanese encephalitis” AND feral AND pig (n = 1) 3: “japanese encephalitis” AND wild AND pig (n = 4) 2: “japanese encephalitis” AND wild AND swine (n = 7) 1: “japanese encephalitis” AND feral AND swine (n = 7)	330
USDA Current Research Information System (CRIS)[4]	"Japanese encephalitis" AND (feral; wild; "free range"; ranging; "free roaming"; game; undomesticated) AND (swine; pig; boar; hog; pork; "sus scrofa")	1249
Articles by Vienna Brown[5]	(“Japanese encephalitis”, “Japanese b encephalitis”, “JEV”, “JE”, “summer encephalitis”, “viral encephalitis”, “viral meningitis”, “Russian autumnal encephalitis”, “viral encephalitis”) OR ((“swine”, “boar”, “hog”, “pig”, “pork”)	33

	AND (“wild”, “feral”, “game”, “free range”, “ranging”, “free roaming”, “sus scrofa”, and “undomesticated”))	
Reference lists of Wildlife Health Australia[6]	(“Japanese encephalitis”, “Japanese b encephalitis”, “JEV”, “JE”, “summer encephalitis”, “viral encephalitis”, “viral meningitis”, “Russian autumnal encephalitis”, “viral encephalitis”) OR ((“swine”, “boar”, “hog”, “pig”, “pork”) AND (“wild”, “feral”, “game”, “free range”, “ranging”, “free roaming”, “sus scrofa”, and “undomesticated”))	92

[0] Resulting number for each source is reported before de-duplication of references

[1]Keyword search will be conducted within each database, using the website search option. https://www.aphis.usda.gov/aphis/home/

[2]Seearch was performed using the “advanced search” option-fields

[3]Wildlife Services Digital Collection (https://nwrc.contentdm.oclc.org/digital/collection/NWRCPubs1); the wild-synonyms “game”, “free range”, “ranging”, “free-roaming”, “undomesticated”, and “non-domesticated” did not find any result.

[4]Search term string was entered in “Full text Terms” field-option, using “Subfile option” as “(Any)”. https://cris.nifa.usda.gov/cgi-bin/starfinder/99451/crisassist.txt

[5] Articles by Vienna Brown include: 1) Brown VR, Bowen RA, Bosco-Lauth AM. Zoonotic pathogens from feral swine that pose a significant threat to public health. Transbound Emerg Dis. 2018 Jun;65(3):649-659. 2) Brown, Vienna R., et al. Current status and future recommendations for feral swine disease surveillance in the United States. Journal of Animal science 97.6 (2019): 2279-2282. 3) Brown, Vienna R., et al. Perspectives on the past, present,

and future of feral swine disease surveillance in the United States. Journal of Animal Science 98.8 (2020): skaa256.

[6]The reference list of the review article was searched for titles referring to Japanese encephalitis in wild pigs and all above mentioned synonyms.

Data management

A single reviewer (VV) will export results from the databases as Research Information Systems (RIS) files and deduplicate the reference list using Covidence AI (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Following relevance screening, full-text pdfs from relevant reference lists will be searched, downloaded, and saved in a single folder by an undergraduate student-worker (ME). Full-text pdf files will be named based on the first Covidence ID number, author's last name, and publication year (first authors having multiple publications in the same year will have the year followed by a unique letter (e.g., 764 - Sympson 2020; 765 - Sympson 2022)). Full-text pdfs will be imported into Zotero (Corporation for Digital Scholarship, Virginia, USA), and then uploaded into Covidence using the bulk upload function (VV).

Relevance Screening/Selection process

The selection process of the primary databases (Table 4) will be performed according to the following steps:

#1: Citation retrieval. Citations from the search strategy will be downloaded as RIS and then uploaded into Covidence as described on the data management section.

#2: Deduplication. Duplicated references will be removed using Covidence's deduplication tool.

#3: Primary relevance screening tool development. A screening tool comprised of a flow chart will be designed based on the POS and the current study objectives. The tool will be piloted using 150 random abstracts (sorted by author in Covidence) and adjusted/edited if necessary to improve clarification of the relevance criteria. If major edits were incorporated, an additional round of screening will be performed in another set of 50 random abstracts. This process will be repeated until clarity of relevance criteria is deemed sufficient by the reviewers (VV and CH). Once the relevance screening tool is finalized, all articles will be screened using the same, final, screening tool.

#4: Primary relevance screening tool calibration. The proposed primary relevance screening tool will be tested for clarity and utility. For the test exercise, a pair of reviewers (VV and CH) will independently review a random sample of 20% of the total titles and abstracts and assess eligibility. Reviewers will compare their results and discuss any differing decisions or questions that arose during the screening. The primary relevance screening tool will be used in its current form only if >80% agreement is achieved between reviewers. If this threshold is not met, then the primary relevance screening tool will be amended based on reviewer recommendations, and another iteration of screening will be performed to another set of 25 citations; this process will continue until at least 80% agreement is achieved.

#5: Title and Abstract screening. Once a final version of the relevance screening tool is decided upon, VV and CH will complete the title and abstract screening. During this step, one reviewer will evaluate each reference (VV) and a second reviewer will check excluded references for inconsistencies (CH). Articles deemed unclear by the primary reviewer will be re-

evaluated by the second reviewer (CH). Only articles deemed unclear by both reviewers during the primary screening will undergo a supplementary screening (full text screening). Disagreements between the primary and verifier reviewer on excluded and unclear articles will be indicated by the verifier with a note explaining the reason for disagreement. Disagreements will be resolved via consensus between the two reviewers (VV and CH). If consensus cannot be achieved, then a third reviewer (NC) will be consulted. Supplementary screening will be performed by the verifier reviewer (CH) using the full text article and the same relevance tool as the primary screening. Studies included in the primary relevance screening will move directly to data extraction, as well as those deemed unclear during the first relevance screening and subsequently identified as relevant after the supplementary relevance screening. References that moved to the supplementary screening phase or extraction phase can still be excluded if deemed not relevant. References excluded during the supplementary screening or extraction phase will receive a tag with the reason for exclusion.

Non-peer-reviewed articles on JEV and feral swine will be excluded from primary relevance screening with a “grey literature” tag. Excluded references containing “grey literature” tags will be evaluated using the grey literature relevance screening process.

The selection process of the grey literature and hand search (Table 5) will be performed according to the following steps:

#1: A search strategy will be defined according to each electronic source based on search resources/restrictions available in each electronic database.

#2: Results obtained from each combination of words in each database will be screenshot and saved as a record of search terms used and resulting references obtained.

#3: The relevance screening of grey literature (i.e., governmental organizations databases) and hand search (i.e., reference list of reference review articles) will be performed by accessing the relevance of titles first. Only titles that include either JEV (or synonymous), or wild swine (or synonyms) will be further investigated for relevance, using the full text file.

#4: Relevant literature will be downloaded and included for data extraction.

Data extraction

Data extraction will be performed in ~~Covidence~~ Excel (changed due to the complexity of the data being extracted and Covidence's capacity to extract several outcomes per reference | 11.20.23), using a custom-built data collection form. Data extraction form will be assessed with a calibration exercise, similar to the one performed for the relevance screening tool. After achieving 80% agreement during the calibration exercise, and upon refinement of the data extraction tool, full-text articles will be evaluated for extraction in duplicate by two reviewers (VV and CH) independently. Unresolved discrepancies will be resolved by a third reviewer (NC). Full-text articles can still be excluded during the data extraction process (if deemed irrelevant during extraction phase). Exclusion of studies that moved to the extraction phase will be performed by moving the study back to screening when choosing the Covidence built-in option "Move study to Full text review", then the article will be double-tagged with a 1) reason for exclusion, and 2) "retracted-during-extraction" tags. The following RR approaches will be incorporated to expedite data extraction: 1) Limit data extraction to a minimal set of required data items, and limit the outcomes to cost-effectiveness (Tricco et al., 2015); 2) Use standardized data extraction form piloted elsewhere (Wollscheid and Tripney, 2021); 3) Use data from existing SR to reduce time spent on data extraction; however, the methodological and reporting quality of the existing SR will be assessed (Hamel et al., 2020; Martyn-St James et al., 2017). When comparing the accuracy of extracting

data from an existing SR versus extracting from the primary studies, Martyn-St James et al. (2017) concluded that data in existing reviews were highly accurate, and findings and conclusions did not differ between methods.

Data items

All variables for which data will be sought will be defined (such as POS items, funding sources, location), including prioritization of main and additional outcomes (with rationale), any pre-planned data assumptions and simplifications (Table 6). Experts and/or stakeholders in the topic area will be involved in early stages of the project to ensure the included outcomes are relevant.

Table 6. List of data items that will be extracted from the included reference list of studies

Data item*	**Explanation**
Reference information	Title, all authors, first affiliation, journal, volume, pages, and publication date
Type of evidence	Peer-reviewed or not
Type of evidence – peer-reviewed	Primary research (original papers), review, systematic review, N/A
Type of evidence – non-peer-reviewed	Theses, technical reports, other, N/A
Quality of systematic reviews/scoping reviews	Was there an assessment of the quality of evidence (RoB or GRADE)?
Study characteristics	
Year and season of study	Year and season when the study was conducted, or not reported (NR)

Country and region	Country and region where the study was conducted. If not reported, reviewers will report the main author's institution location.
Study type	Reported study design as review, experimental or observational, or not reported (NR)
Study design – observational: type	Reported study design as case-control, cohort, cross-sectional, other
Study design - experimental: type	Reported study design as RCBD, CRD, split-plot, cross-over, latin-square, ND (used in studies with no design/randomization), or NR
Study design – experimental: randomization method (if RCBD or CRD)	If the study design is reported as RCBD, then reported randomization method used for the study, or N/A (if not a randomized study), or NR
Study design - experimental: type of exposure	Reported type: laboratory natural, field natural , Lab challenge, Field challenge, or not reported (NR)
Study design - experimental: preventive intervention	Vaccine, quarantine, mosquito-control, testing of new animals, segregation, sanitation, NR, or N/A
Study design - experimental: curative intervention	Management of positive animals (segregation, euthanasia and disposal, other) disposal of contaminated material (placenta, stillborn piglets), treatment of positive animals, NR, N/A
Study design – experimental: treatment structure	Reported treatment structure as one-, two-, three-way factorial, or NR

Total number of EU	Number of experimental units (unit of replication) used in the study, or NR
Number of EU/treatments	Number of EU per treatment (replication), or NR
Blinding	Was the use of blinding reported? Single-blind, double-blind, triple-blind, no, or unclear
Blinding: level	Data collectors, data collectors & data analysist, NR
Confounding	Is confounding addressed and accounted for? Yes, No, or Unclear
Sample size determination	Is there a sample size determination conducted? (this will address the "imprecision" domain of quality of evidence (to add in discussion section). Yes, No, or Unclear
Outcomes	
JEV case definition	Method used to confirm disease (diagnostic test, clinical signs, other, NR)
JEV case definition: diagnostic test	What diagnostic test was used (ELISA, HIA (hemagglutination inhibition assay) HIA+SNT (seroneutralization test), PCR, RT-PCR, other, NR or N/A
JEV case definition: clinical signs	Combination of clinical signs used to declare as positive JE case, NR or N/A

JEV seroprevalence	Reported prevalence (%, proportion, measures of association, etc.) and test used for prevalence determination; NR, or N/A
JEV morbidity (prevalence based on clinical signs)	%, proportion, etc; NR, or N/A
Infection rate in swine	Infection rate (also known as "R(t)") is the estimated number of new swine that become infected during a specific time period; NR, or N/A
Incubation period in swine	The number of days between infection and manifestation of clinical signs; NR, or N/A
Routes of transmission in swine	The pathway through which JEV enters the organism to infect a susceptible host; NR, or N/A
Pathological lesions in swine	Anatomical changes caused by the pathological agent during course of disease; NR, or N/A
Clinical signs in swine	Signs associated with the manifestation of disease; NR, or N/A
Swine demographics	Sex, age, breed, and genetic markers; NR, or N/A
JEV immunization status of swine herd	What JEV vaccines were administered to the herd? Commercial name, doses, route of administration; NR, or N/A
Production size	One time capacity of the entire farm, NR, or N/A.
Barn size	Total number of animals per barn, NR, or N/A

Pen size	no of animals/pen, NR, or N/A
Farm location	Urban, peri-urban, rural, NR, or N/A (as reported by the authors)
Type of operation	Type of swine operations will be described as: confined commercial or research; opened commercial or research; semi-opened commercial or research; or subsistence farming (“backyard pigs”), NR, or N/A
Type of production	Farrow to finish, farrow to wean, feeder pig production, wean to finish, seedstock production, or purebred production, NR, or N/A
Production system	Conventional or alternative/organic (antibiotic-free, and hormone-free raised pigs, other), NR, or N/A
Biosecurity/hygiene procedures applied at the farm (in general and specific to JEV)	Quarantine, segregation, personnel standard procedures, animal-sourcing, conveyance management , testing, mosquito control, in-house surveillance/testing, NR, or N/A
Effectiveness of farm biosecurity measures	Include measure of effectiveness, NR, or N/A
JEV surveillance strategies	Mosquito trapping, use of sentinels, etc.; NR, or N/A
Effectiveness of surveillance	Critical evaluation of the effectiveness of JEV surveillance programs used to detect and monitor JEV in endemic regions; NR, or N/A
Genotype	I, II, II, IV or V; NR, or N/A

R0	Reproductive number; estimate of JEV contagiousness; NR, or N/A
Vaccine efficacy/effectiveness	Degree to which a vaccine prevents disease; NR, or N/A
Type of diagnostic test	Type (antibody, antigen, etc.), name; NR, or N/A
Diagnostic test performance	Sensitivity, specificity, likelihood ratios, predictive values, and/or other accuracy measures reported for a diagnostic test; NR, or N/A

*RCBD = randomized complete block design; EU = experimental unit; JEV = Japanese encephalitis virus; R0 = R-naught

Risk of bias assessment (RoB)

Upon determining all relevant articles, an independent reviewer (NC) will evaluate the risk of bias for these articles and document the results. A second reviewer will be available to discuss uncertainties brough up by the primary reviewer. This step will be implemented concurrently with the initiation of the data extraction step. To accelerate this process, we will implement the RR approaches suggested by Garrity et al. (2021) when conduction the RoB rating, which include: 1) limit RoB assessment to only primary outcomes, and 2) use a valid RoB assessment tool specific to the study designs included (https://www.riskofbias.info).

Data synthesis

Methods for summarizing the data around the POS question framework elements with findings grouped by key questions, population of interest, and outcomes, will be implemented. We will use a combination of 1) minimal evidence synthesis (described by Haby et al. (2016) as "a locally prepared, short, contextually framed, narrative report in which the results of the

systematic review were described and locally relevant factors that could influence the implementation of evidence-based guideline recommendations were highlighted"), and 2) tabular synthesis of data (for narrative and quantitative data syntheses).

Identification and characterization of knowledge gaps

We will use a framework (Figure 1; Robinson et al., 2013) developed to systematically identify research gaps from systematic reviews. This framework facilitates the classification of where and why the current evidence falls short and includes two elements: (1) characterization of the gaps and (2) the identification and classification of the reason(s) for the research gap (Robinson et al., 2013).

The PICOS (in our case POS) structure can be used to describe questions or parts of questions inadequately addressed by the evidence synthesized in the RR. The second element of the framework consists of classifying the reasons behind a research gap. For each research gap (row of the worksheet: "Serial no."), the reason(s) that most preclude conclusions from being made in the RR will be chosen by the reviewer completing the framework. Reasons for research gaps will be categorized as per Robinson et al. (2013): A. Insufficient or imprecise information, B. Biased information, C. Inconsistent or unknown consistency, and D. Not the right information (See Figure 1 footnote). Insufficient information (A) will be used when only a limited number of studies or none are identified, or if the sample sizes in the available studies are too small to allow conclusions. Biased information (B) will be concluded based of the aggregate risk of bias (dependent on risk of bias of the individual studies). Consistency (C) will be evaluated based on the effect size directionality of included studies (i.e., inconsistency will be attributed to a research gap when the reported effect sizes of included studies appear to go in opposite directions). Lastly, lack of right information (D) will be assigned to research gaps which result from included studies that are not applicable (e.g., different population, different research setting), do not include/report outcomes of interest for the review, whose duration of study period is insufficient, or other reasons that may be categorized as "D".

In the worksheet table, the person conducting the identification and characterization of the knowledge gap (VV and CH) should identify the project name, date of completion, worksheet page number (out of total number of pages), and the key question number. Christy Hanthorn and VV will work concurrently in the knowledge gaps, each addressing a different research gap (i.e., this step will not be conducted in duplicate).

Figure 1. JHU EPC Frameworks Project: Research Gaps Worksheet and Instructions (Original)[+]

<Example Project Name> **Completed by – V. Veloso**

Research Gap Worksheet **Date – 08.10.22**

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Key Question – 2 (What is the JEV seroprevalence in pigs (domestic and feral)?)

Serial no.	Reason(s) for gap*	Population (P)	Intervention (I)	Comparison (C)	Outcomes (O)	Setting (S)	Free text of gap	Notes
Ex. 1	B1	Domestic pigs (sow)			seroprevalence	-		Study used wrong diagnostic test
Ex. 2	D1, D4	Feral swine in the US	-	-	-			
Ex 3	A3	Domestic pigs (barrow)			seroprevalence			

***Reasons for Gap: A) **Insufficient or Imprecise Information -> A1**=No studies, **A2**=Limited number of studies, **A3**=Sample sizes too small, **A4**=Estimate of effect is imprecise

B) **Biased Information** -> **B1**=Inappropriate study design, **B2**=Major methodological limitations in studies

C) **Inconsistency or Unknown Consistency** -> **C1**=Consistency unknown (only 1 study), **C2**=Inconsistent results across studies

D) **Not the right information** -> **D1**=Results not applicable to population of interest, **D2**=Inadequate duration of interventions/comparisons, **D3**=Inadequate duration of follow-up, **D4**=Optimal/most important outcomes not addressed, **D5**=Results not applicable to setting of interest

[+](https://www.ncbi.nlm.nih.gov/books/NBK126708/pdf/Bookshelf_NBK126708.pdf)

Meta-biases (for systematic reviews): Meta-bias will not be implemented in this RR.

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