Title

~~Assessment of data on~~ Vector and host competence for Japanese encephalitis virus: A systematic review and meta-analysis update of Oliveira et al. 2018

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Contributions of the authors

Natalia Cernicchiaro is the guarantor. Study protocol was initially drafted by VV, AD, and NC, and all authors provided feedback. AD will conduct the search and deduplication. AD and SE will conduct screening and respective data extraction. AO performed the original systematic review and will conduct the ROB. AD and SE will conduct data synthesis. AD will conduct the meta-analysis

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Rationale

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). JE is an untreatable and incurable disease that, in humans, can result in inflammation of the brain (encephalitis) causing fever, headache, respiratory signs, gastrointestinal signs, confusion, seizures, coma, and, in some cases, death (Fischer et al., 2012; Kliegman et al., 2015).

The United States (US) is considered a susceptible region with great potential for JEV introduction, given the availability of competent insect vectors, susceptible maintenance (avian) hosts, large populations of susceptible, amplifying hosts (domestic and feral pigs), intensive travel and trade activities to and from JEV-affected countries, and areas with similar climatic and environmental conditions to countries where the virus is epidemic. To investigate the risk of JEV introduction and establishment, Oliveira and colleagues performed a risk assessment (Oliveira et al., 2019) supported by a systematic review of vector and host competency for JEV (Oliveira et al., 2018).

Although Oliveira et al. (2019) found the risk of introduction of JEV in the US through entry of infected mosquitoes via airplanes to be very high, the risk of establishment was considered negligible; yet, increases in international trade and globalization, as well as changes in climate and land use, and the recent incursion of a new JEV genotype into areas previously free from disease, as observed in Australia with the invasion and expansion of JEV (Genotype IV) in the eastern and southeastern states, warrants the need for an update of the review and risk assessment. The objective of this review is to update the systematic review (Oliveira et al., 2018) on host and vector competence of transmission of the Japanese encephalitis virus.

Objectives

The primary objective of this study is to update the systematic review by Oliveira et al. (2018) by conducting a systematic review comprising the appraisal of scientific literature published from 2016 to ~~2022~~ 2023[1] on host and vector competence for the transmission of JEV. The research question is: what information is available on vector and host competency and abundance for JEV transmission arising from peer-reviewed published literature from 2016 to ~~2022~~ 2023[1]?

Registration and amendments

This protocol has been drafted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) and 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

[1] A meta-analysis was included and the time period was lengthened to include as many reports as possible and keep the update as timely as possible (AD - JAN 8 2024)

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

The eligibility criteria will follow those set out in the original review, except the time frame will be restricted to 2016 to ~~present~~ December 31, 2023[1].

Table 1. Relevance screening criteria for inclusion and exclusion of articles – adapted from Table 1 Oliveira et al. (2018).

	Inclusion criteria	**Exclusion criteria**
Language	English	Other than English
Time period	2016 to ~~2022~~ 2023[1]	Published before 2016
Types of evidence	Peer-reviewed articles	Non-peer reviewed articles, conference proceedings, thesis dissertations, and other non-peer reviewed publications
Location	Any country	-
Vector AND/OR Host Competence to JEV		
	Inclusion criteria	**Exclusion criteria**
Population (P)	Vectors (mosquitoes, other insects) and/or Hosts (vertebrate hosts)	Vectors other than insects and non-vertebrate hosts.
Outcomes and outcome measures (O)	Transmission efficiency, feeding patterns, host preference, infectiousness, susceptibility to infection, incubation time, duration of viremia	Vector and/or host competence for other Flaviviruses transmitted by ticks[a]
Study type (S)	Challenge trial (laboratory and field), field studies (e.g., trapping, capture), observational or experimental studies	Non-primary research (thesis) and literature reviews

[a] Tick-borne flaviviruses such as the causative agents of tick-borne encephalitis, Kyasanur Forest disease, Alkhurma disease or Omsk hemorrhagic fever, ~~but other mosquito borne Flaviviruses (West Nile, St. Louis Encephalitis, yellow fever, dengue fever, and Zika) were included.~~[2]

Information sources

To best replicate the original search, we will search the same electronic databases (Web of Science and Pubmed), as well as Scopus to capture the following privately searched journals: The American Journal of Tropical Medicine and Hygiene, Journal of the American Mosquito Control Association, Journal of Medical Entomology, and Vector-Borne and Zoonotic Diseases. The Armed Forces Pest Management Board will be searched separately. Table 2 describes the electronic databases that will be searched, the interface used, and the time frame.

Table 2. Electronic databases, interface used, and time frames for the search.

Database	Interface	Dates included
Web of Science Core Collection; KCI-Korean Journal Database; MEDLINE; SciELo Citation Index	Web of Science	2016 – ~~2022~~ 2023[1]
PubMed	National Library of Medicine	2016 – ~~2022~~ 2023[1]
Scopus	Scopus, Elsevier	2016 – ~~2022~~ 2023[1]
The Armed Forces Pest Management Board	The Armed Forces Pest Management Board	2016 – ~~2022~~ 2023[1]

Search strategy

We will utilize the searches from the original paper for the previously searched electronic databases (WOS, PubMed, and the Armed Forces Pest Management Board) and create a separate search based on these search terms for Scopus. AD will perform the search. Table 3 reports the

[2] Papers that specifically focused on non-JEV mosquito-borne Flaviviruses were excluded as it was deemed these papers were out of the scope of the review (AD - DEC 22 2022)

search strategies for each electronic database from Oliveira et al. (2018), Supplementary Materials Appendix 1.

Table 3. Search strategy for each electronic database using the search strategy from Oliveria et al. (2018) – S1 appendix.

Database§	**Keyword search***
WOS	TS: ((Japanese encephalitis OR viral encephalitis OR JE OR JEV) AND vector competence AND mosquito AND host competence)
PubMed	All Fields: (Japanese AND encephalitis) AND ((vector OR host) competence)£
Scopus	TITLE-ABS-KEY((vector AND competence) OR (mosquito AND vector AND competence) OR (host AND competence)) AND (TITLE-ABS-KEY(“japanese encephalitis” OR (viral AND encephalitis) OR “je” OR “jev”)
Armed Forces Pest Management Board	Find results in AFPMB website (http://www.afpmb.org/content/search-afpmborg) with all the words: Japanese Encephalitis

* All searches were limited to the timeframe 2016 - ~~2022~~ 2023[1] and to the English language.
§ 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.
£ This search string differs from the original - “mosquitoes” was replaced by “(vector OR host) AND competence)” - as this better captured the information we were interested in.

Data management

AD will export the database results as Research Information Systems (RIS) files into the systematic review software, Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Database results will be de-duplicated using the Covidence de-duplication tool. AD and SE will perform the title and abstract screening and data extraction in Covidence. Following the relevance screening of the titles and abstracts, the full-texts of the relevant papers will be imported into Zotero (Corporation for Digital Scholarship, Virginia, USA), and then uploaded into Covidence using the bulk upload function.

Relevance Screening/Selection process

The selection process 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 Data management section.

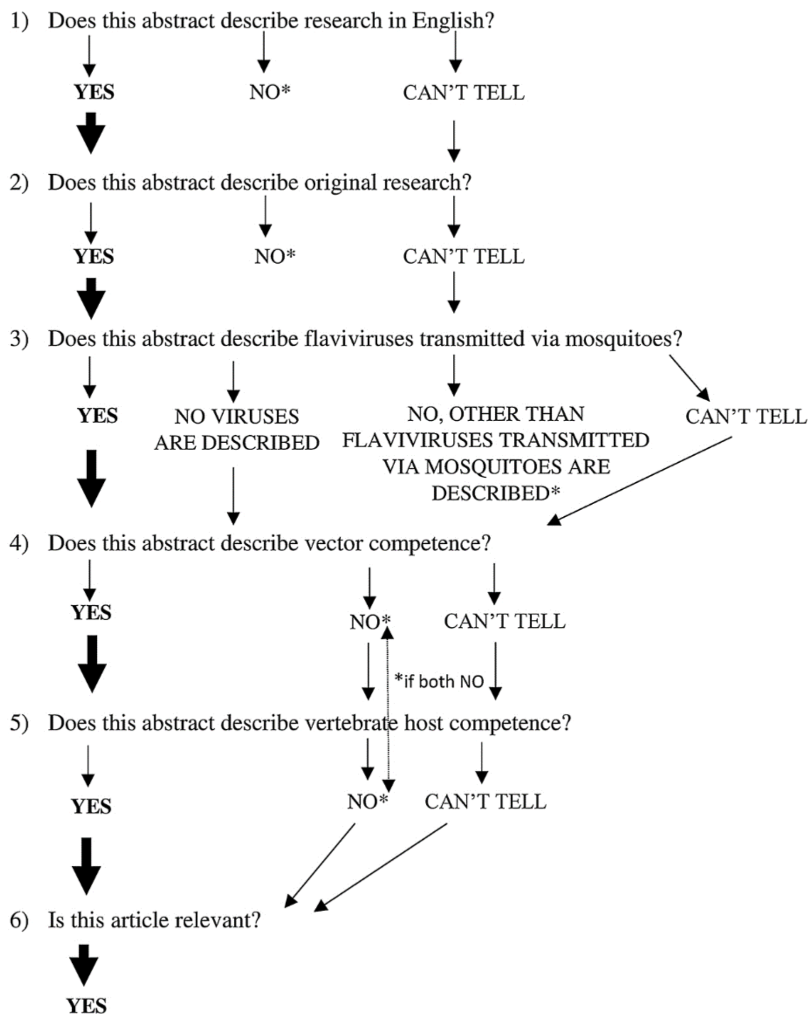
#2: Deduplication. Duplicated references will be removed using Covidence's de-duplication tool.

#3: Relevance screening tool-development. The screening tool comprised of a flow chart (Figure 1 below from Oliveira et al. 2018) will be used.

#4: 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 (AD, SE) will independently review a random sample of 20% of the total titles and abstracts. Reviewers will compare their results and discuss any differing decisions or questions that arose during the screening. The agreement of the two reviewers will be calculated and if there is at least 80% agreement, the version of the screening tool in question will be utilized for the final relevance screening. If this threshold is not met, then the 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 Screen. Once a final version of the relevance screening tool is decided upon, AD and SE will complete the title and abstract screen in duplicate. If it is unclear from the title and abstract if the article is relevant, the article in question will undergo a second full-text review. Otherwise, all relevant articles will move onto data extraction. Any relevant literature reviews will be set aside, and the reference list hand-searched to identify any missing publications, from within the time frame of 2016-~~2022~~ 2023[1], that were missed by the search.

Figure 1. Relevance screening chart from Oliveira et al. (2018)



*Stop answering the other questions of the tool – abstract NOT RELEVANT
Arrows in bold represent which answers lead to a RELEVANT paper.

Data extraction

Data extraction will be performed in Covidence, creating a data collection form based on Table 2 from Oliveira et al. (2018). Since the original review was conducted, there have been several studies conducting to evaluate vector-free transmission of JEV. As the previous extraction form was not originally designed to extract this information, we created an addendum to extract data items pertinent to vector-free transmission from relevant papers. From experimental papers, additional administration route types were added (feeding, intradermal, intranasal, intravenous, intradermal and intravenous, or vector-free), the sample type (oronasal, vaginal/preputial, eye swab, rectal swab, or blood and/or serum), the viral titer, the duration of viremia/viral detection, and the duration of infectiousness. For viral titer, the duration of viremia/viral detection, and the duration of infectiousness, the value, units, value of variation, measure of variation, and P-value were also extracted if available. For observational studies, the sample type (see above for categories) was also collected.[3] Data extraction will be performed in duplicate by two reviewers (AD and SE).

Data items

Table 4. The data items to be extracted, adapted from Table 2 of Oliveira et al. (2018).

	Data item	**Explanation**
Vectors		
Transmission efficiency[a]	Infection rate	Infection rate is the sum of individual/pool of mosquitoes that are JEV-positive divided by the total number of mosquitoes/pools tested in experimental studies.
	Dissemination rate	Dissemination rate is the proportion of mosquitoes with virus in their legs, irrespective to their infection status (Golnar et al. 2015)
	Transmission rate	Transmission rate is the proportion of mosquitoes with a disseminated infection that transmits the virus during refeeding (Golnar et al 2015)
Host preference	Host species preference	The host species from which the mosquito blood meals originated.
Susceptibility to infection	Proportion of JEV infection	The proportion of JEV infection is the total of positive mosquito pools divided by the total number of pools tested (observational studies)
	Minimum infection rate (MIR)	MIR is the ratio of positive mosquito pools to the total number of mosquitoes in the sample (assumption: only one infected individual is present in a positive pool) (Bustamante and Lord, 2010)

[3] The data extraction addendum was added Nov 2022. (AD - DEC 22 2022)

	Maximum likelihood estimate (MLE)	MLE is the proportion (parameter of a binomial distribution) of infected mosquitoes that maximizes the likelihood of pools of a specific size being positive (Bustamante and Lord 2010)
Hosts		
Susceptibility to infection	Proportion of JEV infection	The proportion of positive vertebrate hosts is the sum of positive samples divided by the sum of samples tested

[a]Administration routes included: oral feeding (pledgets/membranes or hosts), intrathoracic inoculation, or vertical transmission (parents infected either intrathoracically or by oral feeding).

Risk of bias assessment (RoB)

RoB assessment will be performed by a third reviewer (either AO or NC) using the previous framework in Oliveira et al. (2018) for experimental (Table 3) and observational studies (Table 4). A second reviewer (AD) will be consulted if any report sections are unclear.[4]

Data synthesis

Tables 6-11 of Oliveira et al. (2018) will be updated. An additional table synthesizing the results from the studies evaluating vector-free transmission will be included.[5]

Meta-~~biases~~ analysis

~~No meta-analyses will be performed for this update.~~

We will update the analyses from Oliveira et al. (2017, 2018a), specifically the outcomes of the proportion of JEV infection in vectors and hosts and minimum infection rate and maximum likelihood estimator of JEV in vectors (see Oliveira et al. 2017) and vector infection, dissemination, and transmission rate of JEV (see Oliveira et al. 2018a) using random-effects models. Meta-regressions to identify heterogeneity (I^2) and associations with predictors of

[4] (AD - JAN 8 2024)
[5] Added in NOV 2022 (AD - DEC 22 2022)

interest will be updated according to the model building methodology reported in the respective articles.

If there are enough studies, a meta-analysis evaluating the outcome of viral titer and duration of viral detection in hosts from experimental studies will be evaluated using sub-group analysis for each species. A meta-regression will be used to identify heterogeneity (I^2) and associations with predictors of route of administration, sample type, incubation period. [6]

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[6] (AD – JAN 8 2024)
[7] (AD – JAN 8 2024)

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