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Assessment of data on vector and host competence for Japanese encephalitis virus: A systematic review of the literature

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ABSTRACT

Japanese encephalitis virus (JEV) is a virus of the *Flavivirus* genus that may result in encephalitis in human hosts. This vector-borne zoonosis occurs in Eastern and Southeastern Asia and an intentional or inadvertent introduction into the United States (US) would have major public health and economic consequences. The objective of this study was to gather, appraise, and synthesize primary research literature to identify and quantify vector and host competence for JEV, using a systematic review (SR) of the literature.

After defining the research question, we performed a search in selected electronic databases and journals. The title and abstract of the identified articles were screened for relevance using a set of exclusion and inclusion criteria, and relevant articles were subjected to a risk of bias assessment, followed by data extraction.

Data were extracted from 171 peer-reviewed articles. Most studies were observational studies (59.1%) and reported vector competence (60.2%). The outcome measures reported pertained to transmission efficiency, host preference, and vector susceptibility to infection within vector competence; and susceptibility to infection within host competence. Regarding vector competence, the proportion of JEV infection reported across all 149 mosquito species in all observational studies ranged from 0 to 100%. In experimental studies, infection, dissemination, and transmission rates varied between 0 and 100%. Minimum infection rates (MIR) varied between 0 and 333.3 per 1000 mosquitoes. Maximum likelihood estimation (MLE) values ranged from 0 to 53.8 per 1000 mosquitoes. The host species in which mosquitoes mostly fed consisted of pigs and cattle (total of 84 blood meals taken by mosquitoes from each of these host species). As for host competence, the proportion of JEV infection varied between 0 (in rabbits, reptiles, and amphibians) and 88.9% (cattle).

This SR presents comprehensive data on JEV vector and host competence, which can be used to quantify risks associated with the introduction of JEV into the US.

1. Introduction

Japanese encephalitis (JE) is a mosquito-transmitted disease that may result from infection by the Japanese encephalitis virus (JEV), an arbovirus (arthropod-borne virus) of the *Flavivirus* genus. Virus transmission extends from Southeastern Asia to the Western Pacific islands. Japanese encephalitis virus is among the most important causes of encephalitis worldwide, with approximately 68,000 JE human cases occurring every year, particularly in children (Campbell et al., 2011; Weaver and Barrett, 2004). The mechanism of transmission is based on interactions between vectors (over 30 species of mosquitoes) and hosts (pigs and ardeid birds) that maintain an enzootic cycle not yet fully understood (Le Flohic et al., 2013).

According to previous work (Le Flohic et al., 2013), JEV can easily shift between the domestic and the wild cycles, with no viral adaptation needed, if competent hosts and vectors are present, which is consistent with the observed geographical expansion of the virus to contiguous regions. This expansion puts the more than three billion people who live in currently JE-endemic countries at risk of infection (Le Flohic et al., 2013). The spread of JE is also related to the exponential human population growth in the affected regions, the increase in the number of pig production systems, and the changes in land usage and agricultural

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practices. Changes in agricultural practices are related to an increase in rice production, leading to more opportunities for mosquito breeding, as rice paddy fields are a suitable and prolific habitat for the development of mosquito vector populations (Erlanger et al., 2009; Mackenzie et al., 2004).

The most competent JEV vectors are *Culex* mosquitoes, such as *Culex tritaeniorhynchus, Culex annulirostris*, *Culex annulus*, *Culex fuscocephala*, *Culex gelidus*, *Culex sitiens*, and the *Culex vishnui* species complex, which are widely distributed over the JEV-endemic areas, thus contributing to further maintaining the transmission cycle. Regarding vertebrate host species, the most competent amplifying and reservoir hosts are wild ardeid birds, especially egrets (*Egretta garzetta*) and herons (*Nycticorax nycticorax*), and pigs, both feral and domestic. The rise in intensive pig farming observed in East and Southeast Asia over the past decades also contributes to JEV transmission, as it increases the number of susceptible vertebrate hosts available (Le Flohic et al., 2013).

To date and despite many reviews describing the susceptibility of hosts, vectors, and environmental parameters that can sustain the introduction of the virus and its further spread in JEV-free countries, such as the United States (US), the role of different vectors and hosts, and their competence, has not been quantitatively evaluated (Huang et al., 2015; Nemeth et al., 2012; Nett et al., 2012; Reeves and Hammon, 1946).

Furthermore, other authors (Lord et al., 2015) refer to the fact that the basis of our current knowledge about the JEV transmission cycle was established during the initial research in the 1950s in Japan, and that it reflected the context of the region and time period when it was carried out. Japanese encephalitis virus transmission should therefore be reconsidered for other regions where the transmission context differs from the one first described in Japan. Limited evidence supporting the need for viral adaptation between different cycles, as well as recent evidence that vector-free transmission between pigs without the intervention of arthropod vectors is possible (Ricklin et al., 2016), further reiterate knowledge gaps. A better understanding of the relative importance of vectors and hosts will determine optimal mitigation strategies, such as JEV vaccination or insect vector control, but will depend on the accurate assessment of parameters that include vector and host abundance, mosquito host preference, and vector competence for JEV (Lord et al., 2015; Le Flohic et al., 2013).

Globalization and increasing international travel create additional opportunities for the introduction of exotic pathogens into new regions of the globe. In the US, specifically, the rapid spread of the West Nile virus after its introduction in 1999, and the inability of the public health services to control the outbreaks and prevent the establishment of the disease raised an important issue regarding the emergence of exotic vector-borne diseases in the country. Agencies responsible for the prevention and control of the introduction of foreign pathogens and the timely response to potential outbreaks, should they occur, require comprehensive information regarding the previously mentioned parameters, of which vector and host competence play a major role (Huang et al., 2015; Nemeth et al., 2012; Nett et al., 2012; Reeves and Hammon, 1946).

A systematic review (SR) of the literature provides a replicable, transparent, and reliable method of identifying, assessing, and summarizing available evidence on a research question, with reduced bias (Sargeant and O'Connor, 2014; Sargeant et al., 2006). The objective of this study was therefore to identify research gaps and information regarding vector and host competence for JEV worldwide, using a systematic review of the literature.

2. Materials and methods

Steps of the SR consisted of posing a research question, searching the literature, conducting a relevance screening, extracting data, assessing the risk of bias, as well as analyzing and presenting the extracted data.

2.1. Research question

The original research question was as follows: Which vectors and hosts are competent for Japanese encephalitis virus transmission in the United States?

Due to the low number of publications originating from the US, the research question and search were refined to include peer-reviewed literature worldwide.

Because the research question was related to descriptive parameters (competence of vectors and hosts), rather than interventions, we used a PO (population, outcome) question format to define the research question (O'Connor et al., 2014b). Population (P) referred to vectors and hosts, while outcomes (O) concerned competence, in terms of transmission efficiency, host preference, and susceptibility to infection.

The working team was comprised of four reviewers (AO, LE, ES, NC), each participating in different steps of the review.

We followed the protocols and guidelines for performing systematic reviews in veterinary medicine (O'Connor et al., 2014a; O'Connor et al., 2014b; Sargeant and O'Connor, 2014; Sargeant et al., 2006), and the Cochrane group's guidelines (adapted) to conduct the risk of bias assessment (Higgins and Green, 2011).

2.2. Searching the literature

The search was restricted to the English language, without limitations to year of publication, and was performed using eight electronic databases and journals. The journals included in the search (Armed Forces Pest Management Board, The American Journal of Tropical Medicine and Hygiene, Journal of the American Mosquito Control Association, and Vector-Borne and Zoonotic Diseases) were selected based on the relevance of the topics covered, which are aligned with our research question. Databases were accessed in March and April 2016 and the search terms were related to the PO components. A complete list of the search terms, and their combinations, used for each database and journal is available in S1 Appendix (supplementary materials).

A hand-search was also used to identify additional articles cited in the reference list of nine articles considered as key publications by the reviewers based on a priori identification of relevant articles (Huang et al., 2014; Le Flohic et al., 2013; Misra and Kalita, 2010; Erlanger et al., 2009; Nett et al., 2012; van den Hurk et al., 2009a; Mackenzie et al., 2004; Weaver and Barrett, 2004; Solomon et al., 2000). Only peer-reviewed articles were considered for further evaluation. All articles were given a unique number that was kept throughout the SR for identification purposes.

2.3. Relevance screening

To determine their relevance, the title and abstract of all identified articles were subjected to a set of inclusion and exclusion criteria comprised of language, time period, population, study type, outcome measures, and location fields. A detailed description of the inclusion and exclusion criteria is included in Table 1.

Based on this set of criteria, we created a relevance screening tool composed of six questions, using an Excel® (Microsoft Corp., Redmond WA, 2013) spreadsheet. The first five questions were deemed crucial to establish relevance, and based on the answers to those questions, the abstracts were considered relevant or not.

The first version of the tool was pre-tested by three reviewers (AO, LH, NC) using 10 abstracts. After reviewing the sources of disagreement, we improved the tool and performed a second testing using the same 10 abstracts and three new ones.

Two reviewers (AO, LH) working independently performed the final relevance screening, and compared the answers for conflict resolution. When both reviewers determined that the abstract was not relevant, it was not considered further in the SR. The two reviewers resolved all