Aedes albopictus is a competent vector of Zika virus: a meta-analysis

Benjamin A. McKenzie[1], Alan E. Wilson (wilson@auburn.edu)[2],
and Sarah Zohdy[1,3*]

[1]School of Forestry and Wildlife Sciences, Auburn University, Auburn, Alabama, USA
[2]School of Fisheries, Aquaculture, and Aquatic Sciences, Auburn University, Auburn, Alabama, USA
[3]College of Veterinary Medicine, Auburn University, Auburn, Alabama, USA

*Corresponding authors
Email: zohdy@auburn.edu (SZ) and bam0073@auburn.edu (BM)

Abstract

Background

Much work has been done in recent years to determine the vector competence of *Aedes albopictus* (Skuse) for Zika virus (ZIKV). If competent, *Ae. albopictus* could become an important vector in the spread of ZIKV to areas which until now have been considered safe from the virus. Despite much speculation about *Ae. albopictus'* competence for ZIKV, there have been, to date, no quantitative syntheses of *Ae. albopictus'* competence, nor have the potentially confounding differences between studies been addressed.

Methodology/ Principle Findings

This study represents a quantitative meta-analysis of the literature surrounding this topic by examining infection rates (IR) and transmission rates (TR) among sample populations of *Ae. albopictus* at 7 and 14 days post infection (dpi) across 15 journal articles comprising 23 studies. Our analyses examined potentially confounding variables in the studies contained therein, including: geographic origin of viral strain, geographic origin of mosquito population tested, whether the viral strain and mosquito population tested came from the same geographic region, and freshness of blood meal. Our results suggest 1) *Ae albopictus* is a competent vector for ZIKV and 2) that origin of *Ae. albopictus* population and origin of viral strain had significant effects on the competence of *Ae. albopictus* to transmit ZIKV.

Conclusions/ Significance

These results indicate a need to further explore the effects of methodology on vector competence studies and to examine in more detail the geographic variation in the competence of *Ae. albopictus* for ZIKV as well as the underlying causes of said variation. The ability of *Ae. albopictus* to carry and transmit ZIKV also points to a need to create new vector control strategies in case of a ZIKV outbreak in an area where *Ae. albopictus* is prominent. Finally, this study represents a potential template for future meta-analyses in the field of vector competence, where this type of study has been under-utilized.

Key words: Arbovirus, emerging infectious diseases, pathogen-host, invasive species, mosquito, RNA virus, transmission

Author summary

Here we meta-analytically examine competence of the Asian tiger mosquito, *Aedes albopictus*, one of the most invasive species in the world, for Zika virus (ZIKV). When ZIKV emerged in the Americas in 2015, control and prevention efforts were emphasized in locations with known yellow fever mosquito (*Aedes aegypti*) distributions. However, the potential for other mosquitoes with different distributions to transmit ZIKV remained unclear. We combine all existing laboratory studies on the vector competence of *Ae. albopictus* for ZIKV and determine that the geographic origins of the mosquito populations and viral strains have significant effects on the competence of *Ae. albopictus* for ZIKV. We also highlight the role of meta-analyses as a method to clarify vector competence.

Introduction

Zika virus (ZIKV) is a mosquito-borne flavivirus (family *Flavaviridae*, genus *Flavivirus*) phylogenetically similar to the dengue fever (DENV), West Nile (WNV), Japanese encephalitis (JEV), and yellow fever (YFV) viruses [1]. ZIKV was first isolated in 1947 from a sentinel rhesus monkey (*Macaca mulatta*) in the Zika forest of Uganda [2]. Over the next 60 years, ZIKV was detected several times in serological studies and routine arthropod-borne viruses (or arboviruses) surveillance across Africa and Southeast Asia [3–6]. In 2007, the first large ZIKV outbreak among humans occurred on Yap Island, in the Federated States of Micronesia [7,8]. This outbreak raised a great deal of concern, not because of its severity, but because of its virulence. Nearly 73% of the population op the island was infected during this outbreak [7]. Another outbreak in French Polynesia in 2013 further raised concerns because of the number of people infected and because ZIKV infection was linked in several cases to an autoimmune disease known as Guillaine-Barré Syndrome (GBS), which causes acute or subacute flaccid paralysis [9–11]. Most recently, an outbreak of ZIKV in the Americas, which began in 2015, has infected around a million citizens of Brazil alone and spread to a total of 50 countries and territories by 2017 [12]. Along with GBS, this recent outbreak has also been linked to microcephaly in infants [13–15] and has shown potential for sexual transmission [16–18] making ZIKV an emerging infectious disease of high concern.

Many mosquito species have been implicated as potential vectors of ZIKV. The original vector is thought to be *Aedes africanus* [2], while *Aedes henselli* was implicated in the Yap Island outbreak [7,8], but the primary vector of the outbreak in the Americas is thought to be *Aedes aegypti* [19], which has demonstrated high competence for ZIKV in multiple laboratory tests.

Vector competence, in this case, meaning the ability to be infected by and to transmit a pathogen (Li et a., 2012; Richard et al., 2016; Roundy et al., 2017). In contrast, most other *Aedes* species have shown potential for infection by ZIKV, but low potential for transmission [23,24]. *Ae. aegypti* is a medically important vector as it has a broad distribution, lives largely in urban areas, and has anthropophilic feeding tendencies [25,26]. Along with ZIKV, *Ae. aegypti* is considered the primary vector of DENV, YFV, and chikungunya fever virus (CHIKV) in most parts of the world [27]. A few studies have suggested *Culex quinquefasciatus*, a known vector of WNV, as a potential vector of ZIKV [28,29]. However, *Cx. quinquefasciatus* has largely been discounted as a vector of ZIKV through experimentation and critical review (Liu et al., 2017; Lourenço-de-Oliveira et al., 2018; Roundy et al., 2017). Currently, much of the debate in the field surrounds the species *Aedes albopictus*, which has long been considered the secondary vector of ZIKV even before its competence was experimentally assessed (Ayres, 2016; Gardner et al. 2017; Gardner et al., 2016; Vasilakis & Weaver, 2017). In the past decade or so, *Ae. albopictus*' role as a vector for arboviruses has become more widely recognized [37]. *Ae. albopictus* is already widely considered a competent vector for 26 arboviruses, including viruses from the families *Flaviviridae* (e.g. DENV, YFV, etc.)*, Togaviridae* (e.g. CHIKV, etc.) and *Bunyaviridae* (e.g. La Crosse virus, or LCV, etc.) [37]. In some parts of the world *Ae. albopictus* is even considered to be the primary vector of DENV and CHIKV [38,39].

If competent to carry and transmit ZIKV, *Ae. albopictus* represents a major new threat in the global transmission of the disease (Gardner et al., 2017; Gardner et al., 2016). From the 1980s-2000s, *Ae. albopictus* spread from its native Asian range to occupy a nearly global distribution [40], making it one of the most invasive mosquito species in the world. *Ae. albopictus'* current range stretches across every continent but Antarctica, and it is continuing to spread further into

North America and Europe [26,40]. Thus, if *Ae. albopictus* is a competent vector, areas thought to be safe from mosquito transmitted ZIKV because of the absence of *Ae. aegypti*, especially the US, Europe, China, and Japan, may be at risk (Gardner et al., 2017; Gardner et al., 2016). This means control strategies designed to limit the spread of ZIKV must be broader than if *Ae. aegypti* is the sole vector [33].

While it is thought that *Ae. albopictus* may be a vector of ZIKV, at least in some parts of the world [41,42], there have been no quantitative analyses of *Ae. albopictus'* competence for ZIKV. It is especially important to understand how competence varies across studies, as this may give us insight into potential geographical differences in *Ae. albopictus* ability to carry and transmit ZIKV, which is thought to be variable [41–44], as well as giving us a chance to examine other potential variables in the literature. Studies to date of *Ae. albopictus'* competence for ZIKV vary in methods, mosquito strains, and viral strains among other things. All of these variables are known to impact mosquitoes' vector competence for DENV, CHIKV and other flaviviruses, and it seems likely that they would affect competence for ZIKV as well [22,43,44]. The variation in vector competence among different mosquito populations/viral strains may be due to micro-adaptations in the host-pathogen genome, which could mean co-occurrence of mosquito population and ZIKV strain could affect competence of populations for arboviruses [45]. Laboratory-based infection methods can also cause variation in vector competence results. Richards et al., 2007 [46] and Ciota et al., 2017 [47] suggest that freezing viral blood meals before allowing mosquitoes to feed on them can cause dramatic underestimates of vector competence. Meanwhile, Roundy et al., 2017 [22] suggests that mosquitoes fed on live mice demonstrate higher vector competence than those fed on artificial blood meals. It is important to understand how different methods affect the findings of *Ae. albopictus'* competence for ZIKV.

68 The objectives of this study were to: 1) determine the overall vector competence of *Ae.*
69 *albopictus* for ZIKV and 2) examine the variation in the literature and the effects of geography
70 and methodology on *Ae. albopictus'* competence for ZIKV. Specifically, whether geographic
71 origin of viral strain, geographic origin of mosquito test population, geographic co-occurrence of
72 mosquito population and viral strain, freshness of blood-meal, viral titer (or dose) of blood-meal,
73 and whether the blood-meal was artificial or taken from a live, murine source, have significant
74 effects on *Ae. albopictus* vector competence for ZIKV.

Methods

75 *Ethics statement*

76 N/A

77 *Meta-analysis for vector competence*

78 Despite the widespread use of meta-analyses as a tool in both the medical and ecological fields
79 [48,49], surprisingly, and with a few notable exceptions [50,51], it has not been widely used in
80 synthesizing vector competence research. Here, a meta-analysis of the literature surrounding *Ae.*
81 *albopictus'* competence for ZIKV was used to address objectives associated with determining
82 vector competence, infection rate (IR), and transmission rate (TR) among *Ae. albopictus*' groups
83 subjected to infection by ZIKV. For our purposes, IR is defined as the proportion of the test
84 population of *Ae. albopictus* with traces of ZIKV in their midguts and TR is defined as the
85 proportion of infected *Ae. albopictus* individuals with traces of ZIKV in their salivary glands or
86 saliva. Since these rates vary throughout the incubation time of a virus, IR and TR were used at
87 both 7 and 14 dpi, the most common windows of time at which these metrics are examined.

Identification of studies and inclusion criteria

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2018 Guidelines [52]. Relevant studies were identified using searches of keywords through Clarivate Analytics' Web of Science (http://webofknowledge.com/WOS_GeneralSearch) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) search engines. The search was refined to include only papers published in English between January 2014 and March 2018. The key terms used were as follows: Aedes albopictus, vector, competenc*, transmiss*, dissem*, infect*, zik*. Results were screened initially excluding all studies that did not include *Ae. albopictus* as a study organism. With the study objective to quantify *Ae. albopictus'* competence for ZIKV, results were further refined to include only primary, experimental vector competence studies and exclude field studies. Furthermore, only studies that assessed both IR and TR were included. Since vector competence varies a great deal over the infection period, all papers that did not examine competence at 7 and/or 14 dpi (the most commonly reported sampling times) were excluded. Studies in which mosquitoes were infected with a viral titer of 1×10^7 ffu/pfu/$TCID^{50}$ or lower were also excluded because they were significantly below the typical ID_{50} of *Ae. albopictus* for ZIKV [52]. A few papers (Azar et al. 2017, in particular) reported multiple effect sizes from separate experiments that used different methods, therefore these effect sizes were listed as separate studies in the analysis.

Of the 34 results originally identified by the search criteria, 13 were removed as duplicates. Two additional studies [53,54] were identified through a search of the literature. Three additional papers [54–56], were identified in October of 2018, following the original analysis, using the same keyword search in Google Scholar and refining the search to papers published in 2018. Of

111 the remaining 26 studies screened for eligibility, 10 were excluded, either because they did not
112 include *Aedes albopictus* as a study species or because they did not study competence for ZIKV
113 (Fig 1). Ciota et al., 2017 [50] was excluded because it only reported IR and TR after 21 dpi.
114 This left a total of 15 papers for the analysis. Two papers, Heitmann et al., 2017 [57] and Azar et
115 al., 2017 [56] assessed multiple populations in their studies using different methods, so data from
116 these papers were split into separate studies and tested separately. A full list of studies long with
117 their characteristics, and the models in which they were included can be found in S1 Table. Ten
118 studies from Azar et al., 2017 [56] were excluded because they studied mosquitoes infected with
119 viral titers lower than 1 x 10^7 ffu/pfu/$TCID^{50}$. This left a total of 23 studies. A list of which
120 studies were used in which models can be found in the S1 Table.

Figure 1. The inclusion process for the meta-analysis conducted followed PRISMA guidelines.

This meta-analysis was carried out and reported according to PRISMA guidelines [52]. Search of the databases returned 34 records, while 2 additional records were identified through a search of the literature and 3 more through following . After all duplicates were removed 26 records remained, of which 10 were excluded because they were not relevant to the study. Two articles were excluded because they did not meet the criteria for inclusion. The remaining 13 articles were divided into multiple studies based on the number of separate effect sizes reported and included in different parts of the meta-analysis, depending on which metrics they reported (IR at 7 dpi, IR at 14 dpi, TR at 7 dpi, TR at 14 dpi).

121 *Data extraction*

122 The following study characteristics from the research articles matching inclusion criteria were
123 extracted by a single reviewer and entered into a database: IR at 7 dpi, IR at 14 dpi, TR at 7 dpi,
124 TR at 14 dpi, origin of viral strain, origin of *Ae. albopictus* test population strain, whether
125 infected blood-meal was given to mosquitoes fresh or after having been frozen, log transformed
126 viral titer of blood-meal, and whether the blood-meal was given artificially or taken from a live,
127 murine source. IR and TR were taken directly from tables or extracted from figures using the R

128 package “metaDigitise” [58]. Variation exists between studies in reporting transmission rates,
129 with some reporting TR as the proportion of transmitting mosquitoes in the whole test population
130 instead of the infected population. All data not conforming to our definitions were transformed
131 using information on sample size found in the papers.

132 *Statistical analysis*

133 Because IR and TR are easily comparable between vector competence studies and are inherently
134 meaningful measurements, these raw proportions were used as effect size in this study. Data
135 were compiled into a spreadsheet and analyzed using the R package “metafor” [59]. A mixed-
136 effects restricted maximum likelihood (REML) model was used to determine pooled estimates of
137 IR and TR at both 7 and 14 dpi, using sample size to weight estimates. Since not all studies
138 examined IR and TR at both 7 dpi and 14 dpi, not every study was included in every model.
139 Heterogeneity of IR and TR across studies were assessed using a Cochran Q test ($P < 0.05$ is
140 considered to indicate statistically significant heterogeneity). Because they are easy to analyze
141 and widely understood and utilized, funnel plots were used to look for publication bias, while
142 Egger’s method was used to test for asymmetry. Results of tests for asymmetry can be found in
143 the S1 Figure. The R code for models can be found in the S1 Table. Models were rerun using
144 study characteristics thought to affect outcome (geographic origin of viral strain, geographic
145 origin of mosquito test population, geographic co-occurrence of mosquito population and viral
146 strain, freshness of blood-meal, viral titer (or dose) of blood-meal, and whether the blood-meal
147 was artificial or taken from a live, murine source) as moderators.

Results

148 The pooled estimated IR of *Ae. albopictus* was 0.79 (95% CI 0.69-0.89) and 0.81 (95% CI 0.72-
149 0.90) at 7 and 14 dpi, respectively (Fig 2). Significant heterogeneity in IR estimates at both 7 and
150 14 dpi were observed with an I^2 (Cochran's Q test) of 93.6% (P < 0.0001) and 95.1% (P <
151 0.0001), respectively. For TR, significantly heterogeneous pooled estimates at 7 dpi of 0.15 (Fig
152 2; 95% CI 0.05-0.24; I^2 = 90.3%; P < 0.0001) and at 14 dpi of 0.29 (Fig 2; 95% CI 0.16-0.42; I^2
153 = 94.9%; P < 0.0001) were detected.

Figure 2. Mean infection rate and transmission rate (± 95% CI) of *Ae. albopictus* for ZIKV at 7 and 14 dpi.
Ae. albopictus shows high infection rates at both 7 dpi (IR = 0.79, 95% CI = 0.69-0.81) and 14 dpi (IR = 0.81, 95% CI = 0.72-0.90). Transmission rates were considerably lower at both 7 dpi (TR = 0.15, 95% CI = 0.05-0.24), and 14 dpi (TR = 0.29, 95% CI = 0.16-0.42).

154 Tests of all moderators showed significant effects only on TR at 14 dpi (Q = 260.1, P < 0.0001).
155 No significant moderator effects were found on IR at 7 dpi (Q = 13.1, P = 0.22) and 14 dpi (Q =
156 15.6, P = 0.11) or TR at 7 dpi (Q = 10.0, P = 0.44). Among moderators, geographic origin of *Ae.*
157 *albopictus* test populations had significant TR at 14 dpi (Fig 3), as did origin of viral strain (Fig
158 4). Using mosquitoes from East Asia/Oceania as a reference group, models show that European,
159 North American and South American mosquitoes displayed significantly lower TRs 14 dpi (P =
160 0.0025, P = 0.0002, P = 0.0013). Origin of viral strain also had significant effects on TR at 14
161 dpi (Fig 4), with East Asian/Oceanic, North American and South American viral strains showing
162 significantly lower TRs than the reference African strains (P = 0.0079, P < 0.0017, P < 0.0001).
163 Origin of blood meal also had a significant effect on TR at 14 dpi, with mosquitoes that fed on
164 mice exhibiting higher TRs (P = 0.002; Fig 5). Finally, freshness of blood meal, artificial or

murine source of blood-meal, log viral dosage, and co-occurrence of mosquito population and viral strain had no significant effects on IR or TR at any stage.

Figure 3. Scatter plot showing mean IR and TR for ZIKV (± 95% CI) of geographically separated populations of *Ae. albopictus* at 7 (A) and 14 (B) dpi.
East Asian/ Oceanic and North American *Ae. albopictus* demonstrated higher IRs than other *Ae. albopictus* populations at both 7 dpi (IRs: East Asian/ Oceanic = 0.71, 95% CI = 0.50-0.92; European = 0.50, 95% CI = 0.28-0.72; North American = 0.90, 95% CI = 0.80-1.00; South American = 0.65, 95% CI = 0.37-0.93) and 14 dpi (IRs: East Asian/ Oceanic = 0.87, 95% CI = 0.70-1.04; European = 0.57, 95% CI = 0.41-0.74; North American = 0.91, 95% CI = 0.81-1.01; South American = 0.65, 95% CI = 0.37-0.93) though these results were not statistically significant. East Asian/ Oceanic and European *Ae. albopictus* showed the highest TRs at 7dpi (TRs: East Asian/ Oceanic = 0.31, 95% CI = 0.01-0.60; European = 0.33, 95% CI = 0.05-0.62; North American = 0.11, 95% CI = -0.03-0.24; South American = 0.05, 95% CI = -0.23-0.34) while East Asian/ Oceanic *Ae. albopictus* showed significantly higher TRs than other strains at 14dpi (TRs: East Asian/ Oceanic = 0.82, 95% CI = 0.61-1.03; European = 0.17, 95% CI = -0.01-0.35; North American = 0.21, 95% CI = 0.10-0.31; South American = 0.05, 95% CI = -0.19-0.28).

Figure 4. Scatter plot showing mean IR and TR (± 95% CI) of *Ae. albopictus* infected with geographically separated strains of ZIKV at 7 (A) and 14 (B) dpi.
African and South American strains of ZIKV demonstrated significantly higher IRs than other ZIKV strains at both 7 dpi (IRs: African = 0.95, 95% CI = 0.74-1.17; East Asian/ Oceanic = 0.61, 95% CI = 0.46-0.76; North American = 0.84, 95% CI = 0.67-1.01; South American = 0.90, 95% CI = 0.71-1.10) and 14 dpi (IRs: African = 0.97, 95% CI = 0.73-1.2; East Asian/ Oceanic = 0.69, 95% CI = 0.54-0.84; North American = 0.81, 95% CI = 0.66-0.97; South American = 0.92, 95% CI = 0.72-1.13). African strains of ZIKV also demonstrated the highest TRs at 7 dpi (TRs: African = 0.42, 95% CI = 0.26-0.57; East Asian/ Oceanic = 0.06, 95% CI = -0.01-0.13; North American = 0.08, 95% CI = 0.01-0.14; South American = 0.06, 95% CI = -0.02-0.13) while African and East Asian/ Oceanic strains of ZIKV demonstrated the highest TRs at 14 dpi (TRs: African = 0.79, 95% CI = 0.56-1.03; East Asian/ Oceanic = 0.36, 95% CI = 0.20-0.52; North American = 0.15, 95% CI = 0.01-0.30; South American = 0.06, 95% CI = -0.13-0.25).

Discussion

This meta-analysis, assessed 15 papers, divided into 23 studies, to determine the suitability of *Ae. albopictus*, an invasive Asian mosquito species which is found in high densities on all continents except Antarctica, as a competent vector to both carry and transmit ZIKV. The studies included in this paper and the analysis performed conclude that *Ae. albopictus* is a competent vector to

both carry and transmit ZIKV in laboratory settings. Infection rates of ZIKV in *Ae. albopictus* at both 7 dpi (IR = 0.80; 95% CI 0.70-0.92) and 14 dpi (IR = 0.83; 95% CI 0.72-0.92) are high, on par with those found in similar studies of *Ae. aegypti* [22]. Transmission rates for ZIKV in this mosquito at 7 dpi (TR = 0.15; 95% CI 0.05-0.26), and 14 dpi (TR = 0.3; 95% CI 0.16-0.45) are low compared to *Ae. albopictus'* competence for other RNA viruses [60,61], but are still similar to numbers reported in many studies that examined *Ae. aegypti*'s competence for ZIKV [21,22,44].

Studies have suggested that geographically disparate populations of *Ae. aegypti* vary in their competence for ZIKV [22,62]. This meta-analysis suggests that *Ae. albopictus'* competence for ZIKV varies geographically as well. The reasons for geographic variation in vector competence of *Ae. aegypti* and *Ae. albopictus* for ZIKV has been hypothesized to be a barrier that prevents infection of epithelial cells in the midgut [44,47,62,63]. This barrier may be related to mosquitoes' microbiome [64,65]. One genus of bacteria in particular, *Wolbachia*, has been implicated in mitigating the ability of mosquitos to transmit ZIKV by limiting the lifespan of *Aedes* mosquitoes, while specific strains have demonstrated the ability to directly interfere with the infection of hosts by RNA viruses such as ZIKV [66–68]. The mechanism for this antiviral interference is still not entirely understood, but may have to do with structural changes that some strains of *Wolbachia* make to the endoplasmic reticulum, the preferred site for RNA viral replication [69]. Recent studies have also identified the existence of a salivary gland barrier in both *Ae. albopictus* and *Ae. aegypti*, which may prevent transmission of ZIKV from the salivary gland to a host [43,55]. Other interactions, including those between viral and mosquito genomes, may also drive mosquito competence for a multitude of arboviruses, including ZIKV [45,70]. Since vector competence is thought to be influenced by regional micro-adaptions in the genome

194 [45,70], a significantly positive effect of co-occurrence of ZIKV viral strain and *Ae. albopictus*
195 population on the competence of *Ae. albopictus* for ZIKV was expected, however, none of the
196 models in this meta-analysis support this. The lack of correlation may be due to the broadness of
197 our geographic characterizations (continent scale) or to a small sample size.

198 Models of both IR and TR at 7 and 14 dpi suggest that East Asian/Oceanic populations of *Ae.*
199 *albopictus* have the greatest capacity to carry and transmit ZIKV (Fig 2). This may be because
200 East Asian/Oceanic *Ae. albopictus* population would have been the first to be infected by ZIKV
201 as the virus spread from Africa eastward, giving the virus more time to adapt to its host in this
202 part of the world. The greater capacity of East Asian *Ae. albopictus* to carry and transmit ZIKV
203 may have direct public health ramifications, as there is evidence that *Ae. albopictus* may already
204 be the primary vector of DENV and CHIKV in some parts of Asia [71]. In these areas it seems
205 likely that in the event of an outbreak, *Ae. albopictus* will also act as the primary vector for
206 ZIKV, and thus vector control strategies should include *Ae. albopictus*. Furthermore, *Ae.*
207 *albopictus'* ability to carry and transmit ZIKV highlights the need to understand the its
208 distribution, making vector surveillance of the species a high priority everywhere the species
209 does or may occur.

210 Test of moderators for TR at 14 dpi also suggests that African strains of ZIKV have the highest
211 potential to infect *Ae. albopictus* (Fig 3), which is in line with similar studies carried out on
212 *Aedes aegypti* [70]. This study indicates a need to determine the potential of these strains to
213 spread to areas with large populations of *Ae. albopictus,* such as Europe, North America, and
214 Asia.

215 We expected to see a significant positive effect of fresh blood meals (vs. previously frozen blood
216 meals) on *Ae. albopictus* TR, as described in previous papers [46,52], which we did not observe.

Nor did we observe a significant difference between mosquitoes infected by feeding from live, murine blood meals and mosquitoes infected with artificial blood meals. This may be because of co-linearity between fresh vs. frozen blood meal categories and the artificial vs. live blood meal categories in this study, or because of small sample size. The lack of effect of viral titer on IRs suggests that likelihood of infection for *Ae. albopictus* is not increased above a certain threshold, possibly around 1 x 10^7 pfu/ffu/$TCID_{50}$. These results demonstrate the necessity of evaluating the methods by which vector competence studies are carried out and creating a consensus regarding best practices for evaluating vector competence. This standardization could help to increase the speed with which the scientific community identifies vectors of emerging diseases and thus allow us to create effective vector control strategies in a timely manner.

There are also possible ecological barriers to *Ae. albopictus'* potential as a critical vector for ZIKV. Unlike the primary vector of ZIKV, *Ae. aegypti*, *Ae. albopictus* tends to take one large bloodmeal as opposed to several smaller ones, which limits *Ae. albopictus'* ability to transfer viruses from one organism to another [72]. *Ae. albopictus* has also been shown to be more opportunistic in its feeding behaviors than the largely anthropophilic *Ae. aegypti*, though this seems to somewhat vary geographically [73–77]. This more catholic feeding behavior may make *Ae. albopictus* a less critical vector than *Ae. aegypti* for ZIKV and other viruses since they are less likely to feed on humans. However, opportunistic feeding may also make *Ae. albopictus* a better bridge vector, carrying diseases such as ZIKV between humans and wildlife reservoirs, thus increasing its potential importance as a vector [37].

Strengths and limitations

ZIKV emerged as a global threat to public health in 2016, therefore at the time of this study, relatively few studies of vector competence have been carried out on the disease, and most of

them were done within a short time frame (Summer 2016 – Winter 2017). With an increasing number of studies, higher resolution analysis can be conducted that may provide insight into how ZIKV is evolving and adapting to new hosts and new environments. The high level of unexplained heterogeneity across studies currently available may be due to small sample size (especially for TR at 7 dpi), exclusion criteria (for instance, exclusion of studies using viral titers below 1×10^7 pfu/ffu/$TCID_{50}$), or the influence of variables we did not consider in our models. Furthermore, considering the potential significance of a salivary gland barrier to transmission, this study's inclusion of studies that measured TRs by the salivary glands instead of expectorated saliva may contribute to inflated estimates of TR. Hopefully, future studies will allow re-examination the moderators in this meta-analysis in more detail and to evaluate their significance more robustly.

Conclusion

The results of our study indicate that *Ae. albopictus* has the potential and competence to be a vector of ZIKV across the globe. The identification of *Ae. albopictus* as a competent vector for ZIKV raises multiple other points of concern, such as the continuation of *Ae. albopictus'* spread across North America and Europe [26,40], the high densities in which *Ae. albopictus* establishes itself [37,78], and the increasing realization that *Ae. albopictus* may either be growing more anthropophilic or may have always been more anthropophilic than previously thought [37,44]. Questions of vector competence are typically difficult to resolve given differing laboratory conditions and pathogen and vector sources. Here, we highlight the underutilized method of meta-analyses to clarify issues of vector competence, given that this method has the potential to synthesize findings from existing studies, and unlike any individual study, allows researchers to incorporate a wide range of moderators. This meta-analysis suggests that *Ae. albopictus* should be seriously considered as a potential vector of ZIKV. Efforts to understand the ecology of both ZIKV and *Ae. albopictus* must be strengthened to understand what other, non-physiological, factors may still prevent *Ae. albopictus* from acting as a major vector for the disease. Finally, efforts at rural and sylvatic surveillance for ZIKV should increase. If *Ae. albopictus* can be infected by, and transmit ZIKV, there is more potential for the disease to become established in areas where monitoring systems are not looking for it.

Acknowledgments

We'd like to thank the Auburn University School of Forestry and Wildlife Sciences, and the Office of the Vice President for Research and Economic Development for supporting this work. We'd also like to thank Todd Steury of Auburn University for his help and input on the meta-analyses used in this study.

References

1. Kuno G, Chang G-JJ, Tsuchiya KR, Karabatsos N, Cropp CB. Phylogeny of the Genus Flavivirus. J Virol. 1998;72: 73–83.

2. Dick GW., Kitchen S., Haddow A. Zika Virus (I). Isolations and serological specificity. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1952;46: 509–520. doi:10.1016/0035-9203(52)90042-4

3. Marchette NJ, Garcia R, Rudnick A. Isolation of Zika Virus from Aedes Aegypti Mosquitoes in Malaysia*. The American Journal of Tropical Medicine and Hygiene. 1969;18: 411–415. doi:10.4269/ajtmh.1969.18.411

4. Moore DL, Causey OR, Carey DE, Reddy S, Cooke AR, Akinkugbe FM, et al. Arthropod-borne viral infections of man in Nigeria, 1964–1970. Annals of Tropical Medicine & Parasitology. 1975;69: 49–64. doi:10.1080/00034983.1975.11686983

5. Simpson DIH. Zika virus infection in man. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1964;58: 335–338. doi:10.1016/0035-9203(64)90200-7

6. Weinbren MP, Williams MC. Zika virus: Further isolations in the zika area, and some studies on the strains isolated. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1958;52: 263–268. doi:10.1016/0035-9203(58)90085-3

7. Duffy MR, Chen T-H, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika Virus Outbreak on Yap Island, Federated States of Micronesia. New England Journal of Medicine. 2009;360: 2536–2543. doi:10.1056/NEJMoa0805715

8. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ, et al. Genetic and Serologic Properties of Zika Virus Associated with an Epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis. 2008;14: 1232–1239. doi:10.3201/eid1408.080287

9. Cao-Lormeau V-M, Roche C, Teissier A, Robin E, Berry A-L, Mallet H-P, et al. Zika Virus, French Polynesia, South Pacific, 2013. Emerg Infect Dis. 2014;20: 1085–1086. doi:10.3201/eid2006.140138

10. Musso D, Nilles EJ, Cao-Lormeau V-M. Rapid spread of emerging Zika virus in the Pacific area. Clinical Microbiology and Infection. 2014;20: O595–O596. doi:10.1111/1469-0691.12707

11. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastère S, Valour F, et al. Zika virus infection complicated by Guillain-Barré syndrome – case report, French Polynesia, December 2013. Eurosurveillance. 2014;19. doi:10.2807/1560-7917.ES2014.19.9.20720

12. Silva GS, Richards GA, Baker T, Hidalgo J, Jiménez JIS, Amin P. Zika virus: Report from the task force on tropical diseases by the world Federation of Societies of intensive and critical care medicine. Journal of Critical Care. 2018; doi:10.1016/j.jcrc.2018.03.030

13. Calvet G, Aguiar RS, Melo ASO, Sampaio SA, de Filippis I, Fabri A, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. The Lancet Infectious Diseases. 2016;16: 653–660. doi:10.1016/S1473-3099(16)00095-5

14. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. The Lancet. 2016;387: 2125–2132. doi:10.1016/S0140-6736(16)00651-6

15. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika Virus Associated with Microcephaly. New England Journal of Medicine. 2016;374: 951–958. doi:10.1056/NEJMoa1600651

16. Duggal NK, Ritter JM, Pestorius SE, Zaki SR, Davis BS, Chang G-JJ, et al. Frequent Zika Virus Sexual Transmission and Prolonged Viral RNA Shedding in an Immunodeficient Mouse Model. Cell Reports. 2017;18: 1751–1760. doi:10.1016/j.celrep.2017.01.056

17. Gaskell KM, Houlihan C, Nastouli E, Checkley AM. Persistent Zika Virus Detection in Semen in a Traveler Returning to the United Kingdom from Brazil, 2016. Emerg Infect Dis. 2017;23: 137–139. doi:10.3201/eid2301.161300

18. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau V-M. Potential Sexual Transmission of Zika Virus. Emerg Infect Dis. 2015;21: 359–361. doi:10.3201/eid2102.141363

19. Guerbois M, Fernandez-Salas I, Azar SR, Danis-Lozano R, Alpuche-Aranda CM, Leal G, et al. Outbreak of Zika Virus Infection, Chiapas State, Mexico, 2015, and First Confirmed Transmission by Aedes aegypti Mosquitoes in the Americas. J Infect Dis. 2016;214: 1349–1356. doi:10.1093/infdis/jiw302

20. Li MI, Wong PSJ, Ng LC, Tan CH. Oral Susceptibility of Singapore Aedes (Stegomyia) aegypti (Linnaeus) to Zika Virus. PLOS Neglected Tropical Diseases. 2012;6: e1792. doi:10.1371/journal.pntd.0001792

21. Richard V, Paoaafaite T, Cao-Lormeau V-M. Vector Competence of French Polynesian Aedes aegypti and Aedes polynesiensis for Zika Virus. PLOS Neglected Tropical Diseases. 2016;10: e0005024. doi:10.1371/journal.pntd.0005024

22. Roundy CM, Azar SR, Rossi SL, Huang JH, Leal G, Yun R, et al. Variation in Aedes aegypti Mosquito Competence for Zika Virus Transmission. Emerg Infect Dis. 2017;23: 625–632. doi:10.3201/eid2304.161484

23. Diagne CT, Diallo D, Faye O, Ba Y, Faye O, Gaye A, et al. Potential of selected Senegalese Aedes spp. mosquitoes (Diptera: Culicidae) to transmit Zika virus. BMC Infectious Diseases. 2015;15: 492. doi:10.1186/s12879-015-1231-2

24. O'Donnell KL, Bixby MA, Morin KJ, Bradley DS, Vaughan JA. Potential of a Northern Population of Aedes vexans (Diptera: Culicidae) to Transmit Zika Virus. J Med Entomol. 2017;54: 1354–1359. doi:10.1093/jme/tjx087

25. Christophers S. Aëdes aegypti (L.) the Yellow Fever Mosquito: its Life History, Bionomics and Structure. Aëdes aegypti (L) the Yellow Fever Mosquito: its Life History, Bionomics and Structure. 1960; Available: https://www.cabdirect.org/cabdirect/abstract/19602901825

26. Kraemer MU, Sinka ME, Duda KA, Mylne AQ, Shearer FM, Barker CM, et al. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus. eLife Sciences. 2015;4: e08347. doi:10.7554/eLife.08347

27. WHO | Vector-borne diseases. In: WHO [Internet]. [cited 17 Apr 2018]. Available: http://www.who.int/mediacentre/factsheets/fs387/en/

28. Guedes DR, Paiva MH, Donato MM, Barbosa PP, Krokovsky L, Rocha SW dos S, et al. Zika virus replication in the mosquito *Culex quinquefasciatus* in Brazil. Emerging Microbes & Infections. 2017;6: e69. doi:10.1038/emi.2017.59

29. Guo X, Li C, Deng Y, Xing D, Liu Q, Wu Q, et al. *Culex pipiens quinquefasciatus*: a potential vector to transmit Zika virus. Emerging Microbes & Infections. 2016;5: e102. doi:10.1038/emi.2016.102

30. Liu Z, Zhou T, Lai Z, Zhang Z, Jia Z, Zhou G, et al. Competence of Aedes aegypti, Ae. albopictus, and Culex quinquefasciatus Mosquitoes as Zika Virus Vectors, China. Emerg Infect Dis. 2017;23: 1085–1091. doi:10.3201/eid2307.161528

31. Lourenço-de-Oliveira R, Marques JT, Sreenu VB, Atyame Nten C, Aguiar ERGR, Varjak M, et al. Culex quinquefasciatus mosquitoes do not support replication of Zika virus. J Gen Virol. 2018;99: 258–264. doi:10.1099/jgv.0.000949

32. Roundy CM, Azar SR, Brault AC, Ebel GD, Failloux A-B, Fernandez-Salas I, et al. Lack of evidence for Zika virus transmission by *Culex* mosquitoes. Emerging Microbes & Infections. 2017;6: e90. doi:10.1038/emi.2017.85

33. Ayres CFJ. Identification of Zika virus vectors and implications for control. The Lancet Infectious Diseases. 2016;16: 278–279. doi:10.1016/S1473-3099(16)00073-6

34. Gardner L, Chen N, Sarkar S. Vector status of Aedes species determines geographical risk of autochthonous Zika virus establishment. PLoS neglected tropical diseases. 2017;11: e0005487.

35. Gardner LM, Chen N, Sarkar S. Global risk of Zika virus depends critically on vector status of Aedes albopictus. The Lancet Infectious Diseases. 2016;16: 522–523. doi:10.1016/S1473-3099(16)00176-6

36. Vasilakis N, Weaver SC. Flavivirus transmission focusing on Zika. Current Opinion in Virology. 2017;22: 30–35. doi:10.1016/j.coviro.2016.11.007

37. Paupy C, Delatte H, Bagny L, Corbel V, Fontenille D. Aedes albopictus, an arbovirus vector: From the darkness to the light. Microbes and Infection. 2009;11: 1177–1185. doi:10.1016/j.micinf.2009.05.005

38. Vazeille M, Moutailler S, Coudrier D, Rousseaux C, Khun H, Huerre M, et al. Two Chikungunya Isolates from the Outbreak of La Reunion (Indian Ocean) Exhibit Different Patterns of Infection in the Mosquito, Aedes albopictus. PLOS ONE. 2007;2: e1168. doi:10.1371/journal.pone.0001168

39. Zhao H, Zhang F-C, Zhu Q, Wang J, Hong W-X, Zhao L-Z, et al. Epidemiological and Virological Characterizations of the 2014 Dengue Outbreak in Guangzhou, China. PLoS One. 2016;11. doi:10.1371/journal.pone.0156548

40. Benedict MQ, Levine RS, Hawley WA, Lounibos LP. Spread of The Tiger: Global Risk of Invasion by The Mosquito *Aedes albopictus*. Vector-Borne and Zoonotic Diseases. 2007;7: 76–85. doi:10.1089/vbz.2006.0562

41. Boyer S, Calvez E, Chouin-Carneiro T, Diallo D, Failloux A-B. An overview of mosquito vectors of Zika virus. Microbes and Infection. 2018; doi:10.1016/j.micinf.2018.01.006

42. Zika Virus. In: CDC [Internet]. 5 Nov 2014 [cited 30 Apr 2018]. Available: https://www.cdc.gov/zika/vector/range.html

43. Calvez E, O'Connor O, Pol M, Rousset D, Faye O, Richard V, et al. Differential transmission of Asian and African Zika virus lineages by Aedes aegypti from New Caledonia. Emerging Microbes & Infections. 2018;7: 159. doi:10.1038/s41426-018-0166-2

44. Uraki R, Hastings AK, Gloria-Soria A, Powell JR, Fikrig E. Altered vector competence in an experimental mosquito-mouse transmission model of Zika infection. PLOS Neglected Tropical Diseases. 2018;12: e0006350. doi:10.1371/journal.pntd.0006350

45. Lambrechts L, Chevillon C, Albright RG, Thaisomboonsuk B, Richardson JH, Jarman RG, et al. Genetic specificity and potential for local adaptation between dengue viruses and mosquito vectors. BMC Evolutionary Biology. 2009;9: 160. doi:10.1186/1471-2148-9-160

46. Richards SL, Pesko K, Alto BW, Mores CN. Reduced infection in mosquitoes exposed to blood meals containing previously frozen flaviviruses. Virus Res. 2007;129: 224–227. doi:10.1016/j.virusres.2007.06.019

47. Ciota AT, Bialosuknia SM, Zink SD, Brecher M, Ehrbar DJ, Morrissette MN, et al. Effects of Zika Virus Strain and Aedes Mosquito Species on Vector Competence. Emerg Infect Dis. 2017;23: 1110–1117. doi:10.3201/eid2307.161633

48. Egger M, Smith GD. Principles of and Procedures for Systematic Reviews. Systematic Reviews in Health Care. Wiley-Blackwell; 2008. pp. 23–42. doi:10.1002/9780470693926.ch2

49. Stewart G. Meta-analysis in applied ecology. Biol Lett. 2010;6: 78–81. doi:10.1098/rsbl.2009.0546

50. Lambrechts L, Scott TW, Gubler DJ. Consequences of the Expanding Global Distribution of Aedes albopictus for Dengue Virus Transmission. PLOS Neglected Tropical Diseases. 2010;4: e646. doi:10.1371/journal.pntd.0000646

51. Oliveira ARS, Cohnstaedt LW, Strathe E, Etcheverry L, McVey DS, Piaggio J, et al. Meta-Analyses of Japanese Encephalitis Virus Infection, Dissemination, and Transmission Rates in Vectors. The

American Journal of Tropical Medicine and Hygiene. 2018;98: 883–890. doi:10.4269/ajtmh.17-0622

52. McInnes MDF, Moher D, Thombs BD, McGrath TA, Bossuyt PM, Clifford T, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA. 2018;319: 388–396. doi:10.1001/jama.2017.19163

53. Vazeille M, Dehecq J-S, Failloux A-B. Vectorial status of the Asian tiger mosquito Aedes albopictus of La Réunion Island for Zika virus. Medical and Veterinary Entomology. 32: 251–254. doi:10.1111/mve.12284

54. Lozano-Fuentes S, Kenney JL, Varnado W, Byrd BD, Burkhalter KL, Savage HM. Susceptibility and Vectorial Capacity of American Aedes albopictus and Aedes aegypti (Diptera: Culicidae) to American Zika Virus Strains. Journal of Medical Entomology. 2018; doi:10.1093/jme/tjy114

55. Garcia-Luna SM, Weger-Lucarelli J, Rückert C, Murrieta RA, Young MC, Byas AD, et al. Variation in competence for ZIKV transmission by Aedes aegypti and Aedes albopictus in Mexico. Armstrong PM, editor. PLOS Neglected Tropical Diseases. 2018;12: e0006599. doi:10.1371/journal.pntd.0006599

56. Knecht H, Richards S, Balanay J, White A, Knecht H, Richards SL, et al. Impact of Mosquito Age and Insecticide Exposure on Susceptibility of Aedes albopictus (Diptera: Culicidae) to Infection with Zika Virus. Pathogens. 2018;7: 67. doi:10.3390/pathogens7030067

57. Heitmann A, Jansen S, Lühken R, Leggewie M, Badusche M, Pluskota B, et al. Experimental transmission of Zika virus by mosquitoes from central Europe. Eurosurveillance. 2017;22: 30437. doi:10.2807/1560-7917.ES.2017.22.2.30437

58. Pick JL, Nakagawa S, Noble DW. Reproducible, flexible and high throughput data extraction from primary literature: The metaDigitise R package. 2018; doi:10.1101/247775

59. Viechtbauer W. Conducting Meta-Analyses in *R* with the **metafor** Package. Journal of Statistical Software. 2010;36. doi:10.18637/jss.v036.i03

60. Sardelis MR, Turell MJ, O'Guinn ML, Andre RG, Roberts DR. Vector competence of three North American strains of Aedes albopictus for West Nile virus. J Am Mosq Control Assoc. 2002;18: 284–289.

61. Vega-Rúa A, Zouache K, Girod R, Failloux A-B, Lourenço-de-Oliveira R. High Level of Vector Competence of Aedes aegypti and Aedes albopictus from Ten American Countries as a Crucial Factor in the Spread of Chikungunya Virus. J Virol. 2014;88: 6294–6306. doi:10.1128/JVI.00370-14

62. Chouin-Carneiro T, Vega-Rua A, Vazeille M, Yebakima A, Girod R, Goindin D, et al. Differential Susceptibilities of Aedes aegypti and Aedes albopictus from the Americas to Zika Virus. PLOS Neglected Tropical Diseases. 2016;10: e0004543. doi:10.1371/journal.pntd.0004543

63. Azar SR, Roundy CM, Rossi SL, Huang JH, Leal G, Yun R, et al. Differential Vector Competency of Aedes albopictus Populations from the Americas for Zika Virus. The American Journal of Tropical Medicine and Hygiene. 2017;97: 330–339. doi:10.4269/ajtmh.16-0969

64. Jupatanakul N, Sim S, Dimopoulos G. The Insect Microbiome Modulates Vector Competence for Arboviruses. Viruses. 2014;6: 4294–4313. doi:10.3390/v6114294

65. Weiss B, Aksoy S. Microbiome influences on insect host vector competence. Trends in Parasitology. 2011;27: 514–522. doi:10.1016/j.pt.2011.05.001

66. Aliota MT, Peinado SA, Velez ID, Osorio JE. The *w*Mel strain of *Wolbachia* Reduces Transmission of Zika virus by *Aedes aegypti*. Scientific Reports. 2016;6: 28792. doi:10.1038/srep28792

67. Moreira LA, Iturbe-Ormaetxe I, Jeffery JA, Lu G, Pyke AT, Hedges LM, et al. A Wolbachia Symbiont in Aedes aegypti Limits Infection with Dengue, Chikungunya, and Plasmodium. Cell. 2009;139: 1268–1278. doi:10.1016/j.cell.2009.11.042

68. Walker T, Johnson PH, Moreira LA, Iturbe-Ormaetxe I, Frentiu FD, McMeniman CJ, et al. The *w*Mel *Wolbachia* strain blocks dengue and invades caged *Aedes aegypti* populations. Nature. 2011;476: 450–453. doi:10.1038/nature10355

69. White PM, Serbus LR, Debec A, Codina A, Bray W, Guichet A, et al. Reliance of Wolbachia on High Rates of Host Proteolysis Revealed by a Genome-Wide RNAi Screen of Drosophila Cells. Genetics. 2017; genetics.116.198903. doi:10.1534/genetics.116.198903

70. Rico-Hesse R. Microevolution and virulence of dengue viruses., MICROEVOLUTION AND VIRULENCE OF DENGUE VIRUSES. Adv Virus Res. 2003;59, 59: 315, 315–341. doi:10.1016/S0065-3527(03)59009-1

71. de Lamballerie X, Leroy E, Charrel RN, Ttsetsarkin K, Higgs S, Gould EA. Chikungunya virus adapts to tiger mosquito via evolutionary convergence: a sign of things to come? Virology Journal. 2008;5: 33. doi:10.1186/1743-422X-5-33

72. Hawley WA. The biology of Aedes albopictus. J Am Mosq Control Assoc Suppl. 1988;1: 1–39.

73. Haddad N, Mousson L, Vazeille M, Chamat S, Tayeh J, Osta MA, et al. Aedes albopictus in Lebanon, a potential risk of arboviruses outbreak. BMC Infectious Diseases. 2012;12. doi:10.1186/1471-2334-12-300

74. Kamgang B, Nchoutpouen E, Simard F, Paupy C. Notes on the blood-feeding behavior of Aedes albopictus (Diptera: Culicidae) in Cameroon. Parasites & Vectors. 2012;5: 57. doi:10.1186/1756-3305-5-57

75. Kim KS, Tsuda Y, Yamada A. Bloodmeal Identification and Detection of Avian Malaria Parasite From Mosquitoes (Diptera: Culicidae) Inhabiting Coastal Areas of Tokyo Bay, Japan. J Med Entomol. 2009;46: 1230–1234. doi:10.1603/033.046.0535

76. Ponlawat A, Harrington LC. Blood Feeding Patterns of Aedes aegypti and Aedes albopictus in Thailand. J Med Entomol. 2005;42: 844–849. doi:10.1093/jmedent/42.5.844

77. Richards SL, Ponnusamy L, Unnasch TR, Hassan HK, Apperson CS. Host-Feeding Patterns of Aedes albopictus (Diptera: Culicidae) in Relation to Availability of Human and Domestic Animals in

Suburban Landscapes of Central North Carolina. J Med Entomol. 2006;43: 543–551. doi:10.1093/jmedent/43.3.543

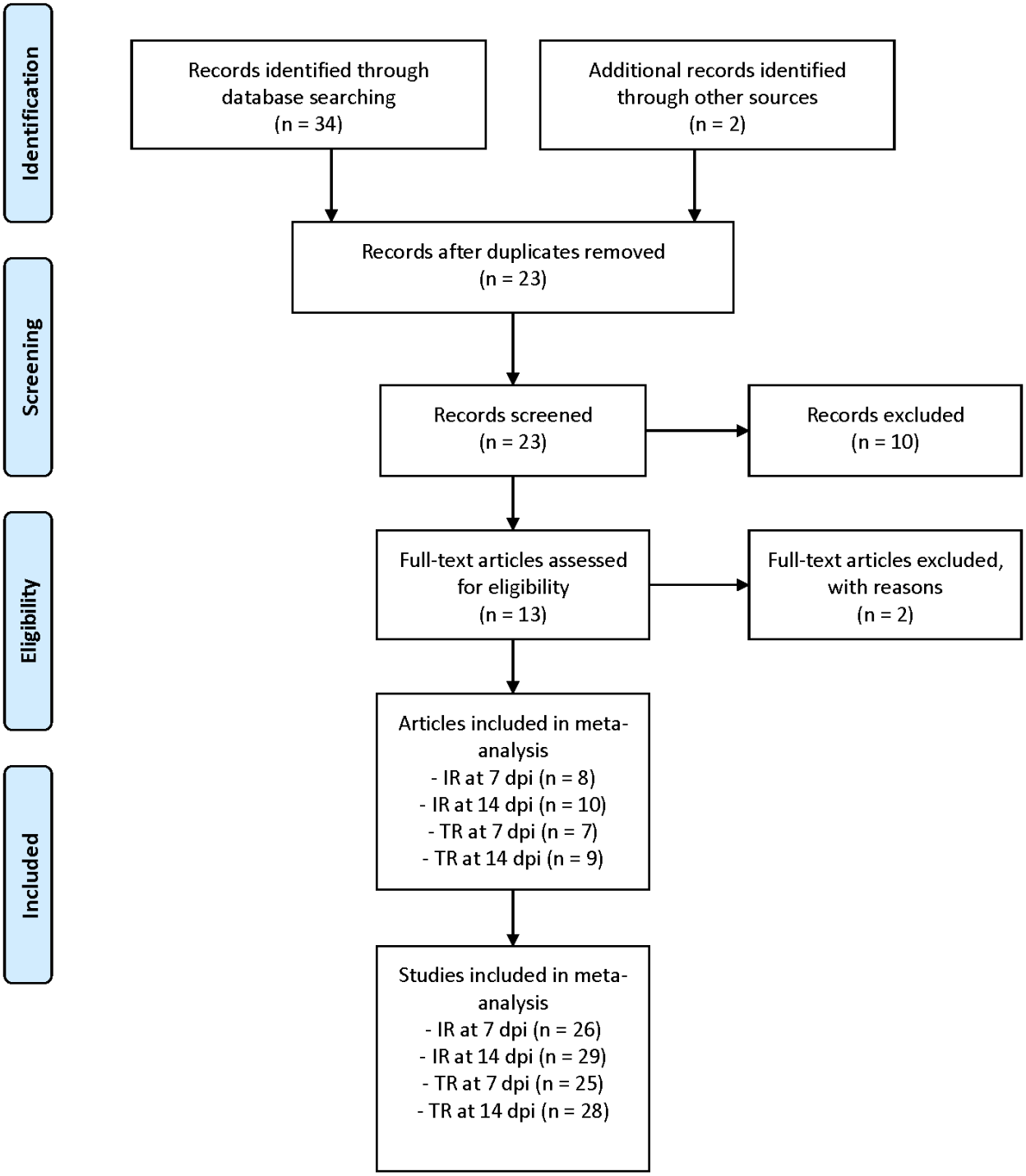
78. Gratz NG. Critical review of the vector status of Aedes albopictus. Medical and veterinary entomology. 2004;18: 215–227.

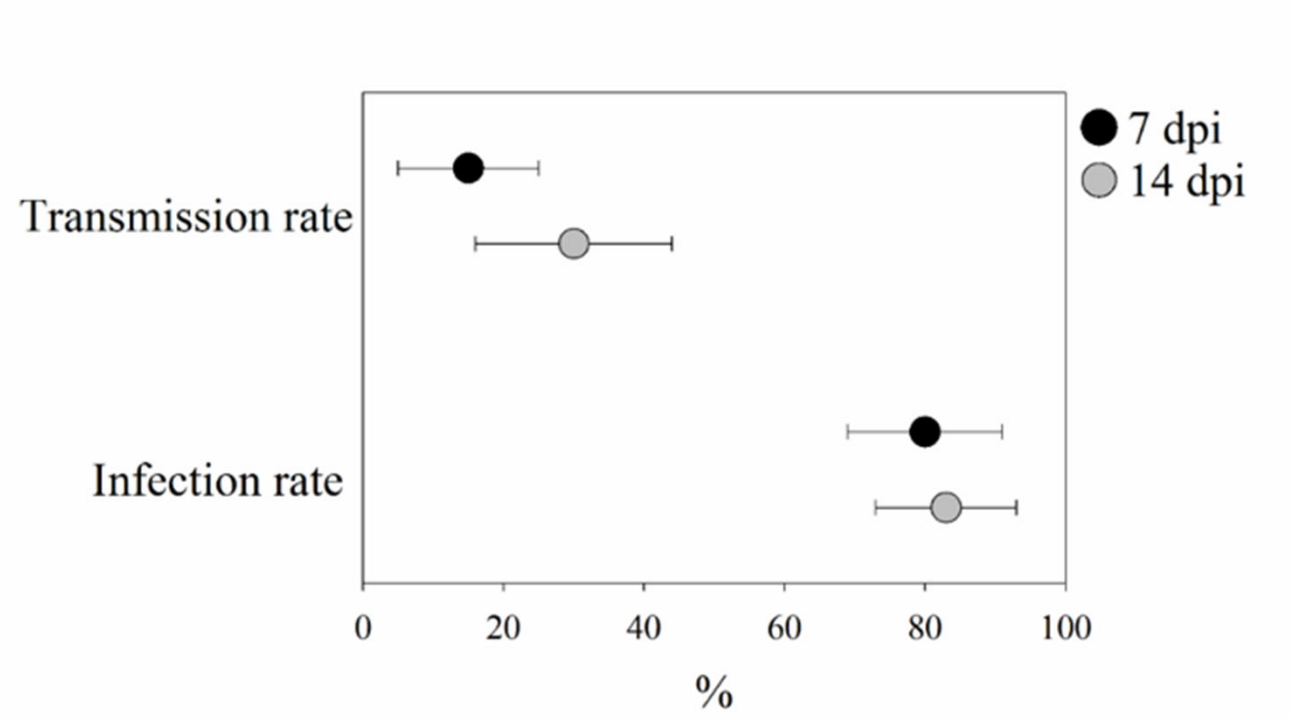
Supporting Information

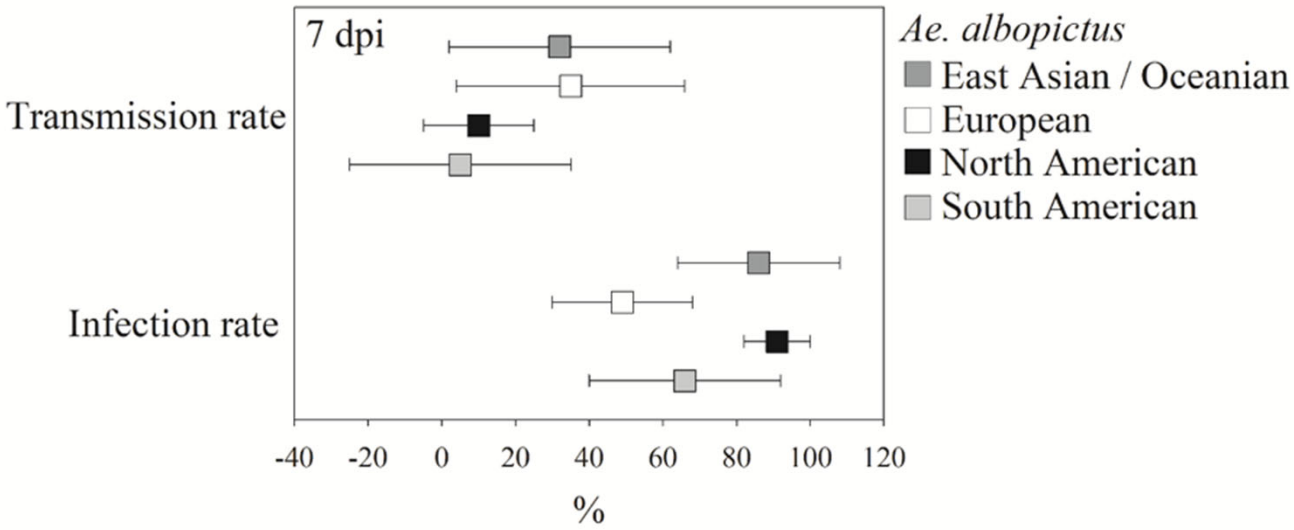
S1 Fig. Funnel plots tended to have an asymmetrical shape, with the exception of the funnel for TR at 14 dpi (S1 Fig). Egger's tests likewise suggested significant asymmetry for all funnel plots except for TR at 14 dpi (for IR at 7 dpi, $P < 0.0012$; for IR at 14 dpi, $P < 0.0001$; for TR at 7 dpi, $P < 0.0001$; for TR at 14 dpi, $P = 0.23$).

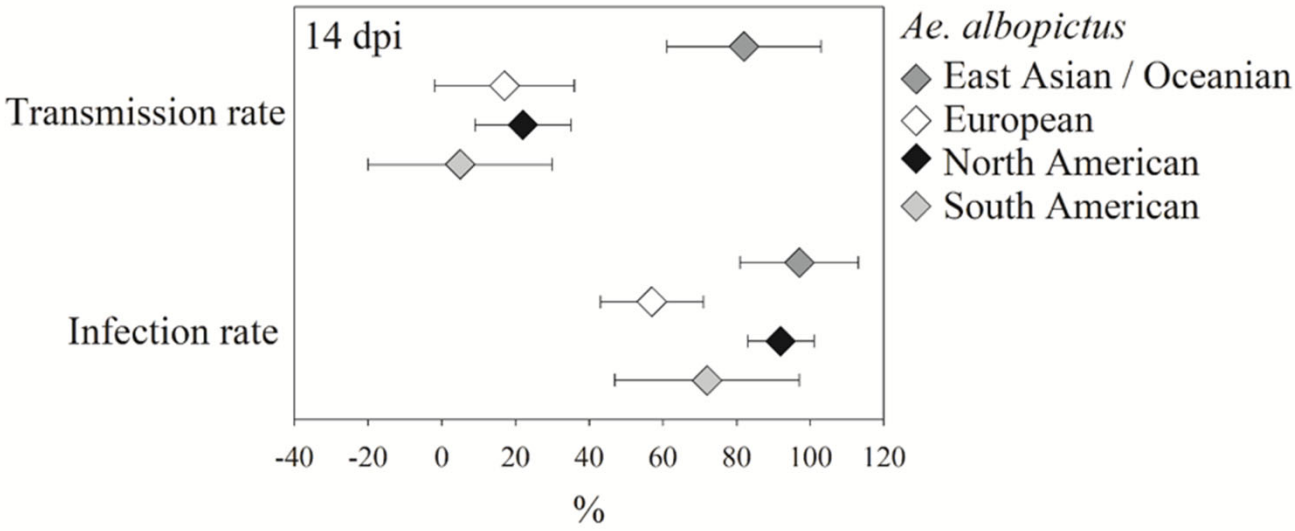
S1 Table. Data used in the meta-analysis presented here.

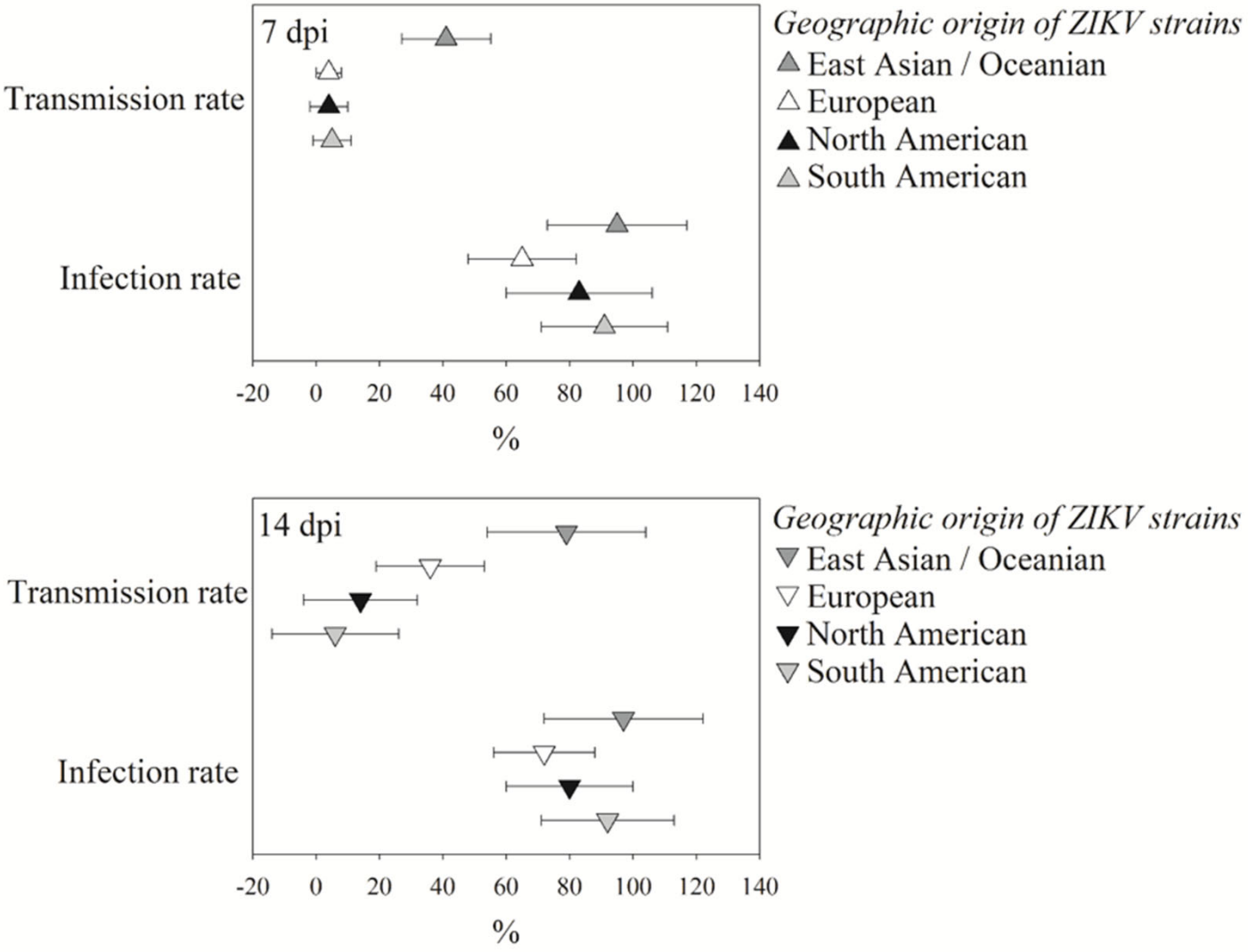
S1 Checklist: PRISMA Checklist

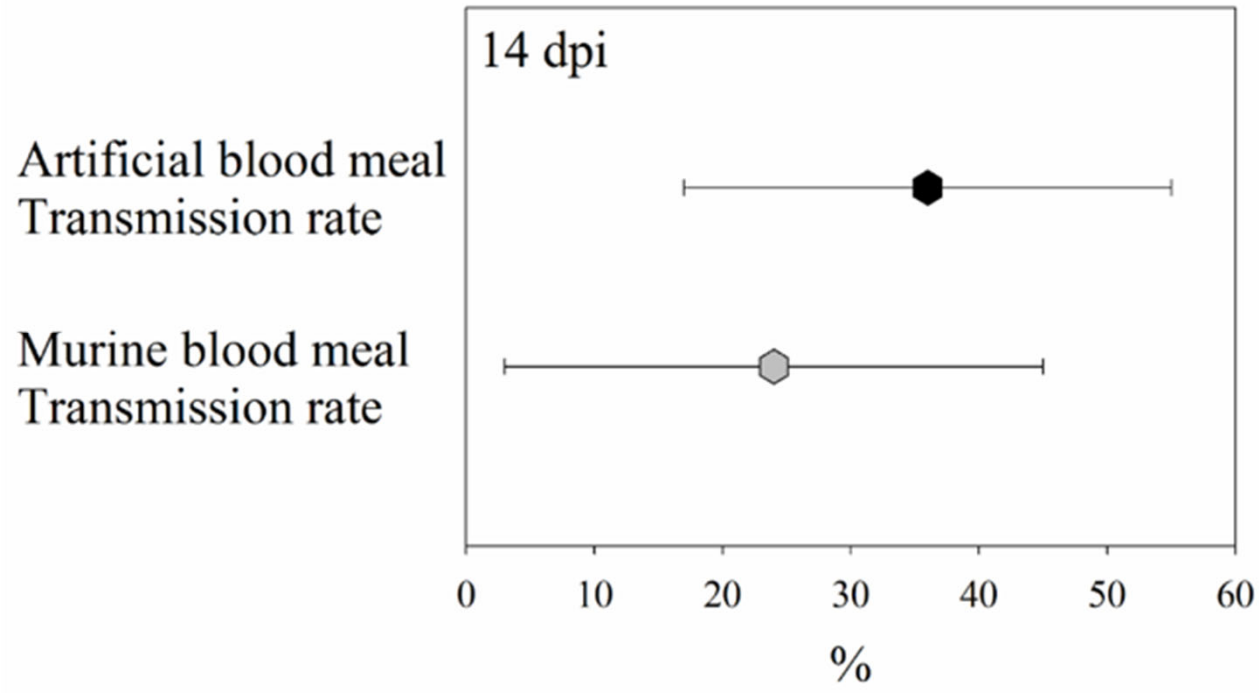

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 34)
Additional records identified through other sources (n = 2)
Records after duplicates removed (n = 23)
Records screened (n = 23)
Records excluded (n = 10)
Full-text articles assessed for eligibility (n = 13)
Full-text articles excluded, with reasons (n = 2)
Articles included in meta-analysis
- IR at 7 dpi (n = 8)
- IR at 14 dpi (n = 10)
- TR at 7 dpi (n = 7)
- TR at 14 dpi (n = 9)
Studies included in meta-analysis
- IR at 7 dpi (n = 26)
- IR at 14 dpi (n = 29)
- TR at 7 dpi (n = 25)
- TR at 14 dpi (n = 28)


7 dpi
14 dpi
Transmission rate
Infection rate
0
20
40
60
80
100
%


7 dpi
Transmission rate
Infection rate
-40
-20
0
20
40
60
80
100
120
%
Ae. albopictus
East Asian / Oceanian
European
North American
South American


14 dpi
Transmission rate
Infection rate
-40
-20
0
20
40
60
80
100
120
%
Ae. albopictus
East Asian / Oceanian
European
North American
South American


7 dpi
Transmission rate
Infection rate
-20
0
20
40
60
80
100
120
140
%
Geographic origin of ZIKV strains
East Asian / Oceanian
European
North American
South American
14 dpi
Transmission rate
Infection rate
-20
0
20
40
60
80
100
120
140
%
Geographic origin of ZIKV strains
East Asian / Oceanian
European
North American
South American


14 dpi
Artificial blood meal
Transmission rate
Murine blood meal
Transmission rate
0
10
20
30
40
50
60
%