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SHORT COMMUNICATION

Vectorial status of the Asian tiger mosquito *Aedes albopictus* of La Réunion Island for Zika virus

M. VAZEILLE¹, J.-S. DEHECQ² and A.-B. FAILLOUX¹¹Department of Virology, Arboviruses and Insect Vectors, Institut Pasteur, Paris, France and ²Agence de Santé Océan Indien, Lutte anti-vectorielle, Saint-Denis, France

Abstract. La Réunion Island has been the scene of unusually large epidemics of dengue (DENV) and chikungunya (CHIKV) viruses with *Aedes albopictus* Diptera, Culicidae (Skuse, 1894) as the sole vector. The emergence of Zika virus (ZIKV) in 2007 and the spread of the epidemic strain of the Asian genotype through the Pacific region and the Americas, mainly via the vector *Aedes aegypti* (Linnaeus, 1762), has raised concern about its possible introduction to, and transmission in, *Ae. albopictus*-infested areas. We performed an experimental oral infection with the Asian genotype of ZIKV in *Ae. albopictus* from La Réunion and found a strong midgut barrier to dissemination. This result is discussed in the light of previous vector competence assays for DENV and CHIKV performed by our team on other *Ae. albopictus* populations from La Réunion.

Key words. *Aedes albopictus*, arboviral emergence, Zika, La Réunion Island.

La Réunion Island, a French overseas department in the Indian Ocean (21° 06' S, 55° 36' E) 800 km from Madagascar, has been the scene of unusually large epidemics of infections with arboviruses. This small, densely populated island (2500 km² with 700 000 inhabitants) has low mosquito diversity (12 species), yet nearly half of culicid species are major vectors of human pathogens, including *Anopheles ariabiensis* (Patton, 1905), *Culex quinquefasciatus* (Say, 1823), *Culex tritaeniorhynchus* (Giles, 1901), *Aedes aegypti* (Linnaeus, 1762) and *Aedes albopictus* (Skuse, 1894) (Bousses *et al.*, 2013). *Ae. albopictus* is the predominant *Aedes* mosquitoes on the island, with *Ae. aegypti* persisting as residual populations in remote rural areas. The two species co-occurred in urbanized areas until the mid-1950s, when insecticidal control targeting the malaria vector *An. arabiensis* was implemented. Against all expectations, urban populations of *Ae. aegypti* were sharply reduced while *Ae. albopictus* succeeded in occupying the urban niche left vacant by *Ae. aegypti* (Bagny *et al.*, 2009).

Ae. albopictus, originating from the forests of Southeast Asia, was first recorded on La Réunion Island in 1913, but the species was probably introduced in the 18th Century. Imported populations then underwent several processes of differentiation from their ancestral Asian progenitors (Manni *et al.*, 2017). Today, *Ae. albopictus* from La Réunion is described as genetically close to populations from Madagascar, America and metropolitan France, suggesting the replacement of the original population

through migratory events from Madagascar (Mousson *et al.*, 2005). *Ae. albopictus* is known to experimentally transmit more than 26 arboviruses and has been identified as the sole vector of dengue (DENV; family *Flaviviridae*, genus *Flavivirus*) and chikungunya viruses (CHIKV; family *Togaviridae*, genus *Alphavirus*) during the last outbreaks on La Réunion (Paupy *et al.*, 2009).

The first documented outbreak of DENV on La Réunion took place in 1978 and involved the DENV-2 serotype, with an estimated attack rate of 30%. The virus was probably introduced from the neighbouring Seychelles Island, where a DENV outbreak was ongoing from December 1976 to September 1977. On both islands, *Ae. albopictus* was incriminated as the epidemic vector. After this major outbreak, DENV was not detected until 2004, when a smaller DENV-1 outbreak with only 228 cases occurred on La Réunion Island (http://www.invs.sante.fr/publications/2005/jvs_2005/poster_13.pdf). Since 2004, improved surveillance has resulted in continuous detection of sporadic autochthonous cases with some small peaks of transmission (231 cases in 2016). Shortly after the DENV re-emergence in 2004, the first cases of CHIKV were recorded, which were the beginning of an epidemic of unprecedented size, affecting ~38% of the population from March 2005 to June 2006. During the course of this outbreak, a CHIKV strain with a single amino acid substitution (substitution of alanine by valine at position 226) in the E1 glycoprotein was selected. This

Correspondence: Marie Vazeille, Department of Virology, Arbovirus and Insect Vectors, Institut Pasteur Paris, 25 rue du Dr Roux, 75015 Paris, France. Tel: +33 1 40 61 37 15; E-mail: marie.vazeille@pasteur.fr

new mutated strain enabled better transmission by the atypical CHIKV vector *Ae. albopictus* (Vazeille *et al.*, 2007). While it was often regarded as a mild disease, CHIKV infection on La Réunion Island was responsible for more severe symptoms (meningo encephalitis, encephalopathy and fulminant hepatitis), which were probably detected by the careful monitoring of cases during the outbreak. Between the DENV-1 and CHIKV outbreaks, co-infections were also detected in patients and co-transmission of both viruses by local *Ae. albopictus* has been demonstrated experimentally (Vazeille *et al.*, 2010).

Zika virus (ZIKV; family *Flaviviridae*, genus *Flavivirus*), originally isolated in Uganda in 1947, emerged in 2007 outside its natural range of distribution in Africa and Asia. It was initially reported in the Pacific Region on Yap Island (Micronesia), and then subsequent epidemics occurred in French Polynesia in 2013, New Caledonia in 2014 and the Americas in 2015, initially being detected in northeastern Brazil. Subsequently, 22 American countries reported ZIKV transmission. These outbreaks produce a heavy human health burden, being responsible for Guillain–Barre syndrome in the Pacific Region and birth defects, specifically microcephaly in newborns, in South America (Passi *et al.*, 2017). Currently, the ZIKV strains are classified into two major genotypes, African and Asian; genetic analysis has revealed that the Asian genotype of ZIKV was responsible for the last outbreaks in the Pacific Islands and the Americas (Lancioti *et al.*, 2016). With the exception of sexual transmission, ZIKV is primarily transmitted to humans through the bite of an infected *Aedes* mosquito. *Ae. aegypti* has been implicated as the major vector in recent outbreaks (Chouin-Carreiro *et al.*, 2016). The peculiar situation of La Réunion Island, where *Ae. albopictus* is the main anthropophilic vector of DENV and CHIKV, raises the question of its possible role in local transmission of ZIKV. Therefore, we orally infected one population of *Ae. albopictus*, collected in 2016 on the west coast of La Réunion, with a strain of the Asian genotype of ZIKV collected in New Caledonia in 2014, and discuss the results in the light of already published results on vector competence of *Ae. albopictus* from La Réunion for DENV or CHIKV.

Ae. albopictus mosquitoes assessed in this study were collected as eggs from the field in 2016 on the west coast of the island then reared in an insectary. F1 females were infected via a bloodmeal containing 10^7 TCID₅₀/mL (50% Tissue Culture Infective Dose/mL) of ZIKV, strain NC-2014-5132, isolated from a patient in April 2014 in New Caledonia. The bloodmeal was composed of two-thirds washed rabbit erythrocytes and one-third viral suspension supplemented with ATP at a final concentration of 10 mM (Vazeille-Falcoz *et al.*, 1999). Engorged females were kept in cardboard containers and maintained at 28 °C with 10% sucrose solution as food. Mosquitoes were analysed at 3, 6, 9 and 14 days post-infection (dpi) to estimate the infection rate (IR: the proportion of mosquitoes with an infected midgut among the examined mosquitoes) and the disseminated infection rate (DIR: the percentage of mosquitoes with an infected head among the analysed mosquitoes). Bodies and heads were homogenized individually in cell culture medium and infectious particles were detected by determining plaque-forming units (PFUs) on Vero cells (Jupille *et al.*, 2016).

As shown in Fig. 1A, infection rates for ZIKV assessed at 3, 6, 9 and 14 dpi were < 50%, with a maximum of 42.1%

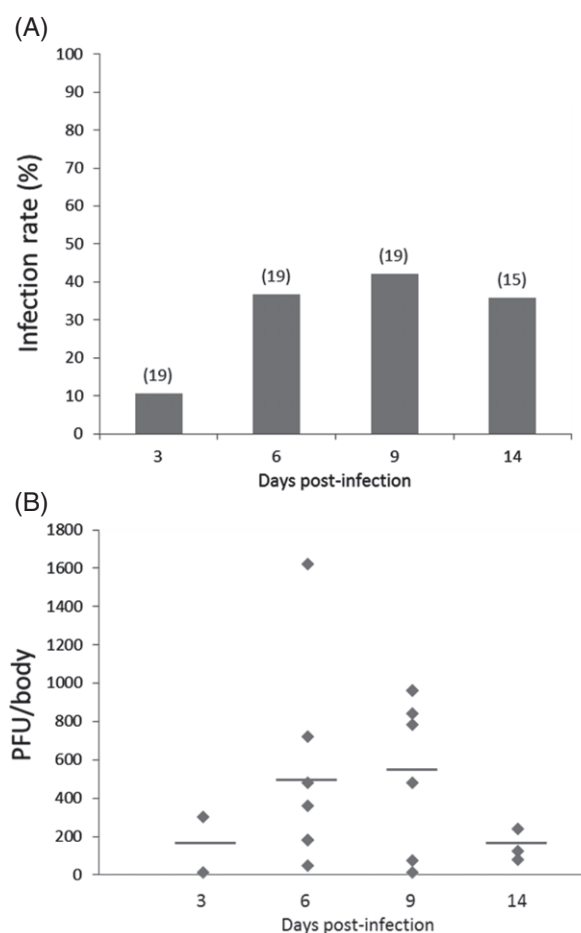


Fig. 1. *Aedes albopictus* from La Réunion assessed for viral infection at days 3, 6, 9 and 14 after oral exposure to Zika virus (ZIKV) NC-2014-5132 provided at a titre of 10^7 TCID₅₀/mL (50% Tissue Culture Infective Dose/mL). (A) Infection rates (%); (B) body titres of infected females [plaque-forming units (PFU)/body] with mean value.

(eight of 19) at 9 dpi. Body titres of infected females (Fig. 1B) ranged from 12 to 1620 PFU/body, with a maximum mean titre obtained at 9 dpi of 586 PFU/body. No dissemination in infected females was observed at these same time-points. Figure 2 shows an absence of dissemination at day 14 for ZIKV and compares this result with DIR obtained in two previous studies at 14 dpi for samples of *Ae. albopictus* from La Réunion (west coast) collected in 2006. In the first study (Vazeille *et al.*, 2007), F1 females from eight populations were tested for viral dissemination of two CHIKV strains collected in 2005 on La Réunion: (1) CHIKV strain 05.115, isolated in June 2005 from a patient on La Réunion presenting classical CHIKV symptoms; this strain, belonging to the East-Central-South-African (ECSA) genotype, has an alanine at position 226 in the E1 glycoprotein (E1-226A); and (2) CHIKV strain 06.21, isolated in November 2005 from a patient on La Réunion presenting meningo-encephalitis symptoms; this strain, belonging to the ECSA genotype, has a valine at position 226 in the E1 glycoprotein (E1-226V) and was selected during the course of the epidemic by the atypical CHIKV vector, *Ae. albopictus*. Both viral strains were provided

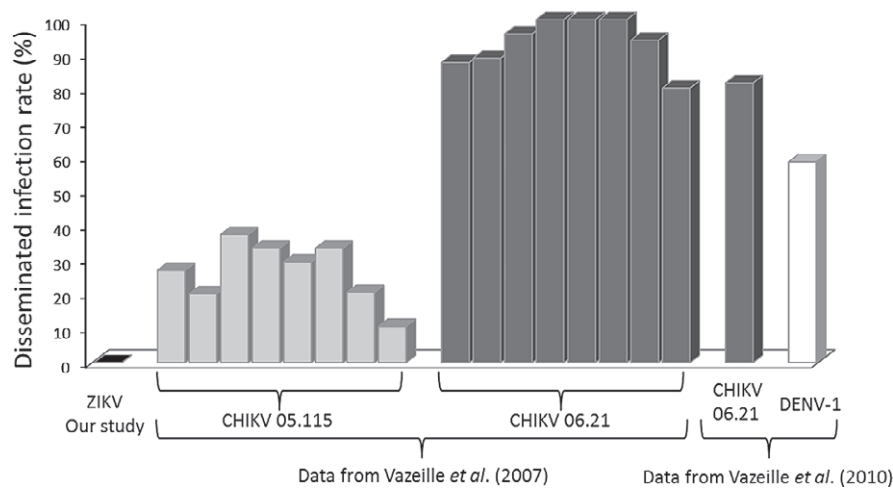


Fig. 2. Disseminated infection rates for Zika virus (ZIKV), chikungunya virus (CHIKV) and dengue virus (DENV) in *Aedes albopictus* from La Réunion at day 14 post-infection, expressed as a percentage (%). ZIKV NC-2014-5132, isolated in 2014 in New Caledonia, was provided at a titre of 10^7 TCID₅₀/mL (50% Tissue Culture Infective Dose/mL) (this study). CHIKV 05.115, isolated in 2005 in La Réunion, and CHIKV 06.21, the epidemic strain also isolated in 2005 in La Réunion, were provided at a titre of 10^7 plaque-forming units (PFU)/mL (from Vazeille *et al.*, 2007). CHIKV 06.21 was also provided in a co-infected meal with DENV-1185/04 isolated in 2004 in La Réunion at respective titres of 10^6 FFU/mL (Focus Formit Unit/mL) for CHIKV and $10^{5.9}$ FFU/mL for DENV (from Vazeille *et al.*, 2010).

at a titre of 10^7 PFU/mL (Plaque Formit Unit/mL). In the second study (Vazeille *et al.*, 2010), one population (F6 females) was co-infected with CHIKV 06.21 and DENV-1 1185/04, isolated in May 2004 from the plasma of a patient on La Réunion Island; this strain belongs to the Brazilian group of the Pacific genotype. CHIKV 06.21 was provided at a titre of 10^6 FFU/mL (Focus Formit Unit/mL) and DENV-1 at $10^{5.9}$ FFU/mL. The first study demonstrated that even the original CHIKV strain 05.115 could disseminate in *Ae. albopictus*, but with a lower DIR (10.5–37.5%) than the mutated CHIKV 06.21 (80.5–100%). In the second study, DENV-1 was provided at a lower titre than ZIKV in our study and in the presence of CHIKV could disseminate in > 50% females. This DENV strain was isolated during the course of the 2004 outbreak causing 228 cases. Therefore, *Ae. albopictus* from La Réunion could, as expected, be considered an efficient vector for both CHIKV and DENV-1 under laboratory conditions.

In contrast, *Ae. albopictus* with the same geographical origin was not able to disseminate the Asian genotype of ZIKV, which has emerged in the Pacific Region in 2007 and spread to the Americas. This result suggests a strong midgut barrier to dissemination in this mosquito–virus system and could indicate an improbable autochthonous transmission of ZIKV on La Réunion Island. Indeed, the recent major outbreaks of ZIKV seem to have been sustained mainly by *Ae. aegypti* in locations where *Ae. albopictus* is also present. For example, in Brazil, ZIKV was isolated from naturally infected *Ae. aegypti* but not from *Ae. albopictus* (Ferreira-de-Brito *et al.*, 2016) and the latter has demonstrated a much lower receptivity to experimental infections. However, dissemination and even transmission could be observed in *Ae. albopictus* from Brazil and from Vero Beach (Florida, USA) at 7 dpi, the latter being at least two times more susceptible to ZIKV (Chouin-Carneiro *et al.*, 2016). Two populations of *Ae. albopictus* from the south of France

also show a reduced competence for this same ZIKV Asian genotype compared with *Ae. aegypti* from the island of Madeira, but they were nevertheless able to disseminate the virus to some extent (Jupille *et al.*, 2016). Variation in results obtained for *Ae. albopictus* of various geographical origins underlines differences depending on the specific pairing of vector and pathogen genotypes and is an example of genotype-by-genotype (G × G) interactions (Lambrechts & Scott, 2009). Our results demonstrate an absence of dissemination and transmission of the ZIKV Asian genotype in a population of *Ae. albopictus* collected on La Réunion Island in 2016; however, we should keep in mind several parameters. First, migration events or selection under insecticide pressure may modify the *Ae. albopictus* population genotype, leading to a new G × G interaction that could be more favourable for the outcome of infection. Secondly, the ZIKV African genotype seems to be more easily transmitted by *Ae. albopictus* than the Asian genotype (Wong *et al.*, 2013). Under this scenario, it would be advisable to test *Ae. albopictus* of La Réunion with the ZIKV African genotype. Finally, we know that *Ae. albopictus* from La Réunion selected the epidemic variant of CHIKV responsible of the 2004–2005 outbreak, demonstrating the ability of this mosquito to enhance viral transmission and emergence. Therefore, our assessment should be improved by using more *Ae. albopictus* populations from La Réunion and other genotypes of ZIKV for experimental infections. ZIKV, like most arboviruses, may evolve rapidly, so the utmost caution should be exercised before excluding any scenario of emergence, as for CHIKV in 2004–2005.

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The authors declare that there is no conflict of interest.

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