JMID/
Journal of Microbiology and Infectious Diseases

2022; 12 (1):19-26
doi: 10.5799/jmid.1085937

RESEARCH ARTICLE

# Arthritogenic *Arbovirus* in Madagascar: State and Epidemic Risk

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## ABSTRACT

**Objectives:** We aimed to determine the epidemiological risk of the arthrogenic Arbovirus in Madagascar, where the epidemiological situation seems to be unclear.

**Methods:** A systematic review of the literature based on the PRISMA method was performed for 15 months. We include each publication reporting the presence of arthrogenic Arbovirus in Madagascar. We found 107 publications witch 54 were included.

**Results:** Seven arthrogenic arbovirus (Chikungunya, Dengue, Rift Valley Fever, Bunyamwera, Sindbis, West Nile and Wesselbron) were found. Two types of vectors (mosquitos and tick) and two types of a host (mammalian and bird) complete the epidemiological chain of the virus. In addition, three arboviruses were identified within an epidemic situation: Chikungunya, Dengue, and Rift Valley Fever.

**Conclusion:** The epidemic risk of this virus seems high. The discrepancies between the theoretical result and the "reality" need further studies. *J Microbiol Infect Dis 2021; 11(4):19-26.*

***Keywords:*** *Arthrogenic arbovirus, Madagascar, Viral arthritis*

## INTRODUCTION

Arbovirus or "arthropod-borne virus" literally means a virus carried by an arthropod. According to the WHO, the Arbovirus is a virus disseminated in nature transmitted to the sensible vertebrate by an arthropod. The epidemiological chain of this kind of virus contains a vector (the arthropod), a host (vertebrate human or not), and the virus himself [1]. From a clinical view, all the Arbovirus have a common initial clinical manifestation type flue syndrome with fever and polyalgia. After this initial condition, specific manifestations like the osteoarticular manifestation came in. The arthrogenic Arbovirus is then a disease caused by Arbovirus with an articular tropism [7,8]. At the word scale, Arbovirus represents a global problem and a constant threat by the permanent risk of a pandemic [2,3]. The last decade has seen an increase in the number and geographical distribution of arbovirus outbreaks [4], especially for the Chikungunya who strike the Indian Ocean before reaching the other continent [5,6]. The situation in Madagascar seems to be unclear. There is evidence that many Arbovirus are present on the island, and numerous arthropods are evolving in a favorable environment. However, only a few outbreaks have been reported and the surveillance system related only a few cases per month. Therefore, we aimed to do a systematic review of the literature to identify all the arthrogenic Arbovirus present in Madagascar and the other element of the epidemiological chain to deduce the epidemiological risk.

## METHODS

We did a systematic review of the literature based on the Preferred Reported Items for Systematic review and Mata Analysis (PRISMA). There was no restriction about the date or the language of publication. PubMed,

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Received: 01 September 2021 Accepted: 19 December 2021

Google Scholar, Medline, Embase, Cochrane review, and the Pastor Institute of Madagascar archives were the data sources. Keywords were: "Madagascar and Arthrogenic arbovirus" and "the Indian Ocean and Arthrogenic arbovirus."

All the obtains publications passed then by several criteria were defined as eligible for all publications that mention "Madagascar and/or Arbovirus" in his title or his abstract was defined as including all the eligible publications read integrally and who report the presence of one or more arthrogenic Arbovirus in Madagascar. From the eligible publication, we studied the identified Arbovirus, the viral cycle, the clinical and biological manifestation of the corresponding Arbovirus.

**RESULTS**

***Selection of the publication***

We found 107 publications, among which 54 were included (figure 1). The oldest publication was edited in 1947, and the most recent one was in 2018. We found:

- o 39 journal article
- o 3 thesis
- o One WHO communicate
- o 10 activity report
- o One citation
- • Identified virus

Three families of arthrogenic Arbovirus devised in 4 genera and 7 species were found (Table 1).

***Arbovirus identification circumstance***

The principal circumstance of identification was seroprevalence and survey studies (Table 2)

***Arbovirus identifications methods***

The association serology/virology was the principal identification method (33 within the 57 publications retained). The serologic study was used for 32 publications (immunofixation and hemagglutination), and 14 publications report the identification via the direct virological method (viral culture and PCR).

***Hosts and vectors***

Two types of arthropods were found mosquitoes and ticks. In addition, many genera of mosquitoes were identified, like Anopheles, Aedes, Mansonia, Culex, and Eretmapotides (table3).

Concerning the hosts, primates (human and Lemurian) were the identification species of 6 of 7 arboviruses (excepted BUN, who was identified in a tick). The zebu was the principal host of RVF and bird for WN (table 4)

***Arbovirus identification areas***

All the arthrogenic Arbovirus was isolated in the East part of the island, an area with hot and rainy weather all along the year. However, all the other part was concerned, from the hot and desert south part, the Savana of the middle west to the cold temperature of the highland (Figures 2 to 8).

***Clinical manifestations***

None of the publications found was reporting the incubation periods of the arthrogenic Arbovirus. The clinical signs of Chikungunya and Dengue were mostly reported, and only these two infections present arthralgia within the principal signs reported (two publications each other). Dermatological and ophthalmologic manifestations were also reported. For the RVF, Dengue-like syndrome, hemorrhagic manifestations, and encephalitis were reported.

None of the retained publications report information about the exploration of the articular system. Only three cases of fulminant hepatitis due to RVF report paraclinical information. Each patient has anemia associated with thrombopenia. All present biological signs of cytolysis and severe hepatic failure. The histological study post mortem showed hepatic necrosis in one patient.

One publication reported the case of encephalitis due to WN. The cerebrospinal fluid examination showed a pleocytosis predominantly lymphocytic, hyperproteinorachie up to 170 mg/dl with a normal glycorrachie.

The evolution of the disease was reported in only three publications; all the encephalitis due to WN led to the death of all cases. The evolution of RVF infection was also reported for 21 infections cases; five died, one remained whit neurologic sequela, and 15 recovered.

**DISCUSSION**

The epidemiological risk of the Arbovirus in Madagascar seems to be very high, at least theoretically. All the conditions (climatic, ecologic, socio-economic) are present for the resurgence of the periodical outbreak in Madagascar, but this circumstance is not what the literature report. We confirm the circulation of seven arthrogenic arboviruses in Madagascar, three host types, and two arthropods. However, only a few outbreaks were reported, and a few cases of arbovirus infections are mentioned by the national surveillance system (at least 1%). There is a discrepancy between what the literature reports about the epidemiological risk and the risk in the real world.

Table 1. The Virus distribution.

| Family | Genra | Virus | No. publications |
|---|---|---|---|
| Togaviridae | *Alphavirus* | Chikungunya<br>Sindbis | 27<br>9 |
| Flaviviridae | *Flavivirus* | Dengue<br>West Nile<br>Wesselbron | 19<br>16<br>8 |
| Bunyaviridae | *Bunyavirus* | Bunyamwera | 2 |
| | *Phlebovirus* | Rift Valley Fever | 27 |

The weakness of the health system could explain the limited case of diagnosing patients. The paucisymptomatic presentation of the disease or its manifestation as a flu-like syndrome leads the diagnostic difficulty outside an outbreak context. The diagnostic needs serologic or virologic confirmation. The sentinel sites of the epidemiologic veil were operational only in 2007, which explains the few publications before this time. Also, the virologic laboratory of the Pastor Institute of Madagascar is localized in the capital. Identifying the case and the rooting of the sample from far-off regions could restrain virological studies. Rapid Test of Diagnostic (RTD) for Dengue and Chikungunya have good sensibility and sensitivity, but there are not available or used in everyday practice [10].

To the late identification and report of the case, the clear definition of the case causes another bias, especially for Dengue and Chikungunya. The systematic exclusion of patients with RTD positive to malaria is a source of bias. The co-infection between Arbovirus and malaria is frequently reported (47,8%). Their symptoms are typically the same (fever, headache, polyarthralgia, stiffness) [11].

The feeble rate of frequentation of health centers could also hide an outbreak's presence. For the example of Chikungunya, this Arbovirus is symptomatic in more than 90% of the infected patients, with articular manifestation in 70% to 90% [12-13]. Therefore, diagnosing seems to be accessible during an outbreak phase. In 2006, 250.000 persons (25% of the population) were infected by Chikungunya in Réunion island [14]. All the islands of the Indian Ocean were involved in this outbreak between 2005-2006 and in 2010. In 2006, 55 patient serum samples with a Dengue-like syndrome during the outbreak in the town of Toamasina were analyzed (virologic and serologic): 38 (69%) were positive for Chikungunya or Dengue, and 10 (18%) had a co-infection by the two viruses. Retrospective studies among 4242 people living in the city find out that 67,5% of them have clinical criteria of Dengue-like syndrome during the outbreak period. This data confirms that Dengue and Chikungunya are present in Madagascar, and clinical presentation stack to the serological state of the population. However, according to the monthly activities report, this outbreak did not have any impact on the frequentation rate of the health center of the osteoarticular problem [15]. Therefore, the outbreak was present but did not have any statistical incidence.

On the other hand, host sensibility and clinical expressivity can significantly change from one ethnicity to another [16]. The spatiotemporal interaction, host susceptibility toward a virus, and their capacity to infect the host are crucial elements for the infection and the outbreak [17]. This situation could explain the feeble intensities of symptoms in Malagasy people falsifying or explaining the statistical data reported by the health center. In children less than 15 years old, Longchamp and al. Found a seroprevalence of West Nile infection up to 2,1% at Ambositra and 10,6% at Mahajanga between 1996 and 1999 [18]. The Arbovirus is an immunizing disease. The early contact could lead to antibodies protecting against severe and symptomatic form in the adult age [17].

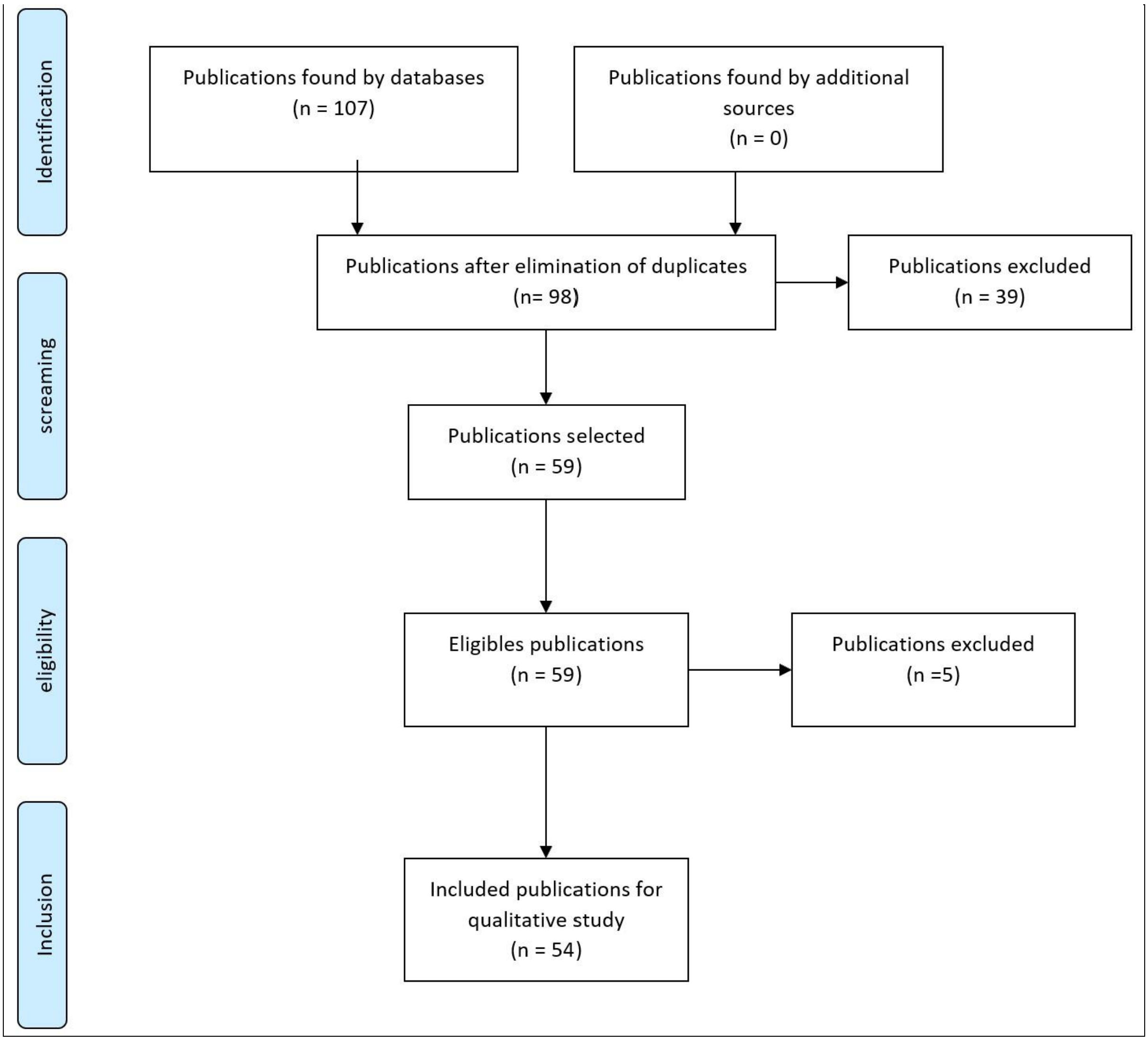


Figure 1. The process of article search.

Table 2: Types of studies allowing the identification of arthritogenic arboviruses in Madagascar

| Virus | Seroprevalence | Outbreak | Survey | Clinical report | Other |
|---|---|---|---|---|---|
| CHIK | 6 | 8 | 9 | - | 2 |
| DEN | 2 | 4 | 6 | 1 | - |
| WN | 11 | - | 3 | 2 | 4 |
| FVR | 9 | 7 | 1 | 2 | 2 |
| WSL | 4 | - | 2 | - | - |
| BUN | 1 | - | - | - | - |
| SIND | 7 | - | - | - | - |

CHIK= Chikungunya, DEN= Dengue, WN= West Nile, RVF= Rift Walley Fever, WSL= Wesselbron, BUN= Bunyamwera, SIND= Sindbis

Table 3. Table showing the number of publications and the vectors listed according to the viruses identified in Madagascar.

| *Viruses* | CHIK | DEN | WN | WSL | BUN | FVR | SIND |
|---|---|---|---|---|---|---|---|
| *Aedes albopictus* | 2 | 1 | - | - | - | - | - |
| *Aedes aegypti* | 3 | 2 | 1 | - | - | 1 | 2 |
| *Aedes neomelaniconion* | - | - | 1 | 2 | - | - | - |
| *Aedes albocephalus* | - | - | 1 | - | - | - | - |
| *Aedes circumlemtum* | - | - | - | 1 | - | | - |
| *Culex. unnivatus* | - | - | 1 | - | - | 1 | 2 |
| *Culex antenatus* | - | - | 2 | - | - | 1 | - |
| *Culex. descens* | - | - | 1 | - | - | 1 | 1 |
| *Culex.quinquevittatus* | - | - | 1 | - | - | 1 | - |
| *Culex tritaenionhynchus* | - | - | 1 | - | - | 2 | - |
| *Anopheles. Funestus* | - | - | - | - | - | 1 | - |
| *Anopheles. Maculapis* | - | - | 1 | - | - | - | - |
| *Anopheles. Paulani* | - | - | - | - | - | 1 | - |
| *Anopheles. Squamous* | - | - | - | - | - | 1 | - |
| *Anopheles. Mascarensis* | - | - | 1 | - | - | - | - |
| *Anopheles. coustani* | 1 | 1 | 1 | - | - | 1 | 1 |
| *Anopheles brunipes* | - | - | 1 | - | - | - | - |
| *Eretemapotides.quinquevittatis* | - | - | - | - | - | 1 | - |
| *Mansonia .uniformus* | 1 | 1 | - | - | - | 4 | 2 |
| *Boophilus .microplus* | - | - | - | - | 2 | - | - |

*CHIK= Chikungunya, DEN= Dengue, WN= West Nile, RVF= Rift Walley Fever, WSL= Wesselbron, BUN= Bunyamwera, SIND= Sindbis*

Table 4. Host and virus found

| Virus | Human n=50 | Lemurians n=12 | Castle n=14 | Rats n=2 | Bats n=3 | Bird n=7 |
|---|---|---|---|---|---|---|
| CHIK n=20 | 18 | 1 | 0 | 0 | 1 | 0 |
| DEN n=13 | 11 | 2 | 0 | 0 | 0 | 0 |
| WSL n=4 | 2 | 1 | 0 | 0 | 1 | 0 |
| FVR n=24 | 9 | 1 | 13 | 1 | 0 | 0 |
| WN n=17 | 6 | 4 | 0 | 1 | 0 | 6 |
| BUN n=0 | 0 | 0 | 0 | 0 | 0 | 0 |
| SIND n=10 | 4 | 3 | 1 | 0 | 1 | 1 |

CHIK= Chikungunya, DEN= Dengue, WN= West Nile, RVF= Rift Walley Fever, WSL= Wesselbron, BUN= Bunyamwera, SIND= Sindbis

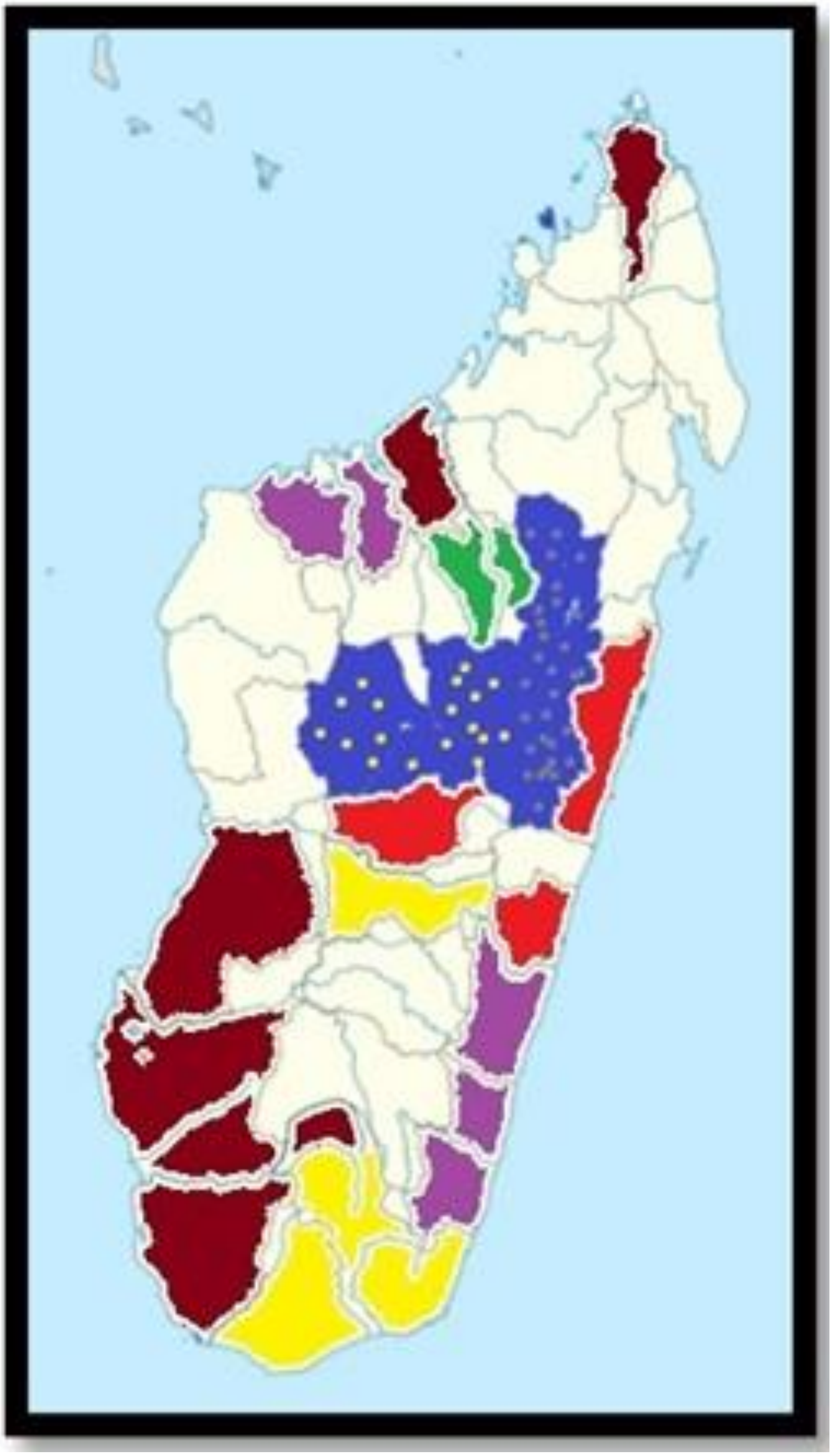

Figure 2. Identification zone of the arbovirus in Madagascar.

Blue= Sindbis, Red= Chikungunya, Brown and Brown Dots= Dengue, Yellow and Yellow Dots= Rift Valley Fever, Violet= West Nile, Green= Bunyamwera, Grey Dots= Wesselbron

Through different period, all part of the island was an identification zone for the Arbovirus, but three arboviruses were epidemic: Chikungunya, Dengue, and Rift Valley Fever. This outbreak capacity is explained by the virus's phylogenetic parameters and the host's immune parameters. The phylogenetic studies about the RVF showed that the outbreak reported in Madagascar was all due to a different phylogenetic virus different from the Malagasy type. They were imported viruses [19,20]. The population's immune system would be naïf of the virus and lead to the development of an outbreak in very localized regions.

The virus mutation can occur in the emergency of an outbreak. For example, the A226V mutation of the Chikungunya virus causes a better adaptation of the virus to a new vector (Aedes albopictus) who was more aggressive than Aedes aegypti, the traditional vector of the virus in the Indian Ocean area [21]. The permanent interaction and a subtle modification of one of the elements of the cycle can drastically improve the epidemical risk [22].

The threat of transmission between two different host species is also real. This is the case for the RVF, an anthropozoonosis whose principal hosts are zebu. The outbreak of this virus started in the area where zebu is the primary resource, especially in the south part of the country [23-25]. The clinical case was reported, and all the patients were in close contact with zebu. In Madagascar, the promiscuity between humans and cattle makes the transmission easy. Many studies conclude that one part of the transmission occurs in the trades road of cattle [26, 27]. However, the serological survey of the cattle is rare, and there is no protection measure for the risky job [28].

At least, the lack of commitment of the population in the fight against the Arbovirus and its vector and the lack of national politics is a parameter that cannot be neglected. In addition, poverty and a weak education level are also linked to increasing the epidemiological risk of the [29,30].

This study is the first, as we know to search all the Arbovirus and all his epidemiological chain in Madagascar through a literature review. Elsewhere there is some limitation. Like all literature reviews, publication bias remains one of the significant limitations. After that, we assume that the main limitation of this study is his inability to make a clear explanation between the theoretical epidemiological risk and the real-life risk due to the absence of a clear serological status of the population. This should lead to another study to search for the real seroprevalence of the population.

## Conclusion

Seven arthrogenic arboviruses are present in Madagascar, and six were identified in humans. Three lead to an epidemic situation. Many competent vectors are present, especially mosquitoes. Those vectors share life space with humans, Lemurian, and zebu. The epidemic risk seems high, all the elements of the epidemic cycle are omnipresent, and the socio-economic and ecological factors are extraordinarily favorable to the dissemination of the vectors and the disease. The weakness of the sanitary system can hide the reality of the epidemic situation. However, the week number of outbreak.

## ACKNOWLEDGMENTS

**Declaration of conflicting interest:** The author(s) declare no potential conflicts of interest concerning this article's research, authorship, and/or publication.

**Financial disclosure:** No financial support was received for this study

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