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Japanese encephalitis in Bali, Indonesia: ecological and socio-cultural perspectives

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ABSTRACT

The increasing number of cases of acute encephalitis syndrome, a key presenting clinical sign of Japanese encephalitis infection in humans, along with increasing laboratory confirmed cases in Bali over recent years have led to the Indonesian government developing a national program of vaccination against Japanese encephalitis virus. In order to inform multidisciplinary management, a review was conducted to assess Japanese encephalitis virus-related cases in humans and animals including their determinants and detection in vectors. Along with published literature, key data from local authorized officers in Bali have been used to convey the recent situation of the disease. Related surveys detected up to 92% of the local children had antibodies against the virus with the annual incidence estimated to be 7.1 per 100,000 children. Additionally, reports on young and adult cases of infection within international travellers infected in Bali were documented with both non-fatal and fatal outcomes. Further seroprevalence surveys detected up to 90% with antibodies to the virus in animal reservoirs. The detection of the virus in certain *Culex* mosquito species and high levels of seropositivity may be associated with greater risk of the virus transmission to the human population. It was also highlighted that local sociocultural practices for agriculture and livestock were potentially associated with the high density of the vector and the reservoirs, which then may lead to the risk of the disease transmission in the ecology of Bali.

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Bali; Japanese encephalitis; potential ecological determinants; socio-cultural practices

1. Introduction

Japanese encephalitis (JE) is a potentially fatal, zoonotic viral disease caused by JE virus (JEV) [1]. The virus is grouped within the family *Flaviviridae*, along with other arthropod-borne flaviviruses, including Dengue virus, West Nile virus (WNV), Tick-borne encephalitis virus (TBEV), St. Louis encephalitis virus and yellow fever virus (YFV) [2]. JEV is an enveloped, icosahedral virus, with a diameter of approximately 50 nm, and consists of a single-stranded positive-sense ribonucleic acid genome [3], of approximately 11 kb in length [4]. The open reading frame in the genome encodes a single polyprotein, which is intracellularly cleaved into ten viral proteins, including three structural (envelope/E, pre-membrane/PrM, and core/C) and seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) [5,6].

JEV exists as a single serotype within which are five genotypes, GI–GV [7–9]. The genotypes of JEV have been characterized based on the nucleotide sequence of the viral envelope (E) protein [10]. The E protein is a major structural protein that contains the receptor-binding domain and the neutralization epitopes.

Additionally, Wei et al. [11] also argued that the amino acid variation in the E protein of the JEV may affect virulence and antigenicity.

The transmission of JEV into animals and humans is through mosquito bites. Several genera of mosquitoes can transmit the virus, however, *Culex* spp. are dominant [12,13], primarily *Cx. tritaeniorhynchus* [14,15]. This mosquito vector tends to breed and lay their eggs in irrigated rice paddy fields, associating this farming practice with the increased mosquito populations and subsequent increased risk of JE infection in humans [16].

JEV infection in humans is also associated with the infection in animals, especially pigs and wading birds. Both of the animals have an important role in the ecology of JEV [17]. *Ardeidae* birds, including egrets and herons, are the reservoir hosts of JEV [18,19]. Meanwhile, pigs act as amplifying hosts that producing large amounts of infectious virus during the viraemia phase, resulting in uptake of virus by feeding mosquitoes [20,21]. Most infected mammals and birds are asymptomatic or develop mild clinical signs such

as resolving fever and inappetence, but in infected pregnant sows, the infection may result in abortion, stillbirth and congenital deformity [21,22].

Aside from *Ardeidae* birds and pigs, evidence of JEV infection has been reported in horses, dogs, cats, cattle, snakes, frogs, sheep, goats, monkeys, racoons, fresh water turtles and other birds including chickens and ducks [21,23,24]. The majority of these are dead end hosts, although ducks and chickens are suspected to have a role in disease transmission as they appear to develop viraemia to a sufficient titre to infect feeding mosquitoes [25–27].

Although the incidence of Japanese encephalitis disease has decreased globally due to implementation of vaccination programs, the disease is still a public health threat partly as a result of vector expansion due to climate change [8]. The virus is estimated to infect almost 68,000 humans each year [28] with approximately 75% of cases occurring in children and resulting in development of acute encephalitis syndrome (AES) [29]. The case fatality rate for the disease may reach 30%, and among those patients who survive 30–50% may develop long-term neurological sequelae [30]. In addition, the distribution of the vector and virus indicates around three billion people in the world are at risk of the infection [31], spanning countries in Oceania and Asia, including Indonesia [32].

Indonesia is recognized as a part of Indo-Malayan region where JEV is considered to have originated. The first JE infection was reported in the 1970s and the virus was successfully isolated. JE-related cases have been detected in 29 out of 34 provinces, including the province of Bali [13].

In Bali, clinical and confirmed cases of JEV infection in humans were reported in 2014 increasing until early 2018 when the national vaccination program against JEV in humans was firstly implemented in Bali in March 2018 [33]. However, vaccination in humans cannot eliminate the virus in the environment, as JE is a zoonotic disease with multifactorial elements involved in transmission, such as human agricultural activities, animal reservoirs and the mosquito vector interact in a socio-cultural-environmental ecology. This review was conducted to assess JE-related cases in humans, animals and their determinants, and detection in vectors, including socio-cultural practices of the Balinese, which may associate with the potential risk of Japanese encephalitis infection in the area.

2. Methods

Published articles on JEV that reported predominantly in Indonesia and more specifically in Bali were reviewed. Online search engines, such as PubMed, Google Scholar, Portal Garuda and Indonesian Publication Index, were the databases that used to

find the related articles. Keywords used were “Japanese encephalitis”, “Flavivirus”, “Indonesia”, “Bali”, “epidemiology”, “distribution”, “risk factors”, “humans”, “vector”, “animals”, “ecology” and “social-culture”. Hardcopies of related documents, including seminar presentations and unpublished online data documents from the Health department of Bali Province, the Agriculture Department of Bali Province, and Disease Investigation Centre (*Balai Besar Veteriner*) Denpasar, were also collected, evaluated and summarized to be used in this review based on preferred reporting items for the systematic reviews and meta-analyses (PRISMA) guidelines conducted in October 2020 to February 2021. The short-listed articles or documents were filtered and compiled based on the inclusion criteria focusing on the detection cases of Japanese encephalitis in humans, mosquito vector and animals in Bali including the articles on Balinese socio-cultural practices. When the articles did not meet the criteria, they were excluded (Figure 1).

3. Results and discussion

Bali is an island province which is located between Java and Lombok islands in the Indonesian archipelago. The island is approximately 5,632 km², inhabited mostly by Balinese who are mainly Hindu. Bali is also recognized as an ecotourism destination due to its agricultural landscape and socio-cultural environment. The local traditions and geographical environment have attracted not only national domestic tourists, but also international travellers to visit the island.

3.1. JEV genotypes detected in Indonesia and Bali

Studies on detecting JEV genotypes in Indonesia have been conducted and found four of the five genotypes in the country. A total of 37 isolates gathered between 1974 and 1987 in mosquito and pig samples collected from Indonesian archipelago, the GII, GIII, and GIV were identified [34]. A more recent study found that GI was isolated from *Cx. gelidus* in the province of Jambi, Indonesia [9].

Genotyping studies on JEV in Bali are very limited. To date, GIV is the only genotype found in Bali. In 1980, GIV was isolated from *Cx. tritaeniorhynchus* [34]. Similarly, in 2017, GIV virus was isolated from pig serum samples [35].

3.2. Cases and determinants related to Japanese encephalitis in Bali

A number of the JE-related studies in Bali have been established. A cross-sectional study conducted by Kari et al. [36] described that 34% of 158

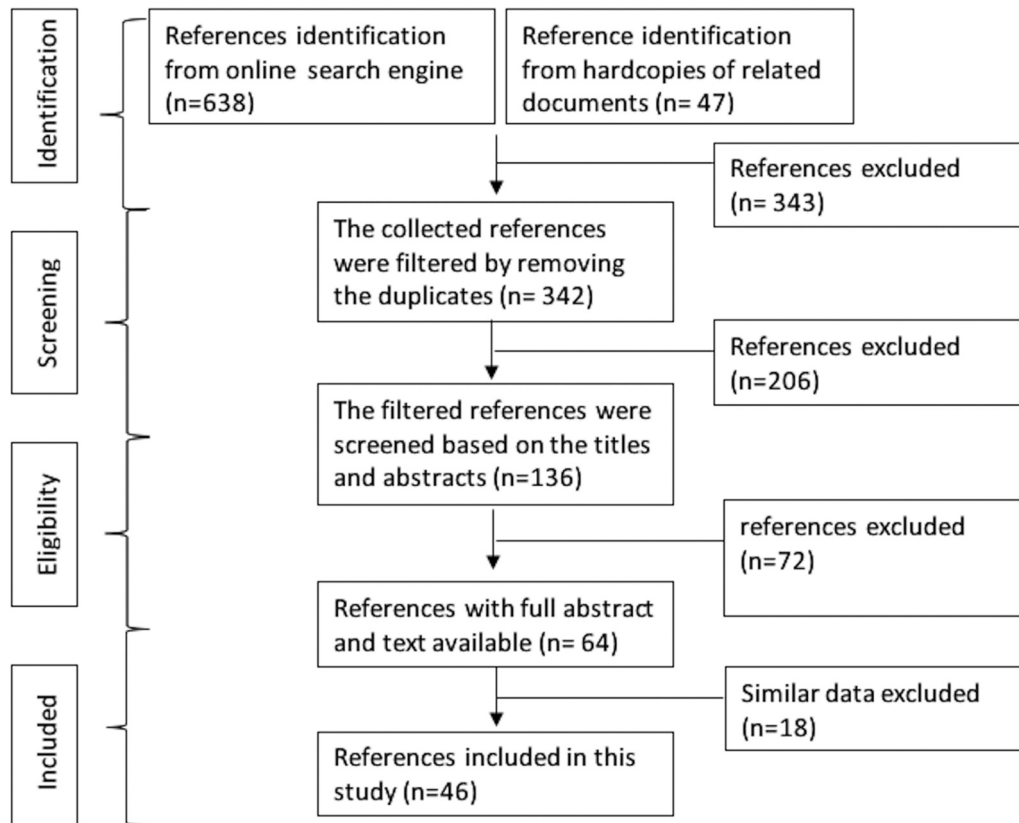


Figure 1. A flowchart of the selection process of related study references used in this review by using preferred reporting items for systematic reviews and meta-analysis (PRISMA).

patients with AES from July 2001 to January 2003 confirmed the evidence of infection by detection of anti-JEV IgM in the patients' cerebrospinal fluid (CSF). The study also assessed risk factors of the infection in which owning pigs and rice farming were significantly associated with the presence of JE [36]. Similarly, a case-control study demonstrated that people with houses located next to rice paddy fields and living in close proximity to pigs were more than four times more likely to be JEV infected [37]. Another study also identified the same associated factors, although some protective factors included window screens, mosquito bed nets and mosquito repellent were also assessed [38].

3.2.1. Japanese encephalitis-related studies in humans in Bali

In 1970s, a JEV serological survey was conducted to detect the antibodies in some areas of Indonesia, such as Pontianak in which antibody prevalence was 26% (25/94), Samarinda 27% (31/121), Balikpapan 22% (37/172), Surabaya (Java island) 2% (1/50), Lombok 16% (18/115), Kupang 2% (2/98), Ujung Pandang 2% (3/174), Jayapura (West Papua) 3% (4/170), Ambon 5% (6/125) and Bali at 52% (48/94) [39,40]. The same antibody proportion was also demonstrated in a survey performed from October 1990 to July 1995 [41].

A two-series survey in humans in Bali was conducted in 1996–1997 and the antibodies were detected [42]. Next survey conducted in 2001 to 2003 also detected the antibodies with annual incidence rate was higher compared to the global incidence rate [43] with 7.1 per 100,000 children, making the virus in Bali hyperendemic [44]. Ninety-two percent of the antibodies was found in children under 15 years old [45], which were distributed in all of the districts and a city areas based on the data gathered from all of the district level and central hospitals in Bali [36].

3.2.2. Japanese encephalitis infected international travellers in Bali

JEV infection not only affects locals but impacts on Bali's key tourism market through the effects on international travellers. Cases that have been acquired by travellers to Bali include fatal and non-fatal encephalitis [13,46]. A ten-year-old girl from Australia had been diagnostically confirmed infected by JEV after returning from a two-week holiday in Bali [47]. Similarly, a 60-year-old Swedish woman [48] and an 80-year-old man were suspected to be infected with the JEV after they had a 2-week holiday on the island [49]. A similar case occurred in a 54-year-old Germany woman [50] and a 45-year-old Australian man after having a holiday in Bali [51] and their serological diagnostics detected the antibodies against JEV. However, fatal

cases of JE infection were reported occurred in a Danish man who had a 12-day holiday [52] and an 59-year-old Australian male who stayed for three months in Bali [53] after their diagnostic tests confirmed that they were infected with the JEV (Table 1).

The reports on JEV-infected travellers in Bali may reveal the intensity of the viral transmission in the area. These traveller cases may also indicate that the virus could not only infect susceptible children but also adults who could reveal related clinical symptoms. To anticipate, the travellers have to prepare themselves having vaccinated against JEV before visiting the JE endemic area. In addition, related travel information has been widely provided online for the travellers to get the vaccine. However, some other international visitors, especially who came from non-JE endemic countries, tended to be vaccinated against JEV in Bali due to its lower price compared to the vaccine price in their own countries [54].

3.2.3. Balinese social-cultural practices in relation to the potential risk of JEV circulation

An important factor that is likely associated with JEV-related cases in Bali is a high density pig population due to its socio-cultural practices. Although local economy and consumption may play less in the demand of local agricultural and livestock sectors, these factors, along with the socio-culture, are likely synergized in forming the risk. The Hindu community in Bali generally uses pigs for local investment, pork for meals and ceremonial requirements. A traditional ceremony called “*Tumpek Kandang*”, periodically held twice a year, is a local tradition offered by Balinese in regard to respect the ecological environment especially animals that live closely with humans [55]. Additionally, most of other traditional ceremonies in Bali in some cases required pigs per ceremony, making pig farming a key occupation [56]. It is estimated that the ratio of humans to pigs in Bali is 4:1 [33,44].

In addition, chickens and ducks are other animals that the Balinese also tend to rear as they are also required for the local ceremonial traditions, such as “*Caru*”, a procession of sacrificing animals in a ceremony in which chickens and ducks are commonly used [57]. Pork, ducks and chickens are not only offered in local Balinese ceremonies, they are also an important part of traditional local food consumption and a key protein source. A social community tradition, called “*Ngelawar*” is an activity implemented mostly by Balinese men to create a local specific type of food “*Lawar*”. It is a traditional food which requires minced meat of pork, ducks, or chickens to be mixed with some

vegetables, coconut, herbs and spices ingredients. This traditional food is offered and consumed to the local community in a special ceremonial event [56].

In regards to the local cultural practices, many local Balinese are raising pigs, chickens or ducks, along with managing their agricultural paddy fields. Some of them rear their ducks in their rice paddy at day time, while at dusk and night the ducks are kept next to their pigpens (Figure 2). In relation to the JEV transmission, these scale and intensity of agricultural and livestock production appear to be the drivers that contribute to the risk of JEV-intensive circulation. Consequently, the close proximity of the pig, chicken and or duck farming, rice paddy fields and the mosquitoes to the community is a key mix of risks for JEV to be amplified and transmitted to susceptible hosts, including humans.

It is really challenging to directly alter the local cultural practices in regards to minimize the risk of JEV exposure and infection. However, related local authorized staff should regularly conduct knowledge, attitude, and practice training program on JEV transmission control and prevention to the community, especially the local farmers. After the training, the community should realize the impacts of the disease on public health and livestock before practicing the JE prevention and control program in their lives. Then, the related knowledge, attitude and practice will gradually change the community’s habit before it becomes culturally accepted.

3.2.4. JEV infection detected in animals in Bali

Surveys on JEV in animals in Bali are sporadic. The first survey was conducted in cattle in 1979 where 70% of 60 samples contained JEV antibodies [58]. Additionally, in 1993–1994, JEV antibodies were detected in 76.4% (107/140) of the pig samples, 95% (19/20) of horses, 43.6% (17/39) of cattle, and 23.8% (5/21) of goats [59]. From May to November 2003, a sentinel seroconversion survey was conducted using ten 2-month-old pigs and 8-month-old cattle in Denpasar, Bali. After eight months of observation, the antibodies were detected in 90% of the pig samples, while only 30% of the cattle seroconverted [60].

In addition, Widarso et al. [39] reported that in 1993–1994, antibodies against JEV were detected in 41.8% of 280 serums of pigs, cattle, goats and birds. The study was continued in 1996–1997, but only pig serum samples were assessed, with a seroprevalence of 46.7% (7/15) contained the antibodies [39]. However, in 2006, a serological survey performed in potential

Table 1. JE-related cases in humans in Bali.

Year study	Findings	Test used	References
	Cases in locals		
1972	52% of human samples in Bali detected to have the antibodies against JEV.	HI	[40]
1990–1995	Antibodies against JEV detected in 40 out of 77 (51.9%) human samples with acute viral encephalitis collected from Sanglah central hospital, Bali.	ELISA	[41]
1993–1997	Most of human samples collected in Bali (up to 90%) had the antibodies against JEV.	HI	[13,39]
1996–1997	Antibodies against JEV were detected in two series surveys of patients with viral encephalitis.	ELISA	[42]
2001–2003	As many as 86 patients confirmed and 4 probable cases of JE identified with incidence rate at 7.1 per 100,000 children under 12 years old.	ELISA	[44]
2001–2003	A cross sectional study found 34% (55/158) of viral encephalitis patients were confirmed with JE infection. The patient samples were gathered from eight district hospitals, Army hospital Denpasar, and Sanglah central general hospital in Bali.	ELISA	[36]
2001–2004	A case control study used 94 confirmed JE cases and 163 aseptic meningitis non JE patients as control conducted to identify the determinants of close proximity to paddy fields and pig ownership.	ELISA	[38]
2005–2007	A total of 46 patients with JE confirmed and non JE encephalitis used to determine the association the risk of infection with paddy fields and the presence of pigs close to the patients houses.	ELISA	[37]
2015	17.7% of 282 Acute encephalitis and complex febrile leisure patients in Bali were confirmed infected by JEV in which 92% of them were children under 15 years old.	ELISA	[45]
	Cases in international travellers in Bali		
1988	A ten-year-old girl from Australia had the JE infection on her 2-week holiday.	HI	[47]
1994	A Swedish woman traveller on 10 days holiday.	PRNT	[48]
1995	A Danish traveller aged 51 years old.	ELISA	[52]
2000	An 80-year-old Swedish man on 3 week holiday in Java and Bali.	IFA	[49]
2011	A 54-year-old German woman had spent a 2-week holiday.	IFA	[50]
2019	A 45-year-old Australian male spent 10 days in Bali in wet season.	Serological test	[51]
2019	A 59-year-old Australian male stayed for 3 months in Bali.	FL-MIA, ELISA, RT-PCR	[53]

HI: haemagglutination inhibition, ELISA: enzyme-linked immunosorbent assay, PRNT: plaque reduction neutralization test, IFA: immunofluorescence assay, FL-MIA: Flavivirus microsphere immunoassay, RT-PCR: reverse transcriptase polymerase chain reaction.



Figure 2. Small holder animal rearing practice in Bali. An example of keeping ducks next to the pigs (personal author's photo collection).

reservoirs of JEV, when the antibodies were identified lower at 32.2% (65/202) serum samples of pigs, including 20.7% (25/125) ducks and 36.7% (72/196) chickens [61].

Studies on detection of antibodies against JEV in animals in Bali were mainly focusing on the pigs as the potential reservoirs or amplifying hosts of the virus. Yamanaka et al. [62] detected the antibodies in 49% (60/123) of the pig samples collected from a subdistrict in Badung regency, Bali [62]. Moreover, a study demonstrated that all of the cattle serum samples collected in Denpasar city (54/54) contained the antibodies in comparison with Tabanan regency at 58.6% (17/29) and Buleleng regency at 47.8% (44/92). Whilst, in the pig serum samples tested, Tabanan had the highest antibody prevalence at 89.3% (25/28) compared to Denpasar at 66.13% (41/62) and Buleleng at 35% (21/60) [63]. More recently, Damayanti et al. [64] and Kuwata et al. [35] also conducted studies related to JE infection in pigs in Bali. The former performing the study in relation to determining the risk of JE infection in children [64], while the latter was to detect the genotype of the JEV circulated in Bali [35] (Table 2).

The consistency of high seropositivity results reported from the animal sero-surveys, especially in pigs is important to be concerned as the animals could be the main sources of the virus circulating in the area. Through the mosquito vector, the JEV in the infected animals may be fed on by the vector and spread the virus to other susceptible hosts, including humans. In consequence, the high proportion of the antibodies detected in the animals may associate with the high number of JE cases in humans [65,66]. Further studies with proper sampling strategy and larger sample size

are needed to evaluate more current prevalence in the pig population of Bali, including its economic impact to estimate the disease burden.

3.2.5. JEV mosquito vector identification in Bali

In Bali, surveys on mosquitoes are somewhat limited, even in relation to their activity as vectors. Based on the related studies that have been performed, *Culex* spp. is the most dominant species found in Bali. In 1975, a survey was conducted to collect mosquitoes in the Indo-Australia archipelago for detecting potential mosquito vectors of arboviruses. Bali was a part of the survey area where *Anopheles barbirostris*, *Aedes vexans*, *Ae. albopictus*, *Cx. tritaeniorhynchus*, *Cx. gelidus*, *Cx. pipiens* and *Cx. pseudovishnui* were collected [40]. Furthermore, a 13-month study conducted to collect mosquitoes for assessing arthropod borne viruses in the south of Bali found 20 species of mosquitoes and several of them were potential JEV vectors, including *Cx. fuscocephala*, *Cx. gelidus*, *Cx. tritaeniorhynchus* [67]. *Cx. vishnui* [60] and *Cx. quinquefasciatus* [68] have also been identified on the island (Table 3).

Those findings proved that the *Culex* spp. mosquito, the main and primary vector of JEV can be found in Bali. In more specific, *Cx. tritaeniorhynchus*, *Cx. fuscocephala*, *Cx. gelidus*, *Cx. pseudovishnui* and *Cx. quinquefasciatus* that captured and identified in the area are the well-known mosquito species to be JEV vector [69]. However, the other species from different genera of mosquito found, such as *Anopheles* spp. and *Aedes* spp., were also reported to have a potential role in transmitting the JEV [70].

Table 2. Studies on antibodies against JEV detection in animals in Bali.

Animal surveyed	Year of study	Findings	Test used	References
Cattle	1979	Antibodies against JEV detected in 70% of the samples.	HI	[58]
Pigs, cattle, goats, and avian	1993–1994	A total of 41.8% (117/280) serum samples were detected to contain the antibodies.	HI	[39]
Pigs, horses, cattle, goats.	1995	The antibodies against JEV were detected in 76.42% of pig serums, 95% horses, 43.6% cattle, and 23.8% goat serums.	HI	[59]
pigs	1996–1997	Antibodies against JEV were observed in 46.7% (7 out of 15) of pig serum samples.	HI	[39]
Cattle and pigs	2003	A sentinel study performed to detect seroconversion antibodies in each 10 of 8 months cattle and 2 months pigs. The antibodies against JEV were started to be detected in the week 3 of the study period in both animals.	ELISA	[60]
Pigs	2003	The antibodies were detected in 70% (280/400) of the collected pig serum samples.	HI	[37,44]
Cattle and pigs	2006–2007	Antibodies against JEV were detected in 77.14% (135/175) of the cattle serums and 58% (87/150) of pig serum samples collected in Denpasar city, Tabanan, and Buleleng regencies, Bali.	ELISA	[63]
Pigs, ducks, chickens	2006	The antibodies were detected in 32.2% (65/202) of pig, 20.7% (25/125) duck, and 36.7% (72/196) chicken serum samples.	ELISA	[61]
Pigs	2008	As many as 49% (60/123) of pig serum samples collected in Mengwi district, Badung regency, Bali were identified to contain the antibodies.	HI	[62]
Pigs	2015	A total of 60% (48/80) of pig serum samples were notified to have the antibodies (IgM & IgG) against JEV.	ELISA	[64]
Pigs	2017	Genotype IV of JEV was identified in 2 out of 5 isolates of 105 pig serums collected in Denpasar, Bali.	RT-PCR	[35]

HI: haemagglutination inhibition, ELISA: enzyme-linked immunosorbent assay, RT-PCR: reverse transcriptase-polymerase chain reaction.

Table 3. Reports on potential JEV mosquito vector in Bali.

Year studies	Findings	References
1975	Potential JE vectors in Bali were collected, such as: <i>Anopheles barbirostris</i> , <i>Aedes vexans</i> , <i>Ae. albopictus</i> , <i>Culex tritaeniorhynchus</i> , <i>Cx. gelidus</i> , <i>Cx. pipiens</i> , <i>Cx. pseudovishnui</i> .	[40]
1980	Genotype IV was isolated from <i>Cx. tritaeniorhynchus</i> .	[34]
1983	<i>Culex fuscocephala</i> , <i>Cx. gelidus</i> , and <i>Cx. tritaeniorhynchus</i> that been incriminated to be involved in the Japanese encephalitis infection.	[67]
2004	<i>Culex tritaeniorhynchus</i> was the dominant mosquito trapped in Denpasar, Bali.	[60]
2015 2016	Survey was conducted in Jembrana regency, Bali and the JEV was detected in <i>Cx. tritaeniorhynchus</i> , <i>Cx. vishnui</i> , <i>Cx. fuscocephala</i> . <i>Cx. tritaeniorhynchus</i> , <i>Cx. gelidus</i> , <i>Cx. fuscophala</i> could be found in Bali.	[13,37]
2018	<i>Cx. tritaeniorhynchus</i> was dominated mosquitoes trapped in the areas of Badung regency, Bali.	[68]

Culex spp. was dominated being collected in Bali as the potential mosquito vector of JEV.

Those female adults of *Culex* spp. found are categorized to be nocturnal, zoophilic and anthropophilic mosquitoes. Instead of being more active at night [71], the mosquitoes found can not only feed blood from animals but from human as well. *Cx. tritaeniorhynchus*, *Cx. vishnue* and *Cx. gelidus* prefer to feed on pigs, cow, birds, including chickens. However, in the absence of those animal hosts, the mosquitoes can also feed on humans [69].

However, some of the *Culex* spp. mosquitoes have difference in their preferred habitats. The *Cx. tritaeniorhynchus*, *Cx. vishnue* and *Cx. gelidus* tend to be found in rural area, where agricultural paddy fields and pig farms are mainly established [15]. Nevertheless, the *Cx. quinquefasciatus* is more known to be urban mosquito. The mosquito prefers to breed in dirty stagnant water or polluted water bodies, for example in sewers, drains and ditches of the metropolitan area [16,72].

3.3. Other mosquito-borne viral diseases detected in Bali

Indonesia is a tropical country where some flaviviruses are circulating; however, the most frequent of the cases is dengue. Dengue fever is also a disease caused by a flavivirus, which can be fatal in infected humans and circulates endemically in the country [73,74], where Java and Bali islands reported as high infection regions. In Denpasar city Bali, the human cases of dengue in 2014 to mid of 2016 reached 6,898 cases with 38 fatal [75].

Other mosquito-borne viral diseases have also been detected in Bali, such as chikungunya and Zika viruses although they do not appear to be endemic. A total of 46.7% (7/15) of patients who suspected of being infected with chikungunya virus was confirmed by laboratory test results [76], while in patients who were suspected of Zika virus infection, only 7% (2/29) of them were confirmed [77] with the additional case report occurred in an international traveller [78]. Other related studies also demonstrated those

infections detected in the area [74,79]. Meanwhile, West Nile, Murray Valley, St. Louis and yellow fever virus have never been reported.

Due to the endemic nature of dengue virus, cross reaction of antibodies with other flavivirus, like JEV does occur, affect the interpretation and validity of the diagnostic test results. To overcome this, testing is conducted against numerous antigens of the JEV serocomplex group to observe which has the highest titre in virus neutralization tests (VNTs) or plaque reduction neutralization tests (PRNTs). The tests are considered to be the gold standard of diagnostic techniques that can be used in the area where two or more flaviviruses circulate [80]. Alternatively, Western blotting or antigen protein microarray can also be used to identify the specific flavivirus antibodies [81].

3.4. Potential strategies for JE prevention and control program in Bali

Vaccination against JEV is considered an important strategy to control and minimize the disease impact on humans and livestock. Although it has not been implemented in animals in Indonesia, the vaccination against JEV in humans has been nationally applied. In the first quarter of 2018, Bali was chosen to be the first area in Indonesia that implemented the Chengdu SA-14-14-2 live-attenuated JEV vaccine targeted in 890,050 local children [33,82]. Almost 94% (95% CI: 92.8–94.9) of the children received the vaccination after the first campaign [83]. Although more studies needed to evaluate the vaccination program, it seems that the JEV infection in local children is getting lower.

Vaccination against JEV in animals is another consideration to prevent and minimize the infection in animals. Application of JE vaccination in pigs in Bali may minimize the virus transmission by decreasing the virus amplification as well as reducing the risk of the reproductive abnormalities in the animals, rate of the mosquito infection, and subsequently risk of transmission to humans. However, such a program would be difficult to be implemented. Although economic

analysis on the related strategy need to be assessed, some reasons why the vaccination program in animals in Indonesia, including Bali has not been implemented, include the high cost of the vaccination, the high turnover of the susceptible pig population [84], and short period between maternal antibody waning (2–4 months) with the age of the pigs being slaughtered (6–7 months) [38], difficulty with cold chain and tracing, and farmers unwillingness to pay because their pigs do not get sick.

Public awareness is crucial, as the disease can be fatal for children and the elderly, with no specific antiviral treatment available to treat JEV infection [85]. A preventive program of JEV infection in public health is important to be applied, as it is a zoonotic disease that can impact on livestock and community. Lack of community knowledge, attitudes and practices (KAP) on the disease is a potential high risk for disease occurrence and spread to wider community [86]. Agricultural rice paddy field and pig farmers including their family members are likely in high risk to be exposed to the virus through the vector bites as they tend to be close contacted with the field and their animals.

Information and education on public to use bed-nets or insect-repellents as their personal protection measures along with implementation of a good sanitation may contribute to reduce contact with the mosquito vector. Similarly, housing the pigs indoor with anti-mosquito nets or screens especially during the peak of vector activity may minimize contact the mosquitoes to the animals [87,88]. Modification of rice paddy fields management for water and fertilizer usage and separating the paddy fields or preventing stagnant water around the pig farms are other strategies that may also limit contact between mosquitoes, pigs and humans.

JE is a vector-borne viral disease that requires to control the mosquito population to prevent the viral transmission and minimize the disease impacts. Limiting contact of the reservoir hosts and humans from mosquitoes or controlling the vector's places for breeding may also support in reducing risk of the viral infection. These approaches are major strategies in controlling the JEV transmission. It is even more effective, when it combines with other related control strategies. Controlling the vector population integrated with public health, livestock and wild life managements is an important multisectoral measure for JEV control and prevention program in order to reduce the risk [89].

JEV infection occurred in the scope of human, environment and animals interaction, which also requires a multisectoral approach for controlling the

disease. This approach has also been suggested to reduce and prevent the vector-borne disease [90]. Interaction in the integrated surveillance system is beneficial for not only being more understood of the disease happened but also assists early warning detection of the disease [91]. To apply this, related institutional and legal framework of the policy-makers should be more active in initiating, promoting and supporting the approach to be more effectively implemented [92].

4. Conclusion

Although the human JEV vaccination has just implemented, the high proportion of antibodies in the residents, the JE confirmed cases from acute encephalitis syndrome happened in children under 15 years old, and the related cases in international travellers recorded indicating high JEV transmission occurred in Bali. Socio-culture and ecology of local Balinese may be involved in the mosquito vector of *Culex* spp. abundance and high proportion of antibodies against JEV detected in the amplifying hosts and dominant livestock in the area. All of the interconnected components are likely contributed to the local viral circulation and consequent proportion of the JE related human cases in the area. This review has identified some key areas to concentrate on JE in Bali, including: a structured surveillance program in the animal reservoirs or livestock, identification of the viral characteristics circulated in the area and its other potential mosquito vector involved, estimation of the disease burden in affected humans and animals, and initiation of collaborative approach in understanding the disease occurrence in the ecological environment and socio-cultural interaction. By evaluating those key areas, it may contribute to better understand JEV transmission ecology and assist the prevention and control program in reducing the risk of the hyperendemic disease threat in the area of Bali.

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Availability of data and materials

All data generated and analysed during this study are included in this manuscript.

Consent for publication

All of the contents, including data in this manuscript, have been checked, discussed and approved to be scientifically published in this journal.

Disclosure statement

All of the authors in this manuscript declare that they have no competing interests.

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Ethics approval and consent to participate

This manuscript is a review article, which used secondary data and therefore, it was not applicable to use the animal and human ethics. However, permission on using the data from local institutions have already been obtained.

Geolocation information

The research location is in Bali province, Indonesia. The Bali's latitude is -18.409518 and its longitude is 115.188919 with the GPS coordinates of $8^{\circ} 24' 34.2648''$ S and $115^{\circ} 11' 20.1084$ E.

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