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Sero-evidence of silent Japanese Encephalitis Virus infection among inhabitants of Ilorin, North-central Nigeria: a call for active surveillance

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ABSTRACT

Infection by Japanese Encephalitis Virus (JEV) causes viral encephalitis in humans. It is endemic in Asia and western Pacific regions with no reported case in Nigeria so far. This study aimed at detecting evidence of circulation and pattern of exposure of individuals in Ilorin, Nigeria to JEV. A total of 139 febrile patients attending outpatient departments of Sobi specialist hospital, Civil service hospital and University of Ilorin health center participated in the study. About 5 ml of venous blood was collected from each participant and the plasma tested for the presence of anti-JEV IgG antibody using Enzyme Linked Immunosorbent Assay (ELISA) technique. Anti-JEV IgG antibody was detected in 32% (45/139) of the participants. Males were more exposed (37%) than female participants (27.3%). Similarly, participants with travel history outside of the country were more exposed (44.4%) than those without travel history (29.5%). Further analysis on the basis of age, marital and working status showed no statistical association between these variables and anti-JEV positivity ($p>0.05$). This study has provided serological evidence of the circulation of JEV among Ilorin inhabitants and therefore calls for active surveillance for the infection in order to forestall any future major outbreak.

KEYWORDS

Japanese Encephalitis Virus; silent infection; evidence; Nigeria

Introduction

Japanese encephalitis (JE) is one of the most important vector-borne and leading causes of epidemic viral encephalitis in humans worldwide. Mostly endemic in much of Asia and western Pacific, [1] the disease has the potential of spreading to other regions of the world. The disease follows infection by Japanese encephalitis virus (JEV), a single-stranded, plus-sense RNA virus which belongs to the family flaviviridae. Water birds (such as pond herons and cattle egrets) are considered the natural reservoirs of the virus. Pigs and ardeidae birds serve as the main amplifying hosts and play vital roles in the maintenance and transmission of the disease agent.[2] Enzootic cycle between the reservoirs and the amplifying hosts is maintained by bite of Culex

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mosquitoes (mainly *Culex tritaeniorrhynchus*). Humans are considered as dead-end host[3] as viremic levels in humans do not reach titers infectious to mosquitoes. Consequently, infections in humans are usually asymptomatic or subclinical as a result of which majority of cases are unlikely to be diagnosed as Japanese encephalitis.[4,5] In all cases however, infection result in development of anti-JEV antibodies which usually persist for life. Detection of these antibodies is used as an indicator of exposure to the virus although cross-reactivity between members of flavivirus genera or vaccination may lead to misleading results.[6,7] In symptomatic cases the mortality is usually high (20–30%)[8] while majority of the survivors suffer long term neuro-psychiatry sequelae causing heavy burden to public health and society.[9] Infection usually occurs among children and young adults mostly in the rural and suburban areas where rice and pig farming co-exist.[10] An estimated 2.4 billion people are known to be at risk for JEV[9] resulting in about 50000 cases and 15000 deaths annually.[11]

Presently, there is no antiviral therapy for the infection hence vaccination remains the only available tool for prevention of the infection.[12,13] Presence of animal reservoirs however has hindered efforts to prevent the circulation of the virus by vaccination.

In Nigeria, there is abundance of migratory water birds such as pond herons and cattle egrets and culex mosquitoes. Also pig and rice farming are widely practiced in the country with Nigeria currently ranked among the leading rice producers in Africa. With these prevailing favorable conditions for the virus transmission, there is a high possibility of silent unreported infections occurring in the country. As a pilot study, we report serological evidence of silent infection of JEV in Ilorin, Nigeria.

Materials and methods

Study population and sample collection

The participants in this study included consenting 139 (73 males 66 females: mean age 28 years) febrile patients (with body temperature usually above 37°C) attending outpatients departments of Sobi Specialist Hospital, Civil Service Hospital and University of Ilorin Health Center Ilorin, Nigeria. The participants were selected irrespective of gender and age; exclusion criteria were; no willingness to participate. Relevant socio-demographic information of the participants was collected using well-structured questionnaire forms. About 5 ml of venous blood sample was collected from each patient into ethylene diamine tetraacetic acid (EDTA) bottle. The sample was spun at 500 g for 5 minutes to separate the plasma from the packed cells. The plasma was aspirated into sterile cryovials, properly labeled and stored at −20°C until analyzed.

Ethical consideration

Ethical approval (MOH/KS/EU/777/275) to carry out the study was obtained from the Ethical Review Committee (ERC) of Kwara state Ministry of Health, Nigeria. The study conformed to Ethics of Human subjects use in research following the Helsinki Declaration. Informed consent was obtained from each participant and from parents (for participants less than 18 years of age) before collection of sample.

Serology

The plasma samples were tested for the presence of anti-JEV IgG antibodies using commercially available Enzyme Linked Immunosorbent Assay (ELISA) kit (manufactured by Diagnostic Automation, Inc., Calabasas, CA, USA). The assay and its interpretation were carried out according to the kit's manufacturer's instructions. The samples with equivocal results were re-tested and samples with repeated equivocal results were excluded.

Data analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS version 21). Pearson's bivariate correlation was used to test association at $p \leq 0.05$ level of significance.

Results

Samples were collected from a total of 139 febrile patients. They included 73 (52.5%) males and 66 (47.5%) females. Stratification on the basis of age shows that majority (47.5%) of the patients were within the age range of ≤20 years while a smaller percentage (18.0%) were 35 years and above. Majority (about 57%) of the participants were in the singles category (not yet married). Data also showed that greater percentage (49%) of the study participants were students while 44% and 7% were working class and unemployed respectively. Less than 20% of the study participants had history of travel outside the country while the rest had no such travel history (Table 1).

Of the 139 febrile patients tested, 45 were found to be positive to anti-JEV IgG antibodies giving a prevalence of 32% while the remaining 94 (68%) tested negative (Figure 1). Table 2 shows the association between anti-JEV status and socio-demographic variables of the study participants. Although higher prevalence (37%) was recorded among male participants than female participants (27.3%), analysis showed no statistical association ($p = .225$) between gender and anti-JEV status. Similarly, higher prevalence (36.4%) was recorded among participants who were ≤20 years of age while age

Table 1. Socio-demographic variables of the study participants.

Variable	Number	Frequency %
Gender		
Male	73	52.5
Female	66	47.5
Age (years)		
≤20	66	47.5
21–35	48	34.5
>35	25	18.0
Marital status		
Married	60	43.2
Single	79	56.8
Working status		
Students	68	48.9
Working class	61	43.9
Unemployed	10	7.2
Travel history		
Yes	27	19.4
No	112	80.6

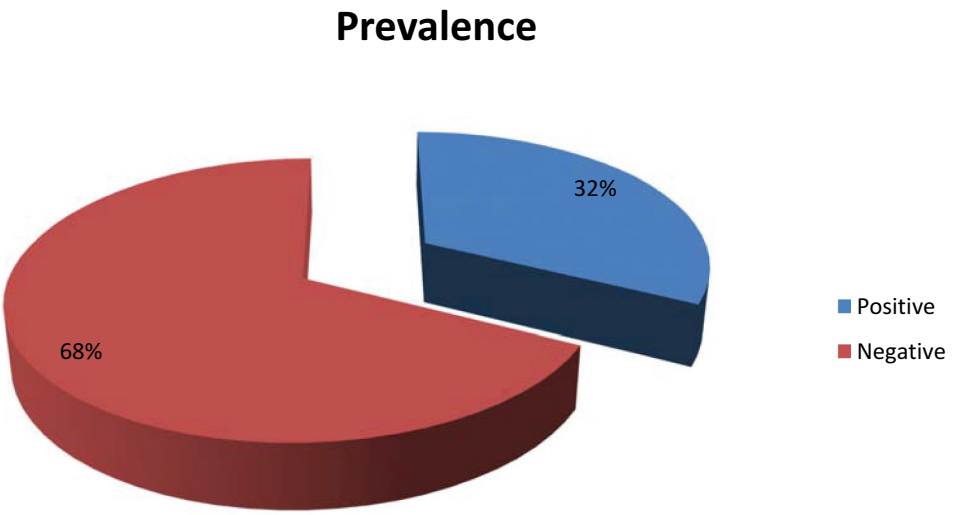


Figure 1. Pie chart of JEV seropositivity among the study participants.

groups 21–35 years and >35 years recorded 29.2% and 28.0% respectively. On the basis of marital status, slightly higher prevalence (33.3%) was recorded among married participants than singles with 31.7%. Furthermore, exposure rate (evidenced by presence of IgG antibodies) was higher among working class participants (36.1%) while students and unemployed participants were least exposed (30.9% and 20.0% respectively). Also participants who had travel history outside the country were more exposed to the virus (44.4%) than their counterparts who had no travel history (29.5%). However, statistical analysis showed no association ($p>0.05$) between these variables and anti-JEV status.

Table 2. Bivariate analysis of JEV status and socio-demographic variables of the study participants.

		JEV status		
Variables	Number tested (%)	Positive n (%)	Negative n (%)	X^2 (*p*-value)
Gender				0.225
Male	73 (100)	27 (37.0)	46 (63.0)	
Female	66 (100)	18 (27.3)	48 (72.7)	
Age (years)				0.374
≤20	66 (100)	24 (36.4)	42 (63.6)	
21–35	48 (100)	14 (29.2)	34 (70.8)	
>35	25 (100)	7 (28.0)	18 (72.0)	
Marital status				0.835
Married	60 (100)	20 (33.3)	40 (66.7)	
Single	79 (100)	25 (31.7)	54 (68.4)	
Working status				0.949
Students	68 (100)	21 (30.9)	47 (69.1)	
Working class	61 (100)	22 (36.1)	39 (63.9)	
Unemployed	10 (100)	2 (20.0)	8 (80.0)	
Travel history				0.137
Yes	27 (100)	12 (44.4)	15 (55.6)	
No	112 (100)	33 (29.5)	79 (70.5)	

Discussion

Japanese encephalitis virus, the known etiologic agent of Japanese encephalitis has become an international public health issue and causes significant morbidity and mortality in endemic countries.[9] The 32% anti-JEV IgG antibody obtained in this study is quite alarming and indicates that the virus has been in circulation in the country albeit silently since no clinical case of the infection has been documented in the country. Furthermore, since the population is JEV vaccine naïve, this figure indicates the level of previous exposure of the population to the virus.

Although the morbidity rate is relatively low (less than 1%) in endemic countries' [9] the absence of any reported clinical case in Nigeria despite the seemingly high seroprevalence obtained in the current study is quite intriguing. Our understanding of RNA viruses could provide some insights into the possible reasons for this finding. RNA viruses are prone to high level of amino acid mutations as a result of lack of proofreading machinery of the RNA-dependent RNA polymerases in these viruses to correct misincorporated nucleotides.[14] Occurrence of these mutations at key loci related to antigenicity and pathogenicity could lead to the emergence of a weakened/attenuated strain with less pathogenic potential. The E protein is believed to have a major role in the determination of virulent phenotype of JEV. A single amino acid substitution in this protein has been implicated for the loss of neurovirulence or neuroinvasiveness in JEV.[15–17]). Hence, a non-virulent strain of the virus might be circulating in the country. The only recorded clinical case of JE in an African country (Angola) so far was as a result of infection by G3 strain of JEV.[18] Hence, the true situation in Nigeria will be better understood by more detailed molecular studies aimed at ascertaining the strain circulating among the virus reservoirs in the country. Such studies

among humans may be a bit difficult considering the transient viremic phase of the infection in humans' [19,20] hence the use of serology in this study. Secondly, some inherent (yet to be explained) genetic factors in the indigenous population as well as prevalent climatic conditions in the country could also be implicated.

Considering the fact that irrigated rice production and pig rearing are key factors in the transmission of JEV[10,21]), detection of significant level of anti-JEV antibodies in Ilorin leaves one wondering. Ilorin is the capital city of Kwara State with significant Muslim population and is located in the guinea savannah region of Nigeria. While rice farming is widely practiced in the area, pig farming is relatively uncommon. The high seroprevalence in Ilorin can therefore partly be explained by the metropolitan nature of the city. The inhabitants of the city come from different parts of the country including the southern regions where pig and rice farming are widely practiced.

Analysis of the different variables in this study showed no positive correlation ($p>0.05$) between the variables and anti-JEV IgG positivity. This notwithstanding, participants with history of travel outside of the country are more exposed to the infection compared to their counterparts with no travel history. Travel to endemic areas has been noted as one of the main risk factors of the infection.[2] Hence some of the infections could have occurred during a trip to some of the more endemic countries. However, this does not pose any risk of potential epidemic in the country since humans are dead-end hosts and possibility of human to human transmission is almost zero.[19]

The risk for possible spread of JEV into the country is however heightened by seasonal migration of birds.[22] Furthermore, with increased availability of transport (especially by air), travel has become much easier with speed thereby encouraging inter-regional and international tourism and business trips. This has further increased the chances of accidental trans-boundary transportation of vectors. With the prevailing favorable conditions for epizootic transmission of the virus, JE could potentially become a major public health issue in non-endemic country like Nigeria. Changes in cultural practices, economy and climate could also be additional contributing factors.[23]

On the other hand, the high seroprevalence in the current study may be attributed to cases of false positives which might have resulted in misleading results. Cases of false positives are known to occur as a result of exposure of the population to other cross-reactive flaviviruses which are known to circulate in JEV-infected countries.[24] This is as a result of shared epitopes between members of flavivirus genera that induce cross-reactive antibodies, leading to difficulty in differentially diagnosing flaviviral infections.[6,25] In Nigeria, circulation of these flaviviruses has been extensively reported.[26–28] Hence the high seroprevalence obtained in this study may partly be as a result of cross-reactivity with other flaviviruses co-circulating in the region and which may have been falsely diagnosed as JEV. On the other hand, occurrence of the other

flaviviruses such as Dengue Fever Virus (DENV) has been speculated to offer cross-protection against JEV.[24,29,30] Therefore exposure of the population to DENV could have resulted in significant level of cross-protection against JEV in the country. Hence, the apparent lack of symptoms in Nigeria may not be far-fetched although this claim has been refuted by some researchers.[25,31]

Conclusion

In view of the foregoing, we hypothesize higher prevalence and incidence in the southern part of Nigeria where pig rearing is widely practiced in conjunction with rice farming. As far as it can be ascertained, this is the first serological evidence of JEV circulation in Nigeria. With this evidence of silent circulation of JEV in Nigeria, there is need to beam our searchlight on this virus in order to fully understand the complex interplay of its ecological factors of transmission. Presence of the virus in domestic mosquitoes and the prevalent animal reservoirs should be investigated in order to determine the circulating strains in our locality. While we cannot advocate for the vaccination of both humans and animal reservoirs as a preventive measure for obvious economic reasons, other forms of prevention can be employed including; effective vector control and active surveillance (including clinical, entomological and veterinary-based sero-surveillance).

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