Infection and Drug Resistance

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REVIEW

Magnitude of Antibody Cross-Reactivity in Medically Important Mosquito-Borne Flaviviruses: A Systematic Review

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Introduction: Flaviviruses are a genus of enveloped single-stranded RNA viruses that include dengue virus (DENV), yellow fever virus, West Nile virus (WNV), Japanese encephalitis virus, and Zika virus. Nowadays, diverse serological assays are available to diagnose flaviviruses. However, infection with flaviviruses induces cross-reactive antibodies, which are a challenge for serological diagnosis.

Objective: This systematic review aimed to assess the magnitude of medically important mosquito-borne flavivirus–induced antibody cross-reactivity and its influence on serological test outcomes.

Methods: This study was designed based on the PRISMA guidelines. It includes original research articles published between 1994 and 2019 that reported serological cross-reactions between medically important mosquito-borne flaviviruses. Articles were searched on PubMed using controlled vocabulary. Eligibility was assessed by title, abstract, and finally by reading the full paper. The articles included are compared, evaluated, and summarized narratively.

Results: A total of 2,911 articles were identified, and finally 14 were included. About 15.4%–84% of antibodies produced against non-DENV flaviviruses were cross-reactive with DENV on different assays. Up to 30% IgM and up to 60% IgG antibodies produced against non-WNV flaviviruses were cross-reactive with WNV on EIA assays. The magnitude of antibodies produced against flaviviruses that are cross-reactive with chikungunya virus (*Alphavirus*) was minimal (only about 7%). The highest antibody cross-reactivity of flaviviruses was reported in IgG-based assays compared to IgM-based assays and assays based on E-specific immunoglobulin compared to NS1-specific immunoglobulin. It was found that preexisting immunity due to vaccination or prior flavivirus exposure to antigenetically related species enhanced the cross-reactive antibody titer.

Conclusion: This review found the highest cross-reaction between DENV and non-DENV flaviviruses, especially yellow fever virus, and the least between chikungunya virus and DENV. Moreover, cross-reaction was higher on IgG assays than IgM ones and assays based on Eprotein compared to NS1protein. This implies that the reliability of serological test results in areas where more than one flavivirus exists is questionable. Therefore, interpretation of the existing serological assays should be undertaken with a great caution. Furthermore, research on novel diagnostic signatures for differential diagnosis of flaviviruses is needed.

Keywords: antibodies, cross-reaction, mosquito-borne flaviviruses, serological diagnosis

Introduction

Flaviviruses are enveloped single-stranded RNA viruses belonging to the genus *Flavivirus* and family *Flaviviridae*.[1] There are 53 recognized *Flavivirus* spp., of which 40 are known to cause disease in humans.[2] The major human pathogenic

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Received: 27 August 2021
Accepted: 7 October 2021
Published: 19 October 2021

viruses under this genera include dengue virus (DENV), yellow fever virus (YFV), West Nile virus (WNV), Japanese encephalitis virus (JEV), Zika virus (ZKV), and others that may cause hemorrhagic fever and encephalitis.[3] These viruses are considered arboviruses, and are transmitted via mosquito bites.[1,4] The term "flavivirus" originates from YFV, the prototype virus for the family. The Latin word *flavus* means "yellow," and YFV in turn is so named because of its propensity to cause jaundice in victims.[1] Infections due to flaviviruses represent a severe global public health problem with major individual, social, and economic consequences,[5] especially in tropical and subtropical countries.[4] DENV alone infects >100 million people annually, and 500,000 people suffer from dengue fever.[3] While many flavivirus infections are asymptomatic, they may begin as an aspecific febrile illness and develop into a severe and life-threatening disease.[1]

Flaviviruses have a worldwide distribution, but individual species are restricted to specific endemic or epidemic areas. For example, YFV prevails in tropical and subtropical regions of Africa and South America, DENV in tropical areas of Asia, Oceania, Africa, and the Americas, and JEV in Southeast Asia. In the last five decades, many flaviviruses, such as DENV, WNV, and YFV, have exhibited dramatic increases in incidence, disease severity, and/or geographic range.[6,7]

The flavivirus genome encodes three structural proteins (capsid [C], premembrane/membrane [prM/M], and envelope [E]) required for the formation of virus particles and 7 nonstructural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) that are not part of infectious virus particles, but are critical for replication of viral RNA by suppressing antiviral defense responses mounted by the host after expression in infected cells.[8] In most flaviviruses the immunodominant antigens are the E, prM, and NS1 proteins, and most serological tools rely on the detection of anti-E and/or anti-NS1 antibodies. The major neutralizing determinants are present in the E protein.[9] Upon folding, each flavivirus E protein monomer is organized into three structurally distinct envelope domains: EDI, EDII, and EDIII.[10,11] Domain III peptides of flavivirus envelope proteins are useful antigens for serological diagnosis and targets for immunization,[12,13] because they contain important antigenic epitopes with strong antigenicity that directly interact with potent neutralizing antibodies.[13] In addition, these epitopes are the main target cell receptor–binding sites that assist viral entry into host cells.[14]

Flaviviruses can be diagnosed using virological, molecular and serological techniques. Virus isolation (virological technique) and/or detection of viral RNA by PCR (molecular technique) are the methods of choice during the acute phase of the infection. However, the virological and molecular techniques are seldom possible, since flaviviruses have a short viremic period and patients mostly-show clinical symptoms after they have passed the viremic phase. On top of this, patients with flavivirus infections often present similar clinical features, and co-occurrence[15] of multiple flaviviruses in several geographic areas is common. Therefore, by taking the nature of flaviviruses and the technical infeasibility of virological and molecular techniques into consideration, diagnosis of infection with a flavivirus largely relies on serological assays.[16]

Nowadays, diverse serological assays are available to diagnose infections with flaviviruses: the plaque-reduction neutralization test (PRNT), microvirus-neutralization test, immunofluorescence assay (IFA), ELISA, and microsphere immunoassay.[17] Currently, the PRNT is considered the gold standard for detecting and quantifying circulating levels of neutralizing antibodies against flaviviruses.[18] Each serological method has its own advantages and drawbacks over the others. Since infections with flavivirus induce cross-reactive antibodies in addition to species-specific antibodies,[9] there is growing concern about the reliability of serological assays for the diagnosis of flaviviruses. Therefore, this systematic review aimed to assess the magnitude of medically important mosquito-borne flavivirus–induced antibodiy cross-reactivity and its influence on serological test outcomes.

Methods

Eligibility Criteria

This systematic review conducted on peer-reviewed original research articles published in English, regardless of date of study (or publication), that met the PICOS (participants, intervention/exposure, comparator, outcomes, and setting/design) criteria. Studies that involved human participants of any age and reported magnitude of antibody cross-reactivity between mosquito-borne flaviviruses, ie, DENV, YFV, ZKV, and WNV, and one alphavirus (chikungunya virus[CHIKV]) irrespective of study design and assay types were included. Studies done on nonhuman primates and articles without full text were excluded. The researchers independently evaluated the eligibility of all retrieved articles.

Design, Information Sources, and Search Strategies

This systematic review was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[19] We searched the PubMed database for articles. EndNote X7 reference-management software was used to download, organize, review, and cite the related articles. A comprehensive search was performed using the search terms "serological [MeSH] OR serological [MeSH] AND cross-reaction [MeSH] OR cross neutralization [MeSH] AND flavivirus [MeSH]" OR dengue [MeSH] OR yellow-fever [MeSH] OR chikungunya [MeSH] OR Zika [MeSH] OR West-Nile [MeSH] AND antibody [MeSH]. Additional relevant articles were manually searched using backward and forward search strategies.

Study Selection

Eligibility assessment of the studies was performed by the investigators first by title, then by reading abstracts, and finally by reading the full papers.

Data-Collection Process and Data Items

After the screening had been completed, relevant data from each included article were extracted using a prepiloted data-extraction format prepared using a Microsoft Excel spreadsheet. The pilot test was performed on two randomly selected papers from the 14 eligible articles and refinements made accordingly. Finally, from each included article, data on name of target flavivirus, source of clinical sample (either flavivirus-infected patient or flavivirus-vaccinated), study design, sample size, target antibody detected, lab method, magnitude of cross-reaction, and factors boosting flavivirus cross-reaction were extracted.

Data Analysis

The articles included in this systematic review were compared, evaluated, and summarized narratively. Due to the heterogeneity of outcome-measurement tools (lab methods) employed in the studies, a meta-analysis was not conducted.

Results

Search Results

The search of PubMed yielded 2,911 records. After removal of irrelevant and duplicate records by title (2,879) and abstract (17) screening, 15 remained. An additional five were identified by forward and backward searches, which made 20 papers eligibile for full-text assessment. Finally, 14 articles published between 1994 and 2019 were included.[16,20–32] Figure 1 is adapted from the PRISMA guidelines[19] and summarizes the search process and results.

Characteristics of Included Studies

As shown in Table 1, the number of samples recruited in the studies included in this systematic review ranged from three to 77. Four target flaviviruses — DENV, YFV, WNV, and ZIKV — and one alphavirus were included. The studies had recruited participants from Okinawa,[20] Thailand,[25] Germany,[21] the Netherlands,[22] Colombia,[23] different countries in Europe, Asia and Africa,[16] Thailand,[32] Singapore,[24] Taiwan,[27] Yap,[28,33] and the US.[27,30] All the articles were cohort studies.

Result of Individual Studies

Cross-Reaction of DENV with Other Flaviviruses

Of the 14 papers included, six[16,21–23,25,32] reported cross-reactivity of DENV with other non-dengue flaviviruses, ie, YFV, ZIKV, JEV, and TBEV. The magnitude of cross-reactivity varied within species of flavivirus, type of assay used, and the target-immunoglobulin class or target-protein type. About 15.4%–84% of antibodies produced against non-dengue flaviviruses were reported as cross-reactive with dengue using different assays (lab methods). Cross-reactivity ranged up to 76.9% with antibodies produced against YFV using IgG ELISA[23] and up to 84% with antibodies produced against one or multiple non-dengue flaviviruses (YFV, WNV, JEV, and TBEV) using IgG EIA assays.[16] With respect to the assay methods employed, the highest cross-reactivity of DENV was reported using IgG-capture ELISA/IFA/EIA over IgM ELISA/IFA/EIA or PRNT and assays based on E-specific immunoglobulin over NS1-specific immunoglobulin. NS1-specific IgG/M-capture ELISA for DENV showed no cross-reaction with ZIKV, unlike E-specific IgG/M-capture ELISA (Table 2).

Cross-Reaction of YFV with Other Flaviviruses

Two papers[16,23] reported cross-reaction of YFV with DENV and sera from DENV/WN/JE patients and TBEV vaccines. Up to 80% antibodies produced against DENV infection were reported as cross-reactive using the PRNT.

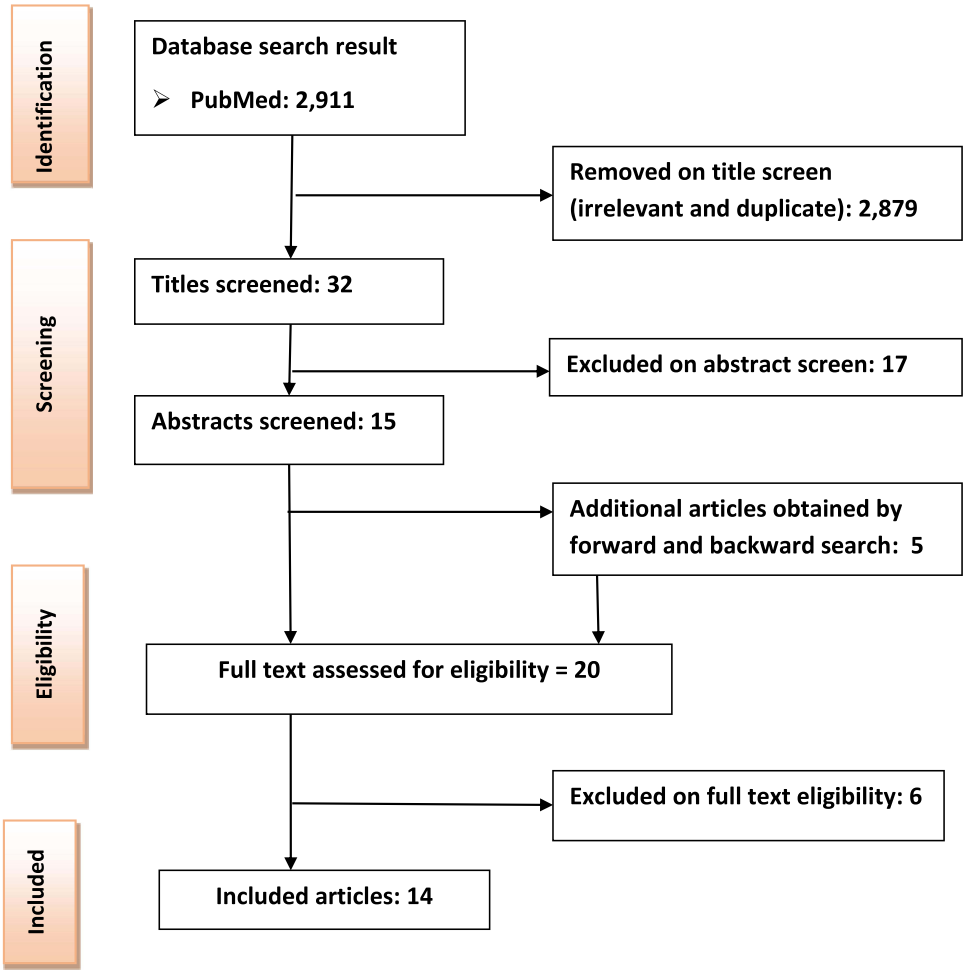

Figure 1 Study-selection flowchart.

Relatively higher cross-reaction was reported using IgG-based assays than IgM assays (Table 2).

Cross-Reaction of WNV with Other Flaviviruses

One paper indicated WNV cross-reactivity with non-WNV flaviviruses to be 10% and 50% using IgM-based IFA and IgG-based IFA, and 30% and 60% using IgM-based EIA and IgG-based EIA respectively.[16] The highest cross-reactivity reported was with IgG-based EIA over IgM EIA and IgG-based IFA over IgM-based IFA. Another study[20] reported 32.1% cross-reaction with antibodies from YFV and JEV vaccines (Table 2).

Cross-Reaction of JEV with Other Flaviviruses

As reported in one paper,[16] 4% and 16% of antibodies induced against non-JEV flaviviruses (sera from YFV and/or WNV and/or JEV patients) were cross-reactive with JEV using IgG-based IFA and IgM-based IFA respectively. Cross-reaction rose to 32% and 74% using IgG-based EIA and IgM-based EIA, respectively (Table 2).

Cross-Reaction of CHIKV (*Alphavirus*) with Flaviviruses

Unlike cross-reaction within the genus *Flavivurus*, very minimal cross-reaction was reported between *Flavivurus and Alphavirus*. As reported in one paper[24] only 6% of antibodies produced against DENV and 7% of antibodies produced against non-DENV flaviviruses were cross-reactive with CHIKV (*Alphavirus*), but up to 58% cross-reaction of CHIKV with other non-CHIKV alphaviruses was reported using the $PRNT_{50}$[24] (Table 2).

Factors Boosting Flavivirus Cross-Reactivity

Studies showed that preexisting immunity due to vaccination or prior flavivirus exposure to antigenetically similar species enhanced serological cross-reactivity.[26,27,29–31] In one study,

Table 1 Characteristics of included studies

	Target flavivirus	Source of sample	Design	Sample size	Country/continent
Mansfield et al[20]	DENV2	JEV- and YFV-vaccinated	Cohort	26	Japan
	WNV	JEV- and YFV-vaccinated	Cohort	28	
Makino et al[25]	DENV	JEV patients	Cohort	13	Thailand
		JEV patients immunized with YFV 17D vaccine	Cohort	3	
Allwinn et al[21]	DENV	YFV-vaccinated (17D vaccine)	Cohort	53	Germany
		TBEV-vaccinated	Cohort	26	
van Meer et al[22]	DENV	ZIKV-infected travelers	Cohort	39	Netherlands
Houghton-Triviño et al[23]	DENV	YFV patients	Cohort	13	Colombia
		YFV vaccines	Cohort	19	
	YFV	DENV patients	Cohort	20	
Koraka et al[16]	DENV	YFV/WNF/JEV patients and TBEV-vaccinated	Cohort	49	Europe, Asia, and African
	YFV	DENV/WNF/JE patients and TBEV vaccinated	Cohort	52	
	WNV	YFV/DENV/JEV patients and TBEV vaccinated	Cohort	50	
	JEV	YFV/WNF/JEV patients	Cohort	50	
Souza et al[32]	DENV and ZIKV	YFV-vaccinated	Cohort	77	Brazil
Kam et al[24]	CHIKV (E2EP3)	Non-CHIKV alphavirus–infected patients	Cohort	19	Singapore
		DENV-infected patients	Cohort	46	
		Non-DENV flavivirus–infected patients	Cohort	14	
Lai et al[26]	DENV	Primary and secondary DENV-infected patients	Cohort	15	Taiwan
Stettler et al[31]	DENV	ZIKV-infected patients	Cohort	20	Not mentioned
Priyamvada et al[34]	DENV	Secondary DENV2 patients	Cohort	4	Yap
Rogers et al[30]	ZIKV	DENV-experienced patients	Cohort	3	USA
Lai et al[27]	DENV	Flavivirus-experienced patients	Cohort	5	USA
Lanciotti et al[28]	ZIKV	DENV-experienced patients	Cohort	23	Yap

secondary flavivirus–infected patients showed a high degree of serological cross-reactivity with other flaviviruses compared to primary flavivirus–infected patients.[28]

Discussion

A number of studies revealed extensive serological cross-reactions between flaviviruses on different assays. This provides a challenge for accurate diagnosis of flavivuruses, especially in areas where multiple species circulate. The magnitude of cross-reaction varied among species, serological assay used, and target antibody for detection.

Within the flaviviruses, the highest cross-reactions were observed between YFV and DENV and between DENV and ZIKV. The magnitude of cross-reactivity for target flaviviruses increased (eg, up to 84% for DENV) in cases of sera taken from participants with a history of infections and/or vaccination with multiple serotypes. The lowest cross-reaction was reported from CHIKV with DENV and non-DENV

Table 2 Magnitude of cross-reaction reported in individual studies

Target flavivirus	Cross-reaction with Abs produced against	Source of sample (serum)	Assay type	Diagnostic marker	Cross-reaction (%)	Reference
DENV2	YFV and/or JEV	JEV- and YFV-vaccinated	PRNT50 (titer at least 1:20)	E-protein	38.5	[20]
DENV	JEV	JEV patients	PRNT50 (titer at least 1:10)	E-protein	15.4	[25]
DENV1–4	YFV and/or JEV	JEV patients immunized with YFV 17D vaccine	PRNT50 (titer at least 1:10)	E-protein	33.3	
DENV	YFV	YFV-vaccinated (17D vaccine)	IgG ELISA	E-protein	15.1	[21]
DENV	TBEV	TBEV-vaccinated	IgG ELISA	E-protein	23.1	
DENV	ZIKV	ZIKV-infected travelers	DENV NS1 antigen ELISA	NS1-protein	—	[22]
DENV	ZIKV	ZIKV-infected travelers	IgM ELISA	E-protein	31.0	
DENV	ZIKV	ZIKV-infected travelers	IgG ELISA	E-protein	54.0	
DENV	YFV	YFV patients	IgG ELISA	E-protein	76.9	[23]
DENV	YFV	YFV patients	IgM ELISA	E-protein	46.2	
DENV	YFV	YFV vaccines	IgM ELISA	E-protein	42.1	
DENV	Non-dengue flaviviruses	YFV/WNV/JEV patients and TBEV vaccines	IgM IFA	E-protein	33	[16]
DENV	Non-dengue flaviviruses	YFV/WNF/JEV patients and TBEV vaccines	IgG IFA	E-protein	71	
DENV	Non-dengue flaviviruses	YFV/WNF/JEV patients and TBEV vaccines	IgM EIA	E-protein	39	
DENV	Non-dengue flaviviruses	YFV/WNF/JEV patients and TBEV vaccines	IgG EIA	E-protein	84	
DENV	YFV	YFV vaccinated	IgG ELISA	E-protein	3.9	[32]
YFV	DENV	DENV patients	PRNT50	E-protein	80	[23]
YFV	Non-YFV flaviviruses	DENV/WNF/JEV patients and TBEV vaccines	IgM IFA	E-protein	10	[16]
YFV	Non-YFV flaviviruses	DENV/WNF/JEV patients and TBEV vaccines	IgG IFA	E-protein	44	
YFV	Non-YFV flaviviruses	DENV/WNF/JEV patients and TBEV vaccines	IgM EIA	E-protein	44	
YFV	Non-YFV flaviviruses	DENV/WNF/JEV patients and TBEV vaccines	IgG EIA	E-protein	65	

(*Continued*)

Table 2 (Continued).

Target flavivirus	Cross-reaction with Abs produced against	Source of sample (serum)	Assay type	Diagnostic marker	Cross-reaction (%)	Reference
CHIKV E2EP3	Non-CHIKV alphaviruses	Non-CHIKV alphavirus–infected patients	PRNT50 (titer at least 1:10)	E-protein	58	[24]
CHIKV E2EP3	DENV	DENV-infected patients	PRNT50 (titer at least 1:10)	E-protein	6	
CHIKV E2EP3	Non-DENV flaviviruses	Non-DENV flavivirus–infected patients	PRNT50 (titer at least 1:10)	E-protein	7	
WNV	Non-WNF flaviviruses	YFV/DENV/JEV patients and TBEV vaccines	IgM IFA	E-protein	10	[16]
WNV	Non-WNF flaviviruses	YFV/DENV/JEV patients and TBEV vaccines	IgG IFA	E-protein	50	
WNV	Non-WNF flaviviruses	YFV/DENV/JEV patients and TBEV vaccines	IgM EIA	E-protein	30	
WNV	Non-WNF flaviviruses	YFV/DENV/JEV patients and TBEV vaccines	IgG EIA	E-protein	60	
WNV	YFV and JEV	JEV and YFV vaccines	PRNT50 (titer at least 1:10)	E-protein	32.1	[20]
JEV	Non-JE flaviviruses	YFV/WNF/JEV patients	IgM IFA	E-protein	4	[16]
JEV	Non-JE flaviviruses	YFV/WNF/JEV patients	IgG IFA	E-protein	16	
JEV	Non-JE FVs	YFV/WNF/JEV patients	IgM EIA	E-protein	32	
JEV	Non-JE flaviviruses	YFV/WNF/JEV patients	IgG EIA	E-protein	74	
ZIKV	YFV	YFV-vaccinated	IgG ELISA	E-protein	—	[32]

flaviviruses (only up to 7%). This variation in the magnitude of cross-reaction might largely depend on the range of antigenic similarities among species. DENV, ZKV, YFV, WNV, and JEV are in the same family (*Flaviviridae*) and genus (*Flavivirus*) with common antigenic determinants, while CHIKV is categorized under another family (*Togaviridae*) and genus (*Alphavirus*).[35]

With respect to lab methods, the highest cross-reactivity was demonstrated with IgG-capture assays (ELISA/IFA/EIA) compared to IgM-capture assays (ELISA/IFA/EIA). Animal-model studies on closely related flaviviruses also demonstrated that IgG-based assays were less specific than IgM-based assays for homologous viruses.[16,36] It was revealed that assays based on the E protein compared to those based on the NS1 protein led to higher cross-reactivity. This variation in the degree of cross-reaction might be due to differences in specificity of methods, which in turn relies on the nature of target-flavivirus proteins used for diagnosis. It was found that the E protein elicited flavivirus cross-reactive neutralization antibodies, while the NS1 protein induced a nonneutralizing virus-specific antibody response.[31] In another flavivirus study, it was also suggested that antibodies to NS1 can be used as diagnostic markers of a flavivirus species–specific infection.[37] In contrast to early studies, which found NS1 to be a species-specific marker in flavivirus serology, one recent study on ZIKV NS1 IgM and IgG revealed significant cross-reactivity with DENV.[38] This raises a question on the specificity of the NS1 marker, and hopefully future research can solve this dilemma. Although currently, the PRNT is considered the gold standard for detecting and measuring antibodies that can neutralize viruses,[18,39] the results of this review indicate it tends to be subject to cross-reactivity, especially in

patients with prior flavivirus infection or immunization history. This finding is incongruent with one study that suggested that the PRNT does not accurately discriminate flavivirus infection in cases of subsequent infection.[40]

The findings of this study showed that preexisting immunity due to vaccination or natural infection to antigenetically related species enhances the serological cross-reaction titer. This evidence is supported by studies that demonstrated relatively higher cross-reactions to ZKV observed in patients with secondary DENV exposure than patients with primary DENV exposure.[22,34] This might be due to reactivation of preexisting memory B cells that target conserved epitopes.[34]

Limitations

This systematic review basically focused on medically important mosquito-borne flaviviruses only, but did not fully address serological cross-reactions within and across all flaviviruses. Despite the endemicity of mosquito-borne flaviviruses in African, Caribbean, and Southeast Asian countries, the review findings do not reflect the situations in this countries, due to a paucity of research in these regions. Furthermore, the sera used for the studies included in this review were not standardized, which might have interfered with patient histories of different flavivirus infections, including tick-borne flavivirus.

Conclusion

The findings of this review revealed that the magnitude of cross-reactivity varies within the species of flavivirus, type of serological assay, and target biological marker. Cross-reactivity was higher between DENV and non-DENV flaviviruses, especially YFV, and the lowest cross-reactivity was observed in CHIKV with DENV and non-DENV flaviviruses. Similarly, cross-reactivity was higher for IgG assays than IgM assays and assays based on the E protein than the NS1 protein. Furthermore, preexisting immunity to antigenetically similar species enhanced the serological cross-reactivity. This can ultimately affect the reliability of serological test outcomes due to false-positive results. Therefore, test outcomes should be interpreted with great caution. Otherwise, it is advisable to use a combination of virological and molecular techniques together with serological investigations to boost the reliability of test results. Researchers in this arena are urged to search for novel diagnostic markers for accurate differential diagnosis of flaviviruses.

Acknowledgments

The authors would like to acknowledge Addis Ababa University for providing systematic review–protocol training to the authors to technically support the review process.

Disclosure

The authors declare no conflicts of interest for this work.

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