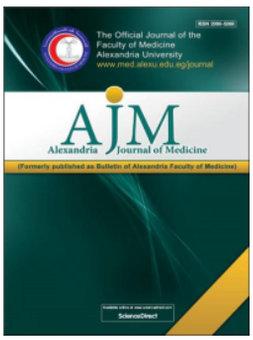

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REVIEW ARTICLE

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Clinical and epidemiological significance of RT-PCR and non-structural glycoprotein-1 assays in the diagnosis of dengue virus infections

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ABSTRACT

Background: Due to the rapid geographic expansion, dengue has attracted much global attention. Hence, many research outputs have emanated from clinical and epidemiological studies. However, most of these studies, especially those from low- and middle-income countries, heavily relied on enzyme-linked immunosorbent assay (ELISA).

Objective: In view of this, we sought to comment and remind dengue researchers within virology, immunology, and epidemiology disciplines regarding the limitations of ELISA protocols in establishing diagnosis of dengue virus (DENV) infections. Subsequently, we provided an update on the current diagnostic algorithm for dengue.

Method: Extensive literature search was done using special key words on "PubMed", "Scopus", "Web of Science" and "Hinari". Suitable articles were selected and subjected to scrutiny for inclusion in this study.

Result: It was discovered that over 90% of published articles from LMICs inferred about dengue mainly from available commercial serological kits, without further confirmation using more accurate, sensitive and specific protocols. In some instances (less than 5%), combination of either RNA positive and anti-DENV IgM or dengue NS1 and anti-DENV IGM were used to diagnose acute primary dengue; while presence anti-DENV IgG and DENV RNA were considered non-primary dengue.

Conclusion: In view of the limitations of every protocol used for investigations of dengue virus infections, its necessary to utilize appropriate combination tests to differentiate primary from non-primary dengue in order to generate reliable clinical and epidemiological inferences.

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KEYWORDS
Dengue; diagnostic algorithm; laboratory protocol

1. Background

Dengue virus (DENV) is a dangerously reemerging and mosquito-borne flavivirus. Dengue (DEN) has been considered a neglected tropical disease by the World Health Organization because it has received insufficient public attention, thrives in tropical and subtropical areas, and mainly affects populations living in poverty [1]. DEN has rapidly spread for the past 60 years and now affects more than half of the world's population. DENV transmission and geographic expansion are expected to rise due to increased international travels, deforestation, industrialization, urbanization, and climatic changes.

Forty-five percent of infected people never had significant symptoms but can still infect mosquitoes, hence sustain the transmission cycle. Infection with DENV confers a serotype-specific and lifelong immunity that does not cross protect against other serotypes [2]. Subsequent exposure to different serotypes could lead to more clinically severe non-primary dengue that could be secondary, tertiary, or quaternary DEN, corresponding with the number of serotypes in the patient. These sequences of increase in incriminating serotypes among infected persons put them at high risk of developing dengue hemorrhagic/shock syndrome [2].

In the last 10 years, DENV infections have become hyperendemic in many countries, as such, several studies have been conucted to ascertain the epidemiology and diagnosis of DEN. Epidemiologically, it is important to have accurate prevalence data of acute dengue virus infection in any setting, as this will assist to speculate the possibility of human-to-mosquito-human transmission of DEN. However, so many studies, especially those from low- and middle-income countries, use commercial anti-DENV IgM and IgG enzyme-linked immunosorbent assay (ELISA) as test protocol for reporting primary and secondary dengue. Based on this, we aimed to provide comments and thus elucidate the recent recommendation test protocols for the diagnosis of dengue.

2. Clinical updates of dengue diagnosis

Our comment with respect to the use of enzyme immunoassay protocols stems from the desire to remind

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virologists, immunologists, and clinicians regarding the possible cross-reaction of ELISA with antigens or antibodies of other viruses co-circulating with dengue [3,4], especially, if IgM/IgG reactive samples are not confirmed by plaque reduction neutralization test (PRNT). PRNT is the U.S. Center for Disease Control and Prevention (CDC) serology gold standard. It is a quantitative assay that measures viral-specific neutralizing antibody titers for DENV, at set tissue culture infective dose 50% (TCID50) [5]. Thus, the major epidemiological concern is the reliability of data generated from studies that solely utilized immunoglobulin-based serology in reporting DENV prevalence data. Aside from the issues of limitation due to cross-reaction, anti-DENV IgM or IgG does not accurately determine acute or recent DENV infection and does not accurately differentiate primary from secondary DEN because no serotypic differentiation can be provided from ELISA.

Dengue, yellow fever, West Nile, and Zika viruses are closely related arthropod-borne flaviviruses with similar nucleotide sequence homology, similar transmission cycles, geographic distribution, and prodromal clinical symptoms including fever, rash, and musculoskeletal pains. IgM and IgG antibody tests are the readily available methods and often the first test of choice in the diagnosis of DENV infection in developing countries. There have been difficulties in the clinical and epidemiological applications of these test results, particularly when determining acute primary infection, as IgM does not rise to detectable level until day 5 after being infected by DENV [6]. For sera collected <7 days after the onset of symptoms, a combo of NAAT and IgM negative results suggests that the individual does not have recent DENV infection. Where there is no NAAT testing, a negative acute IgM antibody test might reflect specimen collection before the development of detectable antibodies, and this does not rule out DENV infection [5].

Moreover, because DENV IgM is often detectable several months after infection, determining the specific time of infection can be difficult, particularly among residents and those who frequently travel to places with risk for DENV [6]. With this, the DENV non-structural glycoprotein-1 (NS1) has been recommended as ideal or in conjunction with IgM in determining acute primary dengue when IgG is seronegative.

NS1 is a highly conserved glycoprotein that is needed for DENV replication and can be detected from the first day to 18 days after the appearance of fever [7]. Therefore, detection of DENV NS1 antigen represents a better approach for the diagnosis of acute DENV in primary infection. Primary DEN is defined when an individual is infected by one of the four serotypes of DENV at a time, while secondary DEN occurs when an individual has a history of DENV infection by two serotypes. Tertiary and quaternary are defined by DENV infection with three or four serotypes, respectively [8]. With this, the ideal protocol for differentiating primary from non-primary DEN is the RT-PCR, probably using multiplex RT-PCR. Nucleic acid amplification tests can provide confirmed evidence of infection and distinguish the specific virus serotypes. Considering the aforementioned evidence, it is recommended that researchers should make use of recommended test protocols in establishing the presence or absence of dengue in any form of study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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