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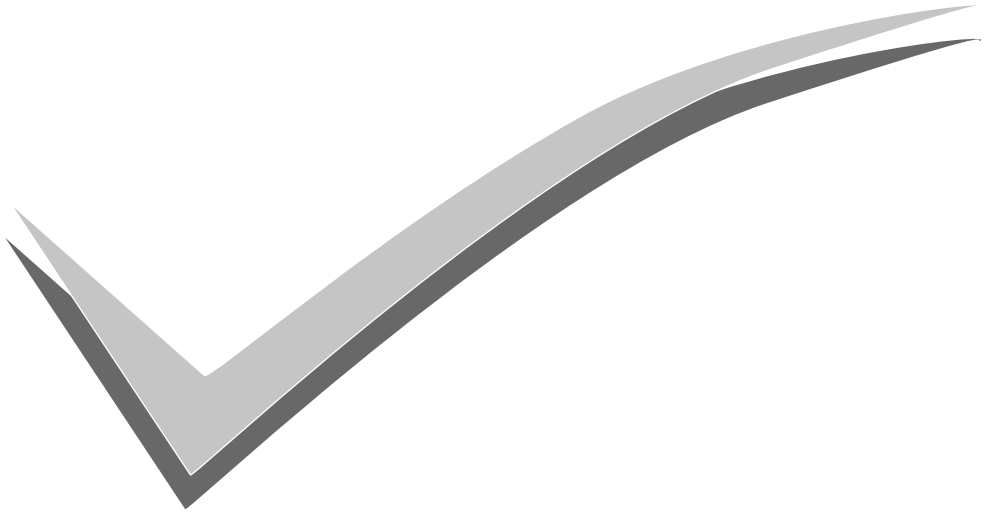

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INDEX		
S. No.	**Name of the Publication**	**Pg Nos**
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S. No.	**Name of the Evaluating Body**
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Rapid test for the detection of NS1 and IgM/IgG antibodies to Dengue virus in serum/plasma

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Diagnostic accuracy of commercially available immunochromatographic rapid tests for diagnosis of dengue in India

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ABSTRACT

Background & objectives: There is limited evidence regarding the accuracy of dengue rapid diagnostic kits despite their extensive use in India. We evaluated the performance of four immunochromatographic Rapid Diagnostic Test (RDTs) kits: Multisure dengue Ab/Ag rapid test (MP biomedicals; MP), Dengucheck combo (Zephyr Biomedicals; ZB), SD bioline dengue duo (Alere; SD) and Dengue day 1 test (J Mitra; JM).

Methods: This is a laboratory-based diagnostic evaluation study. Rapid tests results were compared to reference non-structural (NS1) antigen or immunoglobulin M (IgM) enzyme-linked immunosorbent assay (ELISA) results of 241 dengue-positive samples and 247 dengue-negative samples. Sensitivity and specificity of NS1 and IgM components of each RDT were calculated separately and in combination (either NS1 or IgM positive) against reference standard ELISA.

Results: A total of 238, 226, 208, and 146 reference NS1 ELISA samples were tested with MP, ZB, SD, and JM tests, respectively. In comparison to the NS1 ELISA reference tests, the NS1 component of MP, ZB, SD, and JM RDTs demonstrated a sensitivity of 71.8%, 85.1%, 77.2% and 80.9% respectively and specificity of 90.1%, 92.8%, 96.1 %, and 93.6%, respectively. In comparison to the IgM ELISA reference test, the IgM component of RDTs showed a sensitivity of 40.0%, 50.3%, 47.3% and 20.0% respectively and specificity of 92.4%, 88.6%, 96.5%, and 92.2% respectively. Combining NS1 antigen and IgM antibody results led to sensitivities of 87.5%, 82.9%, 93.8% and 91.7% respectively, and specificities of 75.3%, 73.9%, 76.5%, and 80.0% respectively.

Interpretation & conclusion: Though specificities were acceptable, the sensitivities of each test were markedly lower than manufacturers' claims. These results also support the added value of combined antigen-and antibody-based RDTs for the diagnosis of acute dengue**.**

Key words Dengue; diagnostic accuracy; immunochromatography; rapid diagnostic test; RDT; sensitivity; specificity; India

INTRODUCTION

Dengue is a mosquito-borne disease caused by any of 4 distinct virus serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) of the flaviviridae family. Transmission occurs through the bite of infected *Aedes* mosquitoes, and the disease is endemic throughout the tropics and subtropics. Globally, it is estimated that 96 million suspected dengue infections occur annually, and India alone contributes 34% of the global burden[1]. The Indian National Vector-Borne Disease Control Programme (NVBDCP) reported 101,192 laboratory-confirmed dengue cases and 172 deaths due to dengue in 2018[2]. A recent meta-analysis estimated a 56.9% (95% confidence interval (CI) 37.5–74.4) dengue seroprevalence in the general population, and a case fatality rate of 2.6% (95% CI 2.0–3.4) among laboratory-confirmed patients in India[3].

The revised World Health Organization (WHO) dengue case classification can help in identifying probable dengue cases in endemic areas[4]. The clinical presentation of dengue is non-specific, mimicking several other causes of acute febrile illness, such as leptospirosis, malaria, rickettsiosis, and chikungunya[5]. Progression can be difficult to predict since the majority of patients recover after a self-limiting, non-severe clinical course. However, a small proportion of patients develop hemorrhagic fever/dengue shock syndrome (DHF/DSS), a severe, life-threatening disease typically characterized by plasma leakage with or without hemorrhage. Early and accurate diagnosis of dengue infection and initiation of appropriate observation and treatment are therefore key components in the management of severe dengue infection.

Worldwide, there is a pressing need for highly sensitive, inexpensive, and easily performable point-of-care

diagnostic tools that have a long shelf life in order to aid the early and rapid diagnosis of dengue virus infections. These must be capable of functioning at temperatures above 30°C in the primary health care (PHC) setting and distinguishing between other diseases with similar clinical presentations[6]. Many laboratory methods including virus isolation, nucleic acid detection, antigen detection and serological detection are available. The government of India´s 2015 guidelines are consistent with WHO recommendations in recommending the use of an enzyme-linked immunosorbent assay (ELISA)-based antigen detection test (NS1) for diagnosing the cases from day 1 to day 5 of illness, and the antibody detection test IgM Capture ELISA (MAC ELISA) after the 5th day of disease onset for confirmation of dengue infection[7].

However, these tests are expensive, time-consuming, difficult to perform, technologically demanding, and often unavailable in public health settings. Rapid diagnostic tests (RDTs) are generally more affordable, less time-consuming, user-friendly, easy to perform, and do not always require a cold chain. These RDTs are immunochromatographic assays which detect the presence of NS1 antigen and/or anti-dengue antibodies (IgM and IgG) in the blood of suspected dengue patients. The NS1 glycoprotein is detectable in the sera of dengue-infected patients during the early clinical phases of the disease (i.e., Day 1 to 9 after the onset of symptoms). The IgM antibodies become detectable on Day 3 to 5 of illness in case of primary dengue infection and persist for 2 to 3 months, while IgG antibodies appear by the 14th day and persist for life[8]. RDTs have quickly become essential point of care (PoC) tests in dengue-endemic regions.

Several RDT kits manufactured both in India and elsewhere are registered and commercially available in India. Despite extensive use, the reliability and performance of many of these RDTs are yet to be independently evaluated. An independent laboratory network established by the World Health Organization's Special Programme for Research and Training in Tropical Diseases (WHO/TDR) and the Pediatric Dengue Vaccine Initiative (PDVI) evaluated selected commercial ELISAs and first-generation rapid diagnostic tests in 2009 and found that ELISAs generally performed better than rapid tests[9]. None of the participating laboratories was located within India. The same network later evaluated NS1 antigen-based RDTs and found that both the NS1 and IgM-based tests performed poorly compared to ELISA tests[10]. As such, while the market in India is flooded with a range of newer generation RDTs, there has been no independent evaluation in this country, and there remains very limited evidence on the diagnostic performance of these RDTs in India[11–13].

The present study aimed to address this gap and evaluate the performance of four commercially available RDTs in India that detect both DENV NS1 antigen and anti-DENV IgM, using well-characterized, archived serum specimens already fully characterized with a reference standard ELISA at two tertiary care medical colleges in West Bengal, India.

MATERIAL & METHODS

Study Design

This is a laboratory-based, diagnostic evaluation study, conducted using well-characterized archived clinical specimens from the Calcutta School of Tropical Medicine (CSTM) and Medical College and Hospital, Kolkata, India. The study used 488 stored serum specimens of patients who had presented either at CSTM or Medical College and Hospital, Kolkata with clinical suspicion of dengue between February 2015 and November 2016 and had been subsequently tested with an ELISA test.

Reference test

All samples had been tested with the NS1 antigen ELISA (Panbio Dengue early ELISA, (Brisbane, Australia)) and/or IgM antibody capture-ELISA (Panbio IgM Capture ELISA, (Brisbane, Australia)) as per government recommendations. In general, patients presenting with dengue symptoms for up to 5 days were tested with NS1 antigen ELISA (n=132), while those presenting with symptoms for over 5 days were tested with IgM antibody capture-ELISA (n=214). Some patients with no clear chronology of symptoms were tested with both NS1 and IgM ELISA (n=114). All samples were stored regardless of a positive or negative result.

Of the 488 bio-banked samples identified, 460 sera

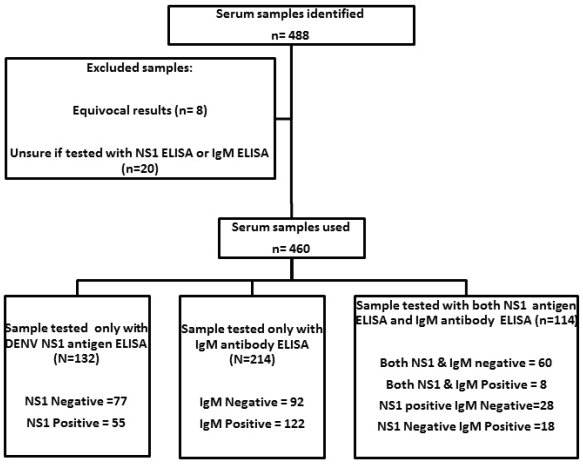

Fig.1: Flowchart describing characteristics of stored serum samples tested with reference standard results NS1 and/or IgM ELISA

Table 1: Characteristics of RDTs under evaluation

	SD BIOLINE Dengue Duo	Dengucheck Combo	Dengue day 1 test	MULTISURE Dengue Ab/ Ag
Manufacturer	Standard Diagnostics, Inc. (SD) Gyeonggi-do, Republic of Korea	Zephyr Biomedical (ZB) Goa ,India	J. Mitra & Co. Pvt. Ltd. (JM) New Delhi, India	MP Biomedicals (MP) California, USA
Assay principle	Lateral flow	Lateral flow	Lateral flow	Reverse Flow
NS1 antigen detection	Yes	Yes	Yes	Yes
IgM and IgG antibody detection	Yes	Yes	Yes	Yes+IgA
Format	Cassette	Cassette	Cassette	Cassette
Number of tests/package	10 or 25	25	10 or 25	20
Antigen	Recombinant DENV 1–4; envelope protein	Recombinant DENV; (serotype not specified)	Recombinant DENV 1–4	Recombinant DENV 1–4
Volume of sample required, ul	NS1-100 IgM/IgG-10	NS1-75 IgM/IgG-5	NS1-70 IgM/IgG-10	25
Storage conditions, °C	2-30	4-30	2-30	2-28
Sample used	Whole blood/ Serum/Plasma	serum or plasma	Serum orPlasma	Whole blood/ Serum/ Plasma
Duration of test, minutes	15-20	15	20	20
Manufacturer claimed sensitivity	92.4% (Dengue NS1 Ag) 94.2% (Dengue IgG/IgM)	100% (Dengue NS1 Ag) 93.5% (Dengue IgG/IgM)	96% (Dengue NS1 Ag) 95% (Dengue IgG/IgM)	94.16%
Manufacturer claimed specificity	98.4% (Dengue NS1 Ag) 96.4% (Dengue IgG/IgM)	100% (Dengue NS1 Ag) 95% (Dengue IgG/IgM)	98% (Dengue NS1 Ag) 97% (Dengue IgG/IgM)	Not Available

were used in the study (Fig. 1). These comprised 231 confirmed positive dengue samples (confirmed with either a NS1 antigen ELISA or an IgM-antibody ELISA detection test) and 229 dengue-negative samples (patients presenting with fever, but testing negative by NS1 and/or IgM ELISA). In total, 246 samples had been tested with the NS1 antigen ELISA and 328 with the IgM capture ELISA. All specimens were stored at -80° C in anonymised aliquots.

Rapid Diagnostic kits under evaluation (index tests)

We evaluated the performance of four lateral flow immunochromatographic test kits, chosen on the basis of their availability in the Indian market and the inclusion of both the NS1-antigen and IgM-antibody detection cassette in the same kit. These tests were the Multisure Dengue Ab/Ag Rapid Test (MP Biomedicals; MP), Dengucheck Combo (Zephyr Biomedicals; ZB), SD BIOLINE Dengue Duo (SD Bioline; SD), and Dengue Day 1 Test (J Mitra; JM). The characteristics of RDTs under evaluation are summarized in Table 1.

Procedure of testing Rapid Diagnostic Test kits

All four RDTs were read in parallel by two experienced laboratory technicians according to the manufacturer's instructions. The technicians were blinded to the results of the reference standard ELISA, and to the results of the RDTs recorded by the other technician. Moreover, digital photographs of all performed tests were taken which were then used by a third independent reader to resolve any discrepancies in interpretation of results.

We planned to test all samples for NS1 antigen, IgM and IgG antibodies in all 4 RDTs. In cases where the sample volume was not sufficient to perform all four RDTs (n=125), the order of testing was randomly shuffled to ensure a fair distribution. Furthermore, in order to determine the repeatability of results, 10% of all samples were tested twice with the same index test. The reproducibility was assessed by comparing the readings of both technicians.

Statistical analysis

We compared the results of each RDT with the reference standard ELISA results to estimate sensitivity and specificity. The sensitivity of the NS1 antigen detection component in each RDT was estimated in comparison to the prior NS1 ELISA result, and sensitivity of the IgM antibody detection component was assessed in samples with known IgM capture ELISA results in 2X2 table. All data was collected on predefined forms and data was entered into a Microsoft Excel database using double inde-

pendent data entry. We carried out analyses of sensitivity, specificity and Cohen's Kappa to determine intra-reader and inter-reader agreement using SPSS version 23 (IBM SPSS statistics). A *kappa* value between 0.6 and 0.8 was considered "good", whereas any value greater than 0.8 was considered "very good". A 95% confidence interval (CI) was also calculated for each parameter. We report the study according to the 2015 STARD guidelines[14].

Ethical statement

This study was approved by the Clinical Research Ethics Committee of the Calcutta School of Tropical Medicine, Kolkata, India, and the Medecins Sans Frontieres (MSF) Ethics Review Board. The study was prospectively registered at the Clinical Trial Registry of India (CTRI/2017/05/008699).

RESULTS

Of the 488 stored serum samples, 59.5% were taken from male patients. Median (IQR) age of the patients was 25 (15–37). The median (IQR) delay between onset of symptoms to presentation at health facility was 4 (3–7) days.

Evaluation of NS1 based assays

A total of 238, 226, 208, and 146 samples with known NS1 ELISA results were tested with the MULTISURE Dengue Ab/Ag (MP), Dengucheck Combo (ZB), SD BIOLINE Dengue Duo (SD), and Dengue day 1 test (JM), respectively for NS1 antigen detection. All RDTs demonstrated sensitivities between 71.8% (MP) and 85.1% (ZB), whereas overall specificities ranged from 90.1% (MP) to 96.1% (SD) as shown in Table 2 and Fig. 2.

Table 2: Overall diagnostic sensitivity and specificities of NS1 antigen RDTs compared with reference standard NS1 ELISA

	MULTISURE Dengue Ab/Ag Rapid Test	Dengucheck Combo	SD BIOLINE Dengue Duo	Dengue day 1 test
Manufacturer	MP biomedicals	Zephyr biomedicals (ZB)	SD bioline (Alare)	J Mitra (JM)
Total samples	238	226	208	146
Sensitivity [95% CI] percent	71.8 [61.4-80.2]	85.1 [76.1 -91.1]	77.2 [66.8-85.1]	80.9 [70.0-88.5]
Specificity [95% CI] percent	96.1 [91.7-98.2]	92.8 [87.3-96.1]	96.1 [91.3-98.3]	93.6 [85.9-97.2]

Evaluation of IgM based assays

A total of 287, 323, 318 and 225 samples tested with reference standard with known IgM ELISA results were tested with MP, ZB, SD, and JM respectively, for IgM antigen detection. All RDTs demonstrated sensitivities between 20% (JM) and 50.3% (ZB). Specificities ranged from 88.6% (ZB) to 96.5% (SD) as shown in Table 3 and Fig. 2.

Table 3: Diagnostic sensitivity and specificities of IgM antibodies RDTs compared with reference standard IgM Capture ELISA

	MULTISURE Dengue Ab/Ag Rapid Test	Dengucheck Combo	SD BIOLINE Dengue Duo	Dengue day 1 test
Manufacturer	MP biomedicals	Zephyr biomedicals (ZB)	SD bioline (Alare)	J Mitra (JM)
Total samples	287	323	318	225
ensitivity [95% CI] percent	40.0 [32.0-49.0]	50.3 [42.4-58.3]	47.3 [39.3-55.3]	20.0 [13.6-28.4]
Specificity [95% CI] percent	92.4 [87.1-95.6]	88.6 [83.1-92.5]	96.5 [92.6-98.4]	92.2 [85.8-95.8]

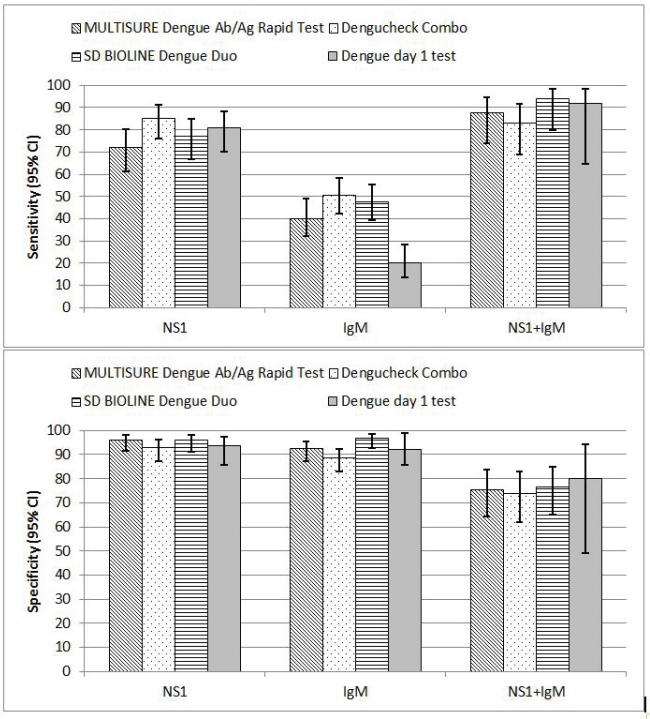

Fig. 2: The diagnostic sensitivity and specificity of different dengue rapid diagnostic test kits using NS1, IgM and Combined NS1+ IgM Approach

Performance of RDTs after combining the results of IgM antibody and NS1 antigen tests

Combining the NS1 antigen and IgM antibody results from assays by the same manufacturer when either assay was considered positive improved overall sensitivities, ranging from 82.9% (ZB) to 93.8% (SD). However, specificities ranged from 73.9% (ZB) to 80% (JM) as shown in Table 4 and Fig. 2.

Table 4: Diagnostic sensitivity and specificities of RDTs when NS1 antigen and IgM antibody results were combined considering a sample positive if either assay positive.

	MULTISURE Dengue Ab/ Ag Rapid Test	Dengu-check Combo	SD BIOLINE Dengue Duo	Dengue day 1 test
Manufacturer	MP biomedicals	Zephyr biomedicals (ZB)	SD bioline (Alare)	J Mitra (JM)
Total samples	113	106	100	22
Sensitivity[95% CI] percent	87.5 [73.9-94.5]	82.9 [68.7-91.5]	93.8 [79.9-98.3]	91.7 [64.6-98.5]
Specificity [95% CI] percent	75.3 [64.4-83.8]	73.9 [62.1-83.0]	76.5 [65.1-85.0]	80.0 [49.0-94.3]

Overall inter-reader agreement was very good with a Cohen's Kappa (*k)* of 0.96.

DISCUSSION

This study examined the diagnostic accuracy of four commercially available RDTs against reference standards and found much lower sensitivities compared to the claims made by the manufacturers (92.0–100%). The results demonstrated that NS1-based assays performed substantially better than IgM-based assays, providing better sensitivity for NS1-based assays (range: 71.8–85.1%) compared to IgM-based assays (range: 20–50.3%). Specificity for all RDTs was in the acceptable range (>88%) for both the NS1-based and IgM-based components. In general, a positive result with these RDTs is highly suggestive of dengue, but a negative result does not always rule out dengue infection.

Multiple studies have evaluated the sensitivities and specificities of dengue RDTs and found a very wide range of accuracy for NS1 antigen (27–99% for sensitivity and 67–100% for specificity) and IgM antibody detection (3-100% for sensitivity and 46-100% for specificity) depending on the test used[9–10, 12, 15–21] the UNICEF/UNDP/ World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) [22–25]. Most authors conclude that commercial RDTs have acceptable specificity, but poor sensitivity, which is consistent with the results of this study. Moreover, several studies confirmed that combining NS1 and IgM diagnostic tests yielded modest increases in sensitivity[18, 22, 26].

However, there are some limitations in our study design. Cross-reactivity with other clinically similar diseases such as chikungunya, typhoid fever, malaria, and leptospirosis was not assessed due to lack of these disease-specific samples. Additionally, the performance of the RDTs may have been affected by the fact that the nature (primary or secondary) and the serotype of infection was unknown[10, 12, 17, 19, 22–24]. However, based on previously published research, we can extrapolate that the majority (88%) of confirmed dengue cases reported in Kolkata were primary in nature[27]. Another study showed that all four types of DENV were circulating in Kolkata during the period of sample collection, where DENV2 (38%) was the dominant serotype followed by DENV1 (28%), DENV3 (22%) and DENV4 (11%)[28].

Based on our findings, suspected dengue patients may benefit from testing by an RDT that combines both IgM and NS1-detection regardless of clinical history, since combining both tests improves sensitivity. Further validation studies are required to determine the field effectiveness of these tests, and there is a need to generate contextualized evidence in the Indian setting without relying solely on assessments conducted by the manufacturers. However, as the quality of newer generations of RDTs improves, these tests have the potential to fulfill the ASSURED criteria (Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users) which has been enumerated by the WHO for point-of-care testing for dengue in endemic settings.

Conflict of interest: None

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A Study on Seroprevalence of Dengue Infection in a Tertiary Care Centre and Role of Rapid NS1 Antigen Test in Early Diagnosis

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Abstract: ***Introduction: Dengue virus infection is one of the most important vector-borne human arboviral infection and has emerged as a notable public health problem in recent decades. AIMS: To study the trend of seroprevalence of dengue infection and to highlight the usefulness of rapid NS1 antigen test in early diagnosis of dengue. Materials and Method: A retrospective study was done in the Department of Microbiology of a tertiary care centre during the study period of October to December in the year 2017, 2018 and 2019. The serum samples were subjected to immuno-chromatographic Dengue NS1 antigen, IgM / IgG Antibodies rapid kit test and Dengue IgM Mac ELISA test. Results: In October to December 2019, 1138 samples of suspected dengue cases were sent to our lab for detection by rapid kit tests. Out of which 161 (14.1%) samples were NS1 positiv, 38 (3.3%) were only IgM positive and 4 (0.4%) were IgG positive. We received 107 samples for Dengue IgM MAC Elisa of which 28 (26.2%) were positive and 25 (23.4%) were equivocal. In October to December 2018, 285 samples were received for detection by rapid kit tests .Out of which 16 (5.6%) samples were NS1 positive, 11 (3.9%) were only IgM positive and 17 (6.6%) were IgG positive ;and 158 samples for IgMMAC Elisa of which 26 (16.5%) were positive and 23 (14.6%) were equivocal. In October to December 2017,out of a total of 165 samples for detection by rapid kit tests ; 18 (10.9%) samples were NS1 positive, 19 (11.5%) were only IgM positive and 5 (3%) were IgG positive; and 261 samples for IgM MAC Elisa of which 21 (0.1%) were positive and 21 (0.1%) were equivocal. Conclusion: This study reported an increasing trend in seroprevalence of Dengue virus which affected many people in recent years and also highlights that the availability of commercial dengue NS1 antigen test kits has provided an additional laboratory diagnostic tool for early detection of Dengue.***

Keywords: Dengue, Seroprevalence, rapid, NS1, IgM, ELISA

List of abbreviations
DENV = dengue virus
DF = Dengue fever
DHF = Dengue haemorrhagic fever
DSS = Dengue shock syndrome
NS = Non - structural proteins

1. Introduction

Dengue virus infection is one of the most important vector-borne human arboviral infection.[1] Denguearboviruses are transmitted by the mosquitoes : Aedesaegypti and Aedesalbopictus.[2]This viral infection may be asymptomatic or may give rise to undifferentiated fever with or without other associated clinical manifestations, namely, Dengue fever(DF), Dengue haemorrhagic fever(DHF),or Dengue shock syndrome(DSS).[3]ClassicDengue fever is presented by a rapid onset of high grade fever, headache, retro-orbital pain, diffuse myalgia, weakness, vomiting, sore throat, an altered taste sensation, and a centrifugal maculo-papular rash.[4]

DENV infection has emerged as a notable public health problem in terms of the mortality and morbidity associated with it in recent decades.[5]According to World Health Organization (WHO), Dengue represents a pandemic threat and is the fastest spreading tropical disease.[6]Appropriate clinical management can reduce the mortality to less than 1% and can save the lives of DHF and DSS patients.[7]Hence early and rapid laboratory diagnosis of Dengue is crucial.

Dengue virus belongs to family flaviviridae and consists of 10 proteins; 3 structural and 7 non-structural.[8]Non-structural protein 1 or NS1 is a highly conserved glycoprotein, which is essential for virus replication. NS1 protein is associated with intracellular organelles and can be transported via cellular secretion pathway to the infected cell surface during the acute phase of DENV infection. NS1 protein was also found to be released from infected mammalian cells and may be found circulating in the sera of patients.[9] The NS1 antigen can be detected on days 0-9 after the onset of symptoms and is found together with endothelium, free or soluble in the serum of patients.[10]There is no cross-reaction of Dengue NS1 protein with those of other related flaviviruses as it was not found in patients with Japanese encephalitis or yellow fever virus infections.[17] Thus,

detection of NS1 has been a promising test to diagnose Dengue in its early febrile stage.[11]

Though dengue IgM detection is a commonly performed test for diagnosis of Dengue, it has limitations due to cross-reactivity between other circulating flaviviruses. Dengue virus specific IgM antibodies appear as early as three days of Dengue viral fever and can persist for 30-60 days and IgG antibodies appear at about seventh day, peak at 2-3 wk and persist for life.[12]

In the present study, we report the trend of seroprevalence of dengue infection in Goa Medical College, a tertiary care centre over a period of 3 consecutive years 2017-2019 in post-monsoon season from October to December and highlight the usefulness of rapid NS1 antigen test in early diagnosis of DENV infection.

2. Materials and Method

A retrospective study was done in the Department of Microbiology of Goa Medical College, a tertiary care centre in Goa over a period of 3 consecutive years during the months of October, November and December in the year 2017, 2018 and 2019. The serum samples obtained from various out-patient departments and in-patient wards obtained during October to December in the above consecutive years were subjected to serological tests to assess the magnitude of dengue infection and the rising or falling trend of seroprevalence over a period. Trend was obtained by calculating the percentage positivity of various serological tests done during the above period in each year.

The samples were subjected to immuno-chromatographic (Dengucheck combo) rapid kit for detection of Dengue NS1 antigen and IgM/ IgG antibodies in human serum. Dengue check combo is a new generation rapid immuno-chromatographic test system for detection in very early stage and differential diagnosis of primary or secondary DENV infection. The procedure and interpretation of test results of the rapid assays were carried out according to the manufacturer's literature guidelines. Also samples sent during above period by clinicians specifically for detection by Dengue ELISA test were tested by Dengue IgM Mac ELISA test by NIV DEN IgM Capture ELISA kit. Elisa test was performed as per the manufacturer's instructions.

The NS1 positivity indicates an acute dengue infection.[13]The primary infection was defined by a visible IgMb and without a visible IgGband, whereas a secondary infection was defined by a positive IgG band with or without a positive IgM band. Specific antibody response to dengue virus enables serodiagnosis and differentiation between primary and secondary dengue infections and detection of potentially life threatening conditions such as DHF and DSS.

3. Results

In October to December 2019, we received a total of 1138 samples for detection by rapid kit tests.Out of which 161 (14.1%)samples were positive for NS1, 38 (3.3%) were only IgM positive and 4 (0.4%) were IgG positive. The positivemalesamples were 136 (67%) and female were 67 (33%) with male: female ratio of 2:1. Amongst the paediatric age group out of 244 samples 30 (12.3%) were positive. 107 samples were received for Dengue IgMMAC Elisa of which 28 (26.2%) were positive and 25 (23.4%) were equivocal.

For the study period in 2018, 285 samples were sent to our lab for detection by rapid kit tests .Out of which 16 (5.6%)samples were positive forNS1, 11 (3.9%) were only IgM positive and 17 (6.6%) were IgG positive. The positive male and female samples were 32 (72.7%), 12 (27.3%) respectively (M:F ratio=2.6:1). 59 samples were paediatric patients of which 3 (5.1%) samples were positive. Out of 158 samples for Dengue IgMMAC Elisa test 26 (16.5%) were positive and 23(14.6%) were equivocal.

In the year 2017 from October to December, out of 165 samples for detection by rapid kit tests; 18 (10.9%) samples wereNS1 positive, 19 (11.5%) were only IgM positive and 5 (3%) were IgG positive. The positive male and female samples were 31 (73.8%), 11 (26.2%) respectively (M: Fratio=2.8:1). 26 samples belonged to paediatric age group of which 1 (3.8%) sample was positive. Amongst 261 samples for Dengue IgMMAC Elisa test 21 (0.1%) were positive and 21 (0.1%) were equivocal.

Table 1: Result of samples of suspected dengue cases received for detection of Dengue by rapid kit tests

Study period	Total samples	Ns1 positive samples	Only IgM positive	IgG positive with/ without IgM
Oct-Dec 2019	1138	161 (14.1%)	38 (3.3%)	4 (0.4%)
Oct-Dec 2018	285	16 (5.6%)	11(3.9%)	17 (6.6%)
Oct-Dec 2017	165	18 (10.9%)	19 (11.5%)	5 (3%)

Table 2: Result of samples of suspected dengue cases received for detection of Dengue by Dengue IgM MAC Elisa

Study period	Total samples	Positive	Equivocal
Oct - Dec 2019	107	28 (26.2%)	25 (23.4%)
Oct - Dec 2018	158	26 (16.5%)	23 (14.6%)
Oct- Dec 2017	261	21 (0.1%)	21 (0.1%)

4. Discussion

Laboratory diagnosis by serological tests is very crucial along with clinical correlation to confirm the diagnosis of Dengue infection.There is a considerable increase in number of suspected Dengue cases and the samples receivedin our tertiary care centre for detection by rapid kit tests. We received 1138 samples during study period of October-December in 2019 compared to 285 samples in 2018 and165 samples in 2017. Dengue has been held to be a disease of high population density tropical urban areas. However, increasing reports of Dengue cases and outbreaks were reported from rural areas of western india.[14] Also, poor sanitation facilities and rapid unplanned urbanization with heavy construction activities contribute to fertile breeding grounds for the mosquitoes.

There is increase in the seroprevalence in 2019 compared to 2018 -17ie. 14.1 % NS1 positive cases indicating acute infection compared to 5.6% and 10.9% in previous years. The trend of distribution of cases and the burden of Dengue

cases during the study period (2017 -2019) is similar to neighbouring states Maharashtra and Karnataka as per the NVBDCP data of *dengue cases and deaths in the country since 2015* showing increase in dengue cases in 2019 compared to previous years.[15]

Dengue IgM MAC Elisa test showed increasing trend of seroprevalence from 2017 to 2019 during the study period. However, there was a decrease in samples received for Dengue IgM MAC Elisa test owing to increased sensitivity and availability of rapid tests like NS1 antigen detection rapid kit in recent years. Samples collected up to day 3 after the onset of symptoms showed more sensitivity byNS1 antigen assay as was showed by a study of Dussart et al.[16] Also there is no cross-reaction of dengue NS1 protein with those of other related flaviviruses as the Dengue NS1 antigen was not found in patients with Japanese encephalitis virus or yellow fever virus infections.[17]The incidence of NS1 positivity i.e. acute infection by Dengue virus has increased considerably in 2019 to14.1% from 5.6% in 2018.

Amongst the paediatric age group the trend of seroprevalence showed that infection rate has increased to 12.3% in 2019 compared to 5.1% and 3.8% in 2018 and 2017 respectively. In some parts of the world, Dengue is mainly a paediatric health problem.[19]

The male female ratio showed male preponderance with ratio around 2:1 in all the three consecutive years and this finding is in concordance with that of an earlier study.[18]Themale preponderance indicates more transmission of Dengue at work sites.However, the study findings are the representation of patients who visited our tertiary care centre during the study period rather the truly infected population.

The study presents the occurrence of Dengue during October –December. It was observed that dengue transmission occurred round the year with highest incidence in the post-monsoon period i.e. to December with a peak incidence around September –October.[18]An increase in Dengue cases in post monsoon months is due to the presence of stagnant water after rainfall which favors the breeding of mosquito vector. Hence, vector control measures should be implemented during the monsoon and post monsoon months.

5. Conclusion

This study reported an increasing trend in seroprevalence of Dengue virus which affected health of many people in recent years; thismay be a warning sign of the future epidemics; hence there is a need to develop vaccine that can protect against all serotypes. The availability of commercial Dengue NS1 antigen test kits has provided an additional laboratory diagnostic tool for early detection of DENV. Such tests may be used in laboratories that have limited resources, lack viral culture, or RT-PCR facilities. Also since most cases were reported during post monsoon period, continued and coordinated efforts coupled with public awareness should be made to control the transmitting vectors to prevent Dengue.

6. Future Scope

Our study provides prevalence based on the patient load in our tertiary care centre alone, hence a more coordinated study including data from all the hospitals and health centres of the state will provide the actual prevalence of the truly infected population.

Source of support-nil

Conflict of interest- nil

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Author Profile

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Performance Evaluations

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EXTERNAL EVALUATIONS

DENGUCHECK® COMBO

Rapid test for the detection of NS1 and IgM/IgG antibodies to Dengue virus in serum/plasma

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NILAI DIAGNOSTIK PEMERIKSAAN IMUNOKROMATOGRAFI CEPAT DENGUECHECK COMBO DARI ZEPHYR BIOMEDICALS PADA PASIEN TERSANGKA INFEKSI DENGUE DI INDONESIA

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Infeksi virus dengue menyebabkan Demam Dengue (DD), Demam Berdarah Dengue (DBD) dan Sindroma Syok Dengue (DSS). Virus dengue termasuk dalam genus *Flavivirus* famili *Flaviviridae* dan mempunyai 4 serotipe yaitu DEN-1, DEN-2, DEN-3, dan DEN-4. World Health Organization (WHO) menyatakan lebih dari 2,5 miliar orang atau lebih dari 40% penduduk dunia berisiko terjangkit penyakit ini. Berdasarkan data WHO, pada tahun 2015 terjadi peningkatan jumlah kasus menjadi 3,2 juta. Di Indonesia pada tahun 2018 terdapat 53.075 kasus dengan *insidens rate* 20,01/100.000 orang dan *case fatality rate* 0,65%. Pemeriksaan NS1-IgG/IgM dengue dengan teknik imunokromatografi cepat merupakan salah satu cara pemeriksan laboratorium untuk mendeteksi adanya infeksi virus dengue.

Penelitian ini berupaya mendapatkan nilai diagnostik kit imunokromatografi Denguecheck Combo dari Zephyr Biomedicals terhadap *Real Time Reverse Transcription-Polymerase Chain Reaction* (rtRT-PCR) dengue. Penelitian ini berlangsung dari Januari 2020 – Mei 2021. Nilai diagnostik ditunjukkan melalui nilai sensitivitas, spesifisitas, nilai duga positif (NDP), nilai duga negatif (NDN), dan akurasi terhadap serum pasien demam akut berusia ≥14 thn dengan kriteria inklusi mengalami demam ≤48 jam. Uji NS1 menggunakan sampel demam hari 1 – 2, sedangkan uji IgG/IgM menggunakan sampel demam hari 5 – 7.

Jumlah partisipan pada penelitian adalah 90 orang. Terdiri dari 60 orang kelompok rtRT-PCR virus Dengue positif dan 30 orang kelompok negatif. Penelitian ini berhasil mendapatkan nilai diagnostik untuk NS1 sebagai berikut, sensitivitas sebesar 90%, spesifisitas 100%, NDP 100%, NDN 91%, dan akurasi 95%. Sedangkan nilai diagnostik untuk IgG/IgM adalah sebagai berikut, sensitivitas sebesar 100%, spesifisitas 100%, NDP 100%, NDN 100%, dan akurasi 100%.

Alat imunokromatografi cepat Denguecheck Combo dari Zephyr Biomedicals mempunyai kemampuan yang sangat baik untuk mendeteksi adanya infeksi virus dengue sejak demam ≤48 jam, sehingga Denguecheck Combo dari Zephyr Biomedicals ini dapat menjadi alat pemeriksaan yang baik dalam menegakkan diagnosis infeksi dengue.

Kata Kunci : NS1 dengue, IgG/IgM dengue, imunokromatografi, rtRT-PCR

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COMMUNITY BASED DENGUE STUDY

SERTIFIKAT

Telah dilakukan penelitian untuk mendapatkan nilai diagnostik imunokròmatografi cepat **Denguecheck Combo dari Zephyr Biomedicals** dengan data penelitian sebagai berikut:

Nomor LOT	: 271104
Waktu penelitian	: Januari 2020 – Mei 2021
Subjek penelitian	: Partisipan dengan demam ≤ 48 jam
Jumlah sampel	: 90 partisipan
Baku Emas	: *Polymerase Chain Reaction* (PCR)

Adapun hasil yang di dapatkan sebagai berikut :

NS-1 dengue

Nilai Diagnostik Sensitivitas	: 90 %
Nilai Diagnostik Spesifisitas	: 100 %
Nilai Duga Positif (NDP)	: 100 %
Nilai Duga Negatif (NDN)	: 91 %
Akurasi	: 95 %

IgG/IgM dengue

Nilai Diagnostik Sensitivitas	: 100 %
Nilai Diagnostik Spesifisitas	: 100 %
Nilai Duga Positif (NDP)	: 100 %
Nilai Duga Negatif (NDN)	: 100 %
Akurasi	: 100 %

Jakarta, 24 Mei 2021

COMMUNITY BASED DENGUE STUDY GROUP

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