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Current Global Status of Dengue Diagnostics

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Authors' contributions

This work was carried out in collaboration between both authors. Authors AA and MDS designed the study. Author MDS performed the literature searches, statistical analysis, and wrote the first draft of the manuscript. Authors MDS and AA edited subsequent drafts together and finalized the manuscript.

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Review Article

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ABSTRACT

Aims: Dengue Virus is a re-emerging infectious disease that is transmitted through mosquitos. Dengue is a significant health concern because of the number of people it affects globally. Clinical diagnosis of dengue is not possible because the symptoms are similar to other febrile-diseases. Therefore, the only way to truly diagnose dengue is via laboratory methods. Many diagnostics tests exist to accomplish this; however, these tests have disadvantages. Rapid, point-of-care, commercially available diagnostic test kits have come onto the market to bridge the gap for those without high tech laboratories and personnel. This paper extends the knowledge of a meta-analysis conducted in 2011 on the performance of commercially available diagnostic tests. The purpose of this review was to compare and contrast the accuracy of commercial dengue diagnostic tests.
Study Design: Systematic Review and Analysis.
Place and Duration of Study: Department of Global Health, University of South Florida, Tampa, Florida, USA between August 2013 and July 2014.
Methodology: A literature review was conducted using multiple database searches using the search terms "dengue diagnostics" and "evaluation".
Results: Only articles written in English evaluating the accuracy, via sensitivity and specificity, of commercially available diagnostics tests were included. Fifteen articles and a meta-analysis were included in this paper for review. Many diagnostic tests were evaluated in these articles. Bio-Rad's STRIP was the most evaluated test. Most tests were evaluated once in a country which doesn't create enough reliability to make any inferences. The best performing test across all studies and

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countries seems to be Bio-Rad's NS1 STRIP.
Conclusion: Overall, these tests perform fairly well and more evaluation needs to occur to get a better idea of the true accuracy of the test.

Keywords: Dengue; diagnostics; commercial; rapid; point-of-care; tests.

1. INTRODUCTION

Dengue virus (DENV) is present in many countries around the world and is continuing to spread [1]. Dengue fever (DF) also known as "break bone fever" is caused by a single-stranded RNA virus that is transmitted through Aedes species mosquitos, primarily *Aedes aegypti*. There are four dengue virus serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) and many different genotypes that occur worldwide. Different genotypes can occur in similar places at different times indicating multiple DENV introductions [2].

1.1 1997 World Health Organization (WHO) Dengue Case Classification System

Dengue virus can lead to the more serious forms of disease severity; dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). These classifications were developed by the WHO[3]. The WHO 1997 case definition for DF include a probable, confirmed, and reportable definition. A probable DF case is an acute febrile illness with at least two of the following signs and symptoms: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestation or leukopenia and supportive serology or in close proximity to a confirmed case's location and time [3]. A confirmed DF case is based on laboratory criteria which would include virus isolation from patient serum or autopsy sample, fourfold or more change in reciprocal immunoglobulin M (IgM), immunoglobulin G (IgG) titers to a dengue antigen, dengue antigen or genome in live or deceased serum, tissue, or cerebrospinal fluid (CSF) via immunochemistry, immunofluorescence, ELISA or RT-PCR[3]. A reportable DF case is one that is either probable or confirmed [3]. The 1997 case definition of DHF requires that a patient present with the following conditions and symptoms; fever or history of one for 2-7 days which can be biphasic, thrombocytopenia (100,000 cells per mm^3 or less), evidence of plasma leakage from vascular permeability because of a rise in haematocrit greater than or equal to 20% above their normal, and one of the following: a positive tourniquet test, petechiae, ecchymoses, purpura, haematemesis, melaena, or a bleeding site [3]. The 1997 WHO case classification system defined DSS as the four criteria for DHF and a rapid and weak pulse with narrow pulse pressure due to hypotension, cold, clammy skin, and restlessness [3]. These definitions are difficult to use because they are not universally applicable, nor are they used consistently thus the development of a new classification system was needed [4,5].

1.2 2009 WHO Dengue Case Classification System

The new 2009 WHO classification system was developed to make the definitions more applicable to children by using signs over symptoms and to make it easier for clinicians to predict patients who may develop severe dengue [6,7]. The 2009 system includes definitions for dengue with or without warning signs and severe dengue. Probable dengue cases include: someone living in or has traveled to a dengue endemic area with fever and experiencing at least two of the following signs and symptoms: nausea, vomiting, rash, aches, pains, positive tourniquet test, any warning sign, and supportive serology or a confirmed case near the location or time [8]. Warning signs include abdominal pain and/or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy, restlessness, liver enlargement of greater than or equal to 2 centimeters, increased haematocrit with rapidly decreased platelet count [8]. A severe dengue case is defined as any of the following: severe plasma leakage, severe bleeding that was evaluated by a clinician, or severe organ involvement [8]. However, these clinical case definitions are sometimes indistinguishable from other febrile illnesses therefore requiring laboratory confirmation [4]. Both of these systems have been reviewed, to further understand their applicability and usefulness, by [9-13].

1.3 Laboratory Tests

Laboratory confirmation can come from a number of different assays or tests. Dengue virus

is comprised of 10 proteins; 3 are structural and 7 non-structural. One of the non-structural proteins, NS1, has been targeted for use in diagnosing dengue in humans because this protein is secreted in the bloodstream and can be found on day 1after the onset of fever [14,15]. This viral antigen can be detected via enzyme-linked immunosorbent assays (ELISA) and immunochromatographic tests (ICT). These tests are available in rapid form and can detect NS1 up to 9 days after onset [16]. NS1 can be detected before viral RNA because it is produced so quickly [17,18]. Furthermore, some studies have shown that NS1 is proportionally associated with disease severity, i.e. the more NS1 is detected, the more severe is the dengue disease [19]. However, other studies have not shown a relationship between NS1 and disease severity and also that the NS1 test could not discern primary and secondary infections from each other [19].

Haemagglutination assays (HA) are also used to detect the presence of dengue virus antigen. ELISAs and ICTs can also use IgM, IgG, and/or immunoglobulin A (IgA) as markers to diagnose dengue. There are two types of ELISA for diagnosing dengue. One detects antibodies (IgM, IgG, or IgA) and the other detects antigen (NS1). However, ELISA, like other serological tests, has issues with specificity and cross-reactivity, but it can be more useful than the haemagglutination inhibition assay (HI) in distinguishing between primary and secondary infections [19,20]. HI can detect anti-dengue antibodies as well. This test has been regarded as a gold standard with great sensitivity while having the same issues as ELISAs regarding cross-reactivity and not being able to identify virus serotype specific antibodies [18,21]. HI also has the ability to screen many samples easily. The principles behind HI and antibody-capture ELISAs are different. Antibody-capture ELISAs sandwich antibodies and antigen on a plate, while HI uses red blood cells to agglutinate antibodies and antigen. Both still however detect the presence of dengue antibodies.

Antibody titers vary throughout the illness and between primary and secondary infections as shown in Fig. 1 [22]. Fig. 1 illustrates the level of various immunological markers that diagnostic tests can use to determine dengue status. Knowing this can help one understand which test to use and why certain tests can only be used during certain points of the disease progression [22]. For instance, if the specimen was collected early in the infection before an antibody response has occurred, then serological tests like ELISA and plaque reduction neutralization test (PRNT) may result in false negatives as shown in Fig. 1 [18,22]. When an antibody response has occurred, PRNT can identify serotype specific antibodies unlike ELISA and HI [18]. PRNT can distinguish between serotypes because each serotype of DENV is tested with the sample individually on a semi-solid media that allows the virus to propagate.

If a sample was collected early enough during viremia, when viral load would still be high, other diagnostic tests can be used to detect the presence of viral RNA to diagnose dengue, such as the reverse transcriptase-polymerase chain reaction (RT-PCR). RT-PCRs can show the results in real time (rRT-PCR), they can be nested (two pairs of primers for one locus) or semi-nested, and they can be simplex (testing for one serotype) or multiplex (testing for multiple) [23]. RT-PCRs can identify the virus's serotype. This test is sensitive, however, it is very technical requiring sophisticated instrumentation in a laboratory setting, highly trained personnel, and is very costly [18]. Virus isolation can also be used for diagnostic and typing purposes, but this approach can take a few days to grow the virus, and dengue is heat-labile which requires care in specimen handling [24]. One major issue with RT-PCR and virus isolation is the short viremic period which is required for diagnosis through these tests [7]. These tests can be used in different situations. RT-PCR, HA, HI, and PRNT require lab settings while ELISAs and ICTs can be used in the field and at point of care settings [18]. A summary of these tests' advantages and disadvantages has already been complied by the WHO Special Programme for Research and Training in Tropical Diseases (TDR) as shown in Fig. 2 [16]. Most of these tests are complex and require some degree of technical expertise and equipment to conduct. Therefore, companies have been creating rapid tests to try and address these issues. These rapid tests are not without their shortcomings however. Therefore, the purpose of this review is to update a meta-analysis, written by Stuart D. Blacksell, by comparing and contrasting how well commercial diagnostic tests perform [22].

Most of these commercially available rapid diagnostic tests can use various bodily fluids and tissues as samples such as whole blood, serum, and plasma, and some can use urine, CSF, and saliva. Serum is most commonly used because

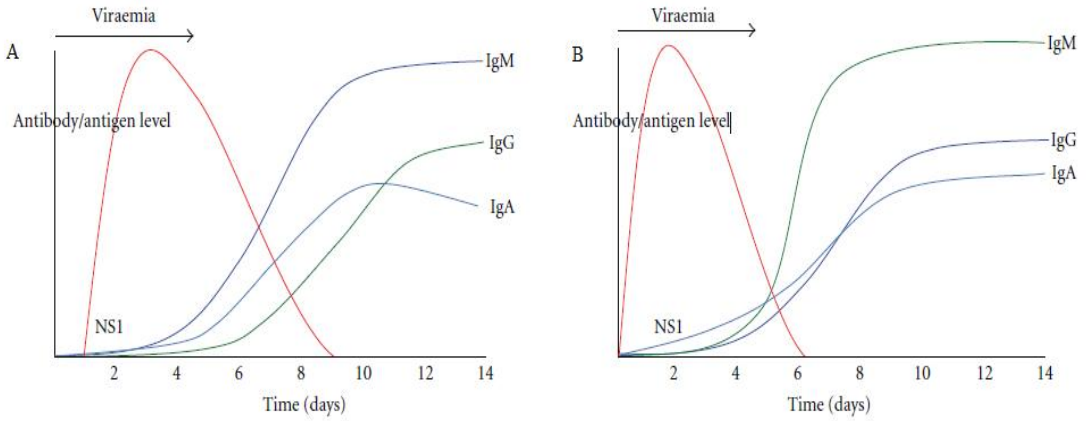

Fig. 1. Antibody and antigen titer change across time. A is during a primary infection and B is during a secondary infection [22]

Diagnostic tests	Advantages	Limitations
Viral isolation and identification	• Confirmed infection • Specific • Identifies serotypes	• Requires acute sample (0–5 days post onset) • Requires expertise and appropriate facilities • Takes more than 1 week • Does not differentiate between primary and secondary infection • Expensive
RNA detection	• Confirmed infection • Sensitive and specific • Identifies serotype and genotype • Results in 24–48 hours	• Potential false-positives owing to contamination • Requires acute sample (0–5 days post onset) • Requires expertise and expensive laboratory equipment • Does not differentiate between primary and secondary infection
Antigen detection		
Clinical specimens (for example, using blood in an NS1 assay)	• Confirmed infection • Easy to perform • Less expensive than virus isolation or RNA detection	• Not as sensitive as virus isolation or RNA detection
Tissues from fatal cases (for immunohisto-chemistry, for example)	• Confirmed infection	• Not as sensitive as virus isolation or RNA detection • Requires expertise in pathology
Serological tests		
IgM or IgG seroconversion	• Confirmed infection • Least expensive • Easy to perform	• IgM levels can be low in secondary infections • Confirmation requires two or more serum samples • Can differentiate between primary and secondary infection*
IgM detection (single sample)	• Identifies probable dengue cases • Useful for surveillance, tracking outbreaks and monitoring effectiveness of interventions	• IgM levels can be low in secondary infections

*Primary infection: IgM-positive and IgG-negative (if samples are taken before day 8–10); secondary infection: IgG should be higher than 1,280 haemagglutination inhibition in convalescent serum.

Fig. 2. Advantages and disadvantages of dengue diagnostic tests [16]

viremia and antibodies can be easily detected and when paired (acute and convalescent samples) can differentiate primary and secondary infections via seroconversion of antibodies [16]. It is also the most well-established, which saliva and urine are not. Urine is also rarely used because it cannot be used for IgM detection, a commonly used analyte [19]. CSF is only used when neurological symptoms have occurred, if not, the antibodies would be too low to detect. The rapid tests generally use serum, plasma, or whole blood for these reasons. These tests are sometimes less accurate and therefore require a confirmatory test.

1.4 Accuracy Calculations

Sensitivity (SN), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) are calculations that can be used to determine the accuracy of a test. The formulas for these calculations are shown in Table 1.

Sensitivity is calculated by dividing the number of true positives (TP) (which is the number of samples that have tested positive and that are truly positive) by the number of samples that are positive for the condition regardless of test's result (which is made up of TP and the number of samples that have tested negative, but are in fact positive with the condition, false negative, FN). Specificity (SP) can be calculated by dividing the number of true negatives (TN), which is the number of samples that have tested negative and are truly negative, by the number of samples that do not have the condition regardless of test results, which is made up of TN and the number of samples that have tested positive, but do not have the condition (false positive, FP). Positive predictive value can be determined by dividing the number of TP by TP plus FP. Negative predictive value can be determined by dividing the number of TN by TN plus FN. Sensitivity and specificity can vary if the populations being tested are dramatically different from one another and if the disease is more severe, easier to see, easier to diagnose, or has increased sensitivity [25]. A limitation of the PPV and NPV calculations is that they can vary depending upon the prevalence of the disease [25].

1.5 Current Diagnostic Methods

Currently, Brazil uses serology to diagnose dengue. They generally do not use RT-PCR or NS1 ELISA often because they are costly and require highly trained personnel [26]. Reference labs in India use MAC-ELISAs to diagnose dengue [27,28]. India also integrated their surveillance system with their sentinel hospital system [29]. Malaysia and Thailand use PCR, HI, and NS1 methods for surveillance and diagnostic purposes in their public health labs [18]. Malaysia has standardized protocols and reporting systems and Thailand's system can generate epidemiological trends [29]. In developing countries, like Mexico, serological testing is commonly used [26]. Dengue is a notifiable disease in Taiwan that is diagnosed via RT-PCR, IgM/IgM ELISA, and/or virus isolation in a reference lab. In August 2008 Taiwan started using the wickstylel CT Dengue NS1 Ag STRIP (Bio-Rad Laboratories, Marnes-la-Coquette, France) for outbreak surveillance [30]. In non-endemic countries such as the United States rRT-PCR, HI, IgM and IgG ELISAs are used to diagnose dengue [21].

2. MATERIALS AND METHODS

The terms, "dengue diagnostics" and "evaluation" were searched on the database Science Direct between 2011-Present. This resulted in 976 relevant articles. The content filter was applied to only produce articles from journals. This left 760 articles which were then organized by relevance. Of the 760 articles the first 100 articles' abstracts were read to determine relevance to this review. Inclusion criteria: Articles that were included in this review mentioned a specific test being evaluated. Only articles written in English were considered for this review. Exclusion criteria: Articles that studied concurrent infections of dengue with another disease were not included. Of the articles reviewed, 10 were additionally included in this report with the meta-analysis [22]. These same procedures were used on the databases PubMed, Academic Search Premier, Google Scholar, and the Directory of Open Access Journals which resulted in an additional 5 articles. This resulted in 16 total articles that are included in this analysis along with the aforementioned meta-analysis. A brief schematic of this is shown in Fig. 3. Fig. 3 shows the process of including and excluding articles that was used for each database search. Among these articles was a meta-analysis. The studies in this meta-analysis were out of the original year range, but were still included in this review for thoroughness.

3. RESULTS AND DISCUSSION

Of the 15 articles and one meta-analysis included in this review 5 were conducted in Thailand, 4 in each Brazil and Vietnam, 3 in Malaysia, 2 each in Martinique, Mexico, India, Singapore, Sri Lanka and Taiwan, and 1 in Bangladesh, China, Colombia, French Guiana, the United States of America (USA), and Venezuela. Most of these countries are endemic with dengue except the USA and China. However, some states in China are endemic [26]. Each of the studies tested the accuracy of at least one commercially available assay as listed in Table 2. Most of the serological/virological tests are either ICT or ELISA. Three tests are molecular real time RT-PCR kits. All of the tests accept serum as the sample material. Not all companies' websites listed the sensitivity and specificity of their tests. Panbio Dengue Early Rapid kit should be used alongside other dengue serological tests [31].

Table 1. Formulas for sensitivity, specificity, PPV and NPV

Calculation	Sensitivity	Specificity	PPV	NPV
Formula	$\frac{TP}{(TP+FN)}$	$\frac{TN}{(TN+FP)}$	$\frac{TP}{(TP+FP)}$	$\frac{TN}{(TN+FN)}$

Legend: TP = true positive, TN = true negative, FP = false positive, FN = false negative

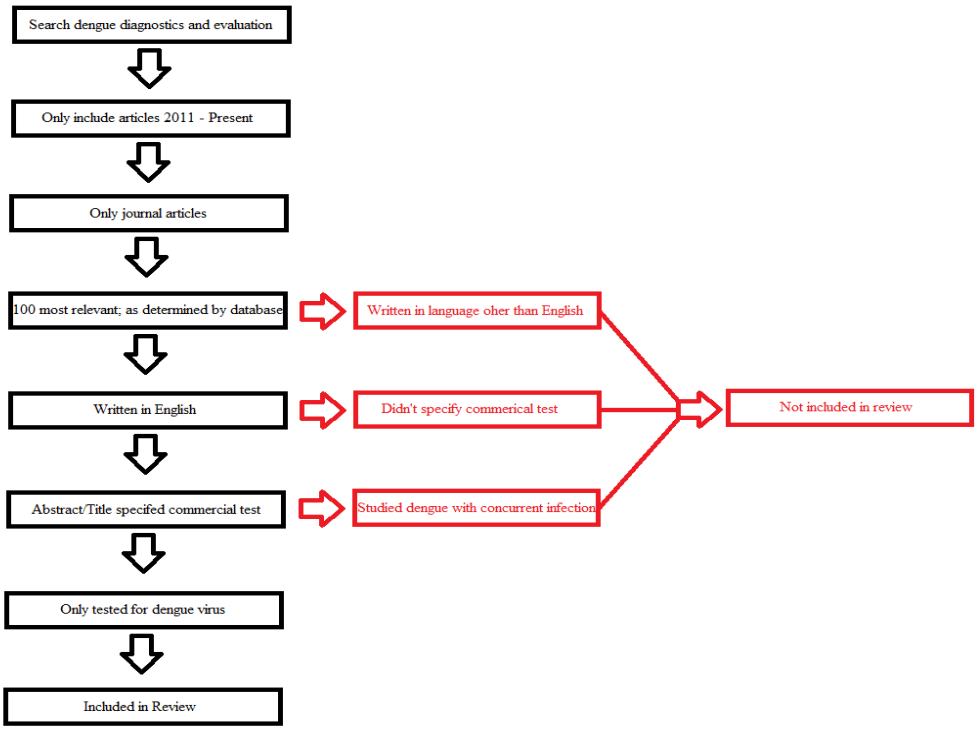

Fig. 3. Schematic view of inclusion and exclusion criteria of articles for this review

Panbio Dengue Duo Cassette simultaneously determines IgM and IgG in a single addition of the sample and differentiates between primary and secondary infections [32]. Panbio Dengue Early ELISA is easy to use because only a single dilution of serum is required and is cost effective because the wells break apart [33]. This test can be used in endemic and non-endemic areas [33]. Panbio Dengue IgG Capture ELISA is used to detect secondary infections of dengue [34].

Panbio Dengue IgM Capture ELISA does not require serial dilutions, has break-apart wells, and color-coded reagents [35]. Panbio Pan-E ELISA has break-apart wells [36]. SD BIOLINE Dengue Duo can detect dengue specific antibodies and antigen simultaneously in acute or convalescent serum, plasma, or whole blood [37]. SD Dengue IgG Capture ELISA and SD Dengue NS1 Ag ELISA include all of the required reagents for the test [38,39]. SD Dengue IgM Capture ELISA has been included in the WHO procurement scheme [40].

Both Bio-Rad products detect NS1 in human serum or plasma [41,42]. Omega's PATHOZYME Dengue IgM kit is an ELISA suitable for screening that has color-coded reagents and coated plates [43]. Geno-Sen's DENGUE 1-4 Real time PCR kit is to be used with the Rotor Gene 2000/300/6000 [44]. Real Star Dengue RT-PCR kit 1.0 can be used with various real-time PCR platforms [45]. Simplexa Dengue Kit is to be used with the 3M Integrated Cycler [46]. DENV Detect IgM Capture ELISA by In BiOS is the first *in vitro* test to have Food & Drug Administration (FDA) approval and was developed with the new generation of CDC licensed recombinants

expressed in mammalian cells [47]. Dengue Fever IgG and IgM combo Device by Merlin can be used to determine primary or secondary infection, but is not allowed for sale or use in the USA [48]. ASSURE Dengue IgA Rapid Test is a rapid point of care test that is the only IgA ICT included in this review [49]. ASSURE, SD BIOLINE Dengue Duo, IMMUNO Quick, and Dengue Eden Test Bioeasy show results in 10-20 minutes unlike Panbio Pan-E ELISA, Panbio Dengue IgM Capture ELISA, and Panbio Dengue Early ELISA which show results in 2 hours and 10 minutes [15,35-37,49,50].

The results of the literature review are summarized on Tables 3-7. The Tables all include the country where the study was conducted, the sample size (n), SN, SP, PPV, and NPV. Tables 4 and 5 include the analyte because these combo tests can use more than one analyte to determine dengue status. Table 7 also includes analyte because many tests are listed and each test has a unique analyte it detects. The country was listed on the Table as a means to conduct comparisons and to understand the population being studied. Sample size was included on all tests as an indicator of validity. Sensitivity and specificity were included because these are the characteristics in which the accuracy of the test is being evaluated in this review. PPV and NPV are included because these calculations also describe the performance of a test, but are not being used for comparison in this review. Table 3 summarizes the results found through the literature review about the STRIP by Bio-Rad. Table 4 is a summary of the studies that evaluated the accuracy of the Platelia Dengue NS1 Ag made by Bio-Rad. Table 5 summarizes what many studies have found when assessing the accuracy of the SD BIOLINE Dengue Duo NS1 antigen and IgG and IgM combo device. Table 6 shows the results of different studies conducted on Panbio Dengue Duo Cassette. Table 7 summarizes many different tests across many studies. Almost every study has included the sensitivity of the diagnostic assays they tested and almost all have included the specificity. About half of the studies reported PPV and NPV. Some of the studies did not report specificity, PPV, and NPV; however they were calculated if the study provided the raw data. Each calculation not included in the original article is marked with an "*" on the Tables. The STRIP by Bio-Rad was the most tested assay according to this literature review (Table 3). Platelia Dengue NS1 Ag (Table 4), BIOLINE Dengue Duo NS1 antigen and IgG and IgM combo device (Table 5), and Panbio Dengue Duo Cassette (Table 6) were also studied very often. The sensitivities and specificities of the Panbio Dengue Duo Cassette and the BIOLINE Dengue Duo NS1 antigen and IgG and IgM combo device were reported on each different analyte and on all of them.

4. DISCUSSION

4.1 Performance by Country

Multiple studies were conducted in Brazil and the Bio-Rad NS1 STRIP had the best overall sensitivity at 99.5%. When evaluated in a different study, this test was only sensitive 91% of the time [26,51-53]. Bio-Rad's Platelia NS1 ELISA came in a very close second (99.3%) with regards to sensitivity [51]. Master Diagnostic's BioEasy Eden, the Bio-Rad NS1 STRIP, and the Panbio Early Rapid were the most specific tests in studies that occurred in Brazil [26,51-53]. In Colombia, the SD BIOLINE Dengue Duo test performed the best with regards to sensitivity and specificity [54]. Platelia NS1 ELISA was the most sensitive test in French Guiana (82.4%) and Panbios's Pan-E Early ELISA was the most specific (97.9%) [55]. In India, the Panbio Dengue Duo Cassette had the best sensitivity when detecting IgG, but when detecting IgM it had the best specificity across both studies (75%) [56,57].The three studies conducted in Malaysia have found that the Bio-Rad NS1 STRIP is the most sensitive (90.4%) and specific test (99.5%) [51,58,59]. All of the tests evaluated in Martinique had 100% specificity except the RealStar RNA kit (98%) and the most sensitive test was the Simplexa RNA kit(93.2%) [60,61]. Since Simplexa is an RNA kit, it would not be efficient in any capacity (cost and ease) to use in Martinique, therefore the best test to use, that is not an RNA kit, would be Bio-Rad's Platelia NS1 ELISA (sensitivity: 61.2%, specificity: 100%) [60].

The SD BIOLINE Dengue Duo was the most sensitive test in Mexico, but it was one of two tests that did not have 100% specificity (89.7%); the other was ASSURE (86.8%) [62,63]. Two studies were conducted in Singapore and the ASSURE IgA test had the best sensitivity (86.7%), while the Platelia and Panbio Early ELISA had the best specificity (100%) [64,65]. When evaluations of commercial assays were conducted in Sri Lanka, Standard Diagnostics BIOLINE Dengue duo test was the most accurate (sensitivity: 92.9%, specificity: 99.4%) [66,67].

Table 2. Summary of commercial tests found in literature review[a]

Manufacturer, country	Product name	Test type[b]	Sample type[c]	Analyte	SN %[d]	SP %[e]
Alere, Australia	Panbio Dengue Early Rapid Kit	LF ICT	S	NS1 Ag	91.9	98.4
	Panbio Dengue Duo Cassette	LF ICT	S/P/WB	IgM/IgG	85.5* 98.8**	91.6
	Panbio Dengue Early ELISA	ELISA	S	NS1	76	98.4
	Panbio Dengue IgG Capture ELISA	ELISA	S	IgG	93.3**	100[NEN]
	Panbio Dengue IgM Capture ELISA	ELISA	S	IgM	55.7 - 94.7*	100
	Panbio dengue virus Pan-E ELISA	ELISA	S	NS1	NR	NR
Standard Diagnostics, South Korea	BIOLINE Dengue Duo NS1 antigen and IgG and IgM combo device	LF ICT	S/P/WB	NS1 Ag IgM/IgG	92.4 94.2	96.4 96.4
	SD Dengue IgG Capture ELISA	ELISA	S	IgG	98.8	99.2
	SD Dengue IgM Capture ELISA	ELISA	S	IgM	96.4	98.4
	SD Dengue NS1 Ag ELISA	ELISA	S	NS1	92.7	98.4
	Dengue Eden Test Bioeasy	ICT	S/P/WB	NS1	92.8	100
Bio-Rad, France	STRIP	W ICT	S/P	NS1 Ag	NR	NR
	Platelia Dengue NS1 Ag	EIA	S/P	NS1	NR	NR
Omega, United Kingdom	PATHOZYME – Dengue IgM	ELISA	S	IGM	99.15	96.92
Genome Diagnostics Pvt, India	Geno-Sen's DENGUE 1-4 Real time PCR kit	RT-PCR	S/P	RNA	95	100
Altona Diagnostics, Germany	RealStar Dengue RT-PCR kit 1.0	RT-PCR	NR	RNA	NR	NR
FOCUS Diagnostics, USA	Simplexa Dengue Kit	RT-PCR	S	RNA	96.7 - 100	92.5 - 100
InBiOS, USA	DENV Detect IgM Capture ELISA	ELISA	S	IgM	91.7	92.8
Biosynex, France	IMMUNOQuick Dengue Fever IgG and IgM	W	S/P/WB	IgM/IgG	NR	NR
Merlin, USA	Dengue Fever IgG and IgM combo Device	LF ICT	S/P/WB	IgM/IgG	NR	NR
MP Diagnostics, USA	ASSURE	LF	S/P/WB	IgA	NR	NR

*[a]As stated on Company's Website [15,32-50][b] LF: lateral flow, W: wickstyle, ICT: immunocchromotographic test, ELISA: enzyme-linked immunosorbantassay,[c]S: serum, P: plasma, WB: whole blood, NR: not reported; [d]SN: sensitivity, NR: not reported, *:sensitivity for primary infections, **: sensitivity for secondary infections;[e] SP: specificity, NR: not reported, *:specificity for primary infections, [NEN]: specificity in non-endemic populations*

Table 3. Summary of results - Strip, Bio-Rad

Country	Source	n	SN %	SP %	PPV %	NPV %
Brazil	[26]	78	91.0	100	100*	62.5*
	[51]	266	99.5	80.0	95.6	97.6
	[52]	450	89.6	99.1		
Singapore	[76]	354	80.5*	100*	100*	87.0*
	[64]	209	78.9	99.0	98.9	81.2
Taiwan	[30]	392	68.4			
	[77]	222	81-84.8	100		
Vietnam	[73]	138	72.8	100		
	[75]	292	61.6	100	100	33.3
French Guiana	[55]	320	76.1-77.6	100	100*	55.9-57.5*
Malaysia	[59]	533	90.4	99.5	99.6*	87.9*
Venezuela	[72]	123	67.8	94.4-100	96.7-100	46.2-54.8
Martinique	[60]	537	49.4	100		
Sri Lanka	[66]	259	58.6	98.8	96.7	79.4
Colombia	[54]	147	57.7-61.5	95.3-93.3	96.8-97	48.2-50.6
Thailand	[69]	104	98.9	90.6		
	[70]	85	70.9*	100*	100*	65.2*

**Study didn't include, but was able to be calculated*

Table 4. Summary of results-Platelia dengue NS1 Ag, Bio-Rad

Country	Source	n	SN %	SP %	PPV %	NPV %
Brazil	[51]	362	99.3	84.1	95.5	97.2
Colombia	[54]	303	70.8	92.3	95.5	57.5
French Guiana	[55]	320	82.4	100	100*	50.0*
Martinique	[60]	538	61.2	100	100	73.2
Mexico	[26]	400	43.8	100	100*	33.3*
Singapore	[64]	209	81.7	100	100	83.3
Thailand	[70]	85	76.4*	100*	100*	69.8*
	[68]	484	56.5	100		
Venezuela	[72]	123	71.3	86.1-100	92.5-100	49.0-55.4

**Study didn't include, but was able to be calculated*

Table 5. Summary of results-Bioline Dengue Duo NS1 antigen and IgG and IgM combo device, Standard Diagnostics (SD)

Country [Source]	Analyte	n	SN %	SP %	PPV %	NPV %
Mexico [63]	NS1/IgG/IgM	399	90.1	89.7	96.9	72.9
Colombia [54]	NS1/IgG/IgM	310	80.7	89.1	94.6	66.1
Vietnam [75]	NS1/IgG/IgM	292	83.7	97.9	99.5	53.5
Malaysia [22]*	NS1/IgG/IgM		88.7	98.8		
Sri Lanka [66]	NS1/IgM	259	92.9	88.8	83.6	95.4
Colombia [54]	NS1/IgM	310	78.4	91.3	95.5	64.1
Vietnam [75]	NS1/IgM	292	75.5	100	100	43.9
Sri Lanka [66]	NS1	259	48.5	99.4	98.0	75.7
Colombia [54]	NS1	310	51.0	96.7	97.4	45.4
Vietnam [75]	NS1	292	62.4	100	100	33.8
Malaysia [22]*	NS1	399	65.4	98.8		
Sri Lanka [66]	IgM	259	79.2	89.4	82.3	87.7
Malaysia [22]*	IgM	399	53.5	100		

**Cited from Meta-Analysis [22], but not in original article [81]*

Five studies were conducted in Thailand and the most sensitive test was Bio-Rad's NS1 STRIP (98.9%), while the most specific tests were Bio-Rad's NS1 STRIP, Platelia NS1 ELISA, and Panbio Early ELISA with 100% specificity [30,68-71]. One study in Venezuela evaluated the Bio-Rad NS1 STRIP, Panbio Early ELISA, and Platelia NS1 ELISA [72]. None of these tests had very good sensitivity, the best being Platelia. (71.3%) [72]. Both the Bio-Rad NS1 STRIP and SD BIOLINE Dengue Duo tests had 100% specificity in Vietnam [51,73-75]. The most sensitive test in Vietnam was the 1st generation SD BIOLINE (90.4%) [51,73-75].

4.2 Performance by Test

Bio-Rad's NS1 STRIP performed the best in Brazil with high sensitivity and specificity across multiple studies averaging a sensitivity of 93.4% and an average specificity of 93% [26,51,52]. The lowest specificity of the NS1 STRIP across all studies was 80% in Brazil, ranging between 80%-100% [26,30,51,52,54,55,59,60,64,68-70, 72,73,75-77]. The sensitivity of the NS1 STRIP varied more than the specificity; between 98.9% in Thailand and 58.6%in Sri Lanka (49.1% in Thailand when urine was the sample material used) [26,30,51,52,54,55,59,60,64,66,69,70,72, 73,75-77]. MP Diagnostic's IgA test ASSURE had the best sensitivity and specificity in Bangladesh, 99.4% and 92.0% respectively [78]. When Panbio Dengue Duo Cassette was used to detect IgM, it was most sensitive in India (81.8%), but the least specific (75%) [57,66,67,74,79]. When Panbio Dengue Duo Cassette was used to detect IgG, it was most sensitive in India (87.5%) and most specific in Vietnam (94.4%) [57,67,74]. When Panbio Dengue Duo Cassette was used to detect IgM and IgG, it was more sensitive in Brazil (78.0%), but more specific in Singapore (93%) [53,64]. The Panbio Early ELISA across multiple studies was not very sensitive, the most sensitive in Singapore (67.0%) and the least sensitive in India (24.1%) [56,64,71,72]. It did however have very high specificity across all studies with 94.4% being the lowest [56,64,71,72]. Panbio Early Rapid was evaluated in four different countries and it performed best in sensitivity and specificity in Brazil, 88.1% and 100% respectively [26,66,80]. Panbio's IgG ELISA had better sensitivity in Mexico (56.4%) and better specificity in Thailand (100%) [63,68]. However, Panbio's IgG ELISA did not have good sensitivity overall (55.2%-56.4%) [63,68]. Panbio's IgM ELISA had the best specificity in Mexico (100%) and was the most sensitive in Brazil (89.5%) [53,63,68,71]. Across all the studies that evaluated Panbio's Pan-E Early ELISA, it performed the best in China (sensitivity: 94.0%, specificity: 100%) [54,55,58,68]. The specificity of Bio-Rad's Platelia NS1 ELISA ranged from 84.1% in Brazil to 100% in French Guiana, Martinique, Mexico, Singapore, Thailand and Venezuela [51,54,55,60,63,64,68,70,72]. Thailand averaged a sensitivity of 66.1% across multiple studies evaluating the Platelia NS1 ELISA which was one of the lowest sensitivities with Martinique at 61.2% and in Mexico with 43.9% [51,54,55,60,63,64,68,70,72]. The Platelia test performed the best in Brazil; sensitivity: 99.3%, specificity: 84.1% [51,54,55,60,63,64,68, 70,72]. When NS1 was the only analyte used in SD BIOLINE dengue duo to diagnose dengue, the sensitivity was very low ranging from 48.5% to 65.4%, but the specificity was high 96.7% to 100% [22,54,66,75]. When both NS1 and IgM were used the specificity remained high (88.8%-100%) and the sensitivity increased to 75.5%-92.9% [54,66,75]. When the SD BIOLINE dengue duo detected NS1, IgG, and IgM the specificity remained high, 89.1%-98.8%, and the sensitivity increased to 80.7-90.6% [22,54,63,75].

It is of interest to note that the companies promote different accuracies for their tests than have been illustrated in this article. Sensitivity varied between a 1% difference to as much as 27%. Companies' statements about test specificty overall are very accurate. However, a few tests were off by 2%-26%.

5. CONCLUSION

A limitation of this review and its analyses is the accuracy of the papers it cites. Some papers were more detailed than others about what tests they used, therefore, including some data in the analysis was impossible. Some articles did not report specificity, PPV, NPV nor the raw numbers (TP, FP, TN, FN) which made it impossible to include these tests in our analysis. Articles also relied on the accuracy of the reference test. These tests may not be 100% sensitive and specific therefore making the accuracy of the tests they reported on higher or lower than its true accuracy and our analysis less meaningful. Another limitation to this review is the limited number of articles evaluating the accuracy of commercial kits in non-endemic areas. Only two studies were conducted in non-endemic countries and one was conducted in the endemic area of the country.

Table 6. Summary of results - Panbio Dengue Duo Cassette, Alere

Country [Source]	Analyte	n	SN %	SP %	PPV %	NPV %
Brazil [53]	IgG/IgM	400	78.0	81.0	80.4*	78.6*
Singapore [64]	IgG/IgM	209	49.5	93.0	88.5	62.8
Thailand [79]	IgM	491	65.3	97.6	98.2	58.8
Vietnam [74]	IgM	200	67.3	91.7	89.7	72.1
India [57]	IgM	138	81.8	75.0	61.0	89.6
Sri Lanka [66]	IgM	259	70.7	80.0	68.6	81.5
Sri Lanka [67]	IgM	549	54.5	95.5	79.5	86.8
Vietnam [74]	IgG	200	66.4	94.4	97.0	51.0
India [57]	IgG	86	87.5	66.6	72.9	83.9
Sri Lanka [67]	IgG	549	62.1	84.5	56.2	87.5

**Study didn't include, but was able to be calculated*

Table 7. Summary of results

Test	**Analyte**	**Country [Source]**	**n**	**SN %**	**SP%**	**PPV%**	**NPV%**
MP ASSURE	IgA	Mexico [62]	225	61.0	86.8	93.8	40.7
	IgA	Singapore [65]	914	86.7	86.1		
	IgA	Bangladesh [78]	204	99.4	92.0	98.9	95.8
Panbio Early	NS1	India [56]	1787	24.1			
ELISA	NS1	Singapore [64]	209	67.0	100	100	73.5
	NS1	Thailand-Myanmar [71]	163	54.2	100	100	73.2
	NS1	Venezuela [72]	123	60.9	94.4-100	96.4-100	41.4-50.0
Panbio Early	NS1	Sri Lanka [66]	259	58.6	92.5	82.9	78.3
Rapid	NS1	Brazil [26]	79	88.1	100	100*	55.6*
	NS1	Vietnam [80]	298	69.2	96.0		
	NS1	Malaysia [80]	293	68.9	96.7		
PanbioIg G	IgG	Mexico [63]	398	55.2	100	100*	38.5*
ELISA	IgG	Thailand [68]	483	56.4	95.3		
PanbioIg M	IgM	Thailand-Myanmar [71]	164	16.7	87.8	52.2	56.8
ELISA	IgM	Mexico [63]	397	62.9	100	100*	43.1*
	IgM	Brazil [53]	400	89.5	89.0	89.1*	89.5*

Test	Analyte	Country [Source]	n	SN %	SP%	PPV%	NPV%
	IgM	Thailand [68]	482	88.6	87.8		
	IgM	Mexico [62]	225	54.1	100	100*	59.8*
Panbio Pan-E	NS1	Thailand [68]	481	55.2	98.6		
EarlyELISA	NS1	China [58]	354	93.9*	100*	100*	96.5*
	NS1	Colombia [54]	310	71.1	89.1	94.0	56.6
	NS1	French Guiana [55]	320	55.1	97.9	99.3*	27.8*
SD BIOLINE	IgM	Thailand [79]	491	21.8	98.8	97.3	39.0
(1stGeneration)	IgM	Vietnam [74]	200	10.6	99.0	91.7	50.5
	NS1	Sri Lanka [67]	549	45.9	97.9	87.3	84.9
	IgG	Vietnam [74]	200	90.4	88.9	95.7	77.4
SD Dengue	NS1	Thailand [68]	478	44.8	98.6		
NS1 AgELISA	NS1	Colombia [54]	310	68.8	94.6	96.8	56.1
	NS1	Malaysia [81]**	399	76.7	98.3	.993	.574
SD Dengue IgG	IgG	Thailand [68]	480	88.9	63.5		
SD Dengue IgM	IgM	Thailand [68]	479	84.9	97.3		
Biosynex	IgM	Sri Lanka [66]	259	79.8	46.3	49.9	78.7
InBiOS	IgM	USA [82]	201	88.7	93.1	87.5*	93.8*
Merlin Combo	IgM	Sri Lanka [66]	259	72.7	73.8	63.2	81.4
Omega	IgM	Brazil [53]	400	83.5	86.5	86.1*	83.9*
BioEasy EDEN	NS1	Brazil [26]	77	94.0	100	100*	71.4*
Geno-Sen's	RNA	Martinique [61]	232	85.2	100	100*	74.5*
RealStar	RNA	Martinique [61]	232	83.3	98.0	100*	72.2*
Simplexa	RNA	Martinique [61]	232	93.2	100	99.3*	86.3*

** Study didn't include, but was able to be calculated*
***Not listed in Meta-Analysis, but in original article*

Overall when evaluating Performance by country, the Bio-Rad NS1 STRIP seems to have performed the best. There may be some bias in this statement because it was evaluated more often than any other test. Also, many factors could have contributed to this bias as well. For example, if the study only used disease-free samples, then they would be less rigorous than the studies that used dengue-negative /Flavivirus-positive samples because of the cross-reactivity that could occur. Flaviviruses can be concurrently endemic, which requires a very sensitive test, and therefore requires this type of rigorous evaluation. Overall when evaluating performance by test, the Standard Diagnostics' (SD) BIOLINE dengue duo was most specific in Vietnam (100%) and most sensitive in Sri Lanka (92.9%) [22,54,63,75]. Standard Diagnostics' (SD) Dengue NS1 Ag ELISA was most sensitive in Malaysia (76.8%) and most specific in Thailand (98.6%) [54,68,81]. That said, the sensitivity of this test was not very good at all (44.8%-76.8%) [54,68,81]. Overall, most tests performed the best in Brazil, but again, this statement is biased due to the fact that Brazil evaluated many tests, which means it has the opportunity to be the best more often.

Infection with dengue virus can lead to severe disease or it can be asymptomatic. Many diagnostic tests are available to help determine the dengue status of individuals. The purpose of this review was to compare and contrast the accuracy of commercial dengue diagnostic tests. The best performing test across all studies and countries seems to be Bio-Rad NS1 STRIP. Those who evaluate the accuracy of commercial tests should consider using the Bayesian Latent class model as described in Pan-ngum et al., 2013 and elsewhere because this model does not assume a perfect test. Taking away this assumption would present a better understanding of the true accuracy of a test. One thing is clear; these commercially available diagnostic tests should be evaluated more often and across more populations in a standardized way to create reliability.

ETHICAL APPROVAL

The authors declare that this work was not against public interest.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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