Rapid immunochromatographic tests for the diagnosis of dengue: a systematic review and meta-analysis

Testes imunocromatográficos rápidos para o diagnóstico da dengue: uma revisão sistemática e metanálise

Pruebas inmunocromatográficas rápidas para la diagnosis del dengue: una revisión sistemática y metaanálisis

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Abstract

Dengue is an important arthropod-borne viral disease in terms of morbidity, mortality, economic impact and challenges in vector control. Benchmarks are expensive, time consuming and require trained personnel. Preventing dengue complications with rapid diagnosis has been based on the testing of easy-to-perform optimized immunochromatographic methods (ICT). This is a systematic meta-analysis review of the diagnostic accuracy of IgA, NS1, IgM and/or IgG ICT studies in suspected cases of acute or convalescent dengue, using a combination of RT-PCR, ELISA NS1, IgM IgG or viral isolation as a reference standard. This protocol was registered in PROSPERO (CRD42014009885). Two pairs of reviewers searched the PubMed, BIREME, Science Direct, Scopus, Web of Science, Ovid MEDLINE JBrigs, SCIRUS and EMBASE databases, selected, extracted, and quality-assessed by QUADAS 2. Of 3,783 studies, we selected 57, of which 40 in meta-analyses according to the analyte tested, with high heterogeneity ($I^2 > 90\%$), as expected for diagnostic tests. We detected higher pooled sensitivity in acute phase IgA (92.8%) with excellent (90%) specificity. ICT meta-analysis with NS1/IgM/IgG showed 91% sensitivity and 96% specificity. Poorer screening performance was for IgM/IgG ICT (sensitivity = 56%). Thus, the studies with NS1/IgM/IgG ICT showed the best combined performance in the acute phase of the disease.

Dengue; Diagnosis; Sensitivity and Specificity; Systematic Review; Meta-Analysis

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Introduction

Dengue is an acute viral disease caused by a virus transmitted mainly by *Aedes aegypti*. This arthropod-borne flavivirus has four distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4, which constitute an antigen complex of the *Flavivirus* genus, Flaviviridae family [1].

Dengue virus is present in more than 100 countries of the Asia-Pacific, Americas, Middle East, and Africa [2,3,4], with 3 billion people (40% of the world population) at risk of infection in tropical and subtropical regions, with 50 to 100 million infections per year [2,4,5]. It is an important arthropod-borne viral disease in terms of human morbidity, mortality and economic impact. Many challenges remain concerning disease control and prevention programs based on vector reproduction and elimination, clinical aspects and pathogenesis [5].

The clinical presentation of dengue infection is highly unspecific varying according to the circulating serotype [5]. Differential diagnosis of dengue in urban areas of large metropolises in Latin America, where malaria is not endemic, includes influenza [6,7]. In Brazil, since 2013 [8], also zika and chikungunya are co-circulating [9], making the diagnosis on a clinical basis unreliable. Thus, diagnostic optimization for adequate clinical management to prevent complications caused by dengue requires better, easier and more efficient rapid tests with good accuracy for case management during the earlier state of infection.

Among the rapid tests, those using the immunochromatographic technique (ICT) to detect the presence of nonstructural protein 1 (NS1) play an important role in early diagnosis of dengue fever (up to seven days from the onset of symptoms) [10]. Reference standards such as virus isolation, PCR or PRNT have the great disadvantages of being laborious, time consuming, require specific reagents, equipment, trained personnel and are high cost. ELISA IgM/IgG has been important for health surveillance and distinguishes between primary and secondary infectious in cases previously confirmed by RT-PCR or virus isolation but presents cross-reactivity with other members of the Flaviviradidae family [6].

We found five systematic reviews with meta-analysis on the subject [4,6,11,12,13]. Alagarasu et al. [11] included only publications on IgA ICT. Another meta-analysis included nine studies on NS1 ICT [4] and the systematic review by Blacksell et al. [6] assessed a single commercial test (Panbio ICT – Abbott Laboratories) in 11 studies, showing wide variability between them. These reviews point out the high specificity of the ICT, but with heterogeneous sensitivities, requiring a critical assessment that includes the various types of ICT and brands available on the market as well as their evaluation in acute and convalescent samples. In fatal cases, NS1 strip showed better sensitivity (78.3%) than ELISA NS1 [10].

A recent systematic review [12] on the economic impact of dengue's ICT favored a relatively obsolete diagnostic strategy based on IgM Panbio for acute cases. However, it identified only two studies, one using primary observational data [14] and the other, a simulation modeling design [15].

In children, when it could be difficult to access blood samples, some studies were carried out in saliva and urine [16,17]. Muso et al. [17] suggested that only 19% of the studies detected zika virus in saliva, concluding that it could not replace blood tests. In a recent review, Colonetti et al. [18] included three studies for dengue diagnosis evaluating salivary IgM, which provided sensitivity of 86% and specificity of 93%. Two included studies evaluating salivary IgA showed a pooled sensitivity of 69% and a pooled specificity of 98%. Despite these results and the low methodological quality of the studies included in the meta-analysis, the authors concluded that it is still soon to claim that IgA is better than IgM to diagnose dengue [18].

This study aimed to review the literature on the accuracy of ICT using as the reference test any type of PCR, ELISA, or virus isolation, in suspected dengue cases with up to seven days since the onset of fever for NS1 ICT and with no restriction on the days of fever for IgA, IgM/IgG, or NS1/IgM/IgG ICT.

Methods

This was a systematic literature review of observational diagnostic studies reported in the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement [19]. The protocol was previously registered on the site PROSPERO number CRD42014009885.

Data sources and search strategy

The research question was: Are point of care immunochromatographic tests accurate for early detection of dengue infection? Does the test performance vary according to age, sex, dengue serotype, reference tests or whether it is a primary or secondary infection, acute or convalescent phases? These questions guided the eligibility criteria expressed in the PICO (Patient, Intervention, Comparison and Outcomes) format:

Population: blood/serum or plasma samples from patients with febrile illness suspected of dengue with up to seven days of fever in the acute phase of the disease and with no time limit in the convalescent phase;

Intervention (index tests): ICTs with detection of IgA, NS1, IgM/IgG, or NS1/IgM/IgG, read within 60 minutes;

Comparator (reference standard): PCR, ELISA NS1 or IgM, virus isolation, or a combination of two or three of these;

Outcome (diagnostic parameters): sensitivity, specificity, likelihood ratios, and positive and negative predictive values in ICTs for dengue, besides the information on time and effect measures, according to the case.

We excluded articles that: use inappropriate reference tests, index test limited to the detection of IgG antibodies or that takes more than 60 minutes to perform, incomplete description or partial examination of sample, small sample size or insufficient data to calculate accuracy parameters.

In case of doubt we directly contacted the authors. We did not limit the search based on study design nor on language of publication.

Two researchers conducted the searches up to October 2019 for journal articles or congress proceedings publications since inception in MEDLINE via PubMed, Science Direct, Scopus, Web of Science, Ovid MEDLINE JBrigs, SCIRUS, BIREME and EMBASE, with no restriction on language or study design. We also searched gray literature using Google Scholar. Our search strategy in MEDLINE via PubMed employed the keywords: ("dengue/diagnosis"[MeSH Terms]) AND (diagnostic reagents and test kits [MeSH Terms]), generating the following strategy: "humans"[MeSH Terms] AND ("Dengue" OR "Dengue Virus") AND (sensitiv*[Title/Abstract] OR specificity[Title/Abstract] OR "sensitivity and specificity"[Mesh Terms] OR "Reference Values"[Mesh] OR diagnosis*[Title/Abstract] OR diagnosis[Mesh] OR diagnosis[Subheading]) AND ((("Serologic Tests" OR Immunoassay OR "Reagent Kits, Diagnostic") AND (Bedside OR Rapid)) OR "Point-of-Care Systems" OR "NS1" OR "NS-1" OR "Viral nonstructural proteins" OR Immunochromatogra* OR Immunochromatography OR bioeasy OR bioline OR bioline OR panbio OR core OR ag-strip OR strip OR Duo OR biorad OR "Reagent Strips"). We used equivalent strategies in the other databases and employed Zotero Standalone 4.0 for Windows (https://www.zotero.org/) in the search and filing of references.

Study selection

Initially, three pairs of reviewers (V.E.M./C.A.F.A., L.V.B.F./S.R.L.P., and Y.H.M.H./S.R.L.P.) independently selected the study abstracts. We held consensus meetings, and in case of disagreement, a third reviewer external to the pair judged the article's relevance. In the second stage, pairs of reviewers (V.E.M./C.A.F.A., V.E.M./S.R.L.P., and Y.H.M.H./S.R.L.P.) read the full-text articles, also independently. Disagreements arising in the consensus meetings of the respective pairs were also resolved with a third external reviewer.

Data extraction and assessment of risk of bias

We designed a standardized form to extract the following variables by the pairs of reviewers: study design, commercial test names, test manufacturing countries, type of detection used, reference test used, number of study participants, number of confirmed dengue cases, non-dengue cases, measures of accuracy, virus serotype, and time since onset of fever.

We used the *Quality Assessment of Diagnostic Accuracy Studies* (QUADAS 2) [20] to assess the quality of the selected articles, risk of bias, and applicability. The tool consists of 14 items distributed across four domains that assess patient selection, index test, reference test, flow and timing.

Data synthesis and analysis

We used the "reference standard" defined in each selected study for comparison with the index test to determine the true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) values. Diagnostic accuracy, sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), positive (LR+) and negative likelihood ratios (LR-), diagnostic odds ratio (DOR). We estimated positive (PP+) and negative post-test probabilities (PP-) in scenarios of 25%, 50%, and 75% prevalence.

For each ICT (IgA, NS1, IgM/IgG, NS1/IgM/IgG), we performed a meta-analysis for each measure of diagnostic accuracy listed above, with the respective 95% confidence intervals (95%CI). The analyses were performed with the Winpepi (http://www.brixtonhealth.com/pepi4windows.html) and Stata XIV (https://www.stata.com) packages using the MIDAS command (*Meta-analytical Integration of Diagnostic Accuracy Studies*) performing the bivariate mixed-effects binary regression modeling framework. Meta-analyses were conducted according to the different analytes and/or brands.

We calculated the I^2 statistic to detect significant overall and inter-subgroup heterogeneity [21]. We considered I^2 values greater than 50% as high evidence of heterogeneity in data. In the presence of I^2 point estimate higher than 50%, we performed meta-analysis using random effects model [22].

We analyzed study heterogeneity graphically and through the I^2 test. We explored possible causes of clinical heterogeneity between studies through subgroup analyses: disease phase (acute or convalescent), by the most extensively assessed brand name, and overall quality of studies according dimensions of QUADAS 2 (low versus high or unclear risk of bias) [20].

Assessment of publication bias used the Deeks graph, where p-value < 0.05 was considered significant [23].

Results

Characteristics of included studies

The initial search identified 3,791 publications. After removing duplicates, we reviewed 3,783 abstracts, and selected 108 articles for reading the full-texts, of which 57 were selected for this review (Figure 1). The studies assessed multiple ICT brand tests with different analytes: five assessed IgA [24,25,26,27,28], 21 NS1 [10,27,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47], 12 IgM/IgG [27,34,48,49,50,51,52,53,54,55,56,57], and 25 NS1/IgM/IgG [29,36,37,40,46,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77] (Table 1). The total number exceeds since some studies evaluated more than one ICT brand tests and type of analyte. Those articles evaluating NS1/IgM/IgG estimated not only the accuracy parameters for the three analytes, but also for each analyte separately.

Although planned, stratified analysis was not available in original studies, except for different analytes.

The 57 studies were performed mainly in Asia (33; 57.9%) and the Americas (18; 31.6%), only one in Oceania and mostly (94.1%) published in English.

The included studies analyzed 29 ICTs, using as the reference tests RT-PCR, real-time PCR, semi-nested PCR, NS1 ELISA, IgM ELISA, IgG ELISA, IgM antibody capture enzyme-linked immuno-

Figure 1

Flowchart of the included studies.
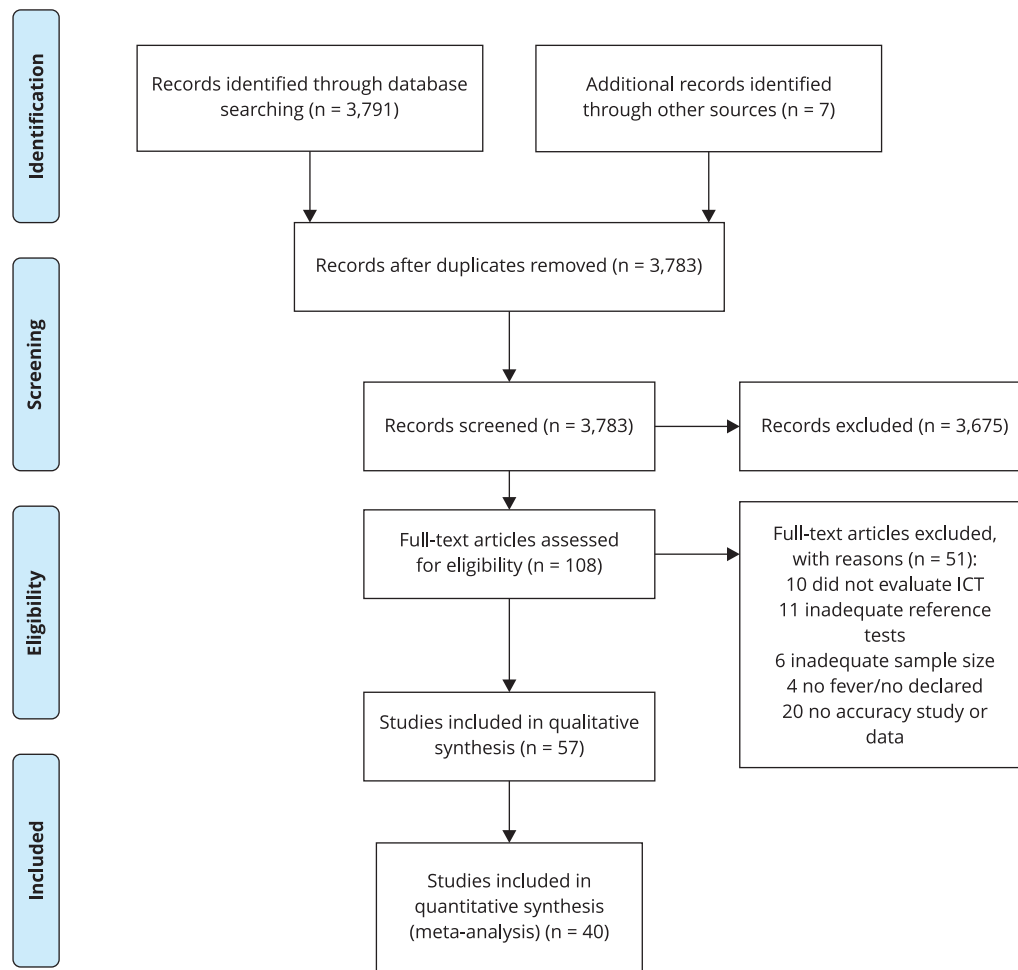
sorbent assay (MAC ELISA IgM), IgG antibody capture enzyme-linked immunosorbent assay (GAC ELISA IgG), or virus isolation (Table 1).

Quality assessment of the studies

According to the assessment of methodological quality conducted with the QUADAS 2 tool, of the 57 included studies, only six [29,30,38,39,69,78] did not show risk of bias, and 25 (43.8%) of the them showed high risk of bias regarding the patient selection process (Figure 2), mainly due to case-control design. Ten of them showed high risk of bias concerning flow and timing, mainly for excluding patients from analysis or for adopting inappropriate intervals between index and reference tests. Concerning reference standard, 31 studies were unclear and three showed high risk of bias, mainly due to not informing about blinding.

However, we did not find any major conflicts that could compromise applicability in relation to patients included, index or reference tests in these studies from those targeted by our review questions.

Table 1

Characteristics and accuracy of rapid immunochromatographic tests (ICT) of the included studies.

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
IgA										
ASSURE	Ahmed et al. [24] (2010)	Bangladesh	CC 1:1 Conval.	424 (179)	86.0 (80.1-90.8) 99.4 (96.9-99.9)	99.2 (97.1-99.9) 92.0 (73.9-98.8)	98.7 (95.2-99.6) 98.9 (96.1-99.8)	90.7 (86.5-93.5) 95.8 (78.8-99.3)	-	ELISA NS1/ IgM/IgG
	Tan et al. [28] (2011)	Singapore	CC -	914 (233)	86.7 (81.7-90.8)	86.1 (83.2-88.6)	68.0 (62.4-73.3)	94.9 (92.9-95.6)	-	ELISA IgM/IgG RT-PCR
	Hernández et al. [26] (2012)	Mexico	CS 5:1 (acute)	225 (172)	61.1 (53.6-68.0)	86.8 (75.2-93.5)	93.8 (88.4-96.7)	40.7 (35.6-46.0)	1 (103) 2 (69)	RT-PCR ELISA NS1/ IgM/IgG
	Naz et al. [27] (2014)	Pakistan	CS 1:1	184 (142)	85.2 (78.3-90.6)	81.0 (65.9-91.4)	93.8 (88.2-97.3)	61.8 (47.7-74.6)	-	ELISA IgM/IgM
Dengue Rapid Test	Hartono & Sari [25] (2012)	-	CS -	100 (70)	82.9 (72.4-89.9)	73.3 (55.6-85.8)	87.9 (80.0-92.9)	64.7 (51.3-76.1)	-	ELISA NS1/ IgM/IgG
NS1										
Bio-Rad	Dussart et al. [32] (2008)	Guiana	CC 1:0	320 (222) Read. 15' Read. 30'	76.1 (70.7-80.8) 77.6 (72.3-82.1)	100.0 (92.6-100.0) 100.0 (92.6-100.0)	100.0 (98.2-100.0) 100.0 (98.3-100.0)	42.5 (33.2-52.1) 44.0 (34.5-53.9)	1 (33) 2 (42) 3 (101) 4 (46)	RT-PCR Viral isolation
	Zainah et al. [47] (2009)	Spain	CC	533 (314)	90.4 (86.7-93.2)	99.5 (97.5-99.9)	99.6 (97.9-99,9)	87.9 (83.2-91.3)	-	ELISA NS1/IgG Viral isolation RT-PCR
	Hang et al. [35] (2009)	Vietnam	Cohort	138 (125)	72.8 (64.4-79.8)	100.0 (77.2-100.0)	100.0 (96.7-100.0)	27.7 (15.6-42.6)	1 (63) 2 (20) 3 (25) 4 (3)	ELISA IgM/IgG RT-PCR
	Ramirez et al. [44] (2009)	Venezuela	CC	147 (87)	67.8 (57.4-76.7)	96.7 (88.6-99.1)	96.7 (89.6-99.0)	67.4 (60.4-73.8)	1 (21) 2 (23) 3 (23) 4 (20)	RT-PCR Viral isolation ELISA IgM
	Chaiyaratan et al. [31] (2009)	Marshall Islands	CC	104 (89)	98.9 (96.8-100)	90.6 (85.6-95.7)	99.0 (96.2-99.7)	90.5 (69.8-96.8)	-	ELISA NS1/ IgM/IgG
	Shu et al. [45] (2009) (blood)	8 Asian countries	CS	850 (22)	77.3 (56.6-89.9)	100.0 (99.5-100.0)	100.0	99.4	1 (9) 2 (3) 3 (5)	RT-PCR ELISA IgM/IgG
	Lima et al. [10] (2010)	Brazil	CC	450 (220)	89.6 (84,8-92.9)	99.1 (96.9-99.8)	99.0 (96.9-99.7)	90.8 (87.1-93.6)	1 (180) 2 (78) 3 (28) 4 (40)	Viral isolation RT-PCR ELISA IgM/IgG
	Pok et al. [43] (2010)	Singapore	Cohort	112 (52)	76.9 (63.9-86.3)	100.0 (94.0-100.0)	100.0	83.3	1 (21) 2 (23) 3 (17) 4 (2)	ELISA IgM/IgG Paired
			CS	209 (109)	78.9 (70.0-86.1)	99.0 (94.6-99.9)	98.9 (96.6-100)	81.2 (73.1-88.2)	-	RNA viral

(continues)

Table 1 (continued)

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
	Osorio et al. [40] (2010) Read. 15'	Colombia	CC	310 (218)	57.7 (47.6-67.3)	95.3 (84.2-99.4)	96.8 (88.8-99.6)	48.2 (37.3-59.3)	1 (13) 2 (17) 3 (7) 4 (5)	Viral isolation RT-PCR ELISA IgM
				Read. 30'	61.5 (51.5-70.9)	93.3 (84.2-99.4)	97.0 (89.5-99.6)	50.6 (39.3-62)		
	Tricou et al. [46] (2010)	Vietnam	Cohort	292 (245)	61.6 (55.2-67.8)	100.0 (93.8-100.0)	100.0 (98.0-100.0)	33.3 (25.6-41.8)	1 (138) 2 (91) 3 (16)	ELISA IgM/IgG RT-PCR
	Blacksell et al. [50] (2011)	Sri Lanka	CC	259 (99)	58.6 (48.2-68.4)	98.8 (95.6-99.9)	96.7 (88.5-99.6)	79.4 (73.1-84.8)	1 (1) 2 (16) 3 (47) 4 (2)	RT-PCR ELISA IgM/IgG
	Najioullah et al. [39] (2011)	Caribbean	CS	537 (264)	49.4 (43.2-55.6)	100.0 (97.3-100.0)	100.0	68.0 (63.4-72.6)	2 (264)	RT-PCR
					83.1 (76.2-88.3)	99.7 (98.5-99.9)	99.2 (85.2-99.8)	93.6 (90.6-95.6)	2 (156)	ELISA NS1
	Ferraz et al. [33] (2013)	Brazil	CS	189 (146)	91.0 (81.8-95.8)	100.0 (72.3-100.0)	100.0	62.5	-	ELISA NS1/ IgM
	Pal et al. [41] (2014)	Peru/ Honduras	CC	241 (200)	79.1 (72.0-84.8)	100.0 (91.2-100.0)	100.0	55.6	1 (67) 2 (26) 3 (45) 4 (62)	Viral isolation RT-PCR ELISA IgM
Panbio	Blacksell et al. [50] (2011)	Sri Lanka	CC	259 (99)	58.6 (48.2-68.4)	92.5 (87.3-96.1)	82.9 (72.0-90.8)	78.3 (71.7-84.0)	1 (1) 2 (16) 3 (47) 4 (2)	RT-PCR ELISA IgM/IgG
	Pan-ngum et al. [42] (2013)	-	CS	549 (135)	54.8 (43.5-65.7)	95.1 (92.7-96.8)	66.7 (54.3-77.6)	92.1 (89.3-94.3)	-	ELISA IgM/IgG
	Ferraz et al. [33] (2013)	Brazil	CS	77 (67)	88.1 (78.2-93.8)	100.0 (72.3-100.0)	100.0	55.6	-	ELISA NS1/ IgM
	Naz et al. [27] (2014)	Pakistan	CS	184 (142)	64.1 (55.6-72.0)	100.0 (91.6-100.0)	100.0 (96.0-100.0)	45.2 (34.8-55.8)	2 (18)	ELISA IgM/IgG
	Pal et al. [41] (2014)	Peru/ Honduras	CC	241 (200)	71.9 (64.3-78.4)	95.0 (83.5-98.6)	100.0	48.8	1 (67) 2 (26) 3 (45) 4 (62)	Viral isolation RT-PCR ELISA IgM
Alere Dengue Earsly	Fry et al. [34] (2011)	Vietnam	CC	298 (198)	69.2 (62.5-75.2)	96.0 (90.2-98.4)	97.2 (93.2-98.8)	61.1 (56.0-66.1)	1 (83) 2 (24) 3 (29)	RT-PCR ELISA NS1/IgM/IgG
		Malaysia	CC	293 (263)	62.0 (56.0-67.6)	96.7 (83.3-99.4)	99.4 (97.1-99.0)	22.5 (20.0-25.7)	1 (101) 2 (21) 3 (23) 4 (16)	RT-PCR ELISA NS1/IgM/IgG
Bioeasy	Ferraz et al. [33] (2013)	Brazil	CS	77 (67)	94.0 (85.6-97.7)	100.0 (72.3-100.0)	100.0	71.4	-	ELISA NS1/ IgM
	Buonora et al. [30] (2016)	Brazil	CS	325 (148)	44.5 (36.4-53.3)	97.8 (94.2-99.4)	94.1 (85.6; 98.4)	68.3 (62.1-74.0)	4 (325)	RT-PCR ELISA NS1 /IgM/IgG

(continues)

Table 1 (continued)

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
	Mata et al. [38] (2017)	Brazil	CS 1:1	144 (120) Read. 15'	76.7 (68.0-84.1)	87.0 (66.4-97.2)	96.7 (90.8-99.3)	42.6(28.3-57.8)	1 (105)	RT-PCR ELISA NS1 (whole blood)
				Read. 30'	78.3 (69.9-85.3)	87.5 (67.6-97.3)	96.9 (91.2-99.4)	44.7 (30.2-59.9)		(whole blood)
				Read. 15'	82.2 (74.1-88.6)	100.0 (85.8-100.0)	100.0 (96.3-100.0)	53.3 (37.9-68.3)		(serum)
				Read. 30'	84.9 (77.2-90.8)	95.8 (78.9-99.9)	99.0 (95.4-99.8)	56.1 (39.8-71.5)		(serum)
Inbio	Pal et al. [41] (2014)	Peru/ Honduras	CC	241 (200)	76.5 (65.1-85.0)	97.4 (86.8-99.6)	98.1	78.4	1 (67) 2 (26) 3 (45) 4 (62)	Viral isolation RT-PCR ELISA IgM
Asan	Lee et al. [37] (2019)	Korea	CC	138 (75)	41.3 (29.0-54.4)	100.0 (95.2-100.0)	100.0 (85.2-100.0)	66.9 (62.2-71.4)	-	PCR-ELISA NS1/IgM/IgG
Asan Ag100	Lee et al. [37] (2019)	Korea	CC	138 (75)	42.9 (17.7-71.1)	99.2 (95.6-99.9)	85.7 (43.7-97.9)	93.9 (90.7-96.0)	-	ELISA IgM
Boditech Med	Lee et al. [37] (2019)	Korea	CC	138 (75)	85.7 (74.6-93.3)	92.0 (83.4-97.0)	90.0 (80.6-95.1)	88.5 (80.7-93.4)	-	PCR-ELISA NS1/IgM/IgG
SD Bioline	Jusoh & Shueb [36] (2017)	-	CC	86 (36)	88.9 (74.7-95.6)	100.0 (92.9-100.0)	100.0	92.6	1 (14) 2 (8) 3 (2) 4 (1)	RT-PCR ELISA NS1
	Pal et al. [41] (2014)	Peru/ Honduras	CC	241 (200)	72.4 (64.8-78.9)	100.0 (91.2-100)	100.0	48.8	1 (67) 2 (26) 3 (45) 4 (62)	Viral isolation RT-PCR ELISA IgM
IgM/IgG										
SD Bioline	Blacksell et al. [29] (2006)	Thailand	CC	491 (326)	21.8 (17.4-26.7)	98.8 (95.7-99.9)	97.3 (90.5-99.7)	39.0 (34.3-43.9)	-	RT-PCR ELISA IgM/IgG
Panbio dengue IC	Branch & Levett [51] (1999)	-	CS	62 (36)	83.9 (72.8-91.0)	100.0 (88.7-100)	75.0	100.0	-	ELISA IgM
Panbio Dengue Duo	Blacksell et al. [29] (2006)	Thailand	CC	491 (326)	65.3 (59.9-70.5)	97.6 (93.9-99.3)	98.2 (95.4-99.5)	58.8 (52.7-64.7)	-	RT-PCR ELISA IgM/IgG
	Cohen et al. [52] (2007)		CS (acute)	723 (132)	19.0 (14.2-24.9)	96.0 (94.0-97.4)	64.4 (52.3-75.0)	75.6 (74.3-76.9)	-	ELISA IgM/ IgG-HI
			Conval.		59.0 (52.1-65.6)	95.0 (92.8-96.6)	81.9 (75.5-87.0)	85.8 (83.7-87.8)	-	
	Congpuong et al. [53] (2008)	Thailand	CS	175 (100)	23.0 (15.8-32.2)	100.0 (95.1-100.0)	100.0	55.0	1 (37) 2 (27) 3 (69) 4 (12)	Real time PCR ELISA NS1/ IgM/IgG
	Martínez-Vega et al. [54] (2009)	Colombia	CS (acute)	100 (65)	52.2 (40.3-64.2)	84.8 (72.6-97.1)	87.5 (77.3-97.7)	46.7 (34.0-59.3)	2 (29)	ELISA IgM paired samples
			Conval.		76.1 (65.9-86.3)	75.8 (61.1-90.4)	86.4 (77.7-95.2)	61.0 (46.0-75.9)	2 (29)	ELISA IgM paired samples

(continues)

Table 1 (continued)

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
	Naz et al. [27] (2014)	Pakistan	CS	184 (142)	72.5 (64.4-79.7)	69.1 (52.9-82.4)	88.8 (81.6-93.9)	42.7 (30.7-55.2)	2 (18)	ELISA IgM/IgG
Alere dengue duo	Fry et al. [34] (2011)	Malaysia	CC	293 (263)	72.5 (67.5-77.0)	96.7 (83.3-99.4)	99.5 (97.5-99.9)	28.7 (24.6-33.3)	1 (101) 2 (21) 3 (23) 4 (16)	RT-PCR ELISA NS1/ IgM/IgG
Dengue Fever	Blacksell et al. [29] (2006)	Thailand	CC	491 (326)	9.5 (6.6-13.2)	97.0 (93.0-99.0)	86.1 (70.5-95.3)	35.2 (30.8-39.8)	-	RT-PCR ELISA IgM/IgG
Dengue check-WB	Blacksell et al. [29] (2006)	Thailand			6.4 (4.0-9.7)	99.4 (96.9-99.9)	95.5 (77.2-99.9)	35.0 (30.7-39.5)		
Core Dengue	Blacksell et al. [29] (2006)	Thailand			22.9 (18.3-27.6)	98.9 (95.7-99.9)	97.4 (90.8-99.7)	39.3 (34.6-44.2)		
Diazyme Combo	Blacksell et al. [29] (2006)	Thailand			17.8 (13.8-22.4)	98.2 (94.7-99.4)	95.1 (86.3-99.0)	37.7 (33.1-42.4)		
Smartcheck Globale Med	Blacksell et al. [29] (2006)	Thailand			62.9 (57.4-68.1)	69.1 (61.4-76.0)	80.1 (74.7-84.8)	48.5 (42.0-55.1)		
Vscan (Minerva)	Blacksell et al. [29] (2006)	Thailand			8.6 (5.8-12.2)	100.0 (97.8-100.0)	100.0 (87.7-100.0)	35.6 (31.3-40.2)	-	RT-PCR ELISA IgM/IgG
Acon	Yusuf et al. [57] (2008)	-	CS	50 (22)	45.8 (31.6-60.7)	100.0 (19.8-100.0)	100.0 (81.5-100.0)	71.0 (56.0-84.0)	-	ELISA
Dengue IgM/ IgG	Aikat et al. [48] (2011)	-	CS	158 (29)	96.4 (85.2-99.4)	98.4 (94.5-99.6)	93.1 (77.6-97.7)	99.2 (96.4-99.8)	1 (1) 2 (16) 3 (47) 4 (2)	ELISA IgM
IgM/IgG (only IgM)										
SD Bioline	Pun et al. [56] (2012)	Nepal	CS	131 (50) acute	70.0 (55.5-81.5)	76.5 (56.2-80.8)	64.8 (51.5-76.1)	80.5 (71.0-87.0)	-	ELISA IgM
	Nga et al. [55] (2007)	Vietnam	CS	200 (162)	10.6 (6.0-18.0)	99.0 (94.3-99.8)	91.7 (64.6-98.5)	80.5 (43.5-57.6)	-	ELISA IgM/IgG
Panbio dengue duo	Berry et al. [49] (1998)	India	CS	43(31)	41.7 (19.3-68.1)	96.8 (83.8-99.4)	83.0 (47.3-96.5)	81.1 (72.4-87.5)	-	ELISA NS1/ IgM
	Nga et al. [55] (2007)	Vietnam	CS Conval.	200 (162)	67.3 (59.7-74.0)	92.1 (79.2-97.3)	97.3 (92.9-99.0)	39.8 (34.2-45.7)	-	ELISA IgM/IgG
	Blacksell et al. [50] (2011)	Sri-Lanka	CS	259 (99)	70.7 (60.7-79.4)	80.0 (73.0-85.9)	68.6 (58.7-77.5)	81.5 (74.6-87.3)	1 (1) 2 (16) 3 (47) 4 (2)	MAC GAC ELISA paired samples
	Pan-ngum et al. [42] (2013)	Sri-Lanka	CS	549 (135)	50.0 (38.9-61.1)	89.5 (86.3-92.1)	46.2 (35.6-56.9)	90.8 (87.8-93.3)	-	ELISA IgM/IgG
	Naz et al. [27] (2014)	Pakistan	CS		63.4 (54.9-71.3)	76.2 (60.5-88.0)	90.0 (82.4-95.1)	38.1 (27.7-49.3)		
	Garg et al. [60] (2019)	India	CC	152 (72)	61.1 (48.8-72.3)	95.1 (87.7-98.6)	91.7 (80.0-97.6)	91.7 (80.0-97.6)	-	RT-PCR ELISA NS1 IgM/IgG
Merlin dengue	Blacksell et al. [50] (2011)	Sri-Lanka	CS	259 (99)	72.7 (62.9-81.2)	73.8 (66.2-80.4)	63.2 (53.2-72.0)	81.4 (74.1-87.4)	1 (1) 2 (16) 3 (47) 4 (2)	RT-PCR ELISA IgM/IgG
Biosynex immunoquick				259 (99)	79.8 (70.5-87.2)	46.3 (38.3-54.3)	49.9 (40.1-55.8)	78.7 (69.1-86.5)		

(continues)

Table 1 (continued)

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
Asan	Lee et al. [37] (2019)		CC	138 (75)	41.3 (29.0-54.4)	100.0 (95.2-100.0)	100.0 (85.2-100.0)	66.9 (62.2-71.4)	-	PCR-ELISA NS1/IgM/IgG
Boditech Medichroma **NS1/IgM/IgG**				138 (75)	85.7 (74.6-93.3)	92.0 (83.4-97.0)	90.0 (80.6-95.1)	88.5 (80.7-93.4)		
SD Bioline Dengue Duo	Osorio et al. [40] (2010)	Colombia	CC	310 (218)	80.7 (75.0-85.4)	89.1 (81.1-94.0)	94.6 (90.8-96.9)	66.1 (59.6-72.1)	-	Viral Isolation RT-PCR ELISA IgM
	Tricou et al. [46] (2010)	Vietnam	Cohort (acute)	292 (245)	83.7 (78.4-88.1)	97.9 (88.7-99.9)	99.5 (97.3-100)	53.5 (42.4-64.3)	1 (138) 2 (91) 3 (16)	RT-PCR ELISA IgM/IgG
	Andries et al. [58] (2012)		Blood (hospital)	157 (58)	85.7 (78.4-91.3)	83.9 (66.3-94.5)	95.6 (90.0-98.5)	59.1 (43.2-73.7)		RT-PCR Viral Isolation IgM and HIA paired
			(laboratory)	157 (57)	94.4 (88.9-97.7)	90.0 (73.5-97.9)	97.5 (93.0-99.5)	77.1 (59.9-89.6)		
	Sanchez-Vargas et al. [70] (2014)	Mexico	CC 1:1.2	397 (310)	90.7 (87.2-94.0)	89.7 (82.7-96.6)	96.9 (94.7-99.1)	72.9 (64.0-81.8)	-	ELISA NS1/ IgM/IgG
	Gan et al. [59] (2014)	Singapore	CS 1:1.1	197 (147)	93.9 (83.9-97.1)	92.0 (82.8-93.2)	97.2 (75.4-90.0)	83.2 (90.6-98.1)	1 (22) 2 (89) 3 (1)	RT-PCR ELISA IgM
	Carter et al. [79] (2015)	Cambodia	CS < 16 years	337 (71)	57.8 (45.4-69.4)	85.3 (80.3-89.5)	52.6 (40.9-64.0)	87.8 (83.0-91.0)	-	ELISA NS1 IgM
	Pal et al. [69] (2015)	Peru/ Venezuela/ Cambodia/ Thailand/ USA	Cohort 1:5 (4-14 days)	1,108 (377)	87.3 (84.1-90.2)	86.8 (83.9-89.3)	77.4 (73.9-80.6)	93.0 (91.0-94.5)	1 (88) 2 (103) 3 (24) 4 (32)	PCR/Viral isolation In-house IgM/ IgG PRNT
	Vickers et al. [77] (2015)	Jamaica	CC 1:3	339 (309)	97.5 (92.9-99.2)	100.0 (86.3-100.0)	100.0 (97.9-100.0)	93.6 (79.3-98.2)	NI	ELISA NS1 IGM
	Jusoh & Shueb [36] (2017)	Malaysa	CC	86 (36)	88.9 (75.8-96.6)	100.0 (92.9-100.0)	-	-	1 (14) 2 (8) 3 (2) 4 (1) 1&2 (1)	ELISA NS1 RT-PCR/viral isolation
	Lee et al. [37] (2019)		CC	138 (75)	82.7 (72.2-90.4)	100.0 (94.3-100.0)	100.0 (93.9-100.0)	82.9 (74.7-88.8)	-	PCR-ELISA NS1/IgM/IgG
	(at least one)		CC	138 (75)	83.7 (78.4-88.1)	97.9 (88.7-99.9)	99.5 (97.3-100.0)	53.5 (42.4-64.3)	-	PCR-ELISA NS1/IgM/IgG
ProDetect Dengue Duo (Mediven)	Jusoh & Shueb [36] (2017)	Malaysa	CC	86 (36)	94.4 (81.9-98.5)	96.0 (86.5-98.9)	94.4 (83.3-98.3)	96.0 (87.7-98.8)	1 (14) 2 (8) 3 (2) 4 (1) 1&2 (1)	ELISA NS1 RT-PCR/viral isolation

(continues)

Table 1 (continued)

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
OneStep NS1 RapiDIP Instatest-Rapicard IgM/IgG	Vickers et al. [76] (2017) (fever 4 days)	Jamaica	CC 1:1.1	339 (174)	99.5 (97.1-99.9)	100.0 (87.5-100.0)	100.0 (98.0-100.0)	96.4 (82.3-99.4)		ELISA NS1 IgM
Asan	Lee et al. [37] (2019)		CC	138 (75)	77.3 (66.3-86.2)	98.4 (91.5-99.9)	98.3 (89.2-99.8)	78.5 (70.6-84.7)	-	PCR-ELISA NS1/IgM/IgG
Boditech Med	Lee et al. [37] (2019)		CC	138 (75)	98.7 (92.8-99.9)	90.5 (80.4-96.4)	92.5 (85.2-96.4)	98.3 (89.0-99.8)	-	PCR-ELISA NS1/IgM/IgG
NS1/IgM/IgG (only NS1)										
SD Bioline Dengue Duo	Osorio et al. [40] (2010)	Colombia	CC	310 (218)	51.0 (44.1-57.7)	96.7 (90.8-99.3)	97.4 (92.5-99.5)	45.4 (38.3-52.7)	1 (13) 2 (17) 3 (7) 4 (5)	Viral isolation RT-PCR ELISA IgM
	Tricou et al. [46] (2010)	Vietnam	Cohort	292 (245)	62.4 (56.1-68.5)	100.0 (93.8-100.0)	100.0 (98.1-100.0)	33.8 (26.0-42.3)	1 (138) 2 (91) 3 (16)	ELISA IgM/IgG RT-PCR
	Blacksell et al. [50] (2011)	Sri Lanka	CC	259 (99)	48.5	99.4	98.0	75.7	1 (1) 2 (16) 3 (47) 4 (2)	RT-PCR ELISA IgM/IgG
	Sandoval et al. [71] (2011)	Cuba	CS	161 (71)	57.8 (45.6-69.9)	98.9 (96.2-100.0)	97.6 (86.8-99.4)	74.8 (66.2-81.6)	1 (53) 2 (21) 3 (1)	ELISA NS1/IgM/IgG
	Tontulawat et al. [75] (2011)	Thailand	CS	237 (126)	70.3 (61.2-78.0)	73.0 (64.7-80.0)	69.6 (62.7-75.8)	73.6 (67.3-79.1)	-	PCR semi-nested ELISA/IgM
	Andries et al. [58] (2012)	Cambodia	CS	126 (31) (blood/hospital)	44.4 (35.6-53.6)	96.8 (83.3-99.9)	98.2 (90.6-100.0)	30.0 (21.2-40.0)	-	RT-PCR Viral isolation ELISA IgM
				(blood/labo-ratory)	45.2 (36.4-54.3)	96.6 (83.3-99.9)	98.3 (92.0-99.7)	30.3 (26.7-34.2)		
	Parham et al. [67] (2013)	Honduras	CS	61 (48)	87.5 (75.3-94.1)	15.4 (4.33-42.2)	79.2 (74.3-83.4)	25.0 (7.8-56.8)	-	RT-PCR
	Gan et al. [59] (2014)	Singapore	CS	197 (147)	81.6 (74.6-87.1)	98.0 (89.5-99.7)	99.2 (99.5-99.9)	64.5 (53.3-74.3)	1 (22) 2 (89) 3 (1)	RT-PCR ELISA NS1 /IgM/IgG
	Sanchez-Vargas et al. [70] (2014)	Mexico	CC 139:171	397 (310)	87.5 (81.6-93.43)	94.6 (91.7-97.6)	89.5 (83.9-95.1)	93.6 (90.4-96.7)	-	ELISA NS1/IgM/IgG
	Krishnanan-thasivam et al. [65] (2015)	Sri Lanka	CC	143 (27)	57.0 (47.1-65.7)	86.7 (59.5-95.9)	97.3 (90.7-99.6)	19.1 (10.6-30.5)	-	RT-PCR ELISA IgM IgG

(continues)

Table 1 (continued)

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
	Hunsperger et al. [62] (2016)		CC	1,678 (1,116)	65.9 (62.2,69.4)	80.9 (77.8,83.8)	-	-	1 (31) 2 (188) 3 (89) 4 (430)	RT-PCR
		Angola		46 (43)	92.9 (76.5-99.1)	22.0 (6.4-47.6)	-	-	1 (29)	
		Marshall Island		796 (430)	66.8 (61.9-71.3)	79.9 (74.3-84.7)	-	-	4 (430)	
		Fiji		302 (148)	84.4 (75.3-91.2)	78.2 (71.8-83.7)	-	-	3 (89)	
		Yap Island		534 (332)	49.7 (42.0-57.4)	89.0 (84.2-92.7)	-	-	2 (175)	
	Garg et al. [60] (2019)	India	CC	152 (72)	100.0 (94.6-100.0.)	100.0 (95.5-100.0)	100.0 (94.6-100.0)	100.0 (95.5-100.0)	-	
	Shih et al. [72] (2016)	Taiwan	CS (acute) Median 17 years	1,607 (1,295)	94.9 (92.1-96.7)	70.9 (63.0-77.8)	89.5 (86.9-91.7)	84.0 (77.1-89.2)	-	
	Huits et al. [61] (2017)	Belgium	Cohort 4:1	308 (52)	82.7 (74.4-93.0)	99.6 (98.8-100)	97.7 (89.6-99.5)	96.6 (94.1-98.1)	-	
	Simonnet et al. [74] (2017)	French Guiana	Cohort (acute)	3,347 (475)	87.6 (84.3-90.2)	98.1 (97.5-98.5)	88.3 (85.3-90.8)	97.9 (97.4-98.4)	-	
	Liu et al. [68] (2018)	Solomon Island	CS 216:14	412 (242)	90.9 (87.0-94.0)	100.0 (98.0-100.0)	100.0 (98.0-100.0)	88.5 (83.0-93.0)	3 (242)	
	Kikuti et al. [64] (2019)	Brazil	CC 45:199	500 (246)	38.6 (32.5-45.0)	98.2 (93.5-99.8)	97.9 (93.2-99.4)	58.8 (56.2-61.2)	1 (18) 2 (113) 4 (49)	
	Lee et al. [37] (2019)	Korea	CC	138 (75)	49.2 (36.4-62.1)	98.7 (92.8-99.9)	96.9 (81.3-99.5)	69.8 (64.4-74.7)	-	PCR-ELISA NS1/IgM/IgG
			CC	138 (75)	57.1 (28.9-82.3)	100.0 (97.1-100.0)	100.0 (63.6-100.0)	95.4 (91.9-97.4)	-	ELISA IgM
	Jang et al. [63] (2019)	Myanmar	CC 1:4	172 (109)	48.6 (38.9-58.4)	100.0 (94.3-100.0)	100.0	52.9		qRT-PCR ELISA IgM/IgG
CTK Biotech	Liu et al. [68] (2018)	Solomon Island	CS 216:14	412 (242)	92.6 (88.6-95.2)	78.8 (72.1-84.3)	86.2 (82.3-89.3)	88.2 (82.7-92.1)	3 (242)	Real-time qRT-PCR
Denguecheck	Garg et al. [60] (2019)	India	CC	152 (72)	100.0 (94.6-100.0)	100.0 (95.5-100.0)	100.0 (94.6-100.0)	100.0 (95.5-100.0)	-	RT-PCR ELISA NS1 IgM/IgG
Dengue day 1					94.4 (86.3-98.4)	100.0 (98.5-100.0)	100.0	95.2 (88.2-98.6)		
	Shukla et al. [73] (2017)	India	CS	249 (128)	93.6 (87.8-96.7)	91.1 (84.8-94.9)	91.4	93.4	1 (79) 2 (85) 3 (85)	RT-PCR
Humasis	Jang et al. [63] (2019)	Myanmar	CC 1:4	172 (109)	63.3 (53.5-72.3)	100.0 (94.3-100.0)	100.0	44.0		qRT-PCR ELISA IgM/IgG
Humasis NS1/IgM	Kyaw et al. [66] (2019)	Myanmar	CS 1:1	202 (140)	68.6 (60.2-76.1)	90.3 (80.1-96.4)	94.1 (87.6-97.8)	56.0 (45.7-65.9)	1 (57) 2 (7) 3 (6) 4 (10)	ELISA IgM/IgG RT-PCR
CareUS	Jang et al. [63] (2019)	Myanmar	CC 1:4	172 (109)	79.8 (71.1-86.9)	100.0 (94.3-100.0)	100.0	74.1		qRT-PCR ELISA IgM/IgG

(continues)

Table 1 (continued)

ICT	Study (year)	Country	Design 1ary:2nd infection	N (dengue cases)	Sn % (95%CI)	Sp % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	DENV (n)	Reference standard
CareUs NS1/ IgM	Kyaw et al. [66] (2019)	Myanmar	CS 1:1	202 (140)	72.1 (63.9-79.4)	87.1 (76.1-94.3)	92.7 (86.0-96.8)	58.1 (47.4-68.2)	1 (57) 2 (7) 3 (6) 4 (10)	ELISA IgM/IgG RT-PCR
Wondfo NS1/ IgM	Kyaw et al. [66] (2019)	Myanmar	CS 1:1	202 (140)	67.1 (58.7-74.8)	91.9 (82.2-97.3)	94.9 (88.6-98.3)	55.3 (45.2-65.1)		
SD Bioline duo	Blacksell et al. [50] (2011)	Sri Lanka	CS	259 (99)	79.2 (70.5-87.2)	89.4 (83.5-93.7)	82.3 (73.2-89.3)	87.7 (81.7-92.3)	1 (1) 2 (16) 3 (47) 4 (2)	RT-PCR ELISA IgM/IgG
	Parham et al. [67] (2013)		CS	61 (48)	82.5 (70.6-90.2)	87.5 (64.0-96.5)	95.9 (87.8-98.7)	58.3 (43.7-71.6)	1 (50) 2 (50) 3 (58)	RT-PCR
	Sanchez-Vargas et al. [70] (2014)	Mexico	CC 1:1.2	397 (310)	60.5 (53.4-67.6)	94.1 (90.6-97.6)	90.8 (85.4-96.1)	71.2 (65.5-76.8)	-	ELISA NS1/ IgM/IgG
	Shih et al. [72] (2016)	Taiwan	CS	1,607 (1,295)	10.0 (7.3-13.5)	66.0 (57.8-73.3)	-	-	-	RT-PCR
	Simonet et al. [74] (2017)	French Guiana	Cohort	3,347 (475)	44.8 (39.9-50.0)	98.3 (97.8-98.7)	75.9 (70.2-80.9)	93.7 (93.1-94.2)	-	Dx select IgM
SD Bioline Dengue Duo	Hunsperger et al. [62] (2016)	Angola	CC	46 (14)	91.7 (61.5-99.8)	85.3 (68.9-95.1)	-	-	1 (29)	ELISA IgM
		Marshall Island		796 (53)	80.0 (61.4-92.3)	92.2 (88.9-94.8)	-	-	4 (430)	
		Fiji		302 (38)	55.3 (38.3-71.4)	78.2 (96.2-99.6)	-	-	3 (89)	
		Yap Island		534 (53)	56.6 (42.3-70.2)	93.1 (91.4-95.9)	-	-	2 (175)	
	Lee et al. [37] (2019)		CC	138 (75)	49.2 (36.4-62.1)	98.7 (92.8-99.9)	96.9 (81.3-99.5)	69.8 (64.4-74.7)	-	PCR-ELISA NS1/IgM/IgG
	Kikuti et al. [64] (2019)	Brazil	CC 1:4.4 (acute)	500 (246)	13.8 (9.8-18.8)	96.3 (90.8-99.0)	89.5 (76.5-95.7)	32.9 (31.5-34.3)	1 (18) 2 (113) 4 (49)	RT-PCR ELISA NS1/IgM paired/ IgG
	Garg et al. [60] (2019)	India	CC	152 (72)	44.5 (32.7-56.6)	100.0 (97.5-100.0)	100.0	66.7 (57.4-75.1)	-	RT-PCR ELISA NS1 IgM/IgG
	Jang et al. [63] (2019)	Myanmar	CC 1:4	172 (109)	60.6 (50.7-69.8)	100.0 (94.3-100.0)	100.0	59.4	-	qRT-PCR ELISA IgM/IgG
Denguecheck	Garg et al. [60] (2019)	India	CC	152 (72)	77.7 (66.4-86.7)	50.0 (38.6-61.4)	58.3 (47.8-68.3)	71.4 (57.8-82.7)	-	RT-PCR ELISA NS1 IgM/IgG
Dengue day 1	Garg et al. [60] (2019)	India	CC	152 (72)	27.8 (17.8-39.6)	65.0 (53.5-75.3)	41.6 (27.6-56.8)	50.0 (40.0-60.0)	-	RT-PCR ELISA NS1 IgM/IgG
Humasis	Jang et al. [63] (2019)	Myanmar	CC 1:4	172 (109)	51.4 (41.6-61.1)	98.2 (91.5-99.9)	98.2	53.9	-	qRT-PCR ELISA IgM/IgG
CareUS	Jang et al. [63] (2019)	Myanmar	CC 1:4	172 (109)	89.9 (82.7-94.8)	100.0 (94.3-100.0)	100.0	85.1	-	qRT-PCR ELISA IgM/IgG

95%CI: 95% confidence interval; CC: case-control study; Conval.: convalescent sample; CS: cross-sectional study; DENV: dengue virus; NPV: negative predictive value; PPV: positive predictive value; Sn: sensitivity; Sp: specificity; Read.: reading time.
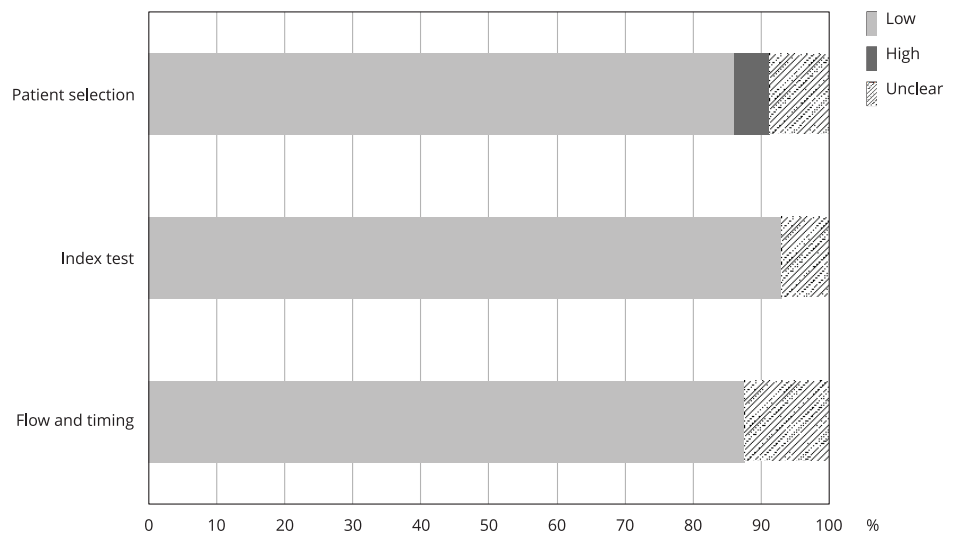
Figure 2

Quality assessment and risk of bias of the selected studies using the *Quality Assessment of Diagnostic Accuracy Studies* (QUADAS 2).

2a) Risk of bias
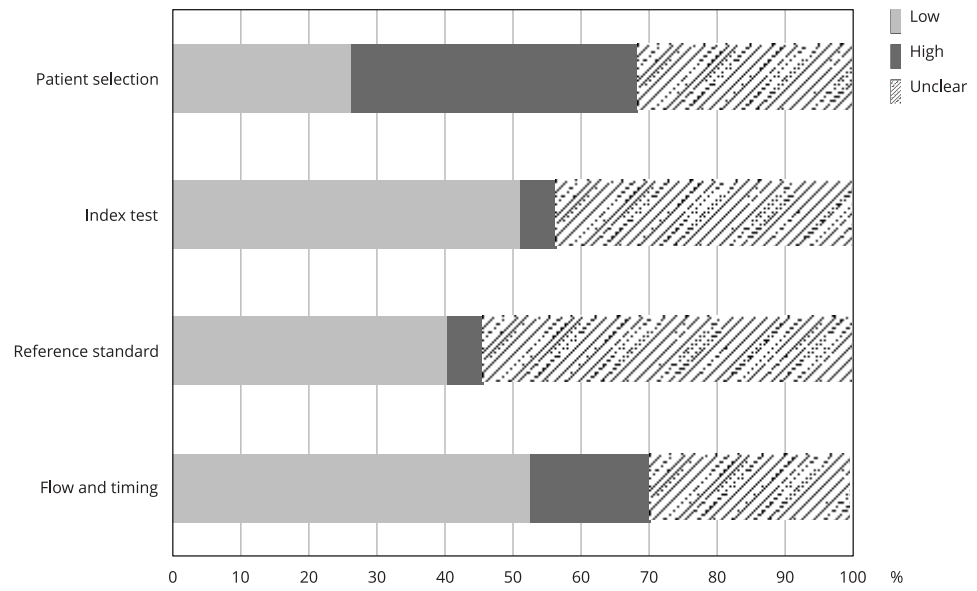
2b) Concerns regarding applicability

Rapid immunochromatographic tests with IgA detection

A total of 2,051 samples from patients with suspected dengue virus infection were analyzed (median 342, interquartile range [IQR]: 100-914) in the five studies selected for this part of the review [24,25,27,27,28]. One of them showed results in acute and convalescent samples [24]. Pooled estimate of the IgA tests showed a sensitivity of 88% and specificity of 90% (Table 2). It was not possible to assess publication bias for these tests due to the small number of studies included in the analysis. The pooled estimate in the acute phase showed slightly higher sensitivity (92.8 vs. 88) and the same specificity (90%) compared with the analysis which included convalescent samples. The performance of this test for screening was better than NS1 or IgM/IgG due to better sensitivity (Table 2), but lower than tests with three analytes.

Forest plots (Figure 3) showed similar results between studies, except for one case-control [26] which included mainly primary infections compared to secondary infections (5:1), despite high statistical heterogeneity (I^2 = 93%). IgA ICT tests in scenarios with prevalence of 25% showed the positive post-test probability still moderately high (75%) compared to conclusive (90% and 96%) results in epidemic scenarios (Table 2). Besides that, the negative post-test probabilities were reasonable up to 12% and 18% even in outbreaks (Table 2).

Only one study [26] reported the serotypes tested (Table 1). This study assessed the performance according to serotype (DENV-1 and 2), showing heterogeneous sensitivities (Sn = 52.4% in DENV-1 and 73.9% in DENV-2).

Three studies [24,26,27] included primary and secondary dengue infection cases without stratified analysis.

Rapid immunochromatographic tests with NS1 detection

Tests based exclusively on NS1 evaluated three brands up to 2014: Bio-Rad, Panbio, Alere/Bio_Easy. These totalized 21 studies up to the seventh day of the disease [10,27,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,50], one of which [34] presented the results of two settings, one in Malaysia and the other in Vietnam. The tests were assessed in 6,618 samples from patients with suspected dengue (median 241). Of 21 studies, 18 reported the serotypes tested, totaling 852 samples of DENV-1, 582 DENV-2, 501 DENV-3, and 510 DENV-4 (Table 1), but did not show stratified performance analysis.

Table 2

Meta-analysis of the accuracy of rapid immunochromatographic tests (ICT) according to the analytes of the diagnostic method.

ICT (samples)	Sn % (95%CI)	Sp % (95%CI)	LR+ (95%CI)	LR- (95%CI)	DOR (95%CI)	PP+ (25%; 50%; 75%)	PP- (25%; 50%; 75%)	I² (%) Sn (95%CI)	I² (%) Sp (95%CI)
IgA all	88.0	90.0	9.1	0.13	69.0	75; 90; 96	4; 12; 28	96.1	91.2
(n = 6)	(73.0-95.0)	(78.0-96.0)	(3.7-22.3)	(0.05-0.33)	(15.0-312.0)			(94.2-98.0)	(85.7-96.7)
NS1 all	76.0	99.0	72.5	0.25	294.0	96; 99; 100	8; 20; 43	94.8	85.3
(n = 23)	(69.0-81.0)	(98.0-100.0)	(34.3-153.3)	(0.19-0.32)	(129.0-669.0)			(93.7-96.0)	(80.9-89.7)
NS1 Biorad	79.0	100.0	175.2	0.21	841.0	98; 99; 100	6; 17; 38	95.9	87.0
(n= 14)	(70.0-86.0)	(99.0-100.0)	(54.2-566.1)	(014-0.30)	(254.0-2,783.0)			(94.8- 97.1)	(81.7-92.3)
NS1 others	70.0	97.0	21.0	0.31	68.0	88; 95; 98	9; 24; 48	91.8	72.2
(n = 11)	(61.0-78.0)	(94.0-98.0)	(12.0-36.8)	(0.23-0.41)	(35.0-133.0)			(88.9-94.7)	(58.2-86.1)
IgM/IgC Panbio	56.0	94.0	9.7	0.47	21.0	76; 91; 97	13; 32; 58	95.8	95.2
(n = 6)	(39.0-72.0)	(86.0-98.0)	(4.1-23.0)	(0.32-0.67)	(8.0-54.0)			(94.0-97.6)	(93.0-97.3)
NS1/IgM/ IgG (n = 11)	91.0	96.0	20.2	0.10	208.0	87; 95; 98	3; 9; 23	93.8	91.4
	(84.0-95.0)	(91.0-98.0)	(9.7-42.2)	(0.06-0.17)	(67.0-646.0)			(91.6-96.0)	(88.0-94.7)

95%CI: 95% confidence interval; I²: I² for heterogeneity; LR: likelihood ratio; PP: positive and negative post-test probabilities assuming dengue prevalence of 25%, 50% and 75%; Sn: sensitivity; Sp: specificity.
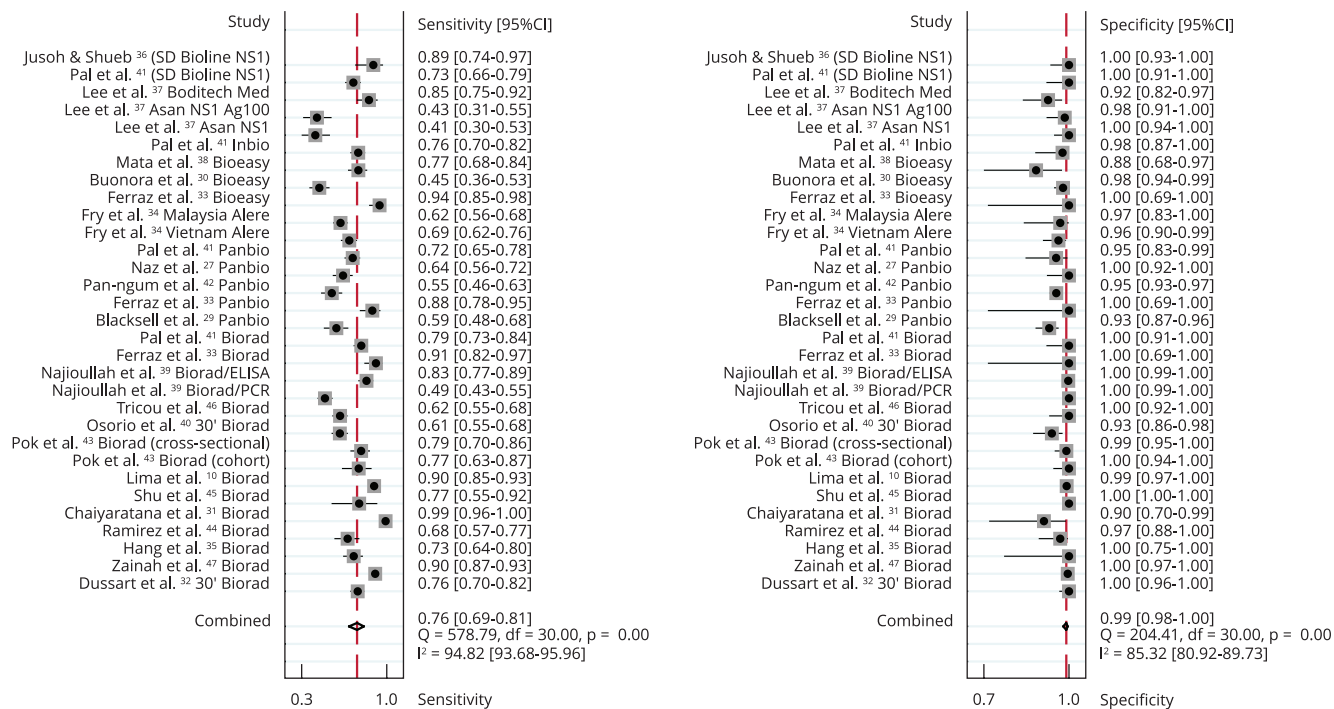
Figure 3

Forest plot for the meta-analysis of rapid immunochromatographic tests (ICT) according to dengue diagnostic analyte.
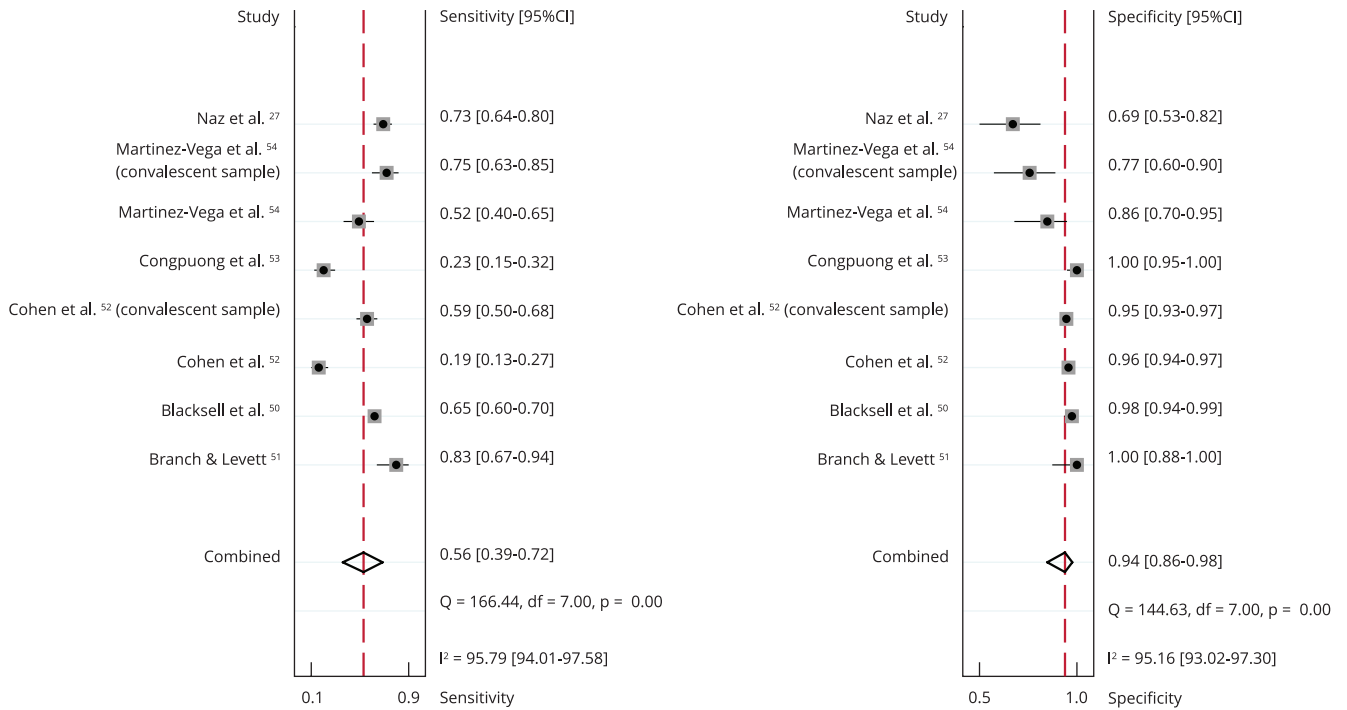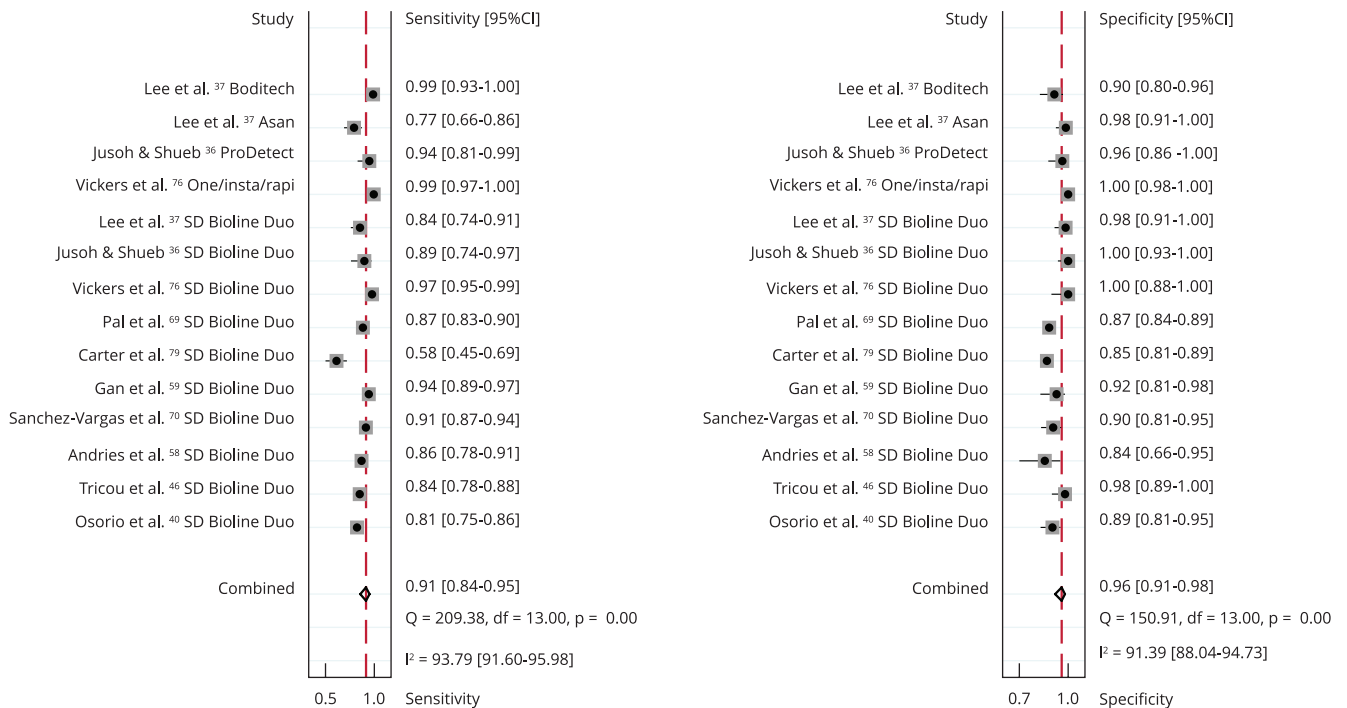
3a) IgA
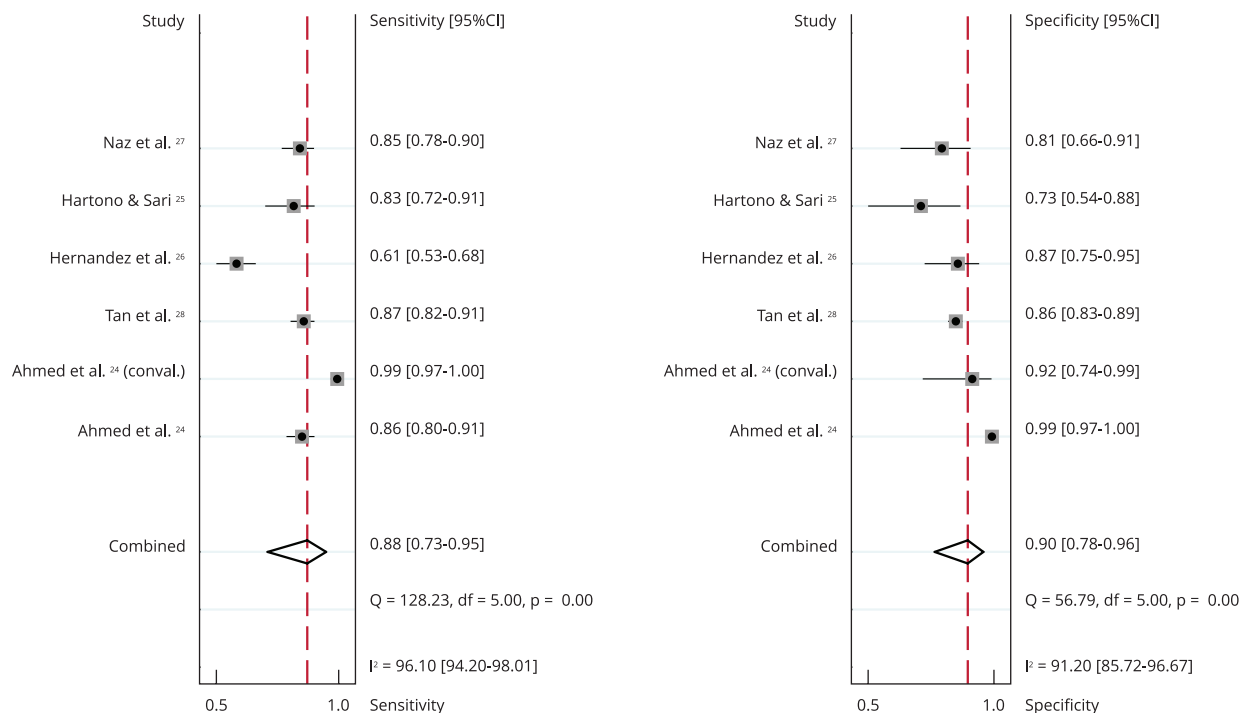
3b) NS1 all tests

(continues)

Figure 3 (continued)

3c) IgM/IgG Panbio

3d) NS1/IgM/IgG.combo test

95%CI: 95% confidence interval; conval.: convalescent sample.

The pooled estimates for all NS1 tests showed sensitivity of 74%, and higher specificity of 99%. The lower sensitivity values were obtained for NS1 Bioeasy in a Brazilian sample of DENV-4 outbreak [30] as well as for the brand Asan [37].

Bio-Rad Dengue Rapid Test was used for NS1 detection in 14 of the 21 studies [10,31,32,33,35,39,40,41,43, 44,45,46,47,50] (4,678 samples). Sensitivity ranged from 49.4% [39] to 98.9% [31] and specificity from 91% [35] to 100% in 8 studies [32,33,35,39,41,43,45,46]. The pooled estimate for the Bio-Rad Dengue Rapid Test showed sensitivity of 79% and specificity of 100% (Table 2). The post-test probability after a positive result in NS1-based ICT was above 95% in three different hypothetical scenarios of dengue prevalence of 25%, 50% and 75%.

Several recent studies tested SD Duo Bioline ICT but only showed NS1 results. We opted to describe these on Table 1, but to exclude them from the meta-analyses since there was not blinding of other analyte results in the same cassette.

Assessment of the individual studies did not show publication bias (p-value = 0.09).

Rapid immunochromatographic tests with IgM/IgG detection

Seven studies assessed tests with both IgM/IgG detection [27,48,50,51,52,53,54], using 2,597 samples (median 178). Seven studies identified the dengue serotypes, with a total of 251 DENV-1, 176 DENV-2, 193 DENV-3, and 77 DENV-4. Most studies except one evaluating exclusively IgM/IgG ICT were published up to 2011 (Table 1).

These tests presented the lowest values of pooled estimates of sensitivity (54%), with inadequate values of negative likelihood ratios (NLR > 0.4) (Table 2). Thus, the post-test probabilities after negative results were inconclusive, particularly for epidemic scenarios of prevalence. In the convalescent phase of the disease, the pooled estimate of accuracy showed, as expected, higher sensitivity (Sn = 62.6%, 95%CI: 36.7-82.9), than in the acute phase, 53.8% (95%CI: 41.4-65.8), and high specificity in all phases of the disease (94% and 94.7%,). Specificity was lower for recent studies [27,54].

Panbio Dengue Duo IgM/IgG was the most widely assessed test, with pooled sensitivity and specificity of 56% and 90% (Figure 3; Table 2).

We detected no publication bias (p = 0.13).

Rapid immunochromatographic tests with simultaneous NS1/IgM/IgG detection

Ten studies that assessed that type of test included a total of 3,361 patients (median 447) with suspected dengue, with 289 DENV-1, 225 DENV-2, 52 DENV-3 and 39 DENV-4 [36,37,40,46,58,59,69,70,77,79] (Table 1).

The best performance was observed for these tests with pooled positive and negative likelihood ratios, of 19.2 and 0.09, respectively. The post-test probability after negative and positive results in endemic (25%) and epidemic (75%) scenarios of dengue prevalence were below 25% and above 85%, respectively. The pooled estimate of sensitivity was 91% and specificity, 96% (Table 2). Carter et al. [79] obtained the poorest performance in sensitivity. After excluding it, the pooled results were unchanged, Sn = 92% (87-95%) and Sp = 96% (92-98%).

Some recent studies also reported results for each analyte separately even when testing ICT composed of a cassette with three analytes. We describe these "only results" on Table 1 without including these meta-analyses, since this was only a statistical analysis and not a practical use of a test with a single analyte in a cassette.

We observed no asymmetry in the assessment of publication bias in the studies (p-value = 0.09).

Discussion

This was a systematic review addressing the dengue virus detection methods in commercially available ICTs, obtained through a search of nine large databases, with 57 studies included. One strategy used to increase the tests' performance was the simultaneous test of the three analytes NS1, IgM, and IgG [40,46,56,58,67,71]. In our review, these ICTs showed high pooled estimates, better than those of IgA ICTs. Among the ICTs with serological detection assessed in this review, those with IgA detection stood out as having the best accuracy, with high pooled sensitivity and specificity in the acute phase compared to IgM/IgG ICT.

IgA tests showed the best performance in triage of patients in acute phase of the disease. They were twice as positive among cases with up to seven days of dengue fever when compared to those in the convalescent phase. Still, these studies did not analyze the tests according to phase of disease (acute/convalescent), thus making it impossible to claim that this same performance would be maintained in the initial days of the disease.

The current review showed an excellent pooled specificity (99%-100%) in the acute phase of the disease in ICTs with exclusive detection of NS1, six times more positive among dengue cases when compared to IgA ICTs during the same phase of the disease. These findings corroborate those of Lima et al. [10], who suggested the best performance of NS1 to confirm dengue cases in the acute phase of disease.

The systematic review published by Alagarasu et al. [11] assessed IgA ICTs, including three studies with lower estimate sensitivity of 72% and similar specificity (89%). However, the wide confidence intervals in the measures of accuracy both in our review and in Alagarasu et al. [11] make its use for screening questionable.

In recent years, several authors have questioned the use of IgM/IgG serology to detect dengue and other flaviviruses, due to the tests' proven cross-reaction with the Zika, yellow fever, and chikungunya viruses, thus limiting their use in scenarios with co-circulation of these viruses [6,80,81].

The systematic review by Zhang et al. [4] showed pooled estimates to these NS1 ICTs similar to our review, with Sn = 71% and Sp = 99%. Both in Zhang et al. [4] and in our review, the performance of NS1 ICT in scenarios with 25%, 50%, and 75% of dengue prevalence pointed to increasing positive post-test probability, ranging from 99 to 100%. When used in screening, these tests should be coupled with a diagnostic algorithm in order to optimize their performance, due to the high number of false-negatives [4].

The accuracy of IgM/IgG ICTs had the worst performance and studies about this ICT were interrupted in 2014. The systematic review by Blacksell et al. [6] assessed the Panbio ICT in the acute phase of the disease and the summary measures were superior to those in our review. Among other factors, these differences can be attributed to the samples' characteristics related to the convalescent phase or samples with mostly primary infection [6,11].

Only two studies included in this review reported a potential conflict of interest [31,46]. Only one [31] reported sensitivity results that differed from the pooled sensitivity in our review.

In addition to the review's originality, one of its strengths was the scope of the literature search, which included all types of commercially available ICTs for dengue detection, with subgroup analysis according to the ICT detection method in each of the principal commercial ICTs, and when possible, according to the phase of the disease (acute/convalescent).

The review's limitations include the low methodological quality of the included studies and the lack of data for adequate characterization of the samples (27/34, 79.4%), either by age bracket (21/34, 61.8%) or dengue serotype (16/34, 47.1%), which prevented such subgroup analyses. Another limitation was the high heterogeneity detected in all the types of ICTs that were assessed, possibly due to the differences between the characteristics of the samples included by the studies. These differences were related to the age of the included patients, predominant type of infection (primary or secondary), serotypes assessed, disease phase assessed by the tests (acute/convalescent), and different reference tests (real-time PCR, RT-PCR, in-house ELISA, MAC-ELISA, among others). This heterogeneity may not be explained by the different reference standards since only three studies did not used at least one test with high specificity (100% for RT-PCR or ELISA NS1) [10]. Thus, the sensitivity of ICTs does not

seem to be penalized by the reference standards. Similarly, the almost perfect specificities of ICTs were not influenced by non-optimal sensitivities (89.5%) of reference tests.

The three systematic reviews that included ICTs pointed to the same limitations described above [4,6,11]. Guidelines like the *Standards for Reporting Diagnostic Accuracy Studies* (STARD) [82] and tools like QUADAS 2 [20] have contributed to the standardization of reporting by accuracy studies, as indicated by Blacksell et al. [83]. We emphasize that peer-reviewed journals and regulatory agencies should require the use of both these guidelines in order to assist future reviews and the elaboration of recommendations or protocols. Future studies should investigate cost-effectiveness, decision tree or a combination of multiple tests, including ICT in the diagnostic algorithm.

In conclusion, IgA ICT and NS1/IgM/IgG ICT showed the best pooled performance in the acute phase of dengue. The last one, as suggested by Pal et al. [69], mainly due to their confirmatory power.

Contributors

All authors participated in the conception and design of this manuscript and have been involved in either drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the final version of this manuscript and agree to be accountable for all aspects of the work.

Additional informations

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Resumo

A dengue é uma importante arbovirose em termos de morbidade, mortalidade, impacto econômico e controle do vetor. Os testes de referência são dispendiosos e demorados e exigem pessoal capacitado. A prevenção das complicações da dengue com o diagnóstico rápido tem tomado como base a testagem com métodos imunocromatográficos (ICT). O estudo é uma revisão sistemática e meta-análise da acurácia diagnóstica de estudos de ICT de IgA, NS1, IgM e/ou IgG em casos suspeitos de dengue aguda ou convalescente, usando uma combinação de RT-PCR, ELISA NS1, IgM IgG ou isolamento viral como padrão de referência. O projeto foi registrado na base PROSPERO (CRD42014009885). Dois pares de revisores realizaram as buscas nas bases de dados PubMed, BIREME, Science Direct, Scopus, Web of Science, Ovid MEDLINE JBrigs, SCIRUS e EMBASE, além da seleção, extração e avaliação de qualidade com a ferramenta QUADAS 2. A partir de 3.783 estudos, selecionamos 57, dos quais 40 foram incluídos nas meta-análises de acordo com o analito testado, com alta heterogeneidade ($I^2 > 90\%$), conforme esperado para testes diagnósticos. Foi detectada a maior sensibilidade conjunta no IgA de fase aguda (92,8%), com excelente especificidade (90%). A meta-análise de ICT com NS1/IgM/IgG mostrou sensibilidade de 91% e especificidade de 96%. O pior desempenho para triagem foi com o ICT de IgM/IgG (sensibilidade = 56%). Portanto, os estudos de ICT com NS1/IgM/IgG mostraram o melhor desempenho combinado na fase aguda da doença.

Dengue; Diagnóstico; Sensibilidade e Especificidade; Revisão Sistemática; Metanálise

Resumen

El dengue es una importante enfermedad arboviral, en términos de morbilidad, mortalidad, impacto económico y desafíos en el control del vector. Las mejores prácticas son caras, consumen mucho tiempo y requieren personal formado. Prevenir las complicaciones del dengue con un rápido diagnóstico se ha basado en pruebas con métodos inmunocromatográficos optimizados fáciles de realizar (ICT por sus siglas en inglés). Se trata de una revisión sistemática de metaanálisis sobre la precisión diagnóstica de estudios de IgA, NS1, IgM y/o IgG ICT en casos sospechosos de fases agudas o convalecientes de dengue, usando la combinación de RT-PCR, ELISA NS1, IgM IgG o el aislamiento viral como referencia estándar. Este proyecto se registró en PROSPERO (CRD42014009885). Dos parejas de revisores investigaron en las bases de datos de: PubMed, BIREME, Science Direct, Scopus, Web of Science, Ovid MEDLINE JBrigs, SCIRUS y EMBASE, seleccionaron, extrajeron, y realizaron la evaluación de calidad mediante QUADAS 2. De 3.783 estudios, se seleccionaron 57, de los cuales 40 fueron metaanálisis, según el analito probado, con una alta heterogeneidad ($I^2 > 90\%$), como se esperaba en las pruebas de diagnóstico. Detectamos una sensibilidad más alta combinada en la fase aguda IgA (92.8%) con una excelente (90%) especificidad. Los metaanálisis ICT con NS1/IgM/ IgG mostraron un 91% de sensibilidad y un 96% de especificidad. Se produjo un rendimiento más pobre en el diagnóstico IgM/IgG ICT (sensibilidad = 56%). De este modo, los estudios con NS1/IgM/IgG ICT mostraron un rendimiento mejor combinado en la fase aguda de la enfermedad.

Dengue; Diagnóstico; Sensibilidad y Especificidad; Revisión Sistemática; Metaanálisis