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Clinical evaluation of a developed paper-based Dengue NS1 rapid diagnostic test for febrile illness patients

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ABSTRACT

Objectives: This study aimed to evaluate a microfluidic paper-based analytical device (DEN-NS1-PAD) based on a rapid NS1 antigen test for diagnosing dengue at the point of care.
Methods: 219 serum samples from suspected dengue cases were tested with the developed DEN-NS1-PAD and commercial RDT by SD BIOLINE. The results were compared with the nested-PCR results.
Results: The limit of detection of DEN-NS1-PAD was 0.78 ng mL^{-1}. It showed 88.89% sensitivity, 86.67% specificity, and a substantial agreement correlation ($\kappa = 0.7522$) compared with nested-PCR. In contrast, SD BIOLINE for NS1 (SD-NS1) detection showed 87.88% sensitivity, 90.00% specificity, and had a substantial agreement correlation with nested-PCR ($\kappa = 0.7788$).
Conclusions: DEN-NS1-PAD is a valuable tool for diagnosing DENV infections, especially for diagnosed patients with early acute phase samples with high viral load. DEN-NS1-PAD has better sensitivity than SD-NS1 but less specificity.

Introduction

Dengue virus (DENV) infection is one of the world's most important neglected tropical diseases and the fastest spreading mosquito-borne disease (Cattarino et al., 2020). About 70 percent of the 3.9 billion people at risk live in Asian Pacific countries, mainly in Southeast Asia (World Health Organization (WHO, 2020). In 2019, Thailand had reported at least 136,000 cases (peak in July) and death for 0.12% of all cases (Department of Disease Control Ministry of Health, 2020), with peak transmission during the rainy season.

The early diagnosis of dengue is essential for clinical assessment (Teparrukkul et al., 2017), investigations, and disease control (Sekaran, 2015). Although, molecular assays were used as the gold standard for diagnosing dengue infection (Lanciotti et al., 1992; Santiago et al., 2018), these methods are expensive, tedious, and need the expertise of technicians, which is unsuitable for point-of-care tests in remote areas (Lai et al., 2007; Shu et al., 2003). Reverse transcriptase-polymerase chain reaction (RT-PCR) is highly sensitive and specific; however, it is not cost-effective to establish in dengue-endemic areas. In contrast, rapid diagnostic tests (RDT) can overcome these drawbacks, thus improving the management of infectious diseases and reducing mortality (Kikuti et al., 2019).

There are many commercial immunochromatographic assays for detecting the NS1 or IgG/IgM of dengue, or a combination of them (Kikuti et al., 2019). RDT based NS1 detection is of interest because it can be applied to blood, serum, plasma, and tissues from fatal cases (Guzman et al., 2016, 2014). Protein NS1 can also be diagnosed before day five (during the viremia phase), so it is suitable for early diagnosis (Guzman et al., 2016; Wilder-Smith et al., 2019).

A simple diagnostic kit for dengue NS1 testing based on a wax-printed microfluidic paper-based analytical device (μPAD), so-called DEN-NS1-PAD (Prabowo et al., 2020), had been developed for sensitive and specific detection of dengue NS1. The main

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objective of this study was to evaluate the performance of the DEN-NS1-PAD for its sensitivity and specificity for dengue NS1 detection among febrile patients. DEN-NS1-PAD performance was compared with SD-BIOLINE as a commercial RDT. The validation was conducted by comparison with nested-PCR.

Materials and methods

Study design

The evaluation study was a retrospective cross-section design, and its reporting followed the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) guidelines (Bossuyt et al., 2015).

Clinical specimens

The 250 dengue-suspected sera samples used in this study were the archived sera of dengue-suspected patients, routinely collected during the peak of the disease epidemic in Thailand, from July to September 2019 at the Phramongkutklao Hospital. Patients' blood samples were routinely tested by a commercial dengue NS1 test kit immediately after collection to diagnose and treat patients. Leftover sera collected on the first day of a hospital visit and stored following good clinical practices at −20 °C were randomly selected for further analysis (nested-PCR and DEN-NS1-PADs), after ethical approval had been granted.

Fabrication and detection by DEN-NS1-PAD

The DEN-NS1-PAD was fabricated from a piece of cellulose paper with a wax pattern as described previously (Prabowo et al., 2020). The DEN-NS1-PAD allows specific interaction between reporter antibodies (rAb) labeled with AuNPs and dengue NS1 protein. This immuno-complex was then captured by capture antibodies (cAb) to produce a colorimetric signal. The positive red zone appears because of the formation of rAb-AuNPs/NS1/cAb complexes. The red color at the control zone appears from the formation of anti-goat IgG/goat antibody-AuNPs complexes. Accumulation of red microspheres on the test and control zones allows for visualization by the naked eye, scanner, and smartphones. The schematic representation of the procedure for dengue NS1 detection by using DEN-NS1-PAD is shown in Figure 1A. The DEN-NS1-PAD can be visually observed on a scale of 0 to 1000 ng mL^{-1} (Figure 1B). Briefly, 50 μL of the test sample was added to the PAD sample zone. Results were captured with a smartphone camera and interpreted by ImageJ software 20 min after the application of the specimen. The cut-off value of 0.1103 from normalized gray intensity was used to distinguish between positive and negative results. The test results were interpreted without knowledge of the results of the SD BIOLINE and nested-PCR test (blinded).

Dengue detection by SD BIOLINE™ Dengue Duo

The SD BIOLINE™, Dengue Duo test, was carried out in accordance with the manufacturer's instructions. To detect NS1, 100 μL of the blood sample was added to the device, and the results were interpreted by two independent research assistants 20 min after the application of the specimen. The appearance of a test line was considered positive in the presence of a control line. The presence of only the control line was considered negative (Abbot, 2019). Discrepancies between first and second interpreters were solved with a third interpreter. The test results were interpreted without knowledge of the results of the DEN-NS1-PAD and nested-PCR test (blinded).

Reference standard and serotyping of DENV

Viral RNAs in serum samples were extracted by using QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany). They were then subjected to RT-PCR using dengue-specific primers (Table S1), and the RT-PCR products were used as templates for the nested-PCR reaction as described previously (Lanciotti et al., 1992). Thermocycling parameters were as follows: reverse transcription at 50 °C for 30 min, inactivation at 94 °C for 5 min, 35 cycles of PCR thermocycler at 94 °C for 15 s, annealing at 55 °C for 30 s and extension at 72 °C for 1 min. Samples were recognized as dengue-positive if the amplified target could be visualized on 1.5% agarose gel electrophoresis. Some nested-PCR products were sequenced to

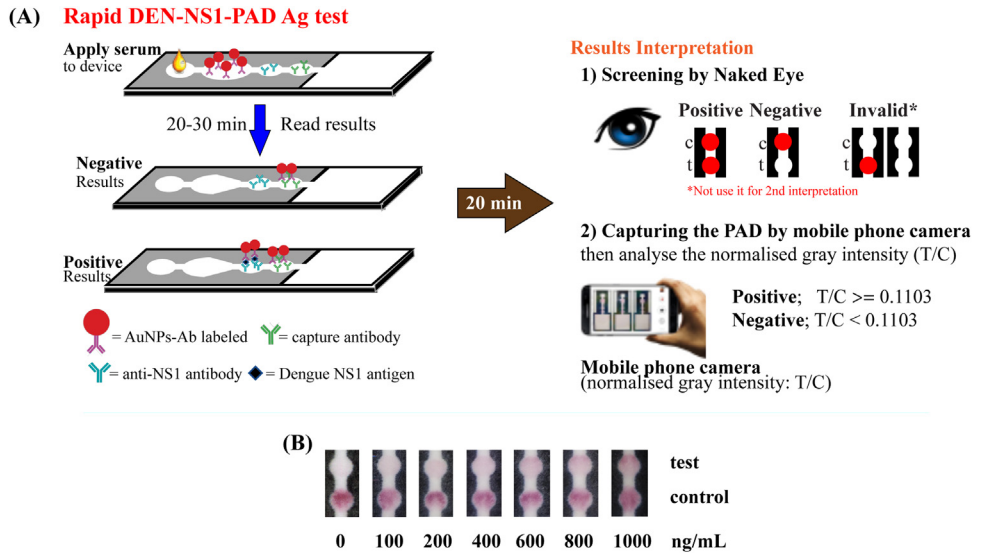

Figure 1. (A) Schematic representation of the procedure for dengue NS1 detection by using DEN-NS1-PAD. The specimen dropped on the sample area wicks through the channel and interacts with the AuNPs-rAb at the conjugate area and with the anti-NS1 capture antibody at the test spot when positive for dengue NS1. At the control spot, the AuNPs-rAb interacts with the control antibody. Red coloration at the test and control spots indicates that the specimen is positive for dengue, which can be detected by the naked eye and digitized images as quantitative values. (B) Signal development of the DEN-NS1-PAD with different concentrations from 0 to 1000 ng mL^{-1}.

specify unclear serotype results from nested-PCR. The researcher performed the assessment blind to the results of the SD-BIOLINE and DEN-NS1-PAD.

Data analysis and quality assessment

Using Open Source Statistics (https://www.openepi.com/DiagnosticTest/DiagnosticTest.htm), the comparative performances of the DEN-NS1-PAD and the SD BIOLINE™ Dengue Duo test were computed. Sensitivity, specificity, positive predictive value, negative predictive value (NPV), diagnostic accuracy, the likelihood of a positive test (LR+), the likelihood of a negative test (LR−), and diagnostic odd and agreement were calculated with this software with two-sided 95% confidence intervals (CI). Cohen's kappa (κ) coefficient was used to describe the degree of agreement between populations or tests (Landis and Koch, 1977). The performance, based on serotype and day of illness (DOI), was also compared for the sensitivity estimates. The diagnostic utility, post-test probabilities (95%CI) of dengue for the positive and negative test were calculated for each assay. The QUADAS 2 was used to review diagnostic accuracy and evaluation criteria for this research. Four aspects: patient selection, index test (for DEN-NS1-PAD and SD-NS1), reference criteria, and process and time were evaluated.

Results

Demographic information of study participants

Out of the 250 dengue-suspected patients who were admitted to the hospital over the study period, there were two commercialized RDT tested, of which 219 were from SD BIOLINE™ Dengue Duo test (considering only NS1; noted as SD-NS1). Therefore, Only 219 were characterized with the DEN-NS1-PAD, SD BIOLINE™ Dengue Duo test, and nested-PCR. The flow of a patient in these studies for the index tests and their results was presented using STARD diagrams (Figure 2). The characteristics of the participants enrolled in this study are shown in Table 1. The study participants were 69% male, with an age range of 1 −>60 years old, with a mean of 29.31 years (SD = 4.31). Upon recruitment, the mean day of fever was 2.98 (SD = 1.70) days, with a range of 1 to 14 days.

Prevalence of dengue infection was 45.21% (95% CI; 49–52.05) by SD-NS1 47.49% (95% CI; 40.72–54.33) by DEN-NS1-PAD and 45.21% (95% CI; 38.49–52.05) by nested-PCR. The results from the nested-PCR were 99 of dengue positive and 120 negative.

All four dengue virus serotypes were identified, among which DENV-1 (54 cases) was the dominant serotype, followed by DENV-2 (36 cases) and DENV-4 (eight cases). DENV-3 (one case) was the least prevalent serotype detected in our testing period. The characteristics of the clinical sample for the given infecting serotype of DENV, graphed over the day after the onset of illness, are shown in Figure 3.

Diagnostic performance of index tests

All the diagnostic accuracy parameters of index tests in these studies are reported in Table 2. DEN-NS1-PAD and SD-NS1 results were compared. The sensitivity of DEN-NS1-PAD was higher than SD-NS1 at 88.89% (95% CI; 81.19–93.68) and 87.88% (95% CI; 80.0–92.93), respectively. The specificity of SD-NS1 was insignificantly higher at 90.0% (95% CI; 83.33–94.19) than that of the DEN-NS1-PAD at 86.67% (95% CI; 79.44–91.62). The DEN-NS-PAD performed greater sensitivity, NPV, and LR -. There was no significant difference between tests for the other parameters except diagnostic odd.

The agreement between test interpreters for the specimens of the DEN-NS1-PAD showed a κ value of 0.7522 (95% CI; 0.6199–0.8845). For SD-NS1, both interpreters substantially agreed with the reference method with a κ value of 0.7788 (95% CI; 0.6463–0.9112). These estimates show that the κ value from DEN-NS1-PAD was lower than that of SD-NS1, but the differences were not statistically significant.

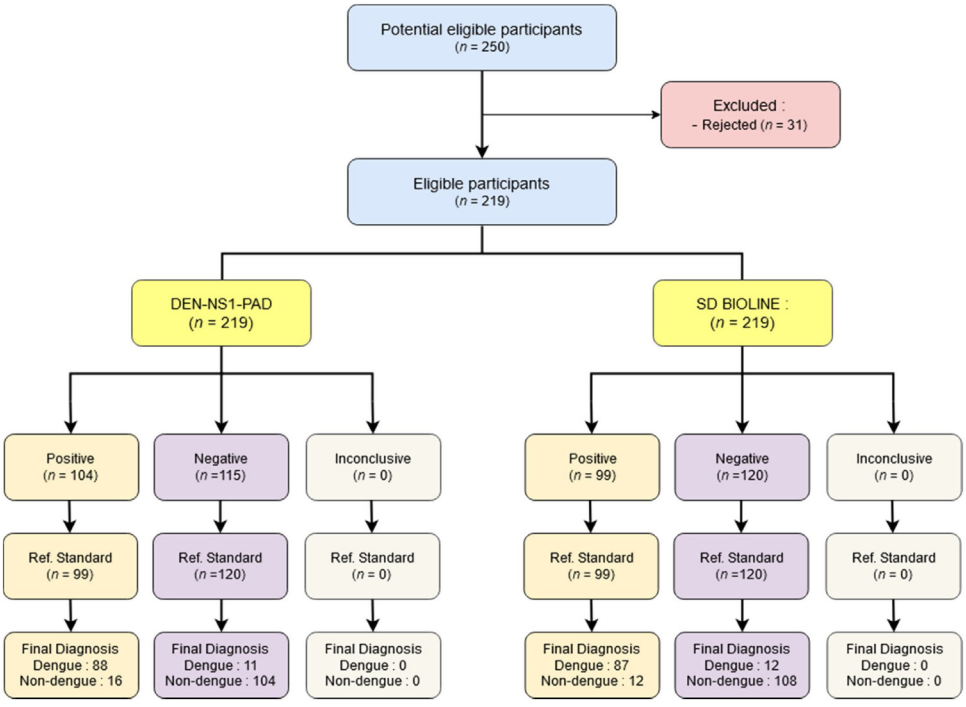

Figure 2. STARD flow diagram for DEN-NS1-PAD and SD BIOLINE™ Dengue Duo.

Table 1
Characteristics of the patients.

Variable	Number
Total patients	219
Age range/Median age range	(1–>60)/(20–30) years
Gender ratio (Male: Female)	(69:31) %
The median date specimen collection after onset of symptom (range)	3 (1–14)
Seasonal period	July–September 2019
Confirmed DENV (nested-PCR)	45% (99)
Non-DENV (nested-PCR)	55% (120)

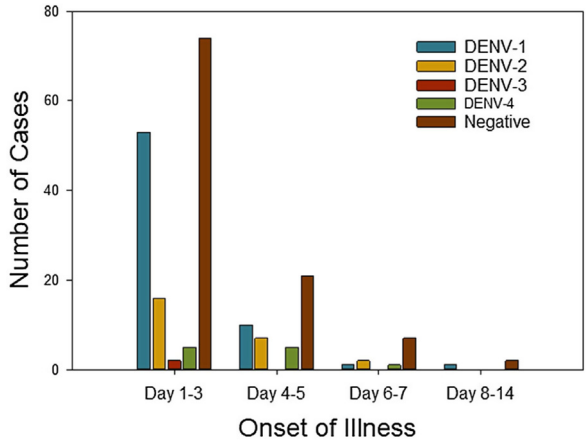

Figure 3. Characteristics of clinical sample for given infecting serotype of DENV graphed over the day after onset illness.

Table 2
Diagnostic performance estimates and their 95% CI for all index tests compared to a reference standard.

Performance	Diagnostic tests (95% CI), *n* = 219	
	DEN-NS1-PAD	SD BIOLINE NS1
Sensitivity	88.89% (81.19–93.68)	87.88% (80–92.93)
Specificity	86.67% (79.44–91.62)	90.00% (83.33–94.19)
Positive predictive value	84.62% (76.46–90.3)	87.88% (80–92.93)
Negative predictive value	90.43% (83.68–94.57)	90% (83.33–94.19)
Diagnostic accuracy	87.67% (82.66–91.39)	89.04% (84.21–92.52)
Likelihood of a positive test	6.667 (5.882–7.556)	8.788 (7.44–10.38)
Likelihood of a negative test	0.1282 (0.107–0.1537)	0.1347 (0.11–0.16)
Cohen's kappa	0.7522 (0.6199–0.8845)	0.7788 (0.6463–0.9112)
Diagnostic odd	52 (22.94–117.9)	65.25 (27.93–152.4)

Sensitivities of index tests

The sensitivities of the diagnostic tests based on the different subgroups are presented in Table 3. Based on serotype stratified, SD-NS1 and DEN-NS1-PAD had the same sensitivity in detecting DENV-3, followed by DENV-1, DENV-2, and DENV-4. The DEN-NS1-PAD was significantly more sensitive than SD-NS1 in detecting DENV-2 and DENV-4. On the other hand, SD-NS1 had significantly higher sensitivity than DEN-NS1-PAD in detecting DENV-1. Based on the DOI stratified (Table 3), the DEN-NS1-PAD had significantly lower sensitivity in the first five days compared to later periods. In contrast, SD-NS1 had higher sensitivity in the first five days compared to later periods. Considering the correlation test (*r*) between the three devices, they were calculated and shown in Table S2 with a high relation (*r* between 0.75 and 0.78).

Table 3
Diagnostic sensitivities and their 95% CI in different subgroups for all index tests.

Assay type	Diagnostic tests (95% CI)	
	DEN-NS1-PAD	SD-NS1
Serotype		
DENV-1	88.89 (48/54) (77.37–95.81)	94.44 (51/54) (84.61–98.84)
DENV-2	88.89 (32/36) (73.94–96.89)	80.56 (29/36) (63.98–91.81)
DENV-3	100 (1/1) (2.50–100)	100 (1/1) (2.50–100)
DENV-4	87.50 (7/8) (47.35–99.68)	75.00 (6/8) (34.91–96.81)
Onset illness		
First 5 days	87.64 (78/89) (78.96–93.67)	88.76 (79/89) (80.31–94.48)
Day ≥6 day	100 (10/10) (69.15–100.)	80 (8/10) (44.39–97.48)

Diagnostic utility of index tests

The pre-test probability of dengue (or proportion of dengue patients among all patients) was 45.20% in this study. The highest post-test probability of dengue for a positive test was achieved by 87.9% (95% CI; 86.0–89.5) SD-NS1, followed by 84.6% (95% CI; 82.9–86.2) DEN-NS1-PAD, and these did not differ significantly from each other (Table 4). In the post-test probability of dengue for the negative test, the DEN-NS1-PAD had a better result than SD-NS1, at 9.6% (95% CI; 8.1–11.3) and 10.0% (95% CI; 8.3–11.7), respectively (Table 4).

Discussion

In this work, we described the diagnostic performance of the DEN-NS1-PAD in comparison to commercial SD Bioline in an endemic area (Bangkok, Thailand). Patient sera were collected between July and September 2019 at Phramongkutlao Hospital within 48 h at −20 °C to avoid any NS1 antigen decay. On-site routine diagnostic testing was performed for all febrile patients enrolled in the study using the nested-PCR for the dengue virus. DENV1 had been the predominant serotype detected in DF patients in Bangkok, Thailand, over several years. Additionally, this data shows an increase in the DENV-4 prevalence compared to a previous report (Klungthong et al., 2004).

Based on clinical parameters used to diagnose, this paper reports the performance of the DEN-NS1-PAD in comparison to standard laboratory diagnostic tests for dengue. Analysis of 219

Table 4
Diagnostic utility estimates and their 95% CI for all index tests.

Parameter	Diagnostic tests (95%CI), n = 219	
	DEN-NS1-PAD	SD-NS1
Post-test probability of dengue for positive test	84.6% (82.9–86.2)	87.9% (86.0–89.5)
Post-test probability of dengue for negative test	9.6% (8.1–11.3)	10.00% (8.3–11.7)

acute phase samples (median day three post-onset of symptoms) from patients with a nested-PCR-confirmed DENV infection revealed an overall diagnostic sensitivity and specificity of the DEN-NS1-PAD of 88.89% and 86.67%, respectively. The actual sensitivity of DEN-NS1-PAD may be better than this since the nested-PCR shows a negative result in the late days of infection. The tested devices' positive and negative predictive values will vary depending on the prevalence and other febrile diseases. However, the PAD provided a positive predictive value (PPV) of 84.62% and an accuracy of 87.67%. The sensitivity and specificity of many commercial RDTs (Chong et al., 2020; Gaikwad et al., 2017; Jang et al., 2019; Lee et al., 2019; Piedrahita et al., 2016; Santoso et al., 2020; Shukla et al., 2017; Simonnet et al., 2017; Suzuki et al., 2019; Thai et al., 2010; Vivek et al., 2017) show variability (Table S3), which might be due to difference in study design, population, reference standard, and other characteristics (Kohn et al., 2013; Leeflang, 2014; Whiting et al., 2011). It is challenging to compare the diagnostic performance between different studies without proper assessment since there were differences in study characteristics. Therefore, diagnostic tests can be directly compared only if the evaluation uses the same study conditions (Leeflang, 2014).

The SD-NS1 performed better detecting dengue infection in the first five days versus $\geq$ 6 days while DEN-NS1-PAD performed in both conditions above. Previous studies showed that the NS1 antigen level fluctuates, and the NS1 can be detected starting from first DOI and peaks around day 4–5 DOI (during primary infections) but decreases in secondary infections (Blacksell et al., 2011). However, a decline in performance at the end of the week might produce a faint test line that is more difficult to be observed by naked eyes (Fry et al., 2011). This condition was related to the status of infection from patients. Based on previous observations, antibodies against DENV NS1 in the patient sample form antigen-antibody complexes and reduce access to the target epitopes for the test articles (Duyen et al., 2011; Miller and Sikes, 2015).

The results for SD-NS1 had lower sensitivity for the detection of DENV-4. Some studies (Hang et al., 2009; Osorio et al., 2010; Pal et al., 2015) reported the sensitivity of RDTs to DENV-4 was low (averaged only 50%), and another reported different sensitivity values for NS1 diagnostic tests for DENV-1 (Ramirez et al., 2009), DENV-2, and DENV-4 (Bessoff et al., 2008). In this study, the sensitivity of the PAD to detect DENV-2 and DENV-4 was better than SD-NS1. This observation might have been caused by the commercial assays' antibody having a less efficient binding with the target (Duyen et al., 2011; Hunsperger et al., 2016) than those used in DEN-NS1-PAD.

In this study, the diagnostic utility using the tested-positive for DEN-NS1-PAD and SD-NS1 showed the probability of dengue infection in a patient around 83.6 and 87.9% and only around 12–16 out of 100 incorrect diagnosed non-dengue patients. If a patient tested negative for any individual assays, the post-test probability of dengue was around 9.8–10%. In other words, at least ten out of 100 dengue patients were a false negative (FN) that might have been misdiagnosed. Dengue false positive (FP) may not be a big concern due to the patient's relatively lower risk. A high number of FN might lead to late diagnosis and delayed treatment for dengue patients. Therefore, it is essential for a dengue diagnostic test or RDT can screening and detect more cases with minimal FN (Chong et al., 2020).

DEN-NS1-PAD has many benefits compared to SD-NS1, as it is easy to fabricate, simple, user friendly, and easy to interpret. This device requires only 50 μl of serum specimen compared to 100 μl required for SD-NS1. This feature is important when the sampling is difficult, and only a small amount can be collected, especially for pediatric patients. The fabrication of DEN-NS1-PAD requires two pieces of equipment, a wax printer and an oven. However, the RDT based on lateral flow assay (LFA) requires expensive machines (lining, spraying, and cutting machine). Moreover, PAD uses only one type of paper to reduce the suffering from separating each piece of paper on LFA. Considering the amount of capture antibody on DEN-NS1-PAD, it was reduced at least half from LFA. The pricing and testing time of DEN-NS1-PAD were 1.5 USD and 20 min, respectively. In addition, its ability to connect and combine with a scanner or smartphone makes the results available immediately to assist quick intervention and increase the analytical sensitivity by 267–400%, depending on the qualities of the image. (Prabowo et al., 2020). Furthermore, this was the first time that the novel DEN-NS1-PAD has been evaluated in this setting to be extensively compared with existing RDTs for a comprehensive understanding of their relative performance. These studies follow STARD-guidelines for quality assurance. The diagnostic utility of the two index tests evaluated in this study can be estimated for any clinical setting (Florkowski, 2008; Mc Gee, 2002).

Our study had several limitations, including the limited number of dengue cases and the variable number of days from the onset of illness at which patients visited the hospital. Also, the diagnostic utility calculated was based on the pre-test probability of disease without considering the hematological result. Further comprehensive evaluations of the DEN-NS1-PAD for the detection of dengue need to be performed and should incorporate a more significant number of primary infections serotype and selected samples collected from both children and adults.

Conclusion

This report showed the performance of the DEN-NS1-PAD to be almost on par with SD-NS1 in detecting dengue infection in acute febrile cases. The device possesses better sensitivity than SD-NS1, especially for the diagnosed patient after day five of illness. The DEN-NS1-PAD can be a potential alternative to existing commercial RDTs in the detection of acute dengue infection in the future.

Author contributions

Conceived and designed the experiments: MHP, SC, PR, PK, TC, KL, and WS. Developed and performed the assay with DEN-NS1-PAD: MHP under the guidance of PR and SW. RDT assay, consent, and documentation: PK, and TC. RT-PCR assay: SC and KL. Data analysis and writing of the manuscript: MHP, SC, PR, PK, TC, KL, and WS. All authors reviewed and approved the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

Ethical approval was obtained by the Ethics Committee of the Institutional Review Board, Royal Thai Army Medical Department, Phramongkutklao Hospital, Bangkok, Thailand (IRBRTA 1218/2562). We have complied with all relevant ethical regulations in carrying out this study.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.05.007.

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