Central African Journal of Public Health
2022; 8(2): 87-90
http://www.sciencepublishinggroup.com/j/cajph
doi: 10.11648/j.cajph.20220802.20
ISSN: 2575-5773 (Print); ISSN: 2575-5781 (Online)

Retrospective Evaluation of the SD BIOLINE Dengue Duo Rapid Diagnostic Test During a Dengue Epidemic in Burkina Faso

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To cite this article:

Cheick Ahmed Ouattara, Tiandiogo Isidore Traore, Bry Sylla, Seydou Traore, Ibrahim Sangare, Clément Ziemlé Meda, Léon Blaise Geswendé Savadogo. Retrospective Evaluation of the SD BIOLINE Dengue Duo Rapid Diagnostic Test During a Dengue Epidemic in Burkina Faso. *Central African Journal of Public Health*. Vol. 8, No. 2, 2022, pp. 87-90. doi: 10.11648/j.cajph.20220802.20

Received: April 8, 2022; **Accepted**: April 30, 2022; **Published**: May 3, 2022

Abstract: The SD Bioline Dengue Duo rapid diagnostic test is the primary means of diagnostic guidance for dengue and in many cases the only one in Burkina Faso. Our objective was to evaluate the performance of this test during the 2017 dengue epidemic. By analysing data from samples during the 2017 dengue epidemic in Burkina Faso for which both rapid test and Real Time Polymerase Chain Reaction and, or Immunoglobulin M capture by Enzyme Linked ImmunoSorbent Assay results were available, the rapid diagnostic test was compared to Real Time Polymerase Chain Reaction and, or Immunoglobulin M detection by Enzyme Linked ImmunoSorbent Assay. The sensitivity and specificity of the tests were calculated and their overall performance was evaluated by the area under the curve. Out of 706 suspected patients, 514 or 72.8% were confirmed by the reference techniques. The positivity rates were 69%, 19% and 26% respectively for NS1 antigen, Immunoglobulin M antibody and Immunoglobulin G antibody. The rapid diagnostic test had a very good sensitivity of 99% for a specificity of 5%. The detection of NS1 antigen by rapid diagnostic test showed the best compromise, with an area under the curve of 0.7. Considering only the results of the NS1 Antigen, the rapid diagnostic test could be a viable solution for the management of dengue epidemics in health centers without a laboratory.

Keywords: Dengue, Serology, PCR, Antigens, Outbreak

1. Introduction

Dengue fever is a neglected tropical disease that currently affects about 390 million people worldwide. It is an arbovirosis caused by the dengue virus, an RNA virus whose four serotypes (DENV1-4) are transmitted to humans mainly by the bites of the *Aedes aegypti* mosquito. This burden is probably greatly underestimated due to asymptomatic forms and even more so in low-income countries where diagnostic facilities are limited [1, 2].

There is currently no licensed vaccine or effective antiviral treatment for dengue. Emphasis should be placed on prevention measures such as surveillance, vector control and early diagnosis. Early diagnosis allows the isolation of the patient and thus breaks the chain of transmission from the cases.

Burkina Faso experienced an outbreak of dengue fever in 2016 and 2017. Since then, it has been included among the diseases under epidemiological surveillance and the fight

against it has been organised around a 2016-2020 strategic plan [3].

The definition of dengue cases in Burkina Faso is based on the WHO classification. A suspected case of dengue fever is a patient presenting with an acute fever, generally high (above 39°C) lasting between 2 and 7 days (with a negative malaria RDT or a positive malaria RDT that does not respond to antimalarial treatment) associated with at least two signs of arboviruses (headache, retro-orbital pain, myalgia-arthralgia, skin rash, haemorrhagic manifestations or shock syndrome). These suspected cases should be tested for dengue by a rapid diagnostic test. They are then classified as probable cases if the rapid diagnostic test is positive. These probable cases should be confirmed by Real Time Polymerase Chain Reaction (RT-PCR) or Enzyme-Linked Immunosorbent Assay (ELISA) [1, 4].

Molecular techniques such as PCR require specialised equipment that is only available in a few facilities. This scarcity, combined with delays in the delivery of samples and results, means that in most cases it is on the basis of a presumptive diagnosis (probable case) that treatment is initiated.

While this may help to anticipate possible severe cases of dengue, it also means that other febrile diseases may be missed. The study of the diagnostic performance of the rapid diagnostic test for dengue in this context may provide reassurance, if not recommendations for a more efficient response. We have not found such an evaluation in Burkina Faso, which is the reason for this study.

2. Methods and Materials

2.1. Data Source

The dengue cases used in this study were notified by the different health facilities in Burkina Faso during the 2017 epidemic. The data were compiled by the Directorate of Population Health Protection of the Ministry of Health. We only included in the analysis data from 706 samples for which both rapid test and RT-PCR (Real Time Polymerase Chain Reaction) and/or Ig (Immunoglobulin) M capture by ELISA (Enzyme Linked ImmunoSorbent Assay) results were available.

2.2. Biological Tests for Dengue

In the diagnostic strategy for dengue in Burkina Faso, any patient presenting with acute fever and a negative RDT (Rapid Diagnostic Test) for malaria or a positive RDT for malaria not responding to anti-malarial treatment with signs of arboviruses is subjected to a rapid immunochromatographic test for dengue "Dengue Duo (NS1 Ag+IgM/IgG) SD (Stantard Diagnostics) Bioline". A patient who is positive for this test (positive Ig M and/or Ig G serology and/or positive NS1 antigen) should have blood drawn for confirmation by positive Ig M serology (ELISA), or increased Ig G titres or virus detection by PCR or isolation [4-6].

2.3. Data Analysis

Data analysis was performed on R software version 4.0.4 [7] and used the EpiR [8] and ROCR [9] packages. The percentages of positive and negative concordance, sensitivity and specificity of the different tests were calculated in relation to the reference method RT-PCR and, or IgM ELISA [10] and the area under the curve was used to estimate their overall performance. All results were expressed with two-sided 95% confidence intervals.

3. Results

3.1. Characteristics of the Study Population

Data from 706 patients who received both the rapid diagnostic test for dengue and the RT PCR were analysed. The mean age of the study population was 29 years with extremes of 1 and 77 years. The sex ratio was 0.9 females to 1 male. The majority of patients resided in Ouagadougou (Table 1). The dates of onset of symptoms and of sampling were well documented for only 295 patients, i.e. 41.8% of cases. The average delay between the onset of symptoms and the consultation was 3.4 days, with extremes of 0 to 15 days.

Table 1. *Distribution of patients by residence.*

Residence	Number	Proportion (%)
Ouagadougou	558	79.03
Bobo Dioulasso	116	16.43
Koudougou	14	2
Dano	6	0.85
Kongoussi	5	0.71
Bogande	3	0.42
Sindou	3	0.42
Orodara	1	0.14

3.2. Dengue Diagnosis Test Positivity Rate

The SD Bioline Dengue DUO RDT identified 706 probable cases of dengue. The positivity rates were 69% [95% CI 65-72], 19% [95% CI 16-22] and 26% [95% CI 23-30] for NS1 antigen, IgM antibody and IgG antibody respectively (Table 2).

Table 2. *Postive rate of dengue diagnosis tests.*

Results	Antigen NS1		Immunoglobulin M		Immunoglobulin G	
	Number	%	Number	%	Number	%
Negative	221	31	570	81	519	74
Positive	485	69	136	19	187	26
Total	706	100	706	100	706	100

Of the 706 probable dengue cases, 458 or 64.9% and 161 or 22.8% were confirmed by RT PCR and ELISA respectively. By combining the two techniques (RT PCR or ELISA or both), 514 cases or 72.8% were confirmed as dengue cases.

3.3. Evaluation of the SD Dengue Duo RDT Kit

3.3.1. NS1 Antigen Detection

The sensitivity and specificity of the detection of dengue NS1 antigen in the RDT was 80% and 50% respectively. This test had a positive and negative predictive value of 84% and

52% respectively (Table 3).

3.3.2. Detection of Immunoglobulin M and G

The sensitivity and specificity of the detection of anti-dengue immunoglobulin M by RDT was 19% and 81% respectively. This test had a positive and negative predictive value of 74% and 24% respectively. Anti-dengue immunoglobulin G had the same sensitivity with a specificity of 53%. Its positive and negative predictive values were 52% and 20% respectively (Table 3).

Among the 514 cases of dengue confirmed by RT-PCR and/or IgM capture by ELISA, 97 or 23.3% were IgG positive. The proportion of secondary dengue was therefore 23.3%.

3.3.3. Combined Detection of NS1 Antigen and Immunoglobulin M

The simultaneous detection of NS1 antigen and anti-dengue immunoglobulin M had a sensitivity of 8% and a specificity of 99%, which corresponded to positive and negative predictive values of 98% and 29% respectively (Table 3).

3.3.4. Detection of NS1 Antigen and/or Immunoglobulin M and/or G

The SD Bioline Dengue DUO RDT had an overall sensitivity of 99% and a specificity of 5%. Its positive predictive value was 74% and its negative predictive value was 64% (Table 3).

Table 3. *Characteristic of the Bioline Dengue DUO RDT compared to RT-PCR and/or IgM-ELISA.*

	Sensitivity (%) [CI à 95%]	**Specificity (%) [CI à 95%]**	**Positive predictive value (%) [CI à 95%]**	**Negative predictive value (%) [CI à 95%]**
NS1	80 [76 -83]	50 [53 - 67]	84 [81 - 87]	52 [46 - 59]
IgM	19 [16 -23]	81 [75 - 87]	74 [65 - 81]	27 [24 - 31]
IgG	19 [16 -23]	53 [46 - 60]	52 [44 - 59]	20 [16 - 23]
NS1 and IgM	8 [6 - 11]	99 [97 -100]	98 [88 - 100]	29 [25 - 32]
NS1 and IgG	5 [3 - 7]	98 [96 -100]	89 [71 - 98]	28 [24 - 31]
IgM and IgG	8 [6 - 11]	92 [87 - 96]	74 [61 - 85]	27 [24 -31]
NS1 or IgM or IgG	99 [98-100]	5 [2 - 9]	74 [70 - 77]	64 [35 - 87]

3.3.5. The Overall Performance of the TDR SD Bioline Dengue Duo

Figure 1 shows the performance of the different markers of the SD Bioline Dengue Duo RDT.

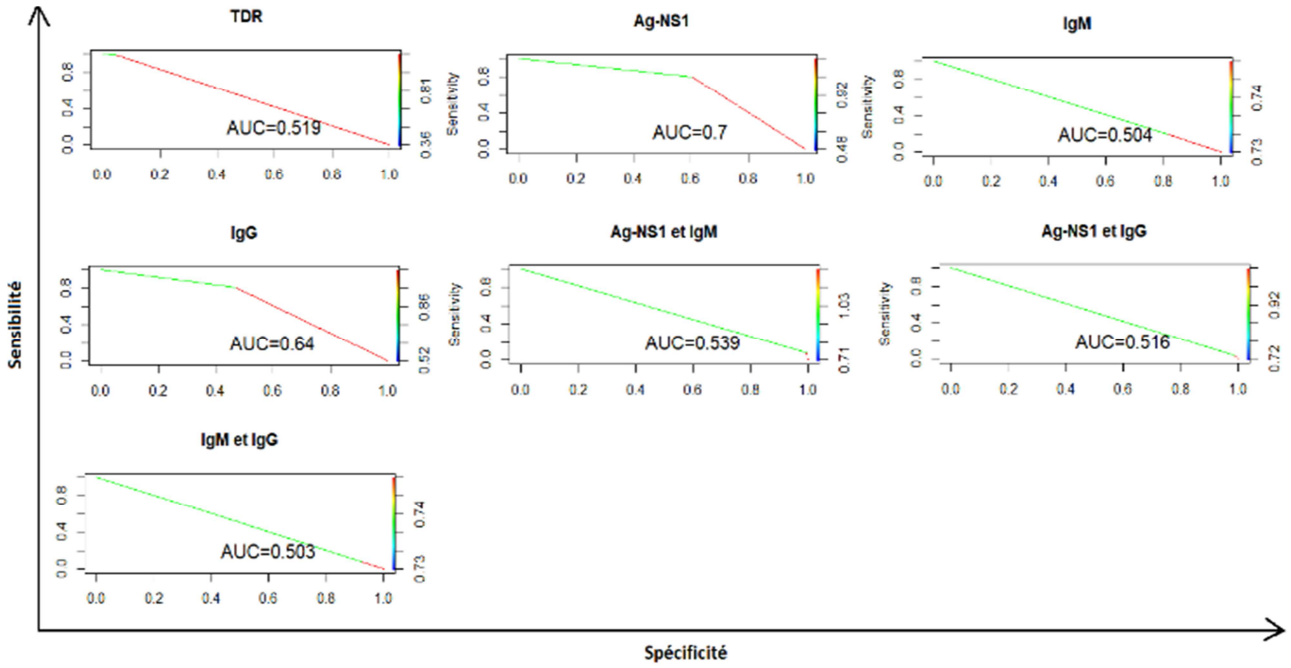

Figure 1. *Suitability of the SD Bioline Dengue Duo RDT for the determination of dengue.*

4. Discussion

More than three out of four patients resided in the city of Ouagadougou. The predominance of dengue cases in Ouagadougou has been reported in other studies [11, 12] and could be explained by the population density and level of urbanisation of Ouagadougou, which is the first and most populated city in Burkina Faso. To this must be added the inequality of access to dengue diagnostic means.

The average age of the patients was 29 years with a sex ratio of 0.9. These results are comparable to those of previous studies in an epidemic context [6].

In the SD BIOLINE Dengue Duo rapid diagnostic test, the NS1 antigen had the highest positivity (69%). This result could be explained by the relatively short consultation time [13, 14].

During an epidemic, media coverage and awareness-raising tend to lead patients to consult earlier and health workers to think more quickly of the current epidemic as a diagnostic alternative.

The presence of at least one of the dengue virus markers (Ag NS1, IgM and IgG) on RDT had the highest sensitivity 99% CI: (98-100). The RDT-based diagnostic strategy in Burkina Faso provides a good estimate of suspected dengue cases during the epidemic period. However, the RDT has a low specificity of 4% [2, 7].

The combination of NS1 antigen and immunoglobulin M in the RDT had the best specificity 98% (95-99).

The proportion of secondary dengue was 23.3%. This rate is comparable to the 25.9% reported by Ouattara et al during the 2016 epidemic in Ouagadougou. It is however lower than the rates reported by other authors in Burkina Faso [14-17]. This difference could be explained by the variability of the study populations on the one hand. On the other hand the quality of the tests used, IgG-ELISA and IgG-TDR.

In clinical terms, the NS1 antigen offered the best compromise with a positive predictive value of 80% (76-83) and a negative predictive value of 68% (62-74). Its diagnostic performance was acceptable with an area under the curve of 0.7.

The main limitation of this study is that we could not correlate the performance of the tests with the duration of disease progression, which was missing. Possible cross-reactions with other flaviviruses or associated infections such as malaria were also not explored.

5. Conclusion

The results of this study showed that the SD Bioline Dengue Duo rapid test had very good sensitivity but low specificity. While it can detect the majority of suspected cases, a combination of NS1, or IgM can compensate for its low specificity. The results also showed that in the event of an epidemic, for the management of dengue in a hospital where laboratory tests cannot be performed, the best compromise was the detection of the NS1 antigen. In the future we will carry out a complementary study taking into account the duration of the disease, associated infections and cross-reactions.

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