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Evaluation of three commercialized rapid point-of-care tests for detection of anti-hepatitis C virus antibodies in Burkina Faso

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This study aimed to evaluate the diagnostic performance of commercially rapid point-of-care (POC) tests used for HCV antibodies detection. This is a case-control study conducted in Ouagadougou between December 2014 and January 2015. Three POC for HCV antibodies detection (*SD Bioline HCV test®, Anti-HCV dipstick®* and *First response® HCV card test*) marketed in Burkina Faso were evaluated. Architect anti-HCV assay and ImmunoComb® II HCV were combined and used as a reference test. All three tests were evaluated with a panel of 62 anti-HCV positive sera and 62 anti-HCV negative sera. The tests performance was calculated using the software OpenEpi. The three rapid POC tests had a specificity of 100% (95% CI: 94.17-100). However, the sensitivities were 33.87% (95% CI: 23.34-46.28) for the *SD Bioline HCV test®*, 41.94% (95% CI: 30.48-54.33%) for *Anti-HCV dipstick®* and 45.16% (95%CI: 33.42-57.47%) for *First response® HCV card test*. The tests evaluated in this study had good specificity but poor sensitivity for the HCV antibodies detection in Burkina Faso. The surveillance of HCV rapid POC tests through the validation of their accuracy in the local context before their approval must be strengthened.

Key words: Hepatitis C virus, point-of-care, diagnostic test.

INTRODUCTION

Hepatitis C virus (HCV) is a hepatotropic RNA virus of the *Hepacivirus* in the Flaviviridae family (Chevaliez and Pawlotsky, 2006). It is responsible for both acute and chronic liver infection. According to the World Health Organization (WHO), more than 71 million people are infected worldwide (WHO, 2019), and new infections

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were estimated at 1.75 million in 2015 (WHO, 2017). Transmission of HCV is mainly through blood (blood transfusion, injection with non-sterile needles, tattoos and other traditional practices, etc.), but it can also be transmitted through sexual intercourse or by an infected mother to her infant (Moosavy et al., 2017). While some infected people may spontaneously clear the virus, the infection progresses to chronicity in 60 to 80% of cases with the appearance of severe liver injury (cirrhosis, and hepatocellular carcinoma) in the long term (Moosavy et al., 2017; Spearman et al., 2019).

The prevalence of HCV remains highly variable from one region to another in Sub-Saharan Africa. Indeed, in a systematic review, the authors estimated HCV seroprevalence in general population in East and South Africa at 0.91% (95% CI: <0.80-1.20), 4.34% (95% CI: 3.99- 4.70) in West Africa and 6.76% (95% CI: 5.98-7.55) in Central Africa (Semugoma et al., 2017). In Burkina Faso, hepatitis C testing on the blood samples collected during the 2010 Demographic and Health Survey (DHS) estimated HCV prevalence at 3.5% (95% CI: 3.0-3.9) (Madiou, 2016). In blood donors, studies have estimated the prevalence of HCV at 8.69% at the Regional Center for Blood Transfusion (CRTS) of Koudougou (Nagalo et al., 2011), and at 4.4% at the CRTS of Ouagadougou (Zeba et al., 2014). This high prevalence of HCV in blood donors justifies the inclusion of screening of this virus in the routine testing of blood donation in the country's blood banks, in addition to HIV, hepatitis B virus and syphilis. The screening for HCV in the blood donation is done using Enzym Linked Immuno Sorbent Assay (ELISA). However, these ELISA technics require relatively expensive laboratory equipment, reagents and relatively long handling times. In the context of frequent blood shortages and emergencies due to traffic accidents and surgical or obstetric complications, rapid HCV tests is often used as an emergency for HCV testing in some blood banks. These tests are very easy to use, provide results in less than 30 min and are less expensive, especially in resources limited contexts (Drain et al., 2014). They do not require highly qualified laboratory technicians, or specific laboratory equipment, or even electricity and cold chain storage. However, even if the manufacturers of these tests reported that they have a very good diagnostic performance (high sensitivity and specificity), the quality and reliability of some of these tests are often questioned (Drain et al., 2014; Khuroo et al., 2015; O'Connell et al., 2013; Scheiblauer et al., 2006; Tang et al., 2017).

Several rapid screening tests from various sources and brands are marketed and used for HCV antibody screening in Burkina Faso, but there are no data comparing these rapid HCV tests with routine ELISA methods practiced in the country's blood banks. This study aimed to assess their diagnostic performance in the screening of HCV antibodies in Burkina Faso. If these tests are efficient, they can be used as an alternative in laboratories in limited resources contexts.

METHODOLOGY

Study design

This is a cross sectional study conducted in Ouagadougou. The evaluation included three (3) point-of-care (POC) tests marketed in Burkina Faso for qualitative detection of hepatitis C virus antibodies.

Rapid POC tests evaluated

Three (3) anti-HCV rapid POC tests marketed in Burkina Faso were evaluated. The POC tests included the following: *SD Bioline HCV test*®, *First response*® *HCV card test* and *Anti-HCV dipstick test*®. All tests were obtained free of charge from the suppliers for the evaluation. The characteristics of the POC tests are presented in Table 1.

Samples collection and laboratory methods

Samples were collected between December 2014 and January 2015 in the Regional Blood Transfusion Center (CRTS) of Ouagadougou, where all blood donations are tested serologically for HIV, hepatitis B, C and syphilis. After consent was obtained from the donor, 10 mL of blood were taken from the tubing of the blood collection bag in two dry tubes 5 mL Vacutainer®, then kept in the refrigerator at + 4 ±2°C while waiting for the results of screening for syphilis, HIV, hepatitis B and C viruses as part of the blood donation.

Once, the infection status of blood donations established through the initial analyzes performed by the CRTS (ELISA test HCV, HBV, HIV and syphilis), the positive samples for anti-HCV and those negative for anti-HCV antibodies were preselected. All reference samples were negative for HIV, syphilis and HBV. The anti-HCV screening as part of the qualification of blood donation at the CRTS was done using the Architect Anti-HCV® automatized assay (Abbott Diagnostics). Architect Anti-HCV assay is an automated test designed for chemiluminescent immunoassay (CMIA) immunoassay for the qualitative detection of antibodies to hepatitis C virus (HCV) in human serum and plasma. Its specificity according to the manufacturer was evaluated at 99.6% (95% CI: 99.45-99.71) and its sensitivity is 99.10% (95% CI: 96.77-99.99) (ABBOTT Diagnostics Division, 2009).

The preselected samples were centrifuged at 3000 rpm for 10 min, and then the serum was put in two 2 mL cryotubes, labeled and stored at -20°C. In order to confirm the presence or absence of anti-HCV in these samples, they were re-tested using the ImmunoComb® II HCV test (Orgenic Ltd). This second testing was performed to avoid inclusion of false positive or false negative samples in the panel, due to the high sensitivity of the Architect Anti-HCV test. The ImmunoComb® II HCV Assay is a sensitive and specific assay for the detection of anti-HCV antibodies. These diagnostic performances have been confirmed in earlier studies in Africa compared to other tests (Njouom et al., 2006)

At the end of this second testing, 62 anti-HCV positive samples and 62 anti-HCV negative samples served as a reference panel for the evaluation.

All rapid POC were evaluated using the panel of samples in accordance with manufacturers' requirements and Good Laboratory

Table 1. Characteristics of the evaluated rapid POC tests according to the manufacturers.

Characteristics	SD Bioline HCV test®	First response® HCV card test	Anti-HCV dipstick®
Manufacturer	Standard Diagnostics, Inc.	Premier Medical Corporation Ltd	CYPRESS Diagnostics
Principle of the test	immunochromatography	immunochromatography	immunochromatography
Antigen	(Core, NS3, NS4, NS5)	(Core, NS3, NS4, NS5).	--
Product code	02FK11	I03FRC	172-050/S
Batch number	02BM14013	39K0214D	B201503056
Expiration date	2016/07/07	2016/05	2017/03
Biological sample	Serum or plasma	Serum, plasma or whole blood	Serum or plasma
Storage	1-30°C	4-30°C	10-30°C
Reading	Visual	Visual	Visual
Time for result	15 min	15 min	15 min
Reading time (stable result)	20 min	20 min	20 min
Consumable required not provided	Pipette	-	-
Sensitivity according to the manufacturer	100%	99.75%	98.7%
Specificity according to the manufacturer	99.4%	99.5%	95.6%

Table 2. Results of the evaluated rapid POC tests on the panel of serum samples.

POC tests	Result	Architect Anti-HCV+ImmunoComb® II HCV	
		Positive (n=62)	Negative (n=62)
SD Bioline HCV test®	Positive	21 TP	00 FP
	Negative	41 FN	62 TN
Total		62	62
First response® HCV card test	Positive	28 TP	00 FP
	Negative	34 FN	62 TN
Total		62	62
Anti-HCV dipstick®	Positive	26 TP	00 FP
	Negative	36 FN	62 TN
Total		62	62

TP, True positive; FP, false positive; TN, True negative; FN, false negative.

Practices (GLP). In order to avoid comparing the results between the tests during the laboratory analysis, each rapid assessment test was tested in a series with all the panel samples before proceeding to another test. The results interpretation was blind, regardless of the results of the reference test.

Data processing and analysis

The test results were entered into Excel 2013 file. For each sample tested, the test results were compared to the positive or negative status of the reference test and categorized as true positive, false positive, true negative and false negative. The sensitivity and specificity of the rapid POC in evaluation were then calculated using free and open source epidemiological statistics software, OpenEpi (http://www.openepi.com,). Cohen's Kappa coefficient (Cohen, 1960) was used to assess the concordance of rapid POC tests with the reference test. Interpretation of the Kappa results was made according to the following criteria: a value ≤ 0 indicating "the absence of agreement" and 0.01-0.20 as a "very weak agreement", 0.21-0.40 as "weak agreement", 0.41-0.60 as "moderate agreement", 0.61-0.80 as "strong agreement" and 0.81-1.00 as "almost perfect agreement"(McHugh, 2012).

RESULTS

The results obtained after the analysis of the 62 anti-HCV positive samples and the 62 anti-HCV negative samples with the index tests are recorded in Table 2. None of the three tests yielded a false positive. In contrast, all three tests each yielded more than 50% false anti-HCV negative.

The evaluated tests diagnostic performance is shown in Table 3. All three rapid POC tests had a specificity of 100% (95% CI: 94.17-100).The sensitivities of these tests were different and varied between 33.87% (95% CI: 23.34-46.28) for the “SD Bioline HCV test®” and 45.16%

Table 3. Diagnostic performance of the tests according to the evaluation.

Parameter	*Anti-HCV dipstick*		*First response® HCV card test*		*SD BIOLINE HCV test*	
	Estimation	**95%CI**	**Estimation**	**95%CI**	**Estimation**	**95%CI**
Sensitivity	41.94%	30.48 - 54.33	45.16%	33.42 - 57.47	33.87%	23.34 - 46.28
Specificity	100%	94.17 - 100	100%	94.17 - 100	100%	94.17 - 100
Diagnosis accuracy	70.97%	62.44 - 78.23	72.58%	64.14 - 79.67	66.94%	58.26 - 74.6
Youden (J)	0. 4194	0.2465 - 0.5433	0.4516	0.2759 - 0.5747	0.3387	0.1751 - 0.4628
Efficiency	0.7096		0.7258		0.6693	
Cohen Kappa coefficient	0.4194	(0.2761 - 0.5627)	0.4516	(0.3044 - 0.5988)	0.3387	(0.2067 - 0.4707)

(95% CI: 33.42-57.47) for the Anti-HCV dipstick Kit. Similarly, the Cohen's kappa concordance with the reference test are respectively 0.3387 (95% CI: 0.1751-0.4628) for the *"SD Bioline HCV test®"*; 0. 4194 (95% CI: 0.2465-0.5433) for the *"Anti-HCV dipstick®"* and 0.4516 (95% CI: 0.2759-0.5747) for *"First response® HCV card test"*.

The study shows a rather simple use of these three (3) tests. However Anti-HCV dipstick is even simpler than the other two because of its strip structure and the absence of migration diluent. In terms of the equipment needed to perform the test, but not provided, only the *"SD Bioline HCV test®"* did not have pipettes in its kit. The time required to obtain the results is identical for the three tests (20 min). The interpretation of the results is very easy, and visual for all three (3) tests.

DISCUSSION

This study shows that the three rapid HCV tests evaluated have very good specificity (100%), but low sensitivity in the detection of HCV antibodies. These tests have low to moderate concordance with the reference test (McHugh, 2012). With a sensitivity of 45.17%, *First response® HCV card test* was the most sensitive of the three tests evaluated. It is followed by *Anti-HCV dipstick®* (41.74%) and then by *SD Bioline HCV test®* (33.87%). This means that each of these three tests yields more than 50% of false negatives in subjects with HCV. If used in blood transfusion, many blood bags would fail to be sensitive, putting the health of recipients at risk.

In this study, all the false results are false negatives, hence a very good specificity observed for the rapid POC evaluated. Most studies confirm the high specificity of rapid tests for anti-HCV (Tang et al., 2017). However, because of their low sensitivity, the diagnostic accuracy of some of them is often poor. The most likely assumption underlying the low sensitivity of the evaluated rapid POC tests for detection of HCV antibodies, is that these tests have a high detection limit compared to the reference test. A study comparing Rapid POC tests with EIA methods had already shown that the sensitivity of rapid HCV antibodies tests decreased with the concentration of anti-HCV in the blood (Montebugnoli et al., 1999). However, the sensitivities found in this study are below those indicated by the tests manufacturers. Indeed, the sensitivities of these three rapid tests according to the manufacturer's instructions are between 95.29 and 100%, and their specificities are between 98.75 and 99.5%. These standards are based on different studies generally conducted under different conditions than those of resource-limited countries in terms of quality insurance. WHO (World Health Organization) has clearly demonstrated the high probability of obtaining false results by using Rapid POC tests in the event of non-compliance with quality assurance (Adler et al., 2015). Nevertheless, the results we obtained from these rapid POC tests suggest that further studies be conducted to establish an algorithm using these rapid POC tests for the detection of HCV infection in Burkina Faso. The literature reports little or no data on the performance of *Anti-HCV Dipstick®* and the *First Response HCV Card test®*, as opposed to the *SD Bioline HCV test®*. In a systematic review and meta-analysis conducted by Mehnaaz et al. (2015), the sensitivity (pooled sensitivity) of SD Bioline HCV was estimated 93.5% with intervals of 73.2 to 98.7%. Which is high compared to the sensitivity found in this study (Khuroo et al., 2015).

However, this study is not the first to report low sensitivity for rapid HCV testing. Mehnaaz et al. (2015) found that the anti-HCV rapid POC tests had good overall accuracy, but this accuracy was very heterogeneous between the individual tests. According to these authors, the sensitivity and specificity of these tests ranged from 16.0 to 99.9% and from 77.8 to 99.7%, respectively (Khuroo et al., 2015). Another study found that the rapid tests evaluated had a sensitivity of 34.5% (95% CI, 25.0-45.1%) for CORE HCV® (CORE Diagnostics, Birmingham B2 5HG, United Kingdom) and 98.8% (95% CI, 94.3-99.9%) for OraQuick HCV® (Meridian Bioscience, Inc. London). However for these tests the specificities were all very high (O'Connell et al., 2013). Added to this are the sensitivities of 49% for the ACON HCV® test (ACON Laboratories, San Diego, CA, USA), 63.1% for the Labmen TM test (Chevaliez et al., 2016a), 64% for the

Hexagon HCV® test (Human Gesellschaft für Biochemica und Diagnostica, Wiesbaden, Germany) in Cameroon (Njouom et al., 2006).

The high variability in the performance of hepatitis C virus rapid POC tests calls for great caution in the selection and use of these tests. Choosing a poorly performing test for HCV screening could have adverse public health consequences, especially when they provide false negative results. Used in a blood bank for the screening of donated blood, these tests of low analytical sensitivity can generate a serious threat to the recipients (Khuroo et al., 2015; Pruett et al., 2015). The sensitivity deficiency of the tests evaluated in this study recommends a prior and serious assessment of HCV Rapid POC tests performance prior to their registration and marketing in resource-limited settings. However, the results should be considered with some contextual limitations. Firstly, there were no conditions of traceability and conservation of these tests were provided free of charge by local suppliers. Although this limit is valid, the results report the performance of routine tests commonly used in laboratories and hospitals across the country, as provided by local distributors. Secondly, it is recognized that HCV has a high genetic diversity with six known genotypes (Chevaliez and Pawlotsky, 2006; Zeba et al., 2014). This genetic diversity could have a significant effect on the diagnostic accuracy of marketed tests. The study did not take into account HCV genetic diversity, but studies are contradictory as to this influence (Khuroo et al., 2015; Scheiblauer et al., 2006; Tang et al., 2017).

In conclusion, the rapid HCV test samples evaluated in this study are poor at detecting anti-HCV. These results challenge the various actors involved in the HCV prevention chain, including health system decision-makers, hospitals, laboratories and reagent providers, to be more vigilant in choosing Rapid POC tests for screening for this virus in Burkina Faso. The high cost and complexity of ELISA and molecular biology methods in the context of limited resources require alternative methods such as Rapid POC tests. However, these Rapid POC tests must be of high diagnostic performance to play their part in HCV testing. It is important that health authorities strengthen the surveillance of HCV rapid diagnostic tests marketed in Burkina Faso, by validating their performance in the local context before their approval.

CONFLICT OF INTEREST

The authors have not declared any conflict of interests.

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