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**Evaluation of two rapid screening assays for detecting hepatitis C antibodies in resource-constrained settings**

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**Abstract**

**Objective:** To evaluate the diagnostic accuracy of the OraQuick HCV rapid antibody test from Ora-Sure and the Multisure HCV antibody assay from MP Biomedicals.

**Methods :** Five seropanel from patients, intravenous drug users and blood donors with and without HCV infection were used on the two rapid immunochromatographic tests. Sensitivity, specificity and predictive values were calculated. In addition, seropanel from 10 seroconverters were used to assess early identification of HCV infection. The study was undertaken in a laboratory at Paul Ehrlich Institute in Germany.

**Results:** Panel 1 contained of 55 positive and 25 negative samples. The OraQuick HCV test had a sensitivity of 100% (95% CI: 93.5–100) and a specificity of 100% (95% CI: 86.3–100). The Multisure HCV test had a sensitivity of 100% (95% CI: 93.5–100) and a specificity of 96% (95% CI: 79.6–99.9). Panel 2 consisted of 193 pre-characterized anti-HCV-positive patient samples. The OraQuick HCV test identified 191 samples correctly and the Multisure HCV 192. The sensitivity was 99.0% (95% CI: 96.3–99.9) for the OraQuick HCV test and 99.5% (95% CI: 97.1–100) for the Multisure HCV test. Panel 3 was composed of seroconversion samples of 10 patients. The OraQuick HCV test detected all of these 10 infections while the Multisure HCV test detected 6 and was indeterminate on 2. Panel 4 included 53 anti-HCV negative blood samples from blood donors. Both tests correctly identified all 53. Panel 5 consisted of 26 samples of HCV/HIV-co-infected patients. The sensitivity of the OraQuick HCV test was 65.2% (95% CI: 42.8–82.8) after 20 minutes and 73.9% (95% CI: 51.3–88.9) after 40 minutes of incubation. The Multisure HCV test had a sensitivity of 96.2% (95% CI: 80.4–99.9).

**Conclusion:** This evaluation revealed good sensitivity for both rapid screening assays, although the MultiSure HCV test detected fewer seroconverters. The OraQuick gave HCV false-negative results in almost 25% of the HIV-positive sera. Therefore the MultiSure test should be used with hesitation (Au: please rephrase) in high incidence settings, while the OraQuick may be less suited in HIV preva-

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lent areas.

**Keywords:** HCV, RDT, POC, OraQuick, Multisure, rapid diagnostic

## Introduction

Hepatitis C is recognized as a major and growing global health problem [1]. It is estimated that 130-150 million people, or almost 3% of the world's population, are chronically infected with the hepatitis C virus (HCV) [2]. HCV is highly variable; 7 major genotypes plus a series of 67 subtypes have so far been described [3]. Genotypes 1a and 1b are most prevalent in Western Europe and the US, followed by genotypes 2 and 3. Genotype 4 is most common in Egypt, genotype 5 in South Africa and genotype 6 in South-East Asia [4].

In Europe and America 31.5 million people are estimated to be infected, and 111 million in Africa and Asia [1, 5–12].

As no vaccine is available for HCV infection, early diagnosis is important for treatment and prevention measures [13]. However, 54% of the world's population lack access to free testing, 3% in high income countries and 82% in low income countries (LICs) [14]. Sub-Saharan Africa is particularly affected, where access to HCV screening tests is nearly non-existent [15–17].

Screening tests for HCV infection are commonly performed with an enzyme-linked immunosorbent assay (ELISA) or a lateral flow immunoassay (LFI). Initially reactive screening test results should ideally be confirmed by HCV nucleic acid amplification testing (NAAT) to test for activity of the infection [14, 18]. HCV viral load (VL) measurements are then needed to monitor treatment success. Both NAAT and VL tests are expensive, have long turnaround times, and require well-trained staff and well-equipped laboratories, all of which contribute to low availability in resource-constrained settings [19].

One possible way forward is through the use of LFI point-of-care (POC) tests. These simplified diagnostic tests can be used at or near the patient without the need for sophisticated laboratory structures. POC testing has the potential to significantly impact health care delivery and to address the challenges of health disparities, especially in resource-constrained settings [19–24].

The WHO has a program of pre-qualification which includes HCV assays including LFIs, but to date, no screening test for HCV has been pre-qualified [25]. Poor accuracy in African and HIV co-infected populations has been reported [19, 26, 27]. The overall sensitivity of HCV donor screening in Africa is only 88% on average [24]. In short, many HCV screening tests do not fulfil the ASSURED criteria [28].

Both tests meet many of the requirements, but knowledge on the performance of the Multisure HCV test is limited [19, 22, 24]. In addition, the OraSure test is not intended for blood donor screening but off-label use is often the best choice available in resource-constrained settings. Thus Médecins sans Frontières (MSF), a medical non-profit organization, commissioned this evaluation from the Paul-Ehrlich Institut (PEI), Langen, Germany. The goal of this evaluation was to gather independent performance data and compare the diagnostic accuracy of the Multisure HCV antibody assay to the already-proven but more expensive OraQuick HCV rapid antibody..

## **Methods**

### ***Evaluation procedures***

The evaluation of both the OraQuick HCV rapid antibody test from OraSure and the Multisure HCV antibody assay from MP Diagnostics was conducted from January 2014 until August 2015 on five serum panels at the Testing Laboratory for In-Vitro Diagnostic Medical Devices at PEI.

Samples of all five serum and plasma panels were stored frozen, thawed and centrifuged before use. Both tests were carried out according to the manufacturer's instructions for use [29, 30]. Samples of panels 1-3 were characterized by several chemiluminescence immunoassays (ChLIA) and microparticle immunoassays (MEIA) including the Architect Anti-HCV test (Abbott, Wiesbaden, Germany), the ADVIA Centaur HCV ADVIA Centaur HCV (Siemens, Tarrytown, USA), Prism HCV test (Abbott, Abbott Park, Illinois, USA) and the AxSYM Anti-HCV version 3 (Abbott, Wiesbaden, Germany). The samples were characterized in addition by ELISA tests including the Innostest HCV Ab IV (Innogenetics, Gent, Belgium), the Ortho HCV 3.0 Enhanced Save ELISA (Ortho Clinical Diagnostics, Raritan, New Jersey, USA) and the Murex anti-HCV Version 4 (7F51) (DiaSorin, Kyalami, South Africa).

### ***Serum panel description***

The first panel (n=82) was procured from ZeptoMetrix, New York, USA and consisted of samples collected from intravenous drug users (IVDU) at high risk for HCV infection. All samples were screened with the Architect Anti-HCV test, the AxSYM Anti-HCV version 3, the Innostest HCV Ab and the Ortho HCV 3.0 Enhanced Save ELISA test.

All positive and discrepant samples were characterized using the Chiron RIBA HCV 3.0 SIA (Novartis Vaccines and Diagnostics, Emeryville, CA, USA) or the Mikrogen *recom*Line HCV IgG (Mikrogen GmbH, München, Germany) as a supplemental test.

A positive status was defined as: i) reactive screening test(s) and positive supplemental test; ii) positive result in several anti-HCV screening tests, negative result in one screening test only and

positive supplemental test. An indeterminate status was defined as reactive screening test(s) and indeterminate supplemental test. A discrepant result was defined as discrepant anti-HCV screening results and negative supplemental test result. A negative status was defined as a negative screening tests and/or negative supplemental test. 55 samples of this first panel were HCV positive and 25 HCV negative; 1 was indeterminate and 1 discrepant. The indeterminate and discrepant samples were excluded from the accuracy analysis.

The second panel (n= 198) originated from the University of Frankfurt, Germany and had been stored at PEI. The HCV genotype (gt) was known for 45 samples (gt1: 2, 1a: 11, 1b: 6, 1a+1b: 1, gt 2: 3, 2a/2c 2, 2b: 1, gt 3: 5, 3a: 10, gt 4: 2 and 4b: 2). All samples were screened with at least one of the following: the Architect Anti-HCV test, the Ortho HCV 3.0 Enhanced Save ELISA, the ADVIA Centaur HCV (Siemens, Tarrytown, USA) and the Murex anti-HCV Version 4. In addition, most samples (121/198) were characterized using the Chiron RIBA HCV 3.0 SIA or the Mikrogen *recomLine* HCV IgG as supplemental tests.

A positive status was defined as: i) reactive screening test(s) and positive supplemental test; ii) reactive screening tests where no supplemental test result was available. An indeterminate status was defined as: i) reactive screening test(s) and indeterminate supplemental test; ii) indeterminate screening test and indeterminate supplemental test; iii) indeterminate screening test and positive supplemental test.

192 samples of this panel were defined as anti-HCV positive; 6 samples were anti-HCV indeterminate or discrepant. The indeterminate and discrepant samples were excluded from the accuracy analysis.

The third panel consisted of seroconversion samples to assess the sensitivity of both index tests in early HCV infection. The samples were purchased from SeraCare Life Sciences, MA, USA (PHV 904, PHV 914, PHV 918, PHV 920) and ZeptoMetrix cooperation, NY, USA (6211, 6214, 6228, 9044, 9047, 9054). Aliquots of these samples had been kept at -70°C at the PEI. These 10 seroconversion panels contained 45 samples in which HCV antibodies could be detected.

All samples were screened with three ChLIAs: the Architect Anti-HCV test, the ADVIA Centaur HCV and the Prism HCV test. Additional screening was performed using the Innostest HCV Ab IV and the Ortho HCV 3.0 Enhanced Save ELISA tests. The results of the Chiron RIBA HCV 3.0 SIA indicated the point of seroconversion.

The fourth panel contained 53 anti-HCV negative samples originating from blood donors of the German Red Cross, Baden-Wuerttemberg - Hessen, Frankfurt, Germany. All 53 samples were characterized by the DS-EIA-Anti-HCV (# C-150) from RPC Diagnostic Systems, Nizhniy Novgorod, Russia.

The fifth panel contained 26 samples from HCV-positive patients known to be co-infected with HIV originating from the HIV Center of the University Hospital of Frankfurt. The HIV status was con-

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firmed at the PEI testing laboratory using up to seven different HIV-1/2 tests per sample. All samples were reactive with the Architect Anti-HCV test.

### ***Index tests***

The OraQuick HCV rapid diagnostic test, OraSure Technologies, Bethlehem, USA (product number: 1001-0270 for 25 tests and 1001-0274 for 100 tests) and the Multisure HCV antibody assay, MP Bio-medicals Asia Pacific, Singapore (product number: 43130-020) are both CE marked LFIs in cassette format.

The OraQuick HCV test contains synthetic peptides and recombinant proteins from the core, NS3 and NS4 regions of the HCV genome in one test area. The Multisure HCV test contains antigens from the core, NS3, NS4 and NS5 regions in single lines on the membrane similar to confirmatory immunoblots.

Both tests were carried out and interpreted according to manufacturer's instructions by two independent readers. If the results were discordant, the result was interpreted in favour of the index tests. Interpretating the MultiSure HCV test is more complicated than the OraQuick HCV test, as the intensity of the various lines is used for interpretation.

### ***Statistical analysis***

Data was entered in an Excel file and analysed using Stata 12.0 statistical software (Stata Corporation, College Station, Texas, USA). Results of panels 1, 2 and 4 were classified as true positives, true negatives, false positives and false negatives. From these categories, sensitivity, specificity and predictive values (for panels 1 and 2 only) were calculated with 95% confidence intervals (CI). Indeterminate results were excluded from further analysis. For panel 3, the seroconversion panel, the number of positive detected samples was calculated and compared.

## **Results**

### ***Panel 1***

The OraSure HCV test identified all 55 positive samples and all 25 negative samples correctly (Table 1). Thus the sensitivity of the OraSure HCV test in panel 1 was 100% (95% CI: 93.5–100), and its specificity was 100% (95% CI: 86.3–100). The positive predictive and negative predictive values at a positivity rate of 69% were 100% (95% CI: 93.5–100) and 100% (95% CI: 86.3–100) respectively.

The Multisure HCV test identified all 55 positive samples and 24/25 negative samples correctly. Thus the sensitivity of the Multisure HCV test in panel 1 was 100% (95% CI: 93.5–100), and its specificity was 96.0% (95% CI: 79.6–99.9). The positive predictive and negative predictive values at a posi-

tivity rate of 69% were 98.2% (95% CI: 90.4–100) and 100% (95% CI: 85.8–100) respectively.

### **Panel 2**

This panel consisted of 198 serum samples, of which 192 samples tested positive, with 6 indeterminate/discrepant. Of the 192 remaining positive samples, the OraSure HCV test identified 190 samples correctly and 2 samples as false negative (Table 2). Thus, the sensitivity of the OraSure HCV test was 99.0% (95% CI: 96.3–99.9).

The Multisure HCV test was used to test 191 positive samples and identified 190 samples correctly and 1 as false negative. Thus, the sensitivity of the Multisure HCV test on panel 2 was 99.5% (95% CI: 97.1–100). All 45 samples for which the genotype was known were detected by both LFIs.

### **Panel 3**

The third panel contained seroconversion serum samples from 10 patients, totalling 242 samples of which 45 were anti-HCV positive. The OraQuick HCV test detected all of these 10 infections and the Multisure HCV test detected 6/10. However, if indeterminate results were added to the positive results of the Multisure HCV test, then seroconversion could be identified in 8/10 patients. Table 3 shows the results of other current screening tests (ELISAs and ChLIAs) in comparison with both index tests. Overall, OraQuick HCV and Multisure HCV Rapid test sensitivities in early HCV infection compared favourably with results of standard ELISAs.

### **Panel 4**

The fourth panel included 53 anti-HCV negative blood donor samples, and both index tests showed a negative result on all samples. The specificity on these 53 samples was 100% (95% CI: 93.3–100) for both index tests.

### **Panel 5**

The fifth panel comprised 26 anti-HCV positive and HIV-positive samples. The OraQuick HCV test was used on 23 samples of which 15 were identified correctly, 8 were false negative after 20 minutes while after 40 minutes two further samples were detected weak reactive, resulting in a sensitivity of 65.2% (95% CI: 42.8–82.8) after 20 minutes and 73.9% (95% CI: 51.3–88.9) after 40 minutes. 25 of 26 samples were correctly identified as HCV-positive by the Multisure test with a corresponding sensitivity of 96.2% (95% CI: 80.4–99.9).

### **Ease of use**

Serum and plasma samples were used on both tests. This allowed the background of the device not to colour and stay white, which has the advantage of easy detection of very weak or faint bands. However, 9 samples of the OraQuick HCV test had to be repeated due to very weak lines.

The MultiSure HCV test had to be repeated on 9 samples at least once due to poor migration on the lateral flow device/membrane. The Multisure HCV test is more suitable for testing smaller series since care needs to be taken that the sample does not migrate beyond the blue indicator line before the addition of chase buffer. Furthermore, the interpretation of the Multisure HCV test takes more time and is complex, as the intensity of the various lines is used for interpretation. Discrepant readings between the 2 readers were fewer than 1% for all seropanel on both tests.

The OraQuick may be read between 20 and 40 min of sample addition. A longer incubation time up to 40 minutes increased sensitivity.

## Discussion

To reduce transmission of HCV in resource-constrained settings, reliable LFIs or other POC tests are required to screen patients and potential blood donors. There are several important factors to consider in selecting a screening test including sensitivity, specificity, ease-of-use of the device, storage requirements, shelf-life, price, and quality-assured manufacturing [28]. Aside from the difficulties of finding a test with these characteristics, another limitation is that most LFIs are not registered for blood donor screening. Thus, most HCV LFIs must be used off-label to allow HCV screening of blood donors in resource-constrained settings.

This evaluation was done to identify a suitable LFI for use in MSF's programmes, most of which are in resource-constrained settings. Both the OraQuick HCV test and the HCV Multisure test had good sensitivities >99.0% in all panels with the exception of the OraQuick HCV having a sensitivity of only 73.9 % in the HCV/HIV-positive panel. Compared with the HCV Multisure test the lower sensitivity in the HCV/HIV-positive panel was not statistically significant but this could be due to the overall small sample size in this panel. Few studies have reported an increased amount of false-negative results with some HCV test assays in the presence of HIV infection [26, 27, 34, 35]. Given the high rate of co-infection of HIV-HCV this is a concern, especially when the test is being used for diagnostic purposes. It is less problematic in blood donor screening as a positive HIV test would exclude a co-infected blood donor. Diagnostic accuracy of HCV POC tests in HIV-co-infected patients should be further investigated in future studies.

Overall, the OraQuick had a good specificity of  $\geq 99\%$ , whereas the Multisure test had a specificity of 96% in the first panel but 100% in the fourth panel. Although this comparison shows lower specificity for the Multisure test, this difference was not statistically significant. It can be concluded

that both tests detect a high number of true anti-HCV positive samples. These results compare well with those of a systematic review and other evaluations of HCV LFIs and POC tests [19, 22, 31–33].

Nevertheless, several important limitations exist. This evaluation was not carried out in the target population and did not include genotype 5 and 6 samples. Thus, in areas such as East and South-East Asia or Southern Africa, where genotype 5 and 6 are circulating, the sensitivities of both tests may be affected. Evaluations including these samples types should follow.

We chose to use existing panels for purely practical reasons as other panels were not accessible and sample collection on-site is costly and time-consuming. Further, this study was not conducted in true field conditions and no whole blood could be used. Instead the tests were conducted at an IVD test laboratory by professional laboratory staff under ideal conditions and results may therefore not be applicable to resource-constrained settings. For example, suboptimal storage conditions or less-trained staff may influence the test's performance [22, 24]. However, evaluation at a professional laboratory gives a good indication of the true performance of rapid tests and how they compare with laboratory ELISAs or automated chemiluminescence assays.

Overall, the OraQuick test seems to be a better screening test for blood donors due to its better detection in early seroconversion, and it is easier to interpret than the Multisure test. However, both assays sometimes display (very) weak lines making interpretation difficult. This is a particular challenge in resource-constrained settings as less-experienced and educated staff may carry out POC testing. The difficulty of reading extremely weak lines has also been encountered by MSF in practice, where the OraQuick test has been used for >1 year [13].

The fact that the OraQuick test is the mostly evaluated LFI for HCV on the market [19] and the only one with FDA approval on venous and capillary blood [36] results in a de-facto monopoly and thus it remains expensive. The cost barrier impacts resource-constrained settings especially, as most of them have no provision for free HCV serology testing [37]. Furthermore, the off-label use of most LFIs for blood donor screening hinders wide use. HCV LFIs should be approved or at least conceived for several relevant indications, including blood donor screening.

In summary, both OraQuick and Multisure HCV tests performed very well in detecting HCV infection when evaluated on serobank panels in the laboratory. Further evaluation is needed to determine the diagnostic accuracy under field conditions, in the target population including HIV co-infected individuals. These evaluations should also include ease-of-use assessment of the assay (including readability and operator agreement) and repeated testing on different lots of the same assay.

This evaluation is an early step in the process of selecting the ideal screening test for HCV infec-



tion. While these results demonstrate that the assays may be used for screening potential blood donors in resource-constrained settings, they may also be used for other purposes such as screening in high-risk populations who inject drugs, HIV infected patients, or those in emergency care.

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**Table 1a.** Accuracy of the OraQuick HCV test compared against reference standard on samples of panel 1: patients at high risk of acquiring HCV infection (i.e. intravenous drug users).

		OraQuick HCV		
HCV ref- erence standard*		Positive	Negative	Total
	Positive	55	0	55
	Negative	0	25	25
	Total	55	25	80

\* Reference standard is composed of the Architect Anti-HCV test (Abbott, Germany), the ADVIA Centaur HCV ADVIA Centaur HCV (Siemens, USA), Prism HCV test (Abbott, USA) and the AxSYM Anti-HCV version 3 (Abbott, Germany) plus the Innostest HCV Ab IV (Innogenetics, Belgium), the Ortho HCV 3.0 Enhanced Save ELISA (Ortho Clinical Diagnostics, USA) or the Murex anti-HCV Version 4 (DiaSorin, South Africa).

**Table 1b.** Accuracy of the MultiSure HCV test compared against reference standard on samples of panel 1: patients at high risk of acquiring HCV infection (i.e. intravenous drug users).

		MultiSure HCV		
HCV ref- erence standard*		Positive	Negative	Total
	Positive	55	0	55
	Negative	1	24	25
	Total	56	24	80

\* Reference standard is composed of the Architect Anti-HCV test (Abbott, Germany), the ADVIA Centaur HCV ADVIA Centaur HCV (Siemens, USA), Prism HCV test (Abbott, USA) and the AxSYM Anti-HCV version 3 (Abbott, Germany) plus the Innostest HCV Ab IV (Innogenetics, Belgium), the Ortho HCV 3.0 Enhanced Save ELISA (Ortho Clinical Diagnostics, USA) or the Murex anti-HCV Version 4 (DiaSorin, South Africa).

**Table 2a.** Accuracy of the OraQuick HCV test compared against reference standard on samples of panel 2: Acquired from the University of Frankfurt, Germany.

		OraQuick HCV test		
		Positive	Negative	Total
HCV ref- erence standard*	Positive	190	2	192
	Negative	0	0	0
	Total	190	2	192

\* Reference standard is composed of the Architect Anti-HCV test (Abbott, Germany), the ADVIA Centaur HCV ADVIA Centaur HCV (Siemens, USA), Prism HCV test (Abbott, USA) and the AxSYM Anti-HCV version 3 (Abbott, Germany) plus the Innostest HCV Ab IV (Innogenetics, Belgium), the Ortho HCV 3.0 Enhanced Save ELISA (Ortho Clinical Diagnostics, USA) or the Murex anti-HCV Version 4 (DiaSorin, South Africa).

**Table 2b.** Accuracy of the MultiSure HCV test compared against reference standard on samples of panel 2: Acquired from the University of Frankfurt, Germany.

		MultiSure HCV test		
		Positive	Negative	Total
HCV ref- erence standard*	Positive	190	1	191
	Negative	0	0	0
	Total	190	1	191

\* Reference standard is composed of the Architect Anti-HCV test (Abbott, Germany), the ADVIA Centaur HCV ADVIA Centaur HCV (Siemens, USA), Prism HCV test (Abbott, USA) and the AxSYM Anti-HCV version 3 (Abbott, Germany) plus the Innostest HCV Ab IV (Innogenetics, Belgium), the Ortho HCV 3.0 Enhanced Save ELISA (Ortho Clinical Diagnostics, USA) or the Murex anti-HCV Version 4 (DiaSorin, South Africa).

**Table 3.** Summary results on anti-HCV testing on the seroconversion panel.

#	# Sero-conversion	# of bleeds per panel	Max. # of positive Ab bleeds	ChLIA A	ChLIA B	ELISA A	ELISA B	ChLIA C	OraQuick HCV test	MultiSure HCV test
				# of positive bleeds detected	# of positive bleeds detected	# of positive bleeds detected	# of positive bleeds detected	# of positive bleeds detected	# of positive bleeds detected	# of positive bleeds detected
1	904	7	5	4	4	3	3	3	3	3
2	914	9	7	5	5	n.d.	4	3	5	6
3	918	8	2	2	1	3	1	1	2	3
4	920	10	7	7	7	7	6	7	7	7
5	6211	40	3	3	3	2	2	3	2	0
6	6214	13	6	6	4	3	5	5	6	0
7	6228	12	4	4	3	0	3	4	2	0
8	9044	6	3	2	3	n.d.	2	2	1	2
9	9047	10	4	4	4	3	43	4	4	3
10	9054	10	2	1	1	2	1	1	1	0
Total # positive samples			45	38	35	23	31	33	33	24
Detection (%)			100	84	78	70*	69	73	73	53

\*Calculated for 8 panels only. ChLIA A = Architect anti-HCV; ChLIA B = Advia Centur anti-HCV; ChLIA C = Prism HCV; ELISA A= Innostest HCV Ab IV; ELISA B = Ortho HCV 3.0 ELISA test system with enhanced SAVE