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Blood Safety: On-Site Verification Of The Screening Of HIV, HBV And HCV By Enzyme Linked Immuno-Sorbent Assay (ELISA) Kits From Bio-Rad Laboratories At The “Centre National De Transfusion Sanguine” (CNTS) Of Lomé In Togo

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Abstract

Background: Blood transfusion improves health and saves lives. Safe blood must be ensured for our populations. Quality assurance is a process that includes a set of coordinated activities in order to achieve the quality objective. Compliance with the quality management rules of medical biology laboratories requires verification of methods prior to their use. This study aimed to verify the on-site verification of the performance of the Enzyme Linked Immuno-Sorbent Assay (ELISA) method performed at the serology laboratory of the CNTS of Lomé.

Methods: The performance of ELISA method performed at the serology laboratory of CNTS for the diagnosis of HIV, Hepatitis B and C with Bio-Rad Genscreen ULTRA-HIV Ag-Ac, Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kits respectively was evaluated on repeatability, reproducibility, sensitivity and specificity according to COFRAC's SH GTA 04 reference.

Results: The evaluation of the repeatability and reproducibility of each kit used in the laboratory resulted in compliant Coefficients of Variation (CV) with manufacturers' ones. Sensitivities obtained with Bio-Rad Monolisa HCV Ag-Ac ULTRA V2, Bio-Rad Monolisa HBs Ag ULTRA and Bio-Rad Genscreen ULTRA HIV Ag-Ac kits were 94.59%, 98.08% and 100% respectively. For specificity tests, we found 86.49% with BIO-Rad Genscreen ULTRA-HIV Ag-Ac kit, 94.34% with Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kit and 97.37% with Bio-Rad Monolisa-HBs Ag ULTRA.

Conclusion: In general, results were compliant except HIV diagnosis specificity. This study appears as a contribution to the establishment of a verification file for ELISA method used at the serology laboratory of CNTS of Lomé.

Keywords: Blood Safety, Quality Assurance, Method Verification, ELISA, Repeatability, Reproducibility, Sensitivity, Specificity

Introduction

Blood transfusion is a very important health procedure. It is therefore the responsibility of the national blood transfusion program to ensure the quality of blood products for a secure clinical use (WHO, 2010). Quality assurance is a process that includes a set of coordinated activities in order to achieve the quality objective (ISO 9000, 2015). When analyses are performed, there is always some degree of uncertainty. The challenge is to reduce the level of inaccuracy as much as possible, and this can only be achieved through mastering analytical systems and methods (Marques-Garcia et al., 2015). In August 2015, Togo Ministry of Health and Social Protection (MHSP) issued a decree N°115/2015/MSPS/CAB/SG to institute ISO 15189 standard as a

reference for all medical biology laboratories in Togo (Cucherat, 2017). In order to meet this challenge outlined above, the standard specifies in its paragraph 5.5.1.3, the requirements for the validation of analytical procedures (COFRAC, 2016). Validation of method is confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled (International Standard Organization, 2005). Compliance with the quality management rules of medical biology laboratories requires verification of methods prior to their use. The “Centre National de Transfusion Sanguine” (CNTS) is the national reference center for blood transfusion in Togo. The biological qualification of donations is done in two laboratories of CNTS, namely serology and immunohematology laboratories. Both must meet the requirements of the ISO15189 standard adopted by the MHSP. Thus, from April 28 to 29, 2016, a diagnostic audit, commissioned by the Division of Laboratories, was carried out in these two laboratories in regard to the above-mentioned reference system. One of the discrepancies noted during this diagnostic audit was the non-verification of methods and analytical procedures. This study responds to this challenge by verifying ELISA method with kits from Bio-Rad Laboratories used in the serology laboratory of the CNTS in order to ensure safe blood to our population.

Methods

This was a descriptive study, from January 15 to February 20, 2018 at the serology laboratory of CNTS in Lomé.

Biological samples consisting of HIV, HBV, HCV positive and negative sera were provided by the National Reference Center (NRC) and CNTS serum bank respectively.

The performance of the ELISA method used at the serology laboratory of CNTS for the diagnosis of HIV, Hepatitis B and C with Bio-Rad Genscreen ULTRA-HIV Ag-Ac, Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kits respectively, has been evaluated on repeatability, reproducibility, sensitivity and specificity according to COFRAC's SH GTA 04 reference (COFRAC, 2015).

Repeatability assessment

To assess the repeatability, negative and positive controls of ELISA kits were tested 17 times under the same conditions by the same scientists and coefficients of variation (CV) were calculated.

Reproducibility assessment

To evaluate the reproducibility, negative and positive controls of ELISA kits were analyzed 17 times under different conditions by changing scientists and coefficients of variation (CV) were calculated.

$$CV = (SD / m) * 100$$

SD = Standard deviation; m = mean

Evaluation of sensitivity and specificity of the methods

For the assessment of sensitivity and specificity, pools of sera known as positive or negative for either HIV, HBV or HCV were tested. Sensitivity and specificity was determined as follow:

$$Sensitivity = TP / (TP + FN) * 100$$

$$Specificity = TN / (TN + FP) * 100$$

Evaluation of predictive values

Positive predictive values (PPV) and negative predictive values (NPV) were calculated as follow:

$$PPV = TP / (TP + FP) * 100$$

$$NPV = TN / (TN + FN) * 100$$

TP = True positive; FP = False positive; FN=False negative; TN= True negative

Statistical analysis

Descriptive statistics were performed using Graph Pad PRISM 5.02 software (GraphPad Software, San Diego California USA).

Results

Evaluation of repeatability

Table 1 shows the results of repeatability test of the ELISA method with different kits. It appears that the CV of negative control (5.28%) and positive control (2.69%) of BIO-Rad Genscreen ULTRA-HIV Ag-Ac dedicated to the diagnosis of HIV, are lower than the manufacturer's ones which are respectively 5.37% and 8.48%. For the diagnosis of Hepatitis B, the negative control of Bio-Rad Monolisa-HBs Ag ULTRA gives a CV of 6.83%, lower than the manufacturer's one (10.6%) and the positive control gives a CV of 2.38%, also lower than the manufacturer's one (6.2%). Regarding the diagnosis of Hepatitis C, the trend is the same with Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 which negative control CV (6.38%) and positive control CV (3.83%) are also lower than the manufacturer's ones (Table 1). These results show that the ELISA method used for the three kits was repeatable.

Table 1. Repeatability of the ELISA method with different kits

Reagent	Samples (Level)	Number of values (N)	Mean	SD	CV (%)	Manufactu-rer CV (%)	Compliant
Bio-Rad Genscreen ULTRA-HIV Ag-Ac	Negative	17	0.089	0.0047	5.28	5.37	Yes
	Positive	17	2.857	0.0768	2.69	8.48	Yes
Bio-Rad Monolisa-HBs Ag ULTRA	Negative	17	0.0205	0.0014	6.83	10.6	Yes
	Positive	17	2.5209	0.060	2.38	6.2	Yes
Bio-Rad Monolisa HCVAg-Ac ULTRA V2	Negative	17	0.069	0.0044	6.38	10.4	Yes
	Positive	17	2.193	0.084	3.83	6.1	Yes

Table 1 shows the means of optical densities of negative and positive controls of Bio-Rad Genscreen ULTRA-HIV Ag-Ac, Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 ELISA kits tested 17 times; their standard deviations, their coefficients of variation and the compliance with manufacturer's values.

Evaluation of reproducibility

The ELISA method reproducibility test with three kits results are presented in Table 2. The BIO-Rad Genscreen ULTRA-HIV Ag-Ac kit negative control CV was 7.33% which is lower than manufacturer's CV (9.9%). Its positive control CV (5.83%) was also lower than manufacturer's CV (17.9%). Similar trends were found for Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCVAg-Ac ULTRA V2 kits controls CV, which were all lower than manufacturer's values (Table 2). These results lead to conclude that ELISA method assayed with the three kits is reproducible.

Table 2. Reproducibility of the ELISA method with different kits

Reagent	Samples (Level)	Number of values (N)	Mean	SD	CV (%)	Manufactu-rer CV (%)	Compliant
Bio-Rad Genscreen ULTRA HIV Ag-Ac	Negative	17	0.086	0.0063	7.33	9.9	Yes
	Positive	17	2.948	0.172	5.83	17.9	Yes
Bio-Rad Monolisa HBs-Ag ULTRA	Negative	17	0.0198	0.0025	12.63	18.1	Yes
	Positive	17	2.870	0.3007	10.48	10.6	Yes

Bio-Rad Monolisa HCV Ag- Ac ULTRA V2	Negative	17	0.069	0.0083	12.03	19.4	Yes
	Positive	17	2.476	0.298	12.04	15	Yes

Table 2 shows the means of optical densities of negative and positive controls of Bio-Rad Genscreen ULTRA-HIV Ag-Ac, Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 ELISA kits tested 17 times; their standard deviations, their coefficients of variation and the compliance with manufacturer's values.

Sensitivity assessment

Table 3 shows the results of sensitivity test with different ELISA kits. The sensitivity obtained with Bio-Rad Genscreen ULTRA HIV Ag-Ac kit was 100% with a positive predictive values (PPV) of 95%. For Bio-Rad Monolisa HBs Ag ULTRA kit, the sensitivity was equal to the PPV, 98.08%. Concerning Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kit, sensitivity was 94.59% with a PPV of 92.11% (Table 3). These results were close to manufacturer's values and showed that the ELISA method was sensitive for the three kits.

Table 3. Sensitivity for different ELISA kits

Reagent		Number of samples	FN	FP	Sensitivity (%)	PPV (%)
Bio-Rad Genscreen ULTRA HIV Ag-Ac	Manufacturer	6038	0	0	100	100
	Our test	132	0	5	100	95
Bio-Rad Monolisa HBs Ag ULTRA	Manufacturer	428	0	0	100	100
	Our test	20	1	1	98.08	98.08
Bio-Rad Monolisa HCV Ag-Ac ULTRA V2	Manufacturer	501	0	0	100	100
	Our test	90	2	3	94.59	92.11

Table 3 shows the number of samples tested per kit, number of false negative (FN) and false positive (FP) obtained, the sensitivities and the positive predictive values (PPV) for Bio-Rad Genscreen ULTRA-HIV Ag-Ac,

Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 ELISA kits.

Specificity assessment

The results of specificity test with ELISA kits are compiled in Table 4. The specificity value for BIO-Rad Genscreen ULTRA-HIV Ag-Ac kit was 86.49% with a Negative predictive Values (NPV) of 100%. With Bio-Rad Monolisa-HBs Ag ULTRA, the specificity was equal to the NPV (97.37%). Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kit gave a specificity of 94.34% with a NPV of 96.15% (Table 4). These results lead to conclude that the ELISA method is more specific for the diagnosis of Hepatitis B and C.

Table 4. Specificity for different ELISA kits

Reagent		Number of samples	FN	FP	Specificity (%)	NPV (%)
Bio-Rad Genscreen ULTRA HIV Ag-Ac	Manufacturer	6038	0	0	100	100
	Our test	132	0	5	86.49	100
Bio-Rad Monolisa HBs Ag ULTRA	Manufacturer	428	0	0	100	100
	Our test	90	1	1	97.37	97.37
Bio-Rad Monolisa HCV Ag-Ac ULTRA V2	Manufacturer	501	0	0	100	100
	Our test	90	2	3	94.34	96.15

Table 4 shows the number of samples tested per kit, number of false negative (FN) and false positive (FP) obtained, the specificities and the negative predictive values (NPV) for Bio-Rad Genscreen ULTRA-HIV Ag-Ac, Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 ELISA kits.

Discussion

The aim of our study was to evaluate the performance of ELISA method at the serology laboratory of Centre National de Transfusion Sanguine (CNTS) of Lomé, for the diagnosis of HIV, Hepatitis B and C. In fact, HIV, HBV and HCV are blood transmittable viruses, so their screening is important for a secure blood transfusion (WHO, 2009). CNTS screen systematically all donors for HBV, HCV, HIV and syphilis. In Togo, Nadjir et al. found among blood donors in CNTS of Lomé, from 2011 to 2015, seroprevalences of

2.63%, 1.58% and 0.92% for HBV, HCV and HIV, respectively (Koboyo Nadjir et al., 2017).

This study was undertaken in order to correct a discrepancy noted during a diagnostic audit conducted according to the requirements of ISO 15189 standard, in 2016: the non-verification of methods and analytical procedures. The study responds to this challenge by verifying ELISA method used in the serology laboratory of CNTS through reproducibility and repeatability assessments, and also evaluation of sensitivity and specificity. In general, results were compliant with manufacturers one, except HIV diagnosis specificity.

A method evaluation or verification is the confirmation that the recognized method is mastered by the laboratory (SADCAS, 2018). Thus, in China, Li et al. evaluated in 2016, the performance of Elecsys Anti - HCV II assay for HCV screening (Li et al., 2016). Kauffmann-Lacroix et al. in 2013 validated ELISA method for the diagnosis of aspergillosis with BIO-Rad kit (C. Kauffmann-Lacroix , M. Arvier , M. Charron, M.-H. Rodier, 2013). Also, in 2015, Elliot et al. evaluated the diagnostic accuracy of blood centers in the screening of blood donors for viral markers in Ghana (Elliot Eli Dogbe, 2015). In general, the literature on ELISA method verification provides a great deal of information on sensitivity and specificity. In our study, we set out to add repeatability and reproducibility to sensitivity and specificity for a better appreciation.

Repeatability and reproducibility are two important parameters in the assessment of a method precision (International Organization for standardization, 2012).

Repeatability is defined as the variation in measurements performed under the same conditions (Berthold, 2011). It is evaluated by calculating the CV. Here, we found that the CV of negative control (5.28%) and positive control (2.69%) with BIO-Rad Genscreen ULTRA-HIV Ag-Ac kit, were lower than the manufacturer's ones, which were 5.37% and 8.48% respectively. With Bio-Rad Monolisa-HBs Ag ULTRA kit, the CV of the negative control (6.83%) and positive control (2.38%) were also lower than manufacturers' CV (10.6%; 6.2%). Same trend was observed with Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kit negative control CV (6.38%) and positive control CV (3.83%) which were lower than manufacturer's CV. These results allowed us to say that ELISA method used at CNTS for the diagnostic of HIV, Hepatitis B and C is repeatable.

On the other hand, Reproducibility is the precision estimate obtained when series of measurements are made under more variable conditions (International Organization for standardization, 2012). We found that BIO-Rad Genscreen ULTRA-HIV Ag-Ac kit negative control CV (7.33%) was lower than manufacturer's CV (9.9%). Its positive control CV

(5.83%) was also lower than manufacturer's CV (17.9%). So were Bio-Rad Monolisa-HBs Ag ULTRA and Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kits controls CV; leading us to conclude that the ELISA method run at CNTS is reproducible.

The accuracy measurements include sensitivity and specificity (Stralen et al., 2009). In our study, sensitivity obtained with Bio-Rad Genscreen ULTRA HIV Ag-Ac kit was 100%. Hwang et al. found in 2006 a sensitivity of 100% for Genscreen ULTRA HIV Ag-Ab kit in Korea (Hwang et al., 2006). Abraham et al. also found in 2019 such a close sensitivity of 99.5% with the same kit in Ethiopia (Abraham, 2019), confirming the high sensitivity of the ELISA method used at CNTS for diagnosing HIV.

With the Bio-Rad Monolisa HBs Ag ULTRA kit, we found a sensitivity of 98.08% whereas Hwang et al. found in Korea in 2006 a sensitivity of 100% with the same kit (Hwang et al., 2006). Maity et al. also obtained in 2012 a sensitivity of 100% with Microscreen HBsAg ELISA kit in India (Maity et al., 2012). So, the ELISA method for HBV screening at CNTS is sensitive but the little difference between sensitivities, when comparing with authors cited above, could be explained by the lowest number of samples (N=20) used to perform our sensitivity test.

Regarding the Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kit, we obtained a sensitivity of 94.59%. In 2007, Alados-arboledas et al. found a sensitivity of 100% with Monolisa HCV Ag-Ab ULTRA in Spain (Alados-arboledas et al., 2007). Hwang et al. found the same sensitivity with the same kit in 2006 in Korea (Hwang et al., 2006). This difference must be due to the largest number of samples (N>1000) used by those authors to perform their test of sensitivity.

In the specificity test, we obtained with BIO-Rad Genscreen ULTRA-HIV Ag-Ac kit a value of 86.49%, which is lower than the one Stanekova et al. found in Slovakia in 2016 (100%) with Genscreen HIV ½ version 2 kit (Stanekova et al., 2016). Maity et al. had also found in India a specificity of 98.9% with ERBA LISA HIV kit (Maity et al., 2012) in 2012. Thus, the ELISA method used at CNTS for the diagnosis of HIV is of low specificity.

With the Bio-Rad Monolisa-HBs Ag ULTRA kit, the specificity was 97.37%. Indeed, by meta-analysis in 2017, Amini et al. found such a close pooled specificity of 98.4% on five studies performed in China, Ghana, Cambodia and Vietnam to evaluate eight enzymatic immune assays for HBs antigen detection (Amini et al., 2017); their results prove that ELISA method for diagnosing HBV at CNTS is specific.

The specificity with the Bio-Rad Monolisa HCV Ag-Ac ULTRA V2 kit was 94.34% while Lambert et al. had found a specificity of 99.86% with the same kit in Europe in 2007 (Lambert, 2007). Also, in 2015, Khuroo

et al. in a meta-analysis found a sensitivity of 99.5% on thirty studies that had evaluated tests to detect HCV antibodies (Khuroo et al., 2015). So, the ELISA method for the detection of HCV at CNTS was not as specific as others but it can be explained by the difference between kits used in each case.

In this study we deplore that we did only 17 tests instead of 30 as recommended by COFRAC, due to lack of funding. Nevertheless, the results will allow to establish a verification file of the ELISA method used at the serology laboratory of CNTS of Lomé.

Conclusion

The verification of analytical methods and procedures is a sine qua non step in the quality approach of a medical analysis laboratory. In this study, the verification of the ELISA method used in the CNTS serology laboratory according to the COFRAC SH GTA 04 reference showed that the method is repeatable, reproducible and sensitive for the diagnosis of HIV and hepatitis B and C. Compared to the diagnostic specificity for hepatitis B and C, the method is less specific for the diagnosis of HIV. Based on these results, this study appears as a contribution to the establishment of a verification file of the ELISA method used at the serology laboratory of CNTS of Lomé.

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Recommendations

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