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External Quality Assessment (EQA) scheme for serological diagnostic test for SARS-CoV-2 detection in Sicily Region (Italy), in the period 2020–2022

https://doi.org/10.1515/dx-2024-0048
Received March 6, 2024; accepted May 26, 2024;
published online July 3, 2024

Abstract

Objectives: Since December 2019, worldwide public health has been exposed to a severe acute respiratory syndrome caused by Coronavirus-2. Serological testing is necessary for retrospective assessment of seroprevalence rates, and the determination of vaccine response and duration of immunity. For this reason, it was necessary to introduce a panel of tests able to identify and quantify Covid-19 antibodies.
Methods: As a Regional Reference Centre, the CRQ Laboratory (Regional Laboratory for the Quality Control) developed and conducted an External Quality Assessment (EQA) panel of assays, to evaluate the quality of various methods, that were used by 288 Sicilian laboratories, previously authorized on behalf of the Public Health Service.
Results: The performance test was based on pooled samples with different levels of concentration of antibodies. 97 , 98, and 95 % of the participating laboratories tested all samples correctly in 2020, 2021, and 2022 respectively. The best performance was observed in the test of total Ig. The general performance of laboratories improved over the years.
Conclusions: The incorrect diagnosis had and could still have important implications on vaccination cycles. Only through the effort of laboratory professionals, and the extension of the EQA scheme, a better harmonization of methods, protocols, and thus results, to guarantee a better healthcare system, will be possible.

Keywords: COVID-19; External Quality Assessment; SARS-CoV-2; serological test performance evaluation

Introduction

The COVID-19 pandemic situation of the last three years had a strong impact on laboratories' management. The high demand for diagnostic tests determined a growing and initially uncontrolled employment of novel diagnostic assays. Different tests, with different targets, are available for diverse diagnostic purposes. In particular, among the applied methods, reverse transcription-PCR (RT-PCR), which amplifies and detects viral genome, is the primary technique for the diagnosis of acute infection [1, 2]. Serological testing, which identifies specific human antibodies, is instead recommended for retrospective assessment of seroprevalence rates for the determination of vaccine or infection response and duration of immunity and gives complementary information to the RT-PCR assay. In fact, serological assays are able to detect various types of antibodies, including IgM, IgG, IgA, total antibodies, and antibodies targeting specific components of the SARS-CoV-2 virus, such as the nucleocapsid protein, the spike protein, and the receptor binding domain (RBD) [3]. Common COVID-19 antibodies identification and quantification methods in human serum or plasma are

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enzyme-linked immunosorbent assays (ELISAs), chemiluminescent immunoassays (CLIAs), or chemiluminescent microparticle assays (CMIAs). The assay design variables show that large differences in test results and interpretations are likely between clinical laboratories [4, 5].

For this reason, laboratory professionals, in compliance with the requirement of ISO 15189:2012, have implemented quality assurance procedures regarding validation and verification of the performance, the definition of the criteria for the results' interpretation, and monitoring of the test performance [6]. In this context, considering the extent of the diagnostic assays, the External Quality Assessment (EQA) became crucial in ensuring the accuracy and high quality of the diagnostic procedures to identify SARS-CoV-2 antibodies [7–11]. All participants in an EQA program blindly analyze the furnished samples and report their test results to an approved and accredited provider that, in case of acceptable results, certifies the laboratories' competence. The aim of the EQA is to acknowledge the existing serological diagnostic tests and performance and to assess standard criteria and recommendations in order to improve the laboratories' executions.

In the context of anti-SARS CoV-2 serological proficiency testing, the CRQ (Centro Regionale Qualità dei laboratori) was an Institutional Public Provider for EQA, accredited and authorized by the Regional Health Service [12]. In this report, the outcome of the three rounds per year EQA conducted in Sicily and the small surrounding islands during 2020, 2021, and 2022 is presented.

Materials and methods

EQA design

The Sicilian EQA system provides mandatory participation in the SARS-CoV-2 EQA for every public and private laboratory that intends to perform SARS-CoV-2 serological tests on patients. The EQA scheme COVS432 has been realized in the period 2020–2022, with three EQA rounds per year. The laboratories that participated in the EQA scheme COVS432 (Serologic SARS-CoV-2) in 2020–2022 were 288. 212, 194, and 209 laboratories participated in 2020, 2021, and 2022 respectively. 115 were the laboratories that took part in the EQA in all three years. The laboratories obtaining the acceptability were then authorized to perform the analysis for the Regional Health System and for COVID-19 antibodies' profiling. The authorization was released from the Regional Government Office after a specific and public selection based on particular, structural, technological, and professional features and confirmed by the EQA results. Thus, the laboratories must have been registered at CRQ and be conformed to the quality control standards. Our research contributes to the ongoing monitoring of laboratories performance and did not involve any form of human experimentation. No human subjects were involved in our study, and thus the Ethics Committee approval was not required.

Participants

Overall, the laboratories that participated in the EQA scheme COVS432 in 2020–2022 were 288 (31 public and 257 private). 213 (24 public and 189 private), 194 (20 public and 174 private), and 209 (17 public and 192 private) laboratories participated in 2020, 2021, and 2022 respectively. Among the laboratories, there were clinical analysis centers, nursing homes, hospital units, and pharmacies. The entire process from registration and anagraphic data collection, to the evaluation of the results, was handled with an in-house platform.

Preparation of simulated samples

The SARS-CoV-2 EQA scheme COVS432 is intended for serological tests on IgG, IgM, and IgA SARS-CoV-2 antibodies. Within the period, new antibodies targeting specific components of the SARS-CoV-2 virus, such as the nucleocapsid protein (IgG nucleocapsid and Ig tot nucleocapsid), the spike protein (IgG S1), and the receptor binding domain (IgG S-RBD and IG tot S-RBD), were added to the panel of the searched antibodies. Every sample to analyze was constituted of two aliquots of 0.3 mL human serum samples (A and B). The stock blood samples of SARS-CoV-2 positive and negative patients were obtained thanks to a vaccination campaign during the COVID-19 pandemic. Three different pools of serum at three levels of concentration (high, low, and negative) of RBD were prepared from the stocked material (stored at −20 °C). Aliquots 1(A) and 1(B) were realized by mixing different ratios of the three pools in order to obtain different concentrations of each antibody. The aliquots were analyzed in triplicate to determine the type and concentration of Ig, with Shenzhen New Industries Maglumi 2000 and Bio-Rad BioPlex 2200 System. The stability of the samples was checked by measuring the antibodies concentration over three months, at the moment of the pool preparation, immediately before the beginning of the VEQ scheme, and after the VEQ scheme. The homogeneity of the samples, and commutability aspects were assessed according to the ISO 17043 guidelines. Blood collection, processing, pooling, aliquoting, capping, freezing, and storage of the serum pools were completed as quickly as possible to ensure the quality of the final product. Pools were prepared from many single donations to reduce the eventual influence of individual samples specific effects.

Data collection and statistical analysis

The CRQ's EQA Platform engine performs statistical analysis, evaluation of the participants, and reporting. The evaluation takes into consideration the overall entered results of each sample and each antibody against target results, and it considers potential sample warnings. The acceptability of the results is based on the peer group consensus value ("trimmed mean value") derived from all results submitted by participants in the scheme for that analyte. This approach was performed only

for groups of at least 10 results. The results for groups of less than 10, were not evaluated. The mean and the standard deviation (SD) for each group were calculated, the results outside the range mean±3SD were excluded and the values recalculated. Accepted results were in the range of mean±2SD, being classified as "*optimum*" values in the range±0.5SD, values presenting a bias between 0.5 and 1 SD from the mean were classified as "good", and presenting a bias between 1 and 2 SD from the mean were classified as "sufficient". Uploaded instrument reports are also evaluated. The produced reports contain information about participants, quality tests, results, targets, and performance evaluation. In the present work, all the results ranging from sufficient to optimum are indicated as acceptable.

Results

Participants

In total, 80 laboratories participated in only one year, 93 participated in the program in two years, and 115 laboratories took part in the EQA in all three years. Participants indicated the use of a variety of methods, including chromatography, colorimetric, and immune-radiometric methods. However, chemiluminescent and immuno-enzymatic, followed by fluorimetric assays were predominant in the three years.

Overall SARS-CoV-2 serological test performance

The blind work setting was necessary to avoid false laboratory results, and thus false reports by the participating authorized laboratories. In 2020, 205 laboratories out of 212 (97 %) received a Positive Performance evaluation (Figure 2A) for the CRQ's EQA scheme COVS432 (252 samples out of 287 processed (88 %) received an acceptable evaluation). In 2021, 191 laboratories out of 194 (98 %) received a Positive Performance evaluation for the CRQ's EQA scheme COVS432 (1,329 samples out of 1,536 processed (87 %) received an acceptable evaluation). In 2022, 198 laboratories out of 209 (95 %) received a Positive Performance evaluation for the CRQ's EQA scheme COVS432 (2107 samples out of 2367 processed (89 %) received an acceptable evaluation). Details about performance per year and analyte are in Figure 1. Overall, 40 % of the laboratories that

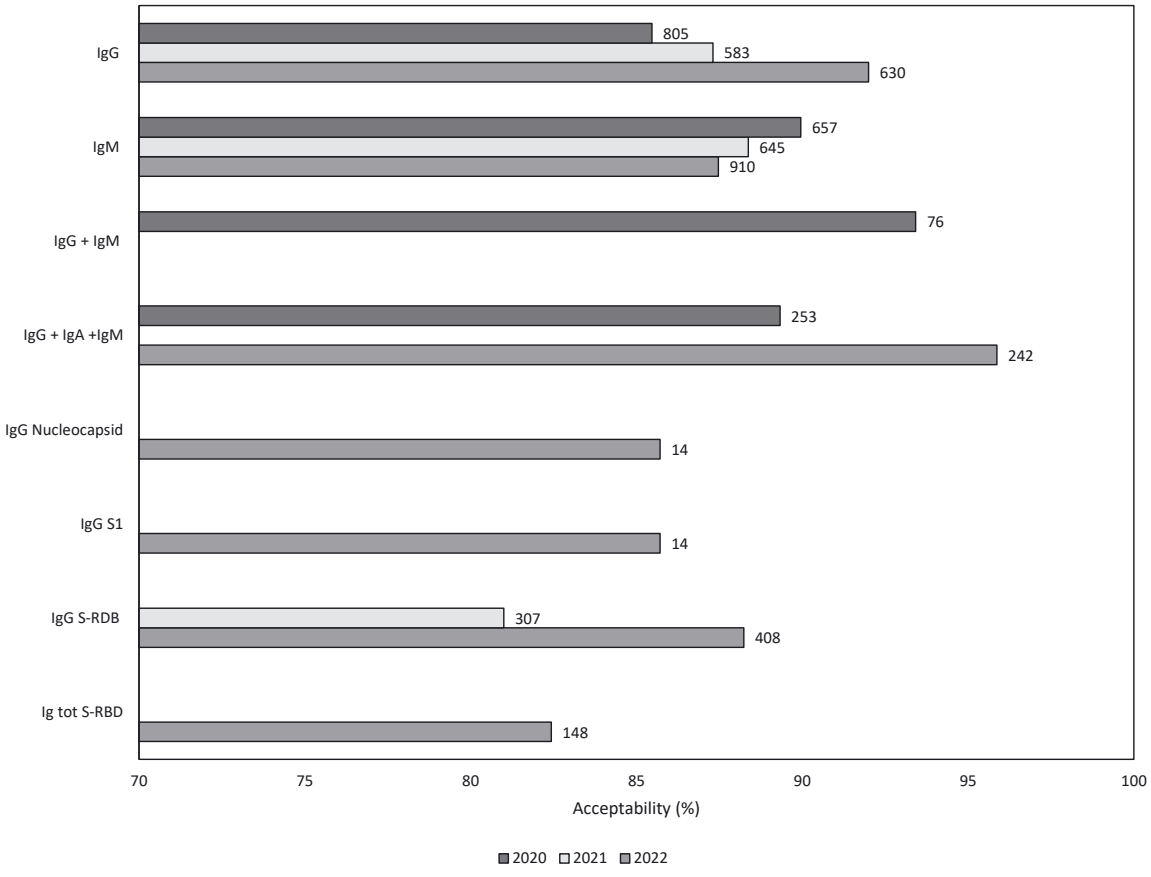

Figure 1: Histogram of the acceptability (%) per analyte and per year. At the top of the bars, the total number of samples is indicated.

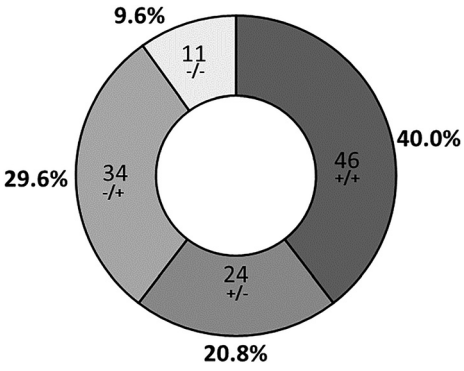

Figure 2: Pie chart of the laboratories' acceptability trend in the period 2020–2022. +/+ indicates that the acceptability was higher in 2021 compared to 2020 and in 2022 compared to 2021 or that the laboratory maintained 100 % acceptance; +/– indicates that the acceptability was higher or that the laboratory maintained 100 % acceptance in 2021 compared to 2020 and lower in 2022 compared to 2021; –/+ indicates that the acceptability was lower in 2021 compared to 2020 and higher in 2022 or that the laboratory maintained 100 % acceptance compared to 2021; –/– indicates that the acceptability was lower in 2021 compared to 2020 and in 2022 compared to 2021. The number in the chart indicates the number of laboratories for each group.

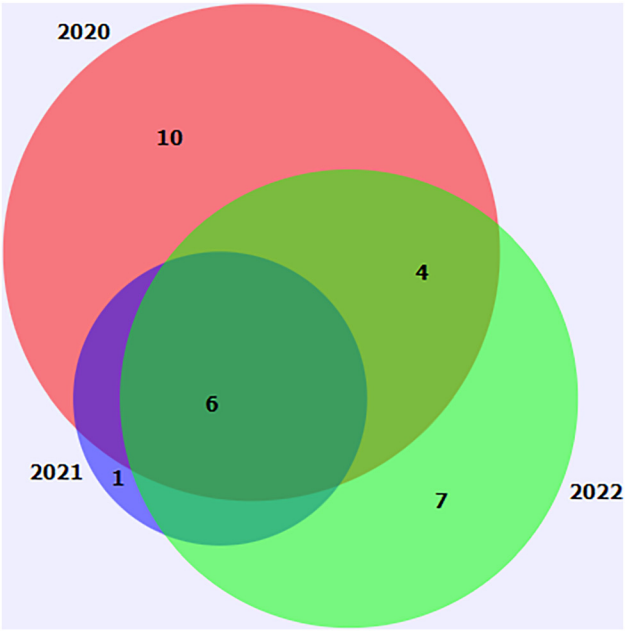

Figure 3: Venn diagram of the reactive kits used in 2020, 2021, and 2022.

were evaluated every year improved their performance over time or maintained the 100 % of acceptance (the mean of improvement was around 27 % in 2021 and around 6 % of 9 in 2022), 34 % of laboratories obtained lower acceptability in 2021 compared to 2020, but then obtained a better result or maintained the 100 % of acceptance in 2022 (the mean of worsening was around –30 % in 2021 and an improvement of around 29 % with a in 2022), in 24 % of the cases the opposite was observed (the mean of improvement was around 28 % in 2021 and a worsening of around 28 % with a in 2022), and 11 % of the laboratories worsened over time (the mean of worsening was around –13 % with a in 2021 and of around 25 % with a in 2022, Figure 2). A total rate of 0.96 for reported results/expected results was achieved, and 0.56 for evaluated results/expected results. The rate of evaluation was mainly linked to the impossibility of reaching the consensus level for certain groups. In the present study, only evaluated results are reported and discussed.

Reagents' kits test performance

A total of 28 different reagent kits, grouped for manufacturers, were used; of them, 20 were used in 2020, 7 in 2021, and 17 in 2022 (Figure 3). The six kits used in all three years were from Abbott Diagnostics, BioMerieux Inc., DiaSorin S.p.A., Diesse Diagnostica Senese Spa, Roche Diagnostics, Shenzhen New Industries Biomedical Engineering Co, while 10, 1, and 4 kits were exclusively used, respectively, in 2020, 2021 and 2022. Four kits were used in 2020 and 2022, but not in 2021 (DEMEDITEC Diagnostics GmbH, Pantec Srl, Siemens (Siemens Healthcare), Zhejiang Orient Gene Biotech Co., Ltd.).

The identification of the total Ig (IgG+IgA+IgM) was mainly performed with Elecsys Anti-SARS-CoV-2 kits, Roche Diagnostics. The identification of IgG was mainly performed with Abbott Diagnostics (SARS-CoV-2 IgG and SARS-CoV-2 IgG II Quant kit), BioMerieux Inc. (VIDAS SARS-CoV-2 IgG kits), Diesse Diagnostica Senese Spa (Chorus SARS-CoV-2 IgG and Enzy-well SARS-CoV-2 IgG kits), and Shenzhen New Industries Biomedical Engineering Co. (Maglumi 2019-nCoV IgG), even if the laboratories considerably reduced the use of this last kit in 2022.

Anti-SARS-COV-2 IgG+IgM analysis was mainly performed with Elecsys Anti-SARS-CoV-2 kit, Roche Diagnostics. Abbott Diagnostic (SARS-CoV-2 IgM kit), BioMerieux Inc. (VIDAS Sars-Cov-2 IgM (9COM)), Diesse Diagnostica (CHORUS SARS-CoV-2 IgM Diesse ENZYWELL SARS-CoV-2 IgM ENZY-WELL SARS-CoV-2 IgM), Shenzhen New Industries Biomedical Engineering Co. (MAGLUMI 2019-nCoV IgM) were the main kits for IgM identification and quantification.

Shenzhen New Industries Biomedical Engineering Co. was also the main producer of anti-SARS-COV-2 neutralizing IgG S-RBD extraction kits MAGLUMI SARS-CoV-2 S-RBD IgG (CLIA) and MAGLUMI SARS-CoV-2 S-RBD IgG II (CLIA). Anti-SARS-COV-2 neutralizing S-RBD total Ig tests were performed only in 2022 by Diesse Diagnostica Senese Spa (CHORUS SARS-CoV-2 ,NEUTRALIZING Ab) and Roche Diagnostics (Elecsys Anti-SARS-CoV-2 S). Further details about acceptability % are reported in Table 1.

Discussion

The level of SARS-CoV-2 antibodies was and is still largely employed for the detection of late infection, monitoring of the immune response, and vaccine clinical trials. Considering the variety of available kits and instrumentation on the market, the existence of a quality assurance tool, such as the EQA scheme, is crucial. Hereby, the EQA scheme for the SARS-CoV-2 serological test assigned to Sicilian clinical laboratories in 2020, 2021, and 2022 is reported. 288 laboratories (31 public and 257 private), previously authorized by the Regional Government to perform COVID-19 serological tests, were involved. During the considered period, the SARS-CoV-2 serological test maintained its importance for COVID-19 diagnosis and vaccine response, and thus the laboratories' participation in the EQA scheme continued to be constant over time. More, new analytes were introduced in 2021 (IgG S-RBD) and 2022 (IgG nucleocapsid, IgG S1, and Ig tot S-RBD) to better characterize individual immune responses. Overall, 97 %, 98 %, and 95 % of the participant laboratories received a positive performance evaluation in 2020, 2021, and 2022 respectively. The most used method was chemiluminescent assay (65 % of the total in 2020, 55 % in 2021, and 54 % in 2022). The performance on the analysis of total Ig and IgG improved over time. In particular, the total Ig analysis in 2022 obtained the absolute highest score of acceptability (95.87 %). On the contrary, the performance on the analysis of IgM decreased over time (89.95 %, 88.37 %, and 87.47 % in 2020, 2021, and 2022 respectively). Generally, the results on new targeted analytes (antibodies S-RBD, S1, and nucleocapsid) presented a lower score of acceptability.

The most used kits for the analysis of IgG were: Abbot, BioMerieux, Shenzhen, and Diesse. The first two kits improved their performance over time, but while the use of the first one was reduced, the use of the second one increased. The other two kits worsened their performance, with the Shenzhen kit significantly reducing their diffusion among laboratories in 2022. Shenzhen and Biomerieux were among the most used kits also for the analysis of IgM, with a reduction in performance over time. Abbot confirmed the high diffusion and performance, both improved over time, with the IgM kit. Diesse IgM kit presented a high level of acceptable results and improved its distribution among laboratories. Kits identifying both IgG and IgM were evaluated only in 2020, with Roche being the most diffused and with good performance. The most common kits for IgG S-RBD were Shenzhen, Roche, and Abbot, with the first two improving their performance and the last one significantly reducing its performance, while contemporarily doubling the number of laboratories using it. The evaluation of the analysis of Ig tot S-RBD was performed only during 2022, and it involved only Roche and Diesse kits, with modest results.

Considering the global evaluation of the laboratories, 70 % of the participant laboratories improved their performance in the last year (40 % performed better in 2021 compared to 2020, while 30 % reduced their performance in 2021 and then improved in 2022), while 30 % of the laboratories reduced their performance in 2022 or both in 2021 and 2022. This result could be linked to the lowest acceptability % on the analysis of the new analytes. The monitoring of performances, especially when dealing with new analytes and methods, is crucial in the healthcare system, highlighting once more the importance of the EQA schemes. The outcomes of the EQA, in fact, are fundamental for the improvement process of the laboratories' performance. Furthermore, the results determine the confirmation of the laboratories' authorization to continue their activities for the diagnosis and certification, incentivizing the laboratories in their amelioration process. The incorrect diagnosis had and could still have important implications on vaccination cycles and the now-expired green pass. Through our EQA, we were able to detect instances of non-compliance that were previously overlooked by standard health governance procedures. The participation and the positive performance of EQA schemes are required for the accreditation of laboratories, together with various guidelines and international technical standards of the sector (ISO/IEC 17025, ISO 15189, Joint Commission, etc.) [13, 14].

Even if it has to be ascribed to the amelioration process, this study presents some limitations that need to be considered. The comparison of the results over the years is affected by the variability of parameters evaluated during

Table 1: List of the most utilized reagents and kits for each assay during the period 2020–2022.

Assay	2020		2021		2022		Total	
	Samples, no	Acceptability, %	Samples, no	Acceptability, %	Samples, no	Acceptability, %	Samples, no	Acceptability, %
IgG	**805**	**0**	**583**	**0**	**630**	**91**	**2,018**	**88**
BioMerieux Inc.	188	87	260	88	386	92	834	89
Abbott Diagnostics	239	84	114	85	134	99	487	88
Shenzhen New Industries Biomedical Engineering Co.	243	93	109	82	12	100	364	90
Diesse Diagnostica Senese Spa	82	93	82	93	78	82	242	89
DiaSorin S.p.A.	18	6	12	100			30	43
Immunostics Inc.	12	83					12	83
NovaTec Immundiagnostica GmbH	10	40					10	40
Beckman Coulter (Immunotech Products)			6	100			6	100
DEMEDITEC Diagnostics GmbH	2	50			4	50	6	50
Zhejiang Orient Gene Biotech Co., Ltd.					6	33	6	33
Guangzhou Wondfo Biotech Co., Ltd					4	100	4	100
Siemens (Siemens Healthcare)					4	50	4	50
Beckman Coulter (Beckman Products)					2	0	2	0
Immunospark	2	50					2	50
Ortho Clinical Diagnostics	2	100					2	100
Pantec Srl	2	100					2	100
Sentinel Diagnostics	2	0					2	0
Shanghai Kehua Bio-Engineering Co. Ltd	2	100					2	100
Beijing Lepu Medical Technology Co., Ltd	1	0					1	0
Zhejiang Orient Gene Biotech Co., Ltd.	6	83					6	83
IgM	**657**	**90**	**645**	**88**	**910**	**89**	**2,212**	**89**
Shenzhen New Industries Biomedical Engineering Co.	254	91	221	87	296	86	771	88
BioMerieux Inc.	182	90	209	86	216	82	607	86
Abbott Diagnostics	108	90	138	92	242	92	488	91
Diesse Diagnostica Senese Spa	73	97	77	91	128	91	278	92
Immunostics Inc.	16	88					16	88
NovaTec Immundiagnostica GmbH	10	70					10	70
AESKU.DIAGNOSTICS					8	100	8	100
DEMEDITEC Diagnostics GmbH	2	0			4	100	6	67
Pantec Srl	2	0			4	0	6	0
Citest Diagnostics Inc.					4	100	4	100
DiaSorin S.p.A.					4	100	4	100
Pishtaz Teb Zaman Diagnostics	4	50					4	50
Zhejiang Orient Gene Biotech Co., Ltd.					4	100	4	100
Immunospark	2	0					2	0
Sentinel Diagnostics	2	100					2	100

Table 1: (continued)

Assay	2020		2021		2022		Total	
	Samples, no	Acceptability, %	Samples, no	Acceptability, %	Samples, no	Acceptability, %	Samples, no	Acceptability, %
Shanghai Kehua Bio-Engineering Co. Ltd	2						2	100
IgG+IgM	**76**	**93**					**76**	**93**
DASIT	6	83					6	83
Roche Diagnostics	57	95					57	95
Screen Italia	4	100					4	100
Siemens (Siemens Healthcare)	3	100					3	100
IgG+IgA+IgM	**253**	**89**			**242**	**96**	**495**	**93**
Ortho Clinical Diagnostics	6	0					6	0
Roche Diagnostics	247	91			242	96	489	94
IgG nucleocapsid					**14**	**86**	**14**	**86**
Bio-Rad Laboratories					14	86	14	86
IgG S1					**14**	**86**	**14**	**86**
Bio-Rad Laboratories					14	86	14	86
IgG S-RBD			**307**	**82**	**408**	**88**	**715**	**85**
Shenzhen New Industries Biomedical Engineering Co.			156	79	226	93	382	87
Roche Diagnostics			90	80	66	88	156	83
Abbott Diagnostics			46	89	96	77	142	81
Diesse Diagnostica Senese Spa			13	92			13	92
Bio-Rad Laboratories					8	100	8	100
DiaSorin S.p.A.					6	100	6	100
DRG International, Inc.					4	50	4	50
Beckman Coulter (Immunotech Products)			2	100			2	100
Fujirebio Inc.					5	50	2	50
Ig tot S-RBD					**148**	**82**	**148**	**82**
Roche Diagnostics					100	82	100	82
Diesse Diagnostica Senese Spa					48	83	48	83
Total	**1,791**		**1,535**		**2,366**		**5,692**	

time (f.e. IgG+IgM and IgG+IgM+IgA were not evaluated in 2021, and nucleocapsid and RBD component quantification was evaluated only in 2022). In addition, the methods used by the laboratories were not standardized, thus a consensus level was not always reached and an evaluation of the results was not always possible. However, one of the aims of an EQA scheme is to identify the best protocols and standardize the processes. Thus, these limitations can be overcome by continuing to perform this kind of scheme.

The results of this study showed that EQA schemes should be adopted as a recognized standard for authorizing and accrediting healthcare services, as well as a means of continuously verifying compliance with necessary requirements. Only through the effort of laboratory professionals, and the extension of the EQA scheme, a better harmonization of methods, protocols, and thus results, to guarantee a better healthcare system, will be possible [15]. This approach would ensure the provision of patient-centered care and support the objectives of healthcare institutions.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: The authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The authors state no conflict of interest.
Research funding: None declared.
Data availability: The raw data can be obtained on request from the corresponding author.

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