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Systematic review of diagnostic accuracy of DiaSorin Liaison SARS-CoV-2 antigen immunoassay

Giuseppe Lippi[1,2], Brandon M. Henry[1,3,4], Mario Plebani[5*], Khosrow Adeli[1,6*]

[1] *IFCC Task Force on COVID-19, Milano, Italy*
[2] *Section of Clinical Biochemistry, University of Verona, Verona, Italy*
[3] *Clinical Laboratory, Division of Nephrology and Hypertension, Cincinnati Children's Hospital Medical Center, Cincinnati OH, USA*
[4] *Disease Intervention & Prevention and Population Health Programs, Texas Biomedical Research Institute, San Antonio, Texas, USA*
[5] *Department of Medicine-DIMED, University of Padova.*
[6] *Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada*
[*] *These authors share senior authorship in this work.*

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Corresponding author:
Prof. Giuseppe Lippi
Section of Clinical Biochemistry
University Hospital of Verona
Piazzale L.A. Scuro, 10
37134 Verona
Italy
Phone: 0039-045-8122970
Fax: 0039-045-8124308
E-mail: giuseppe.lippi@univr.it

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ABSTRACT

Background

Quantification of SARS-CoV-2 antigens by means of rapid, high-throughput and fully-automated techniques has been proposed as a feasible alternative to overcome the current shortage of resources for routine molecular diagnostics. To this end, we provide here a systematic review of diagnostic accuracy of DiaSorin Liaison SARS-CoV-2 antigen immunoassay.

Methods

An electronic search was conduced in Medline and Scopus, with no language or date restrictions (up to January 20, 2022), for identifying all published studies articles in which the diagnostic performance of the DiaSorin Liaison SARS-CoV-2 antigen immunoassay was compared with molecular diagnostic techniques.

Results

The electronic search identified a final number of 11 studies, totalling 4449 oro- and naso-pharyngeal specimens. The pooled diagnostic sensitivity, specificity and area under the curve (AUC) of the Liaison SARS-CoV-2 antigen immunoassay in all samples were 0.51 (95%CI, 0.49-0.54), 1.00 (95%CI, 1.00-1.00) and 0.994 (95%CI, 0.990-0.998), respectively, whilst the overall concordance with molecular diagnostics was 82.1%. The pooled diagnostic sensitivity, specificity and AUC of the Liaison SARS-CoV-2 antigen immunoassay in specimens with high viral load (i.e., cycle threshold values <25-30) were 0.79 (95%CI, 0.75-0.82), 1.00 (95%CI, 0.99-1.00) and 0.911 (95%CI, 0.879-0.943), respectively, whilst the overall concordance with molecular diagnostics in such samples increased to 94.2%.

Conclusion

The results of this systematic literature review suggest that there is sufficient accuracy of the DiaSorin Liaison SARS-CoV-2 antigen immunoassay in samples with high viral loads that would enable its reliable usage for identifying superspreaders, who are responsible for the vast majority of transmission events.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), a life-threatening infectious disease that first appeared at the end of 2019, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and now responsible for the worst human pandemic since the Spanish flu, which emerged over one century ago [1]. High rates of community transmission around the world are driving an extremely high number of daily positive cases and large demand for testing, contact tracing and isolation procedures, which are now further compounded by the emergence of highly mutated and infective variants such as the Omicron (B.1.1.529) lineage [2]. This unprecedented demand for testing has disrupted the capacity of most clinical laboratories to provide an efficient response to these immense test volumes. According to the Coronavirus Resource Center maintained by the John Hopkins University, over 573 million new cases of SARS-CoV-2 infection have been diagnosed up to the end of July 2022 [3], which represents only the tip of the iceberg of the huge number of diagnostic tests that have been performed (between 5- to 10-fold higher). It is hence not surprising to read the results of an ongoing worldwide survey promoted by the American Association for Clinical Chemistry (AACC), which highlights that nearly one-third of all responding laboratories are having issues acquiring reagents and test kits for SARS-CoV-2 diagnostics, and around 30% of labs also have a >1 week turnaround time for processing all the specimens that have been delivered for testing [4]. Moreover, diagnostic labs are also not immune from labor shortages, also in part now driven by widespread transmission of the Omicron variant and need for quarantining. This generated backlog of unanalyzed samples not only delays the diagnosis of several COVID-19 cases who may need timely and early treatment, but also makes it impossible to promptly isolate or quarantine asymptomatic or mildly symptomatic cases, who may be responsible for spreading the outbreak further, especially those bearing high viral loads [5].

One of the major COVID-19 testing challenges is the fact that the reference method for diagnosing SARS-CoV-2 infection encompasses detection (and quantification) of viral RNA in nasopharyngeal specimens, which is unsustainable for clinical laboratories when faced with enormous volumes of diagnostic samples with need for short turnaround time [6]. To overcome this limitation, quantification of SARS-CoV-2 antigens

has been proposed as a possible alternative to viral RNA detection [7]. The use of the so-called antigen rapid detection tests (Ag-RDTs) for quick SARS-CoV-2 diagnostics is now widespread, though the often-insufficient analytical sensitivity, arbitrary interpretation, along with the possibility to obtain only qualitative results are well-recognized and still unresolved drawbacks [8], which may be potentially offset by developing robust, quantitative, accurate and reproducible laboratory-based immunoassays [9].

The DiaSorin Liaison SARS-CoV-2 Antigen test is a fully-automated chemiluminescence sandwich-immunoassay (CLIA) for detection of SARS-CoV-2 nucleocapsid (N) protein in nasal swab and nasopharyngeal swabs. According to manufacturer's specifications [10], the test can be adapted on DiaSorin LIAISON XL and LIAISON platforms, has a throughput of 136 tests per hour (results are available on average in 40 min), the analytical sensitivity (limit of detection [LOD]) is 22.0 Median Tissue Culture Infectious Dose ($TCID_{50}$)/mL, the cut-off is 200 $TCID_{50}$/mL, whilst the overall imprecision is 11-15%. Additional information on preanalytical issues, buffers and biosafety requirements can be retrieved from the package insert [10]. As the DiaSorin immunochemistry platforms are already widespread in many clinical laboratories worldwide, we provide here a systematic review of diagnostic accuracy of DiaSorin Liaison SARS-CoV-2 Antigen Immunoassay. Clearly, defining the diagnostic accuracy of this test will help informing and guiding its clinical use.

MATERIALS AND METHODS

We carried out an electronic search in Scopus and Medline (PubMed interface) using the keywords "Liaison" OR "DiaSorin" AND "antigen" AND "SARS-CoV-2" or "COVID-19" within all search fields and without language or date restrictions (i.e., up to January 20, 2022), aimed at identifying all studies in which the diagnostic performance of Liaison SARS-CoV-2 antigen immunoassay was compared with a reference molecular diagnostic technique. Two authors (G.L. and B.M.H.) screened articles by title, abstract and full text (when available) were identified based on the predefined search criteria, selecting studies in which the rates of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) cases based on manufacturer's recommended cut-off (i.e., 200 $TCID_{50}$/mL) were provided or could be extrapolated from data reported in the study. The reference lists were also hand-searched to screen for further potentially eligible investigations. The data reported in each investigation was then included in a pooled analysis for estimation of diagnostic sensitivity, specificity, and accuracy (Summary Receiver Operating Characteristic Curve; SROC; Agreement; Kappa statistics) with 95% confidence interval (95%CI). A subgroup analysis was performed in samples with higher viral load (when available). A random effects model was used for pooling data, whilst the heterogeneity was calculated using χ^2 test and I^2 statistic. The statistical analysis was carried out using MetaDiSc 1.4 (Unit of Clinical Biostatistics team of the Ramón y Cajal Hospital, Madrid, Spain) [11]. The study was conducted in agreement with the Declaration of Helsinki and within the terms of local legislation.

RESULTS

The search of electronic databases using the predefined criteria allowed for the identification of 54 publications after removing duplicate studies between the two scientific platforms. Forty-three publications were excluded because they did not report specific data regarding the diagnostic performance of Liaison SARS-CoV-2 antigen immunoassay (n=33), did not perform a clinical evaluation (n=9) or were correspondence/letter to the editor (n=1). Thus, a final

number of 11 studies, totalling 4449 specimens, was included in our pooled analysis [12-22].

Table 1 summarizes the principal aspects of all selected studies. Briefly, three studies were conducted in Germany, two each in Italy and Kuwait, and one each in Belgium, France, Spain and the Netherlands. In all but two studies, the diagnostic performance of Liaison SARS-CoV-2 antigen immunoassay was tested in nasopharyngeal swabs, whilst in the two other studies oro-nasopharyngeal swabs [20,22] were employed. The range of viral load (when available) has been summarized in Table 1, together with the sample size which ranged between 119 and 897.

A sub-analysis of diagnostic performance in specimens with high viral load (i.e., Ct values <25-30) could be performed including 7/11 studies (n=2626 specimens), as summarized in Table 2.

Table 1 **Summary of studies that investigated the cumulative diagnostic performance of the fully automated DiaSorin Liaison SARS-CoV-2 Antigen Immunoassay**

Study	Country	Sample matrix	Sample size	Molecular assay (gene targets)	Range of viral load
Alghounaim et al., 2021 (12)	Kuwait	Nasopharyngeal swabs	897	Applied Biosystems TaqPath COVID-19 RT PCR kit (ORF, N and S)	Unspecified
Altawalah et al., 2021 (13)	Kuwait	Nasopharyngeal swabs	300	Thermo Fisher TaqPath COVID-19 multiplex real-time RT-PCR test (Orf1ab, N and S)	11-28 Ct
Baj et al., 2021 (14)	Italy	Nasopharyngeal swabs	119	Abbott real-time SARS-CoV-2 assay (N and RdRP)	3-30 Ct
Fernandez-Rivas et al., 2022 (15)	Spain	Nasopharyngeal swabs	861	Seegene Allplex SARS-CoV-2 Assay (E and N)	11-40 Ct
Fiedler et al., 2021 (16)	Germany	Nasopharyngeal swabs	182	Altona RealStar SARS-CoV-2 RT-PCR Kit (E, N, S and RdRP)	~1×102-~1.5×108 copies/mL
Hartard et al., 2021 (17)	France	Nasopharyngeal swabs	378	In-house - Pasteur Institut (RdRP)	19±5 Ct
Häuser et al., 2021 (18)	Germany	Nasopharyngeal swabs	223	NeuMoDx Molecular SARS-CoV-2 Test Strip (N and Nsp2) and Qiagen QIAamp Viral RNA Mini Kit (E and RdRP)	14-36 Ct

Lefever et al., 2021 (19)	Belgium	Nasopharyngeal swabs	410	Certest Viasure SARSCoV-2 real-time PCR detection kit (N1 and N2)	10-40 Ct
Osterman et al., 2021 (20)	Germany	Oro-nasopharyngeal swabs	410	Multiple assays - Seegene Allplex, Roche Cobas and Cepheid GeneXpert System (unspecified gene targets)	0.8×102-1.6×109 Geq/mL
Salvagno et al., 2021 (21)	Italy	Nasopharyngeal swabs	421	Altona RealStar SARS-CoV-2 RT-PCR Kit (E and S)	16-40 Ct
Van der Moeren et al., 2021 (22)	The Netherlands	Oro-nasopharyngeal swabs	248	Abbott Alinity M SARS-CoV-2 Assay (N and RdRP)	12-39 Ct

Ct, cycle threshold.

Table 2 **Summary of studies that investigated the diagnostic performance of the fully automated DiaSorin Liaison SARS-CoV-2 Antigen Immunoassay in nasopharyngeal samples with high viral load (i.e., cycle threshold values <25-30)**

Study	Country	Sample matrix	Sample size	Cut-off of viral load
Alghounaim et al., 2021	Kuwait	Nasopharyngeal swabs	881	<25 Ct
Altawalah et al., 2021	Kuwait	Oro-nasopharyngeal swabs	300	<29 Ct
Baj et al., 2021	Italy	Nasopharyngeal swabs	94	<26 Ct
Fernandez-Rivas et al., 2022	Spain	Nasopharyngeal swabs	732	<30 Ct
Häuser et al., 2021	Germany	Oro-nasopharyngeal swabs	131	<30 Ct
Salvagno et al., 2021	Italy	Nasopharyngeal & oropharyngeal swabs	421	<30 Ct
Van der Moeren et al., 2021	The Netherlands	Oro-nasopharyngeal swabs	74	<30 Ct

Ct, cycle threshold.

The pooled cumulative diagnostic performance of Liaison SARS-CoV-2 antigen immunoassay in all oro- and naso-pharyngeal samples is shown in Figure 1. The pooled diagnostic sensitivity, specificity and AUC in all samples were 0.51 (95%CI, 0.49-0.54; I^2, 96.4%), 1.00 (95%CI, 1.00-1.00; I^2, 0.0%) and 0.994 (95%CI, 0.990-0.998), respectively. The overall concordance of this immunoassay with a reference molecular technique was 82.1% (kappa statistics, 0.57 and 95%CI, 0.55 to 0.59), thus indicating moderate agreement [23]. The pooled cumulative diagnostic performance of Liaison SARS-CoV-2 antigen immunoassay in specimens with high viral load (i.e., Ct values <25-30) is reported in figure 2. The pooled diagnostic sensitivity, specificity and AUC in these subsets of samples were 0.79 (95%CI, 0.75-0.82; I^2, 68.5%), 1.00 (95%CI, 0.99-1.00; I^2, 74.4%) and 0.911 (95%CI, 0.879-0.943), respectively. The overall concordance of this immunoassay with a reference molecular technique was 94.2% (kappa statistics, 0.84 and 95%CI, 0.81 to 0.86), thus indicating almost perfect agreement in the presence of high viral load [23].

DISCUSSION

Several lines of evidence now attest that providing reliable and timely results of SARS-CoV-2 testing not only enables a more appropriate and rapid management of symptomatic cases, as well as prompt isolation of potentially contagious asymptomatic or mildly symptomatic cases, [24], but also allows to efficiently predict the pressure on healthcare systems in terms of overall hospitalizations, intensive care unit (ICU) admissions and even mortality [25]. The pursuit of these otherwise unquestionably essential outcomes is now becoming an insurmountable effort. In the context of the ongoing COVID-19 pandemic and the attendant challenge imposed by the nearly 3 million new daily infections to laboratory medicine and the healthcare system as a whole, the availability of rapid, high-throughput and accurate techniques continues to be pursued as a primary objective for scaling up diagnostic capacities across many different settings, including in hospital laboratories [26]. Among the various fully automated SARS-CoV-2 antigen techniques that have been recently developed, validated and commercialized, the Liaison SARS-CoV-2 two-step sandwich chemiluminescence immunoassay (CLIA) has the potentiality to provide fast and high-throughput COVID-19 diagnostics in many clinical laboratories equipped with Liaison immunochemistry platforms.

With respect to the clinical performance of this method, the results of our pooled analysis demonstrate an overall satisfactory diagnostic accuracy (AUC, 0.994), absolute diagnostic specificity (i.e., 100%) compared to reference molecular techniques, yet compounded by a limited diagnostic sensitivity - slightly above 50% - which would not allow to conclude that it may be an adequate replacement of nucleic acid amplification test (NAAT), and is probably dependent on the use of a suboptimal (i.e., too high) diagnostic cutoff. Nonetheless, our pooled analysis in samples with high viral load (i.e., Ct <25-30) has evidenced that the still optimal diagnostic accuracy (AUC, 0.911) and specificity (i.e., 100%) are now combined with a satisfactory diagnostic sensitivity (i.e., close to 80%). This is a foremost aspect in terms of epidemic control, since the likelihood of obtaining a positive SARS-CoV-2 culture is strictly dependent on the viral load, with such possibility approximating zero in respiratory samples with Ct ≥30 [27,28]. Accordingly, Hirschfeld et al. reported that the Ct values corresponding to SARS-CoV-2 infectiousness reported in clinical studies would more frequently lie between 29-31, with very low probability that patients with higher Ct values (and thereby lower viral load) would carry a relevant infective risk [29].

A crucial question can hence be finally asked; what could be the value and the most suitable placement of this method within the COVID-19

Figure 1 **Cumulative diagnostic sensitivity, specificity and accuracy (Summary Receiver Operating Characteristic Curve; SROC) with 95% confidence interval (95%CI) of the fully automated DiaSorin Liaison SARS-CoV-2 Antigen Immunoassay for diagnosing SARS-CoV-2 infection in nasopharyngeal samples**

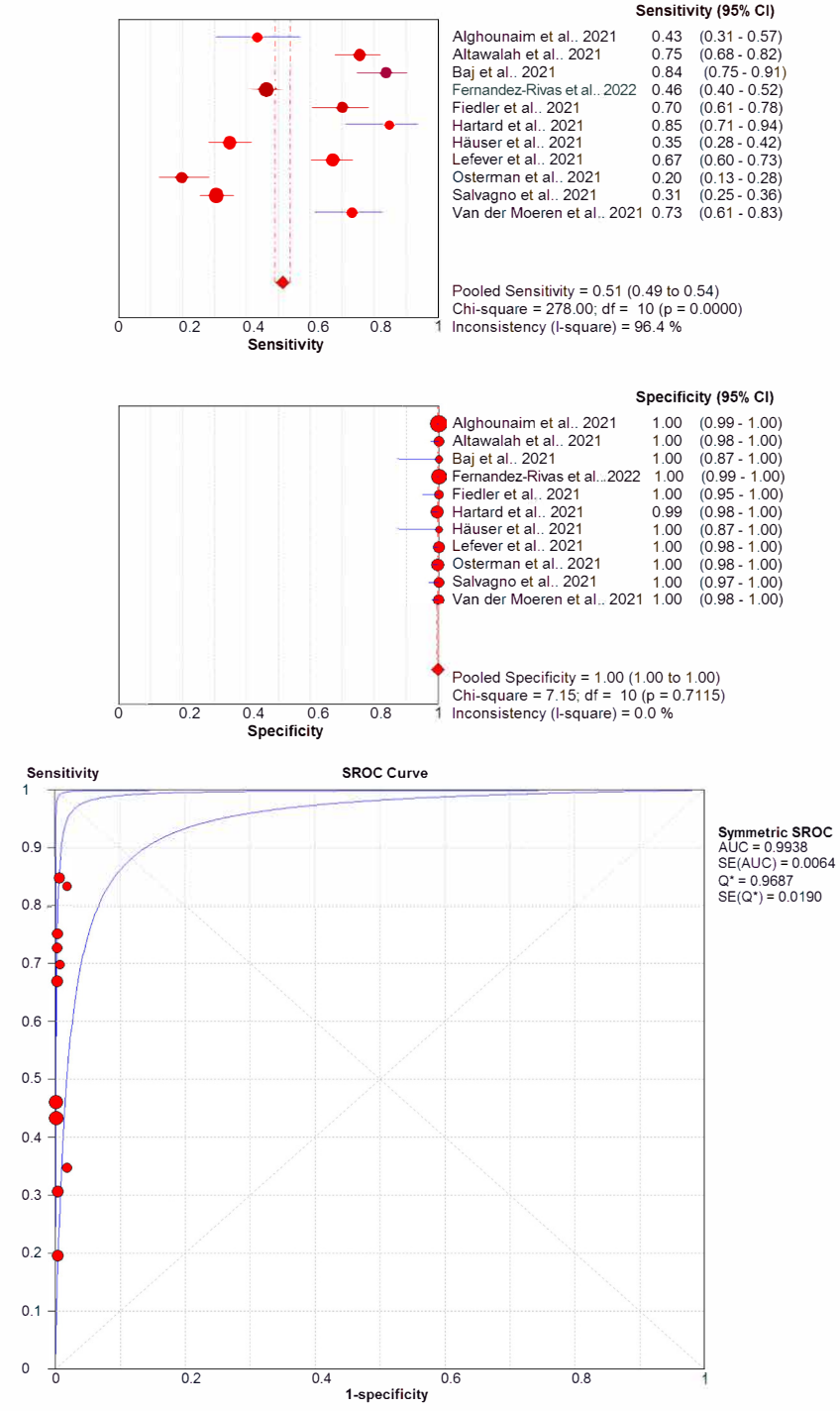
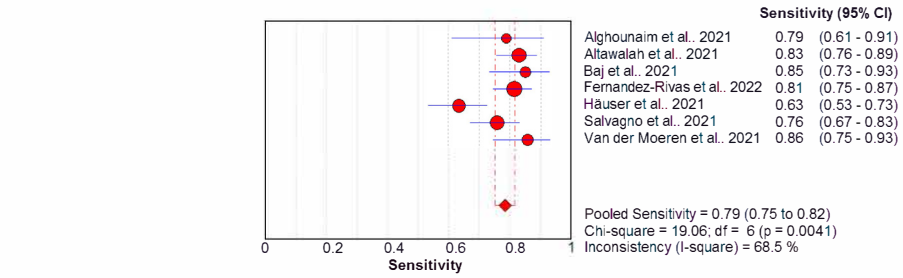
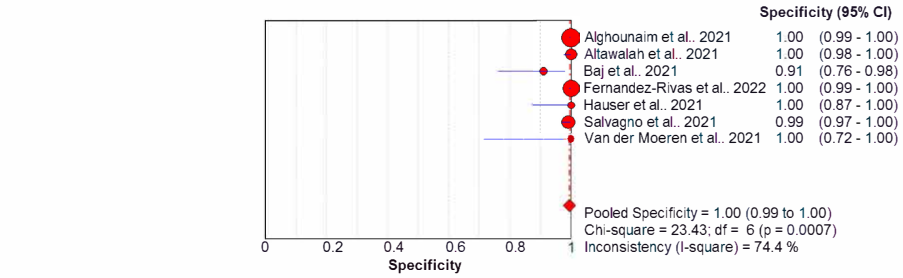
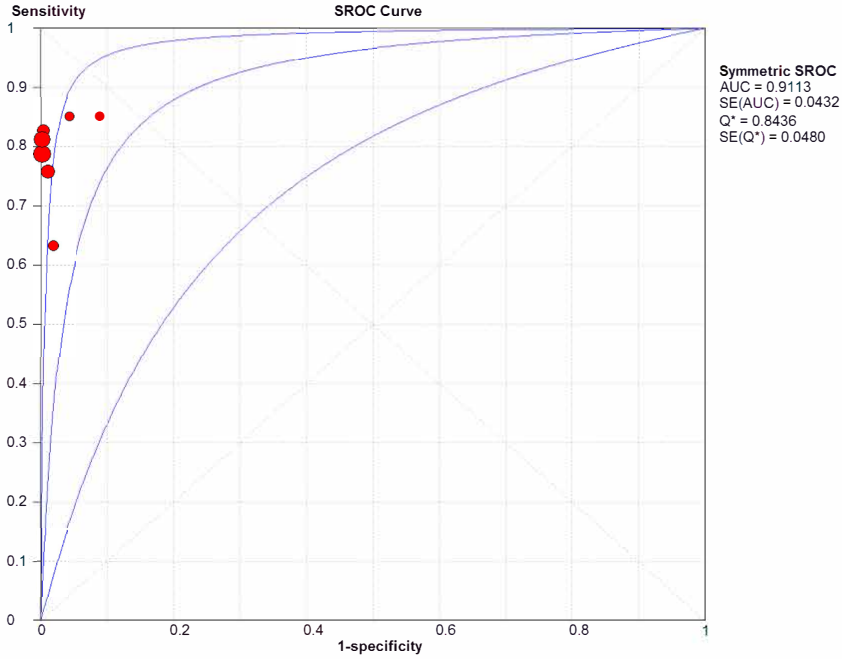


Figure 2 **Diagnostic sensitivity of the fully automated DiaSorin Liaison SARS-CoV-2 Antigen Immunoassay for diagnosing SARS-CoV-2 infection in nasopharyngeal samples with high viral load (i.e., cycle threshold values <25-30). The three lines represent the mean AUC and its 95% confidence interval.**







diagnostic strategy? As noted earlier, it is unlikely that this and other SARS-CoV-2 CLIAs will replace molecular techniques for diagnosing all SARS-CoV-2 infections as they do not have adequate sensitivity. Nonetheless, their higher accuracy at higher viral load thresholds would suggest that SARS-CoV-2 antigen immunoassays could be used for identifying the so called "super(viral)-carriers", who are responsible for the vast majority of transmission events (up to 80%), especially when asymptomatic or pre-symptomatic [5,30], up to the very unwarranted corollary that new infections caused by a "super-spreader" may be more likely to be highly contagious [31]. To this end, the use of these techniques for contact tracing and mass testing or population screening would enable to save precious personnel, technical and economic resources, thus prioritizing molecular testing in those cases where seems more urgently needed (i.e., for diagnosing acute infection in symptomatic or highly suggestive cases). Moreover, the high throughput of this technique can help enable multiple testing over the course of infection (when a first assay has been performed outside a diagnostic window) or several days following a high-risk exposure due to a variable incubation period, as well as be employed in strategies to test out of quarantine. However, it must be clearly noted that a negative results of a SARS-CoV-2 antigen test does not enable to definitely rule out an acute infection, thus the use of a more accurate NAAT would still be advisable in highly suspected cases with equivocal test results. It is also noteworthy that the diagnostic sensitivity of this SARS-CoV-2 antigen immunoassay using the recommended cut-off in samples with high viral load (i.e., 0.79) seems lower than that displayed by automated methods produced by other manufacturers such as Ortho VITROS (i.e., 0.98) [32], Fujirebio Lumipulse (i.e., ~1.00) [33], LumiraDX (i.e., ~1.00) [35], Roche Elecsys (i.e., 0.95) [35] and S-PLEX SARS-CoV-2 N (i.e., ~1.00) [36].

One important aspect that needs to be highlighted is that further studies shall be urgently planned to verify how the analytical and diagnostic performance of this and other immunoassays may be modified by emergence of new variants of concerns such as the former Delta (B.1.617.2) and the new Omicron (B.1.1.529) lineages.

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Ethics statements

This analysis was based on electronic searches in unrestricted, publicly available repositories, so that no informed consent or ethical committee approvals were needed.

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