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Head-to-head comparison of two rapid high-throughput automated electrochemiluminescence immunoassays targeting total antibodies to the SARS-CoV-2 nucleoprotein and spike protein receptor binding domain

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ABSTRACT

Background: Accurate anti-SARS-CoV-2 assays are needed to inform diagnostic, therapeutic, and public health decisions. The first manufacturer-independent head-to-head comparison of two rapid high-throughput automated electrochemiluminescence double-antigen sandwich immunoassays targeting total anti-SARS-CoV-2 antibodies against two different viral proteins, Elecsys Anti-SARS-CoV-2 (Elecsys-N) and Elecsys Anti-SARS-CoV-2 S (Elecsys-S) (Roche Diagnostics), was performed in a routine setting during the exponential growth phase of the epidemic’s second wave.

Methods: The diagnostic specificity of Elecsys-N and Elecsys-S was initially evaluated on a panel of 572 pre-COVID-19 samples, showing 100 % specificity of both assays. Elecsys-N/Elecsys-S head-to-head comparison used 3,416 consecutive blood samples from individuals that were tested for the presence of anti-SARS-CoV-2 within commercial out-of-pocket serologic testing.

Results: Elecsys-N/Elecsys-S head-to-head comparison showed overall agreement of 98.68 % (3,371/3,416; 95 % CI, 98.23–99.03 %), positive agreement of 95.16 % (884/929; 95 % CI, 93.52–96.41 %), and a high kappa value of 0.996 (95 % CI, 0.956–0.976). Previous SARS-CoV-2 PCR positivity was identified in 14/24 (58.3 %) Elecsys-N negative/Elecsys-S positive individuals and in 4/21 (19.0 %) Elecsys-N positive/Elecsys-S negative individuals.

Conclusion: The first Elecsys-N/Elecsys-S head-to-head comparison showed excellent agreement of two highly specific and rapid high-throughput automated anti-SARS-CoV-2 assays. An important question is whether laboratories offering two different antibody assays could benefit from combining the assays; if so, should use be concomitant or sequential—and, in the latter case, in which order? Based on our results, we favor concomitant over sequential Elecsys-N/Elecsys-S use when testing individuals for anti-SARS-CoV-2 antibodies in high-incidence settings; for example, during the exponential or stationary growth phase of the COVID-19 epidemic.

1. Introduction

The availability of assays to detect antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) created excitement and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the public [1]. Unfortunately, early in the pandemic, the global market and hope among the laboratory community, government leaders, and the
Due to the inability of obtaining follow-up sample(s) from in
eligible for PCR-testing; or pure curiosity.

requested out-of-pocket anti-SARS-CoV-2 testing for several reasons:
COVID-19 or clinically compatible but virologically non-confirmed
travel purposes; to check serological response after PCR-confirmed
contrast to SARS-CoV-2 RNA testing [18], which is fully covered by
receptor binding domain (RBD), launched in Europe in September 2020. It received FDA EUA on November 25, 2020, and CE mark on September
17, 2020. The assay has been extensively evaluated by the manufacturer,
showing 99.98 % (95 % CI, 99.91–100 %) specificity on 5,991
samples and 98.8 % (95 % CI, 98.1–99.3 %) sensitivity on 1,423 samples
obtained 14 days or later after SARS-CoV-2 PCR-confirmation. Elecsys-N has also been evaluated in several manufacturer-
independent studies, with diagnostic specificity and sensitivity values spanning claims made by the manufacturer in most studies [1,5,7–16], and it is consequently considered one of the most appropriate assays for seroprevalence surveys, especially in low-prevalence settings [6,17].

Elecsys-S is an assay for quantitative detection (linear range 0.4–250 U/mL) of total anti-SARS-CoV-2 antibodies against the spike (S) protein receptor binding domain (RBD), launched in Europe in September 2020. It received FDA EUA on November 25, 2020, and CE mark on September 17, 2020. The assay has been extensively evaluated by the manufacturer, showing 99.98 % (95 % CI, 99.91–100 %) specificity on 5,991 samples and 98.8 % (95 % CI, 98.1–99.3 %) sensitivity on 1,423 samples obtained 14 days or later after SARS-CoV-2 PCR-confirmation. As far as we know, no Elecsys-S evaluation data have been published in peer-reviewed literature yet.

This study evaluated Elecsys-N and Elecsys-S head-to-head in a routine setting during the exponential growth phase of the epidemic’s second wave. During the 84-day study period, the cumulative number of PCR-confirmed COVID-19 cases in Slovenia increased 18.4-fold, from 6,105 to 112,048 (https://www.nijz.si/sl/dnevno-spremljanje-okuzb-s-
Pneumonia caused by Mycoplasma pneumoniae
Laboratory-confirmed pertussis
PCR-confirmed viral non-SARS-CoV-2 respiratory infections with coronavirus HKU1 (n = 1), NL63 (n = 5), 229E (n = 3), or OC43 (n = 1), influenza virus A (n = 3), influenza virus B (n = 4), respiratory syncytial virus (n = 4), or rhinoviruses (n = 7).

Table 1

| Panel/Cohort | Elecsys-N | Elecsys-S |
|--------------|-----------|-----------|
| Laboratory-confirmed acute human cytomegalovirus (CMV) (n = 6) or Epstein-Barr virus (EBV) (n = 16) infection | 22 | 0 |
| Pneumonia caused by Mycoplasma pneumoniae | 15 | 0 |
| Laboratory-confirmed pertussis | 7 | 0 |
| PCR-confirmed viral non-SARS-CoV-2 respiratory infections with coronavirus HKU1 (n = 1), NL63 (n = 5), 229E (n = 3), or OC43 (n = 1), influenza virus A (n = 3), influenza virus B (n = 4), respiratory syncytial virus (n = 4), or rhinoviruses (n = 7) | 28 | 0 |
| Serum samples collected for different medical reasons (testing for HIV (n = 210) and serological markers of viral hepatitis (n = 290)) before June 2019 | 500 | 0 |
| Total number of samples | 572 | 0 |

Biological Pharmacy Enterprise Co, Beijing, China) detecting total antibodies against the S protein RBD [19–22] and Architect SARS-CoV-2 IgG (Abbott; Abbott Diagnostics, IL, USA) detecting IgG antibodies against N protein [5,8,10,13,14]. Furthermore, 10 % and 5 % randomly selected samples with Elecsys-N/Elecsys-S concordantly positive and concordantly negative results, respectively, were additionally tested by Wantai and Abbott.

A contingency table was constructed to assess overall and positive agreements with 95 % CIs. The level of agreement between both tests was assessed using kappa statistics. All statistical analyses were performed using Excel (Microsoft, Redmond, WA, USA) and R software version 3.2.5 (Free Software Foundation, Boston, MA, USA).

3. Results

Internal evaluation on the panel of 572 pre–COVID-19 samples showed 100 % specificity of both assays (Table 1). As shown in Table 2, head-to-head Elecsys-N/Elecsys-S comparison showed overall agreement of 98.68 % (3,371/3,416; 95 % CI, 98.23–99.03 %), positive agreement of 95.16 % (3,371/3,416; 95 % CI, 94.86–95.46 %) and a high kappa value of 0.996 (95 % CI, 0.996–0.997). A total of 45/3,416 discordant results were observed (Tables 2 and 3).

Of 24 Elecsys-N negative / Elecsys-S positive samples, 23 (95.8 %) tested Wantai positive and all Abbott negative. Previous SARS-CoV-2 PCR positivity was identified in 14/24 (58.3 %) of Elecsys-N negative / Elecsys-S positive individuals (Table 3).

Of 21 Elecsys-N positive / Elecsys-S negative samples, 17 (80.9 %) tested Abbott positive and all but one tested Wantai negative. Previous SARS-CoV-2 PCR positivity was identified in 4/21 (19.0 %) of Elecsys-N positive/Elecsys-S negative individuals (Table 3).
All 124 Elecsys-N/Elecsys-S concordantly negative samples tested also negative using both Wantai and Abbott. Out of 87 Elecsys-N/Elecsys-S concordantly positive samples, 87 (100%) and 85 (97.7%) tested positive using Wantai and Abbott, respectively.

4. Conclusions

Accurate anti-SARS-CoV-2 assays are needed to inform diagnostic, therapeutic, and public health decisions [5,23]. When selecting antibody assays, virologists must consider not only sensitivity and specificity, but also prevalence in the tested population, the intended use of results, sample throughput, test complexity, reagent and instrument availability, and cost per reportable result [5]. Especially assays’ throughput and specificity are crucial parameters if large-scale antibody testing is desirable in a low-prevalence pre-vaccination environment [9,23].

This comparison showed high overall and positive agreement of two highly specific and rapid high-throughput automated assays. Equal distribution of Elecsys-N/Elecsys-S discordant results was observed.

Table 2

| Sample ID | Nasopharyngeal swab collection date (M/D/Y) | Elecsys-N Result | Elecsys-S Result | SARS-CoV-2 RNA PCR Result |
|-----------|--------------------------------------------|------------------|------------------|---------------------------|
| 1 | 10/28/2020 | POS | POS | 09/16/2020 | POS |
| 2 | 10/29/2020 | POS | POS | 09/16/2020 | POS |
| 3 | 10/30/2020 | POS | POS | 09/16/2020 | POS |
| 4 | 11/01/2020 | POS | POS | 09/16/2020 | POS |
| 5 | 11/02/2020 | POS | POS | 09/16/2020 | POS |
| 6 | 11/03/2020 | POS | POS | 09/16/2020 | POS |
| 7 | 11/04/2020 | POS | POS | 09/16/2020 | POS |
| 8 | 11/05/2020 | POS | POS | 09/16/2020 | POS |
| 9 | 11/06/2020 | POS | POS | 09/16/2020 | POS |
| 10 | 11/07/2020 | POS | POS | 09/16/2020 | POS |
| 11 | 11/08/2020 | POS | POS | 09/16/2020 | POS |
| 12 | 11/09/2020 | POS | POS | 09/16/2020 | POS |
| 13 | 11/10/2020 | POS | POS | 09/16/2020 | POS |
| 14 | 11/11/2020 | POS | POS | 09/16/2020 | POS |
| 15 | 11/12/2020 | POS | POS | 09/16/2020 | POS |
| 16 | 11/13/2020 | POS | POS | 09/16/2020 | POS |
| 17 | 11/14/2020 | POS | POS | 09/16/2020 | POS |
| 18 | 11/15/2020 | POS | POS | 09/16/2020 | POS |
| 19 | 11/16/2020 | POS | POS | 09/16/2020 | POS |
| 20 | 11/17/2020 | POS | POS | 09/16/2020 | POS |
| 21 | 11/18/2020 | POS | POS | 09/16/2020 | POS |
| 22 | 11/19/2020 | POS | POS | 09/16/2020 | POS |
| 23 | 11/20/2020 | POS | POS | 09/16/2020 | POS |
| 24 | 11/21/2020 | POS | POS | 09/16/2020 | POS |
| 25 | 11/22/2020 | POS | POS | 09/16/2020 | POS |
| 26 | 11/23/2020 | POS | POS | 09/16/2020 | POS |
| 27 | 11/24/2020 | POS | POS | 09/16/2020 | POS |
| 28 | 11/25/2020 | POS | POS | 09/16/2020 | POS |
| 29 | 11/26/2020 | POS | POS | 09/16/2020 | POS |
| 30 | 11/27/2020 | POS | POS | 09/16/2020 | POS |
| 31 | 11/28/2020 | POS | POS | 09/16/2020 | POS |
| 32 | 11/29/2020 | POS | POS | 09/16/2020 | POS |
| 33 | 11/30/2020 | POS | POS | 09/16/2020 | POS |
| 34 | 12/01/2020 | POS | POS | 09/16/2020 | POS |
| 35 | 12/02/2020 | POS | POS | 09/16/2020 | POS |
| 36 | 12/03/2020 | POS | POS | 09/16/2020 | POS |
| 37 | 12/04/2020 | POS | POS | 09/16/2020 | POS |
| 38 | 12/05/2020 | POS | POS | 09/16/2020 | POS |
| 39 | 12/06/2020 | POS | POS | 09/16/2020 | POS |
| 40 | 12/07/2020 | POS | POS | 09/16/2020 | POS |
| 41 | 12/08/2020 | POS | POS | 09/16/2020 | POS |
| 42 | 12/09/2020 | POS | POS | 09/16/2020 | POS |
| 43 | 12/10/2020 | POS | POS | 09/16/2020 | POS |
| 44 | 12/11/2020 | POS | POS | 09/16/2020 | POS |
| 45 | 12/12/2020 | POS | POS | 09/16/2020 | POS |

Table 3

Overview of anti-SARS-CoV-2 Elecsys-N and Elecsys-S testing results, available SARS-CoV-2 RNA PCR testing results and results of supplemental testing using Abbott and Wantai assays in 45 individuals with Elecsys-N/Elecsys-S discordant results. For SARS-CoV-2 RNA-negative individuals the date of the first recorded PCR positive result is presented, and for SARS-CoV-2 RNA-positive individuals the date of the last recorded PCR negative result is presented. N/A = no record in the national SARS-CoV-2 PCR notification database.
Such distribution of discordant results was confirmed by additional testing using two supplementary assays: Wantai detecting the equivalent total anti-S RBD antibodies as Elecsys-S and Abbott detecting IgG fraction of the total anti-N antibodies targeted by Elecsys-N. The recorded slight Elecsys-N/Abbott discordance is most probably a result of the presence of anti-N antibodies other than IgG detected by Elecsys-N and missed by Abbott. Thus, although we were unable to obtain follow-up sample(s) from individuals with discordant results, we strongly believe that not more than 5% of discordant results are due to false positivity of one of the Elecsys assays. This is supported by: (i) extremely high specificity of both Elecsys assays recorded in the manufacturer’s and manufacturer-independent evaluations [1,5,7–15], including this study; (ii) confirmation of the presence of targeted antibodies using supplementary serological assays in 40/45 samples with Elecsys-N/Elecsys-S discordant results; (iii) confirmation of previous COVID-19 in 18/45 individuals with discordant results through the national SARS-CoV-2 PCR notification database; (iv) distribution of Elecsys-N and Elecsys-S testing values in samples with discordant results not concentrated near the cut-off; and (v) high-incidence study settings in which anti-S-only and anti-N-only responders are not unusual in the early convalescent phase [24–26].

An important open question is whether laboratories offering different antibody assays could benefit from combining the assays; if so, should use be concomitant or sequential—and, in the latter case, in which order? Previous studies showed that a two-assay algorithm improves the positive predictive value compared with an individual assay alone while maintaining the negative predictive value [5,17,27]. Thus, the two-assay approach was recently recommended for identifying potential convalescent-phase plasma donors and assessing candidacy for experimental COVID-19 therapeutics in PCR-negative patients with respiratory symptoms [5]. As far as we know, the Elecsys-N and Elecsys-S manufacturer issued no recommendation for combination use, but the manufacturer’s unpublished data showed that concomitant use of both assays could increase overall sensitivity (some convalescent patients were anti-S-only and some anti-N-only responders) and that of both assays could increase overall sensitivity (some convalescent patients were anti-S-only and some anti-N-only responders) and that of both assays could increase overall sensitivity (some convalescent

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CRediT authorship contribution statement

Mario Poljak: Conceptualization, Methodology, Validation, Investigation, Writing - original draft, Writing - review & editing, Supervision. Anja Oštir-Benk Valencak: Methodology, Validation, Investigation, Data curation, Formal analysis, Writing - review & editing. Tina Stamo: Methodology, Validation, Investigation, Data curation, Writing - review & editing. Katja Seme: Conceptualization, Writing - original draft, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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