Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

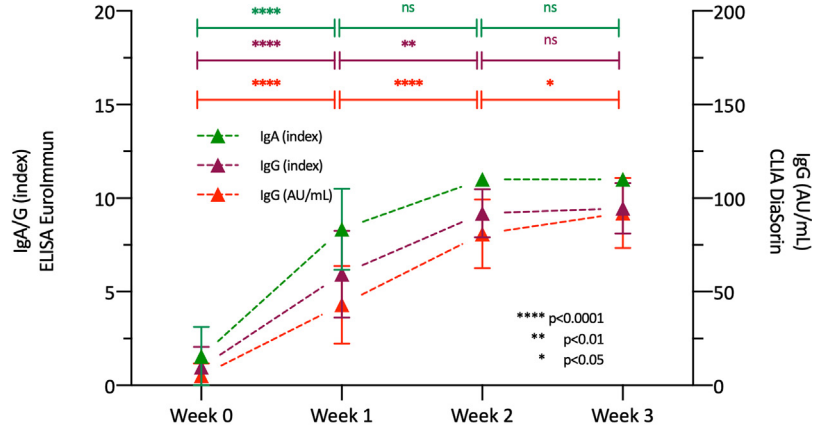
The role of serology for COVID-19 control: Population, kinetics and test performance do matter

To the Editors,

Accumulating evidence in the literature exemplifies the failings of real-time polymerase chain reaction (RT-PCR) as a sole diagnostic method in COVID-19 surveillance, because of its inability to detect past infection.[1-4] The authors of these reports or correspondence highlighted the added value of serological testing, which, if captured within the correct timeframe after disease onset, can detect both active and past infections.[1] By providing estimates of who is and is not immune to SARS-CoV-2, serological data can be used to estimate epidemiological variables, such as the attack rate or case-fatality rate, which are necessary to assess how much community transmission has occurred and its burden.[5] They can also be used to strategically deploy immune health-care workers to reduce exposure of the virus to susceptible individuals or to assess the effect of non-pharmaceutical interventions at the population level and inform policy changes to release such measures.[6] In the near future, serological testing will be required to assess the effectiveness of vaccine candidates and finally, they are also useful to identify individuals who developed a strong immunological response to the virus and whose antibody isolates can be used to treat patients via plasma therapy.[7]

However, several challenges still remain to correctly address the appropriate implementation, validation and interpretation of serological testing. Among them, understanding the kinetics of the antibodies matters as divergent opinion are reported in the literature.[8,9] Our group recently reported the validation of a chemiluminescence immunoassay (CLIA) for IgG determination (LIAISON®SARS-CoV-2, DiaSorin®, Saluggia, Italy) and reported the excellent analytical and clinical performance of the assay. However, data on antibody kinetics and assessment of IgA were not conveyed yet on this cohort.

The sera from 182 symptomatic patients, positive for RT-PCR at admission, were included and assessed at different time points for dosing IgA (ELISA method, Euroimmun Medizinische Labordiagnostika®, Lübeck, Germany) and IgG (ELISA method, Euroimmun Medizinische Labordiagnostika® and CLIA LIAISON®SARS-CoV-2, DiaSorin®). The complete follow-up at the 4 different time points was obtained for 15 of them. Statistical analyses show they are representative of the full cohort.



True positive rate (n/N, %)	Week 0	Week 1	Week 2	Week 3
IgA (adapted cut-off index: 0.438)	**7/15 (50%)**	**15/15 (100%)**	**15/15 (100%)**	**15/15 (100%)**
(manufacturer cut-off index: 1.100)	*4/15 (27%)*	*15/15 (100%)*	*15/15 (100%)*	*15/15 (100%)*
IgG (adapted cut-off index: 0.708)	**4/15 (27%)**	**13/15 (87%)**	**15/15 (100%)**	**15/15 (100%)**
(manufacturer cut-off index: 1.100)	*3/15 (20%)*	*12/15 (80%)*	*15/15 (100%)*	*15/15 (100%)*
IgG (adapted cut-off AU/mL: 6.1)	**2/15 (13%)**	**13/15 (87%)**	**15/15 (100%)**	**15/15 (100%)**
(manufacturer cut-off AU/mL: 15.0)	*1/15 (7%)*	*10/15 (67%)*	*14/15 (93%)*	*14/15 (93%)*

Fig. 1. Antibody kinetics expressed as change from baseline or sensitivity at week 0, 1, 2 and 3 post RT-PCR COVID-19 positivity. *Week 0 corresponds to the day of RT-PCR determination and confirmation of SARS-CoV-2 infection. True positivity rates (sensitivity) have been assessed with the cut-offs adapted from our validation and with the cut-off provided by the manufacturer.*

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Fig. 1 reports the change from the baseline and sensitivity at weeks 0, 1, 2 and 3 for IgA and IgG determinations. Both immunoglobulin levels increase over time and tend to stabilize after two weeks. Using our adapted cut-off, IgA determination shows a sensitivity of 100% after one week while it reaches 87% for IgG testing. The cut-off provided by the manufacturer still shows a sensitivity of 100% for IgA but it diminishes to 80% and 67% for IgG ELISA and IgG CLIA, respectively. After two weeks, all tests demonstrate a sensitivity of 100%, as reported by other groups,[8,10] except when the cut-off provided by the manufacturer were used for IgG detection (i.e. one of our 15 patients was never considered as positive).

These observations are of upmost importance for at least two analytical and clinical matters: first, the selection of the appropriate timeframe is essential for the detection of immunity. Namely, these results show that IgA immunity can be accurately detected one week after the RT-PCR positivity while IgG immunity has to be assessed after two weeks to avoid false negative results. Secondly, adapted cut-offs have to be established by each laboratory in order to improve the sensitivity of the commercial assays. However, this implies that the sera selected to define the adapted cut-off is crucial. In our case, the cut-off was determined on samples from symptomatic patients collected 14 days after the positive RT-PCR. Of note, there is to date no consensus on how to define the disease onset, i.e. date of first COVID-19 symptoms or date of RT-PCR.

Despite being both validated and approved by competent authorities, these results show that the two IgG assays are not similar for determining positivity if measurement is performed at the time of RT-PCR determination (i.e. sensitivity of 7 and 20% for the CLIA and the ELISA method, respectively using the manufacturer cut-off). This further complexifies the interpretation of the results and highlights the need for competent national authorities and learned societies to establish guidance and procedures for serological testing to avoid misinterpretation of too early determination, leading to a high rate of false negative results.

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Authorship

Marie Tré-Hardy, Laurent Blairon, Alain Wilmet, Ingrid Beukinga and Jonathan Douxfils were responsible for data collection, analysis and interpretation. Jonathan Douxfils was responsible for writing the first draft. Marie Tré-Hardy, Jean-Michel Dogné, Hugues Malonne, and Jonathan Douxfils were responsible for the final version.

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