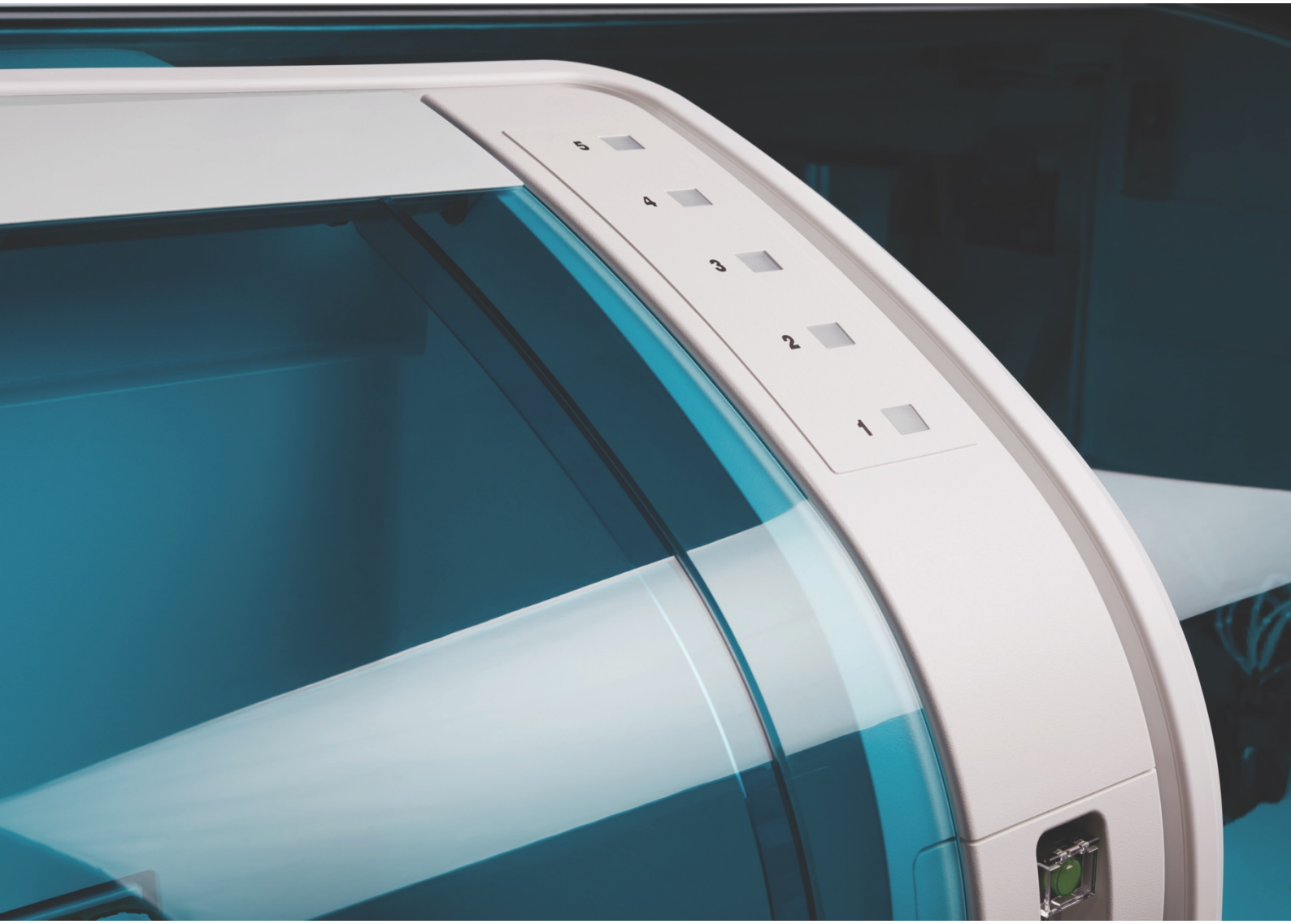
SARS-CoV-2 antibody specificity white paper



Executive summary

The Elecsys® Anti-SARS-CoV-2 assay detects the human antibody response to SARS-CoV-2 infection.[1] A positive antibody response will indicate that a person has previously been infected with SARS-CoV-2. The Elecsys Anti-SARS-CoV-2 test will help health care practitioners understand the extent of exposure and the spread of infection in a population, which is particularly useful as many cases are thought to be asymptomatic.[1-5] During infection with a pathogen, the presence of an antibody response correlates to a certain level of immunity and protection from further infection.

As such, the antibody test may also be used to indicate that a person/team are safe to return to work, depending on their status, and if future evidence will confirm to what extent SARS-CoV-2 antibodies confer immunity.[2,6-8]

When an antibody test will be used to indicate immunity against SARS-CoV-2, it must be highly specific and have as little cross-reactivity with the endemic human coronaviruses as possible, otherwise people may wrongly believe they or their colleagues/community have immunity, potentially leading to an increased risk of infection.

The prevalence of SARS-CoV-2 infection and/or seropositivity in different communities will vary widely.[9-15] In low-prevalence settings, even small reductions in specificity of an antibody assay can lead to large reductions in the positive predictive value (PPV) of a test (i.e. the probability that a positive test result is correct). It is therefore key to have a test with very high specificity. Additionally to specificity, it is very important to power studies with sufficient sample numbers to give confidence in the specificity value and assurance that the PPV will be high in all testing settings, especially when there is a lower prevalence of SARS-CoV-2.

Over the time course of infection, the antibody response becomes more specific through interactions with viral antigens.[6,7] The Elecsys Anti-SARS-CoV-2 assay was designed to preferentially detect, mature, high-affinity antibodies to the highly immunogenic SARS-CoV-2 nucleocapsid (N) protein. The result is a highly specific assay, which shows good correlation to viral neutralizing activity.[16-19]

In most cases IgM is the first specific antibody to be produced in response to a viral infection, followed by IgG, which is assumed to include more mature, high-affinity and neutralizing antibodies. In the case of SARS-CoV-2 infection, IgM and IgG usually appear together early infection, while in some cases IgG might even appear before IgM. As a consequence, targeting only IgG antibodies does not mean specifically mature, high-affinity antibodies are targeted.[2]

Seroconversion panels show that the Elecsys Anti-SARS-CoV-2 assay is highly sensitive for the detection of mature antibodies to SARS-CoV-2.[1]

Contents

1. Principal uses of NAT, antigen and serology testing for SARS-CoV-2

Testing for SARS-CoV-2 involves either:

- Nucleic acid tests (NATs) to detect viral RNA directly, or antigen testing, to detect viral proteins directly, *determining if someone is currently infected with the virus,* or
- Detection of the immune response (antibodies), determining whether someone *has been infected* and developed antibodies in response to viral infection.

NATs or antigen tests are generally used for testing of symptomatic patients and can detect SARS-CoV-2 infection up to one week before symptoms appear (Figure 1).[20]

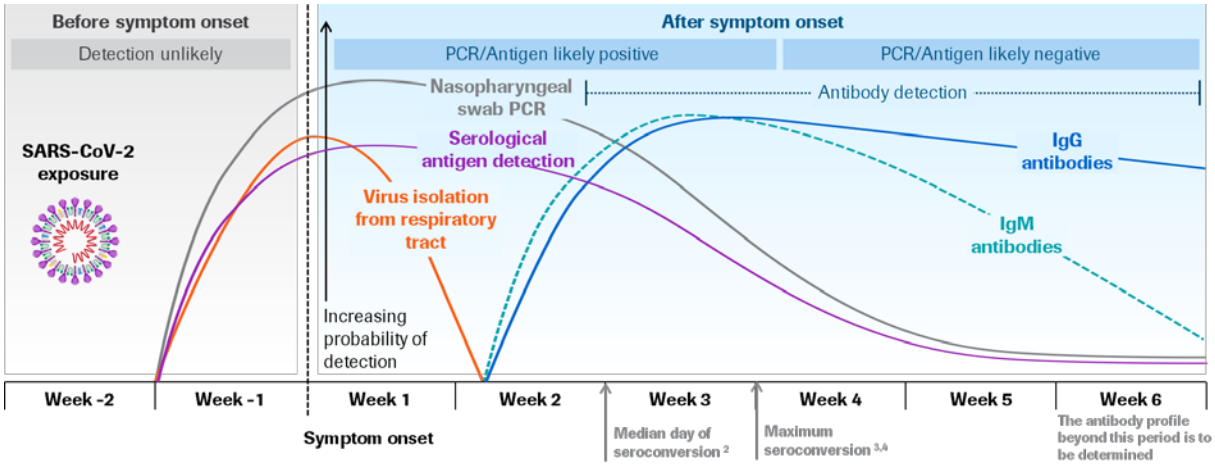


Figure 1. Estimated course of molecular and serological biomarkers during SARS-CoV-2 infection (adapted from reference[2]).

Antibody testing relies upon the detection of IgM and IgG (and other) antibodies that comprise an individual's humoral immune response.

Antibodies against SARS-CoV-2 generally target the viral spike (S) and nucleocapsid (N) proteins, and are typically detectable 8 days post symptom onset (Figure 1, Figure 2).[20-27]

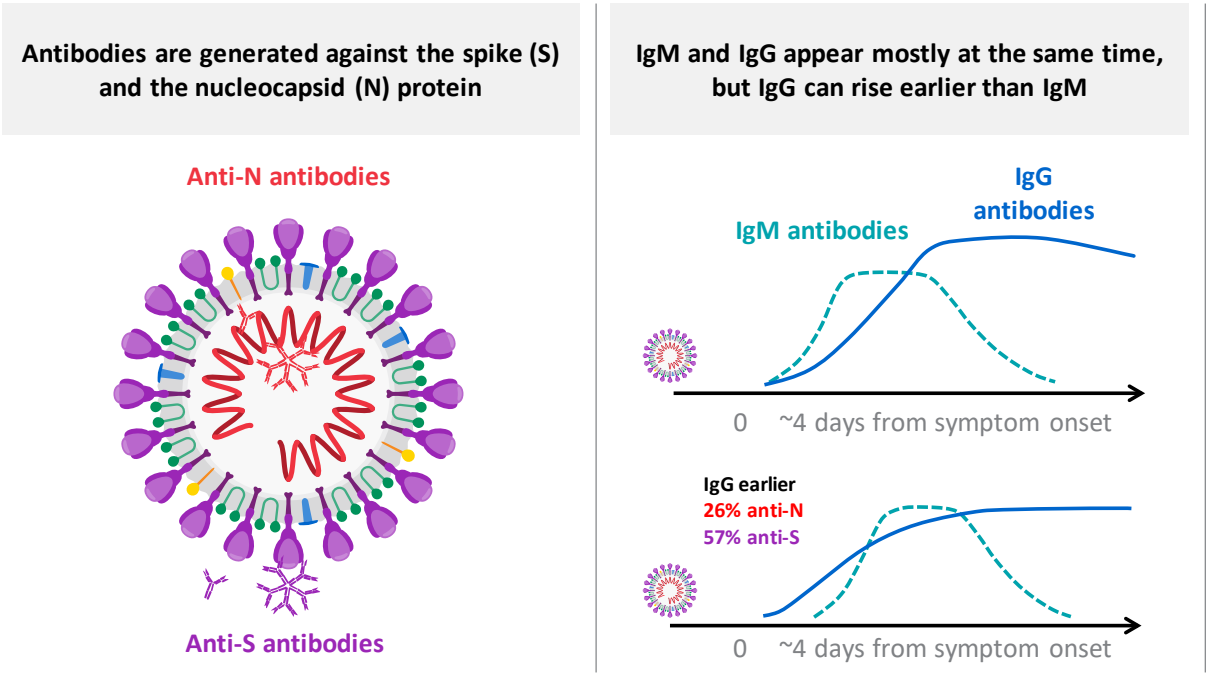


Figure 2. Antibody response during SARS-CoV-2 infection.[16,28,29]

For many other infections, IgM appears before IgG, but in the case of SARS-CoV-2, IgM and IgG appear around the same time, with the IgG response maintained >30 days following symptom onset/PCR positivity; IgM is maintained during that period, but starts to decline afterwards.[16,25,28,30-32] Hence, there are important open questions around IgG maturation and differences in early-appearing IgGs versus those detected later post exposure.

There is also increasing interest in the role of IgA, which develops early, coinciding with IgM response, peaking after 18–21 days, and appearing to be even stronger and more persistent than the IgM response. IgA antibodies are secreted at the surface of body mucosae, and their presence in saliva may be an alternative to blood testing in some circumstances.[33] However, their detection in serum on a routine basis is not recommended.[34]

2. Uses for serology testing: in depth

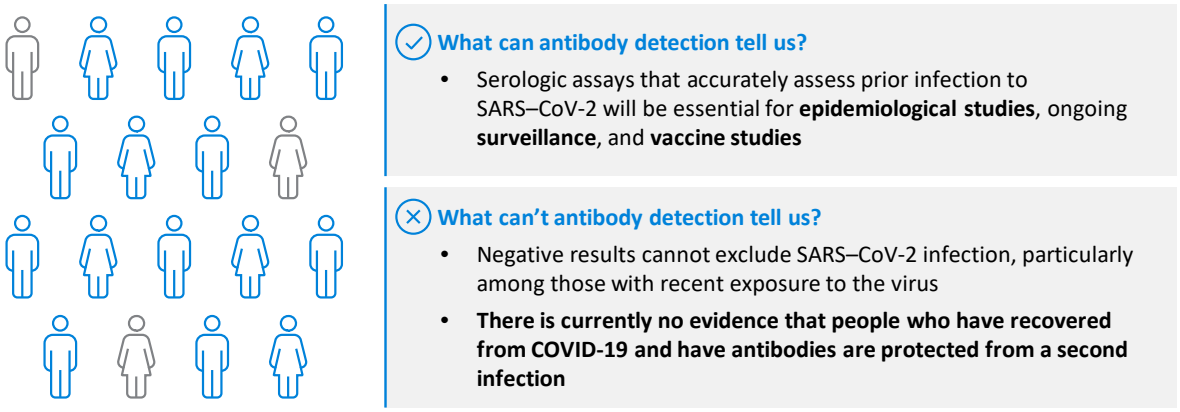


Figure 3. What can an antibody test tell you?[2,8]

Anti-SARS-CoV-2 assays will be useful for: prevalence screening, disease surveillance, contact tracing, vaccine studies and to support return to work strategies. However, currently we do not know:[2,8,35,36]

- Whether antibodies confer reliable immunity
- The duration of any immunity
- At which point a positive antibody test means immunity (e.g. NAT negative, antibody positive) (Figure 3).

The experience with other coronaviruses suggests **that a positive antibody test will indicate that the individual will have some immunity against future infection**. In the case of SARS and MERS, an antibody response is maintained for approximately 2 years following infection, with some CD8+ T-cell memory responses lasting for up to 11 years.[6,7,37-39] A recent study on macaques showed that SARS-CoV-2 infection produced protective immunity against re-exposure in non-human primates.[40] However, it cannot be stated with certainty that these factors prevent reinfection and are equally applicable to SARS-CoV-2.

An antibody test will help to define the real proportion of people infected with SARS-CoV-2, including asymptomatic SARS-CoV-2 cases in the population. Current estimates of this figure vary widely, from 10%[5] to 87.9%.[4] NAT testing is generally only used to assess symptomatic cases and, as such, there is limited knowledge of prevalence within the general population. A true understanding of spread of infection within the general population via antibody testing will not only help determine the infection dynamics within the population but will also play an important role in contact tracing and determining level and duration of quarantine measures as future waves appear.[41,35,42]

3. Requirements for serology testing: high specificity, high sensitivity, and no cross-reactivity

A key requirement of an antibody test is high specificity. Highly specific antibody tests will correctly identify someone who has not been infected and will be unlikely to give a false-positive result (Figure 4).

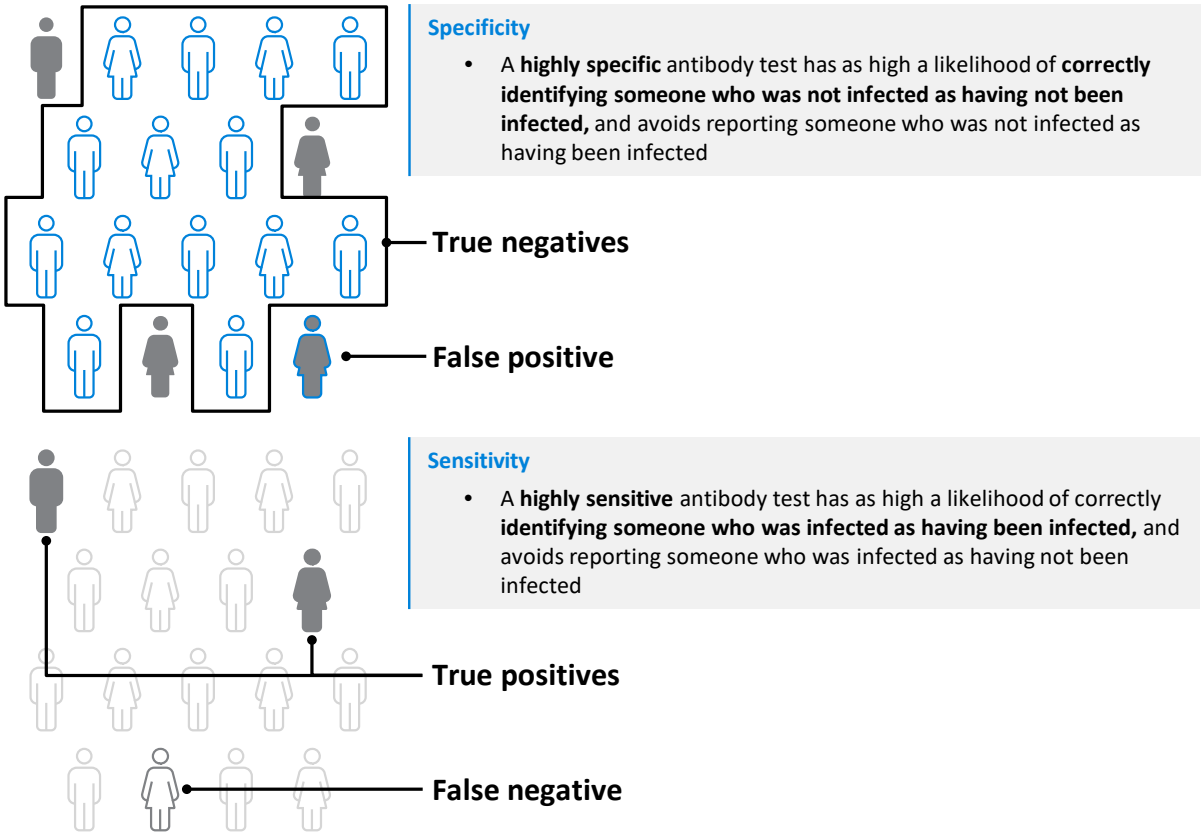


Figure 4. Sensitivity and specificity in diagnostic testing.

High specificity is key: For SARS-CoV-2, false-positive results could lead to individuals believing that they have some immunity, and this could put them at greater risk of infection, possibly infecting others, and resulting in an over-estimation of infection rates within a population, particularly in low-prevalence areas.

Sensitivity is important: The detection of early antibodies may not be useful for serosurveillance of SARS-CoV-2, versus correct detection of mature antibodies, which is more likely to provide correlation with putative immunity. The most sensitive serology test, that detects the earliest antibody response, may also detect immature antibodies that are less specific. Unlike other case settings (such as HIV testing of blood donors), for SARS-CoV-2 antibody testing, false negatives are unlikely to cause harm, only resulting in under-estimation of exposure within a certain population, or that someone continues with

preventative measures. **Hence reducing specificity in favor of sensitivity does not make sense for anti-SARS-CoV-2 testing.**

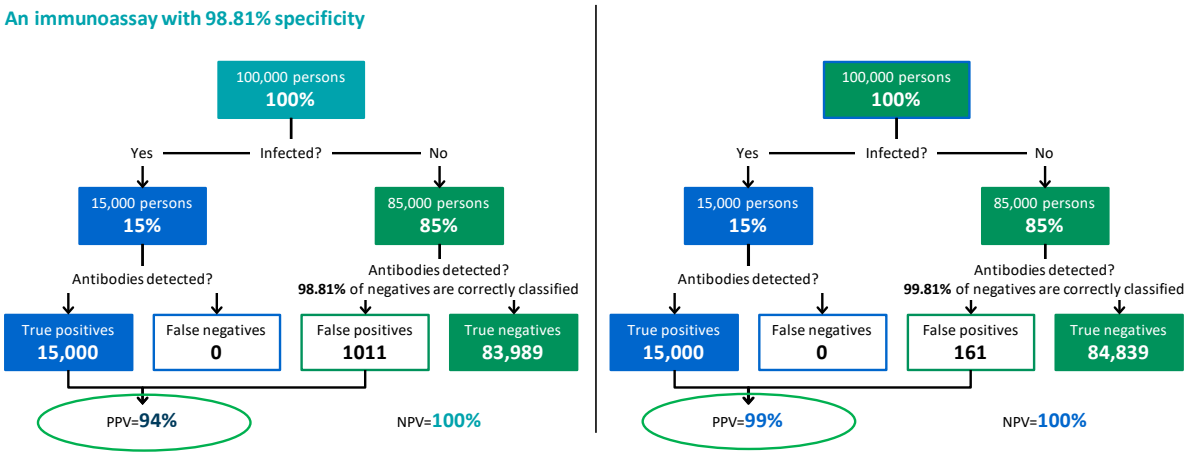
Cross-reactivity must be minimal: Although SARS-CoV-2 infection only emerged in 2019, there are endemic coronaviruses which may cause potentially cross-reactive false-positive antibody results.[8,17] Additionally, SARS-CoV-2 N and S proteins have 90% and 72% homology to the N and S proteins of SARS-CoV-1, respectively; however, SARS and MERS are no longer circulating in the population and therefore cross-reactivity against common, more prevalent coronaviruses (such as those causing common colds) are more relevant.[7,8] **Cross-reactivity with endemic coronaviruses could reduce the specificity of an antibody test**.

4. Positive predictive value

The positive predictive value (PPV) is a measure of the performance that also accounts for the prevalence of the disease in the population, indicating in different prevalence settings how likely someone with a positive test is to be truly positive for infection. In other words, when the test gives a positive result, how confident can one be that the result is indeed positive. The higher the specificity, the better for detecting the true exposure status, particularly in a low-prevalence setting.

As illustrated below (Figure 5), a difference of 1% in specificity can mean a huge difference in terms of PPV in a lower prevalence (for example, 1.5%) region. [5,9-14,43]

15% prevalence



1.5% prevalence

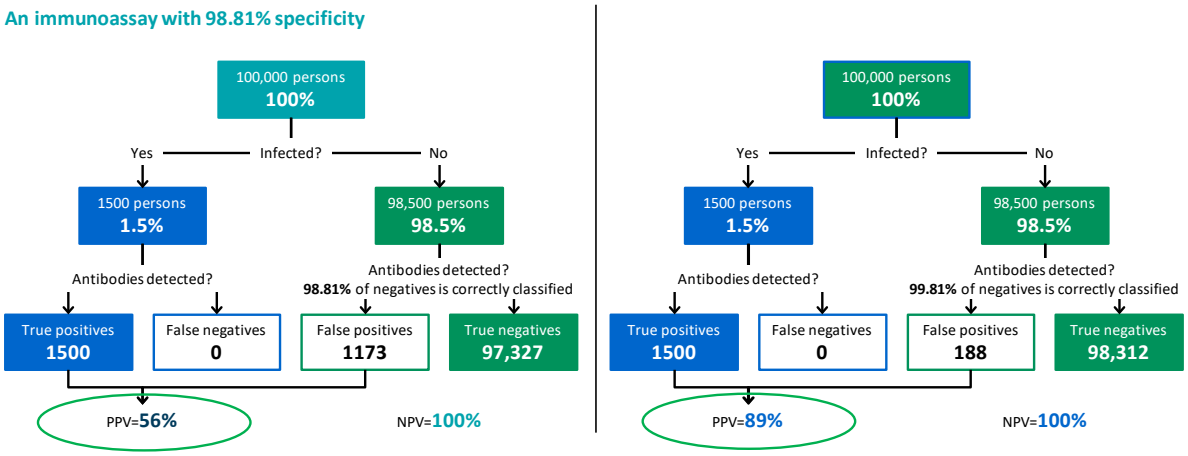


Figure 5. Specificity, sensitivity and PPV in different prevalence settings.

The importance of high PPV has also been recognized by the CDC in the USA, which has recommended that if the PPV of a test in a given prevalence setting is <95%, then the test should be used in combination with another test to bring the PPV up to 95%.[34]

5. Powering a diagnostic performance study

Often, the power of diagnostic studies is not considered; however, studies need to be powered with sample numbers to give confidence in the reported specificity values. Power and sample size estimations are measures of how many patients are needed in a study to show a difference between treatments, as diagnostic and clinical studies assess the performance of a test in a small population and the results are extrapolated to the

whole population. Where the probability of a false-positive result is 5%, and the study has an 80% chance of significant results (power) to obtain and confirm the 'optimal specificities', large sample numbers are needed (Table 1).

Specificity (%)	Sample size needed (N)
99.00	368
99.50	736
99.60	921
99.70	1228
99.80	1843
99.90	3688
99.995	7376

Table 1. Populations needed to provide target specificities when the probability of a false-positive result is 5% and the power (chance of the test having significant results) is 80%.

Among tests being currently developed and validated, only the Roche Elecsys test has been sufficiently powered, by assessment in 10,453 samples, to provide reliable results with a low variance in performance.[1,44-50]

6. Principles of assay design

6.1 Considering cross-reactivity

An assay to detect antibodies against SARS-CoV-2 must be designed so that it does not cross-react with antibodies to any other endemic human coronavirus infections, or any other enveloped RNA viruses.[51,7,8]

6.2 Detection of mature antibodies is key to ensuring a highly specific serology test

How the immune system responds to infection

Detection of mature antibodies is key to ensuring assay specificity. During an infection, SARS-CoV-2 exploits the cellular ACE2 receptors to enter the cell, where it replicates

(Figure 6).[52] The immune system initially responds with non-specific immature antibodies, potentially targeting other antigens from viruses within the same family, depending on a person's prior exposure. As the number of interactions of B cells and T-helper cells with the virus increases, the antibodies become more specific to the virus, via the process of affinity maturation.[53]

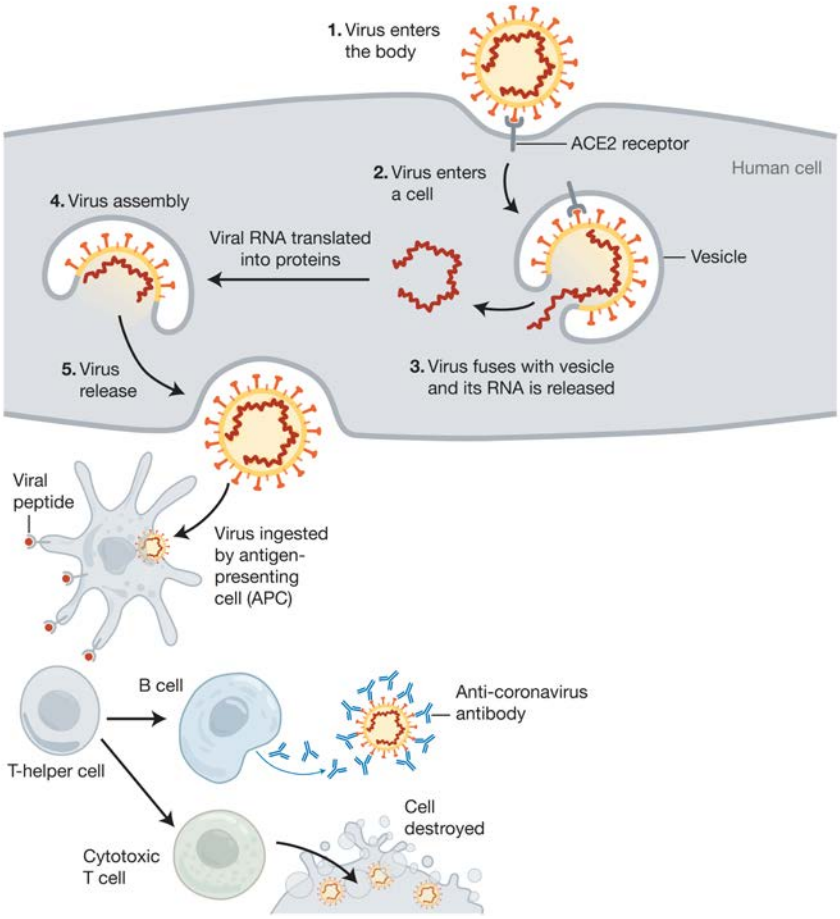


Figure 6. How the immune system responds to infection.[52] The interaction of the virus with B cells and T cells in order to generate the immune response to SARS-CoV-2 infection.

In this schematic of a simplified immune response, specialized 'antigen-presenting cells' engulf the virus and display portions of it to activate T-helper cells. These enable other immune responses including production of antibodies by B cells, and destruction of infected cells by cytotoxic T cells.

Memory B and T cells stay in the body for months or years and may provide long-lasting immunity to further infection.

As mature antibodies evolve, they become more effective at tagging the virus for destruction by cytotoxic T cells. Also, antibodies develop that have neutralizing activity, either blocking the virus from entering the cell (neutralizing anti-S antibodies) or binding to the viral capsid, blocking the uncoating of the viral genome (neutralizing anti-N antibodies; Table 2).[16,28,53-55] In the case of SARS-CoV-2, it is important to note that IgM

and IgG often appear at the same time, thus confounding the nature of early-appearing IgGs versus those that are detected later post exposure.

Antibody main types	Early/immature	Mature	Neutralizing
Description	• Appear in early infection phase • Do not effectively recognize the virus	• Appear in convalescent phase • **Effectively recognize the virus**	• Appear in the convalescent/immunity phase • **Effectively neutralize the virus**
Examples	IgA, IgM, early/immature IgG	Late/mature IgGs	Neutralizing antibodies (subset of mature IgGs)
Relevance/purpose	Initial host response to start understanding the virus	Host memory of the virus for future recognition	Render the virus ineffective against the host
All neutralizing antibodies are mature BUT not all mature antibodies are neutralizing antibodies			

Table 2. Antibody types that evolve during infection.

Which antibodies should an assay detect to ensure specificity?

In a study designed to assess the specificity of the antibodies to each of the antigen targets, where control samples expose any interaction with endemic human coronaviruses, the anti-N antibodies were the most dominant and the most highly specific.[17] This suggested that anti-N antibodies may be the optimal target to ensure specificity (Figure 7). The result was supported by candidate testing strategies at Roche Diagnostics that found, in a pre-pandemic sample cohort of 300 samples, that antibodies against nucleocapsid protein had the highest specificity.

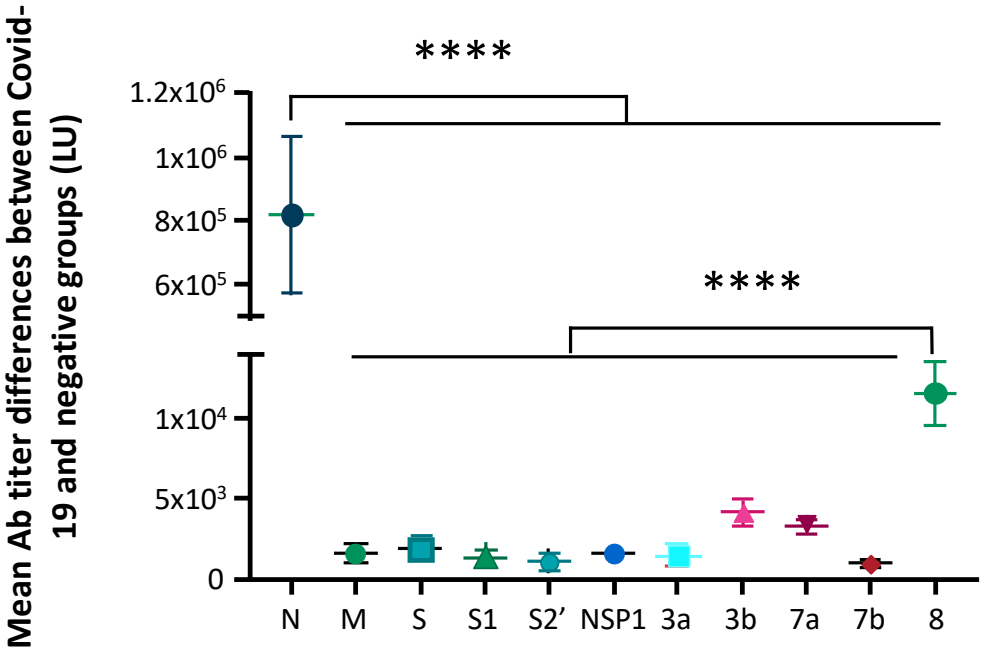


Figure 7. The differences in the antibody titers of different antibodies to SARS-CoV-2 in convalescent versus control patients.[17] Using luciferase immunoprecipitation system

experiments to detect antibody responses in patients recovered from COVID-19 and comparing them with healthy COVID-19 individuals (to subtract any reactivity with endemic human coronaviruses), anti-N antibodies were present/had the greatest difference in convalescent COVID-19 patients versus controls.

A small study assessing the performance of a series of immunoassays for SARS-CoV-2 also found that the assays developed using N antigen had higher specificity compared with the diagnostic tests developed with any other antigen.[19]

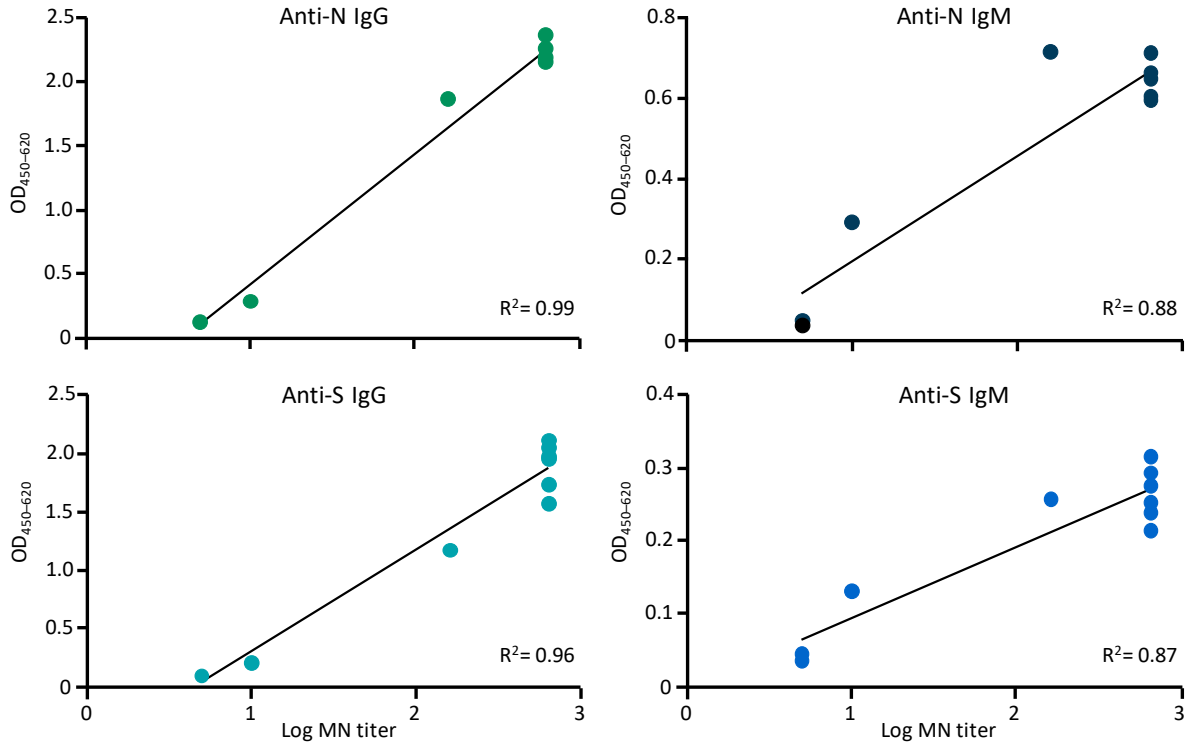


Figure 8. Correlation between microneutralization titers and anti-N or anti-S IgM or IgG. This study of antibodies from patients following COVID-19 infection found anti-N and anti-S IgM and IgG had neutralizing activity, with anti-N IgG having the most neutralizing activity.

For SARS-CoV-2, antibodies against both the viral N and S antigens have been shown to correlate with neutralizing activity (Figure 8), which has also recently been confirmed for the Roche Elecsys Anti-SARS-CoV-2 assay.[8,18,19] Hence targeting mature antibodies against the N antigen ensures a test that is both highly specific and highly sensitive towards those antibodies most likely to correlate with greatest neutralizing activity.

6.3 Assay format can also help to ensure high specificity

There are two key types of antibody assay testing format: the indirect capture and the direct-capture antigen sandwich method. The in-solution double-antigen sandwich

method (Figure 9) used with the Elecsys Anti-SARS-CoV-2 assay requires that antibodies bind to two complementary antigens, one biotinylated and the other ruthenylated. Independent binding events between both antigens and an antibody from the sample are needed for the streptavidin-coated particles to subsequently capture the target antibody and enable generation of the signal. This in-solution chemistry enables specific, preferential detection of late mature antibodies that present high affinity binding under the modified reaction conditions in the assay. By contrast, in the indirect assay format, the fixed antigens on the solid substrate allow high-avidity binding to multiple presenting antigens, and thus potential cross-reactivity to early immature antibodies and/or antibodies against endemic human coronaviruses.

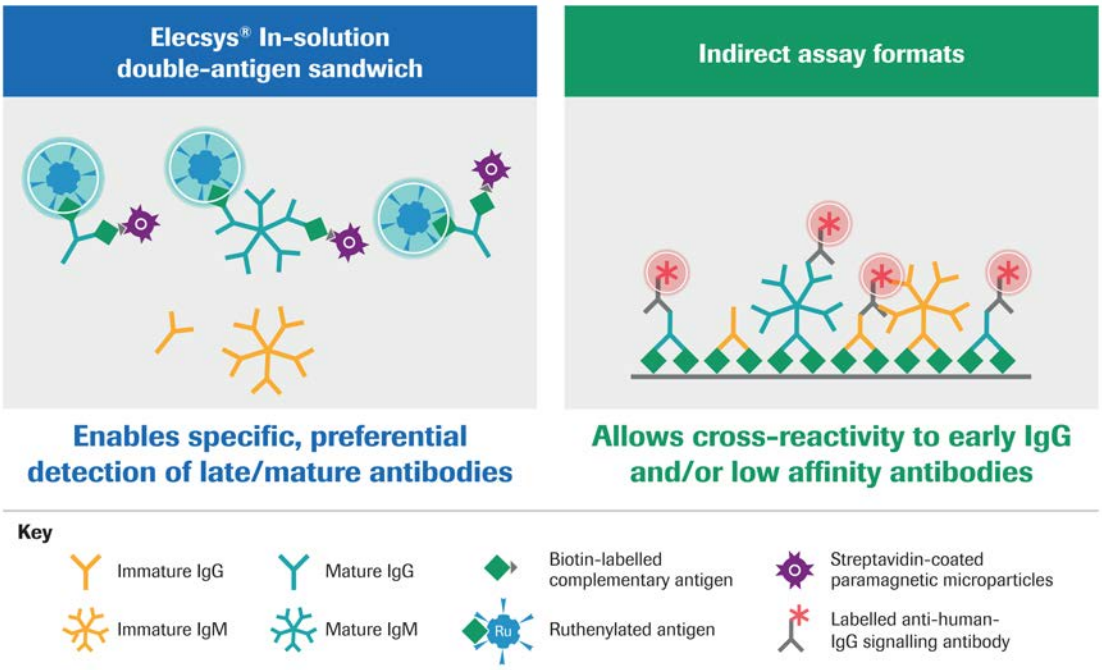


Figure 9. The double-antigen sandwich versus the indirect assay format.

7. The Elecsys Anti-SARS-CoV-2 assay performance

With careful thought and consideration to all the above elements, the Elecsys Anti-SARS-CoV-2 assay has been designed for high specificity detection of mature/late antibodies, which are predominantly, but not exclusively, late-appearing IgGs. It uses a recombinant protein, representing the N antigen, for the determination of antibodies against SARS-CoV-2 using the in-solution double-antigen sandwich assay principle. It is also the only assay that has demonstrated no cross-reactivity against the four common cold coronaviruses.

In a total of 10453 samples assessed using the Elecsys Anti-SARS-CoV-2 assay, there were 21 false-positive samples and an overall specificity of 99.80%. The 95% lower confidence limit was 99.69% (Table 3).

Cohort	N	Reactive	Specificity % (95% CI)
Diagnostic routine	6305	12	99.81% (99.67–99.90%)
Blood donors	4148	9	99.78% (99.59–99.90%)
Overall	10453	**21**	**99.80% (99.69-99.88%)**

Table 3. Diagnostic specificity of the Elecsys SARS-CoV-2 assay.

Assessment of potential cross-reactivity of the Elecsys Anti-SARS-CoV-2 assay with endemic human coronavirus, common cold, or other potentially cross-reacting conditions (cytomegalovirus, Epstein–Barr virus, systemic lupus erythematosus) demonstrated very high specificity for SARS-CoV-2 (Table 4). The Elecsys Anti-SARS-CoV-2 is the only validated SARS-CoV-2 immunoassay assessed across this number of potentially cross-reactive samples.

Cohort	N	Reactive	Specificity % (95% CI)
Common cold panel	40	0	100% (91.19–100%)
Coronavirus panel*	40	0	100% (91.19–100%)
Other potentially cross-reacting samples§	667	4	99.4% (95.6–99.8%)
Overall	**792**	4	**99.47% (98.63–99.85%)**

Table 4. Assessment of the Elecsys Anti-SARS-CoV-2 assay with samples from other potentially cross-reactive conditions.

In keeping with the assay design and goal to preferentially detect late-appearing mature antibodies, the Elecsys Anti-SARS-CoV-2 assay demonstrates an increasing sensitivity with days post-PCR positivity, achieving very high sensitivity 14 days post-PCR positivity, when mature antibodies are expected to be present in the majority of cases (Table 5).

Days post PCR confirmation	N	Reactive	Sensitivity (95% CI*)
0–6 days	161	97	60.2% (52.3–67.8%)
7–13 days	150	128	85.3% (78.6–90.6%)
≥14 days	**184**	**184**	**100.0% (88.1–100%)**

Table 5. Diagnostic sensitivity of the Elecsys SARS-CoV-2 assay following positive PCR for SARS-CoV-2 infection.

8. Conclusions

- A positive antibody response will indicate that a person has previously been infected with SARS-CoV-2, and may be used to understand the spread of infection in the population, contact tracing, for vaccine studies, and for supporting return to work strategies[2,6,7]
- High specificity is needed for an antibody test to be used effectively in these settings; false positive results may lead to an increased risk to people/communities who believe they already have some immunity
- The Elecsys Anti-SARS-CoV-2 assay has a high specificity, as assessed in >10,000 samples, which can provide confidence that the PPV of the test will be high in the relevant prevalence settings, including those with lower infection rates
- Additionally, due to the in-solution double-antigen sandwich assay format of the Elecsys Anti-SARS-CoV-2 antibody test, it preferentially targets highly specific mature antibodies appearing later post exposure. This provides the added benefit of high sensitivity for the antibodies most likely to be correlated with a neutralizing effect

Note: Some information contained in this article is taken from rapidly published articles which have not been peer reviewed

9. References

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Glossary

ACE2	Angiotensin-converting enzyme 2
CDC	Centers for Disease Control and Prevention
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MERS	Middle East respiratory syndrome
N	Nucleocapsid (protein)
NAT	Nucleic acid testing

RNA	Ribonucleic acid
PCR	Polymerase chain reaction
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
S	Spike (protein)