Elecsys Anti-SARS-CoV-2

cobas®

REF		Σ	SYSTEM
09203079190	09203079500	300	**cobas e** 801

English

System information

Short name	ACN (application code number)
ACOV2	10226

Intended use

Elecsys Anti-SARS-CoV-2 is an immunoassay for the in vitro qualitative detection of antibodies (including IgG) to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in human serum and plasma. The test is intended as an aid in the determination of the immune reaction to SARS-CoV-2.

The **e**lectro**c**hemi**l**uminescence **i**mmuno**a**ssay "ECLIA" is intended for use on **cobas e** immunoassay analyzers.

Summary

SARS-CoV-2 is an enveloped, single-stranded RNA virus of the family Coronaviridae, genus Betacoronaviruses. All coronaviruses share similarities in the organization and expression of their genome, which encodes 16 nonstructural proteins and the 4 structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N). Viruses of this family are of zoonotic origin. They cause disease with symptoms ranging from those of a mild common cold to more severe ones such as the Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Coronavirus Disease 2019 (COVID-19). Other coronaviruses known to infect humans include 229E, NL63, OC43 and HKU1. The latter are ubiquitous and infection typically causes common cold or flu-like symptoms.[1,2]

SARS-CoV-2 is transmitted person-to-person primarily via respiratory droplets, but also indirect transmission through contaminated surfaces is possible.[3,4,5,6] SARS-CoV-2 can be isolated from respiratory samples obtained via naso/oropharyngeal swabs or from sputum. The virus accesses host cells via the angiotensin-converting enzyme 2 (ACE2), which is the most abundant in the lungs.[7,8]

The incubation period for COVID-19 is thought to range from 2-14 days following exposure, with most cases showing symptoms approximately 4-5 days after exposure.[3,9,10] The interval during which an individual with COVID-19 is infectious has not yet been clearly established. Transmission from symptomatic individuals, the spread of virus to new hosts shortly before symptoms appear and asymptomatic transmission have all been described; however the evidence is not conclusive.[1,11,12,13,14]

Those infected may exhibit symptoms including fever, cough, fatigue, sputum production, loss of smell and shortness of breath.[15,16,17] The spectrum of symptomatic infection ranges from mild to critical, with most cases being non-severe. Severe illness is characterized by e.g. dyspnea, hypoxia, > 50 % lung infiltrates within 24 to 48 hours and occurs predominantly in adults with advanced age or underlying medical comorbidities such as hypertension, diabetes mellitus and cardiovascular disease. Acute respiratory distress syndrome (ARDS) is a major complication in patients with severe disease. Critical cases are characterized by e.g. respiratory failure, shock and/or multiple organ dysfunction or failure. The proportion of severe or fatal infections vary greatly by location.[16,18,19]

Definite COVID-19 diagnosis entails SARS-CoV-2 detection by nucleic acid amplification technology (NAAT).[20,21,22] Although the underlying technology for NAAT is robust and shows excellent specificity, the outcome directly depends on the viral load acquired during sampling which, among others, can vary with time point of infection, individual patient, sampling method and position as well as sample preparation time.

Consequently, a non-negligible proportion of infected individuals may be missed by screenings based on symptoms and NAAT[23,24,25] and thus form an important source of continued viral spread. Serological assays can contribute to identify individuals exposed to the virus and assess the extent of exposure of a population, and might thereby help to decide on application, enforcement or relaxation of containment measures.[26]

Seroconversion has been observed as early as within 5 days after symptom onset for immunoglobulin M (IgM)[27] and within 5-7 days for IgG.[27,28] Based on still scarce data, anti-SARS-CoV-2 IgA seem to appear at around 3-6 days post-symptom onset.[25,29] Depending on the applied method, seroconversion is observed after a median of 10-13 days after symptom onset for IgM and 12-14 days for IgG.[23,30,31] Maximum seroconversion occurs at 2-3 weeks for IgM,[23,27,28,31,32] at 3-6 weeks for IgG,[23,27,28,33] and at 2 weeks for total antibodies.[31,34] Whereas IgM seems to vanish around week 6-7,[32,35] high IgG seropositivity is seen at that time.[27,32,35] Levels and chronological order of IgM and IgG antibody appearance are highly variable,[23,28,31,36] supporting detection of both antibodies simultaneously.

Neutralizing antibodies targeting spike and nucleocapsid proteins are formed as early as day 9 onwards, showing strong neutralizing response, thus seroconversion may lead to protection at a minimum for a limited time.[29,36,37,38,39] Cross-reactivity with SARS-CoV-2 induced neutralizing antibodies with SARS-CoV was observed, but not with other coronaviruses, suggesting that the vast majority of people are immunologically naive and thus susceptible to this virus.[25,29,36,37,40]

The Elecsys Anti-SARS-CoV-2 assay uses a recombinant protein representing the nucleocapsid (N) antigen for the determination of antibodies against SARS-CoV-2.

Test principle

Sandwich principle. Total duration of assay: 18 minutes.

- 1st incubation: 12 µL of sample, biotinylated SARS-CoV-2-specific recombinant antigen and SARS-CoV-2-specific recombinant antigen labeled with a ruthenium complex[a)] form a sandwich complex.
- 2nd incubation: After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin.
- The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier.
- Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

a) Tris(2,2'-bipyridyl)ruthenium(II)-complex ($Ru(bpy)_3^{2+}$)

Reagents - working solutions

The **cobas e** pack (M, R1, R2) is labeled as ACOV2.

M Streptavidin-coated microparticles, 1 bottle, 16.0 mL:
Streptavidin-coated microparticles 0.72 mg/mL; preservative.

R1 SARS-CoV-2-Ag~biotin, 1 bottle, 18.8 mL:
Biotinylated SARS-CoV-2-specific recombinant antigen (E. coli); preservative.

R2 SARS-CoV-2-Ag~$Ru(bpy)_3^{2+}$, 1 bottle, 18.8 mL:
SARS-CoV-2-specific recombinant antigen labeled with ruthenium complex; preservative.

ACOV2 Cal1 Negative calibrator 1, 1 bottle of 0.67 mL:
Human serum, non-reactive for anti-SARS-CoV-2 antibodies; buffer; preservative.

ACOV2 Cal2 Positive calibrator 2, 1 bottle of 0.67 mL:
Human serum, reactive for anti-SARS-CoV-2 antibodies; buffer; preservative.

Precautions and warnings

For in vitro diagnostic use.
Exercise the normal precautions required for handling all laboratory reagents.
Disposal of all waste material should be in accordance with local guidelines.
Safety data sheet available for professional user on request.

This kit contains components classified as follows in accordance with the Regulation (EC) No. 1272/2008:

Elecsys Anti-SARS-CoV-2

cobas®

Warning

H317 May cause an allergic skin reaction.

Prevention:

P261 Avoid breathing dust/fume/gas/mist/vapours/spray.

P272 Contaminated work clothing should not be allowed out of the workplace.

P280 Wear protective gloves.

Response:

P333 + P313 If skin irritation or rash occurs: Get medical advice/attention.

P362 + P364 Take off contaminated clothing and wash it before reuse.

Disposal:

P501 Dispose of contents/container to an approved waste disposal plant.

Product safety labeling follows EU GHS guidance.

Contact phone: all countries: +49-621-7590

All human material should be considered potentially infectious. All products derived from human blood are prepared exclusively from the blood of donors tested individually and shown to be free from HBsAg and antibodies to HCV and HIV. The testing methods used assays approved by the FDA or cleared in compliance with the European Directive 98/79/EC, Annex II, List A.

The serum containing anti-SARS-CoV-2 (ACOV2 Cal2) was heat-inactivated for 30 minutes at 56 °C.

However, as no inactivation or testing method can rule out the potential risk of infection with absolute certainty, the material should be handled with the same level of care as a patient specimen. In the event of exposure, the directives of the responsible health authorities should be followed.[41,42]

Avoid foam formation in all reagents and sample types (specimens, calibrators and controls).

Reagent handling

For professional use.

The reagents (M, R1, R2) in the kit are ready-for-use and are supplied in **cobas e** packs.

Calibrators:

The calibrators are supplied ready-for-use in bottles compatible with the system.

Store the calibrators at 2-8 °C for later use.

Perform **only one** calibration procedure per bottle.

All information required for correct operation is available via the **cobas** link.

Storage and stability

Store at 2-8 °C.

Do not freeze.

Store the **cobas e** pack **upright** in order to ensure complete availability of the microparticles during automatic mixing prior to use.

Stability of the **cobas e** pack:	
unopened at 2-8 °C	up to the stated expiration date
on the analyzers	72 hours

Stability of the calibrators:	
unopened at 2-8 °C	up to the stated expiration date
after opening at 2-8 °C	72 hours

Stability of the calibrators:	
on the analyzers at 20-25 °C	use only once

Store calibrators **upright** in order to prevent the calibrator solution from adhering to the snap-cap.

Specimen collection and preparation

Only the specimens listed below were tested and found acceptable.

Serum collected using standard sampling tubes.

Li-heparin, K_2-EDTA and K_3-EDTA plasma.

Criterion: Absolute deviation of negative samples ± 0.3 COI (cutoff index) from serum value; reactive samples: recovery within 70-130 % of serum value.

Stable for 3 days at 15-25 °C, 7 days at 2-8 °C, 28 days at -20 °C (± 5 °C). The samples may be frozen twice.

The sample types listed were tested with a selection of sample collection tubes or systems that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube/collection system manufacturer.

Specimens should not be subsequently altered with additives (e.g. biocides, anti-oxidants or substances that could possibly change the pH or ionic strength of the sample) in order to avoid erroneous findings.

Pooled samples and other artificial material may have different effects on different assays and thus may lead to discrepant findings.

Centrifuge samples containing precipitates and thawed samples before performing the assay.

Do not use heat-inactivated samples.

Do not use samples and controls stabilized with azide.

Ensure the samples and calibrators are at 20-25 °C prior to measurement.

Due to possible evaporation effects, samples and calibrators on the analyzers should be analyzed/measured within 2 hours.

The performance of the Elecsys Anti-SARS-CoV-2 assay has not been established with cadaveric samples or body fluids other than serum and plasma.

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

- REF 07299010190, Diluent MultiAssay, 45.2 mL sample diluent
- General laboratory equipment
- **cobas e** 801 analyzer

Additional materials for the **cobas e** 801 analyzer:

- REF 06908799190, ProCell II M, 2 x 2 L system solution
- REF 04880293190, CleanCell M, 2 x 2 L measuring cell cleaning solution
- REF 07485409001, Reservoir Cup, 8 cups to supply ProCell II M and CleanCell M
- REF 06908853190, PreClean II M, 2 x 2 L wash solution
- REF 05694302001, Assay Tip/Assay Cup tray, 6 magazines x 6 magazine stacks x 105 assay tips and 105 assay cups, 3 wasteliners
- REF 07485425001, Liquid Flow Cleaning Cup, 2 adaptor cups to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning Detection Unit
- REF 07485433001, PreWash Liquid Flow Cleaning Cup, 1 adaptor cup to supply ISE Cleaning Solution/Elecsys SysClean for Liquid Flow Cleaning PreWash Unit
- REF 11298500316, ISE Cleaning Solution/Elecsys SysClean, 5 x 100 mL system cleaning solution

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator’s manual for analyzer-specific assay instructions.

Resuspension of the microparticles takes place automatically prior to use.

Place the cooled (stored at 2-8 °C) **cobas e** pack on the reagent manager. Avoid foam formation. The system automatically regulates the temperature of the reagents and the opening/closing of the **cobas e** pack.

Calibrators:

Place the calibrators in the sample zone.

Read in all the information necessary for calibrating the assay.

Calibration

No international standard is available for Anti-SARS-CoV-2.

Calibration frequency:

Calibration must be performed once per reagent lot using ACOV2 Cal1, ACOV2 Cal2 and fresh reagent (i.e. not more than 24 hours since the **cobas e** pack was registered on the analyzer).

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Renewed calibration is recommended as follows:

- after 3 days when using the same reagent lot
- after 3 days when using the same **cobas e** pack on the analyzer
- as required: e.g. quality control findings outside the defined limits

Quality control

For quality control, use controls prepared as follows:

Negative control: Determine the COI of ACOV2 Cal1 by measuring it as a routine sample. Pool serum samples with a COI result of ≤ 150 % compared to the COI result of ACOV2 Cal1 (pooling of ≥ 5 non-reactive samples in this range is recommended). Mix carefully, avoiding foam formation. Prepare aliquots of at least 250 µL from this sample pool and store frozen at -20 °C (± 5 °C) or colder. Use these aliquots to perform regular quality control.
This negative control has a target value range of COI < 0.8 (qualitative assay result "non-reactive").

Positive control: Determine the COI of ACOV2 Cal2 by measuring it as a routine sample. Pool serum samples with a COI result that is higher than the COI result of ACOV2 Cal2 (pooling of ≥ 3 reactive samples in this range is recommended). Dilute the sample pool by adding pooled negative serum (pooling criterion see negative control) or Diluent MultiAssay to obtain a COI between 3 and 15. Mix carefully, avoiding foam formation. It is recommended to confirm calculated reactivity after dilution by a measurement. Prepare aliquots of at least 250 µL from this sample pool and store frozen at -20 °C (± 5°C) or colder. Use these aliquots to perform regular quality control. Upon first use of this control, determine the COI of the control by measurement of the control in triplicate and using a freshly opened **cobas e** pack.
The obtained median of these measurements serves as target value for this positive control. Subsequent measurements of all aliquots of this control material must match this target value ± 45 % (3SD = 45 %, 1SD = 15 %; qualitative assay result "reactive"). In case the quality control fails, thaw a new aliquot and re-assess the performance of the assay.
The target value of the positive control is lot specific and target value assessment as described above has to be performed for every assay lot.

After measurement, discard aliquots with a remaining volume of 250 µL or less, Aliquots with a remaining volume of more than 250 µL can be re-used if sealed tightly and stored immediately at 2-8 °C for max. 3 days. In case quality control fails for any reason, thaw a new control aliquot and re-assess the performance of the assay.

Also pools of plasma samples with similar reactivity can be used, however re-clotting frequently occurs with plasma after thawing. If this occurs, either discard or centrifuge the aliquot before use. Do not mix serum samples and plasma samples to prepare a sample pool.

Controls for the various concentration ranges should be run individually at least once every 24 hours when the test is in use, once per **cobas e** pack, and following each calibration.

The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

If necessary, repeat the measurement of the samples concerned.

Follow the applicable government regulations and local guidelines for quality control.

Note: The controls should be run like external controls. All values and ranges have to be entered manually. Please refer to the section "QC" in the operator's manual or to the online help of the instrument software. Only one target value and range for each control level can be entered in the analyzer. The reagent lot-specific target values have to be re-entered each time a specific reagent lot with different control target values and ranges is used. Two reagent lots with different control target values and ranges cannot be used in parallel in the same run.

Calculation

The analyzer automatically calculates the cutoff based on the measurement of ACOV2 Cal1 and ACOV2 Cal2.

The result of a sample is given either as reactive or non-reactive as well as in the form of a cutoff index (COI; signal sample/cutoff).

Interpretation of the results

Results obtained with the Elecsys Anti-SARS-CoV-2 assay can be interpreted as follows:

Numeric result	Result message	Interpretation
COI < 1.0	Non-reactive	Negative for anti-SARS-CoV-2 antibodies
COI ≥ 1.0	Reactive	Positive for anti-SARS-CoV-2 antibodies

The magnitude of the measured result above the cutoff is not indicative of the total amount of antibody present in the sample.
The individual immune response following SARS-CoV-2 infection varies considerably and might give different results with assays from different manufacturers. Results of assays from different manufacturers should not be used interchangeably.

Limitations - interference

The effect of the following pharmaceutical compound on assay performance was tested. Interference was tested up to the listed concentration and no impact on results was observed.

Endogenous substance

Compound	Concentration tested
Biotin	≤ 4912 nmol/L or ≤ 1200 ng/mL

Criterion: For samples with a COI ≥ 1.0, the deviation is ≤ 20 %. For samples with a COI < 1.0, the deviation is ≤ 0.2 COI.

Potential endogenous interferences e.g. hemolysis, bilirubin, rheumatoid factors and pharmaceutical compounds other than biotin have not been tested and an interference cannot be excluded.

No false negative results due to a high-dose hook effect were found with the Elecsys Anti-SARS-CoV-2 assay but occurrence of high-dose hook effect cannot be completely excluded.

In rare cases, interference due to extremely high titers of antibodies to analyte-specific antibodies, streptavidin or ruthenium can occur. These effects are minimized by suitable test design.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

A negative test result does not completely rule out the possibility of an infection with SARS-CoV-2. Serum or plasma samples from the very early (pre-seroconversion) phase can yield negative findings. Therefore, this test cannot be used to diagnose an acute infection. Also, over time, titers may decline and eventually become negative.

Specific performance data

Representative performance data on the analyzers are given below. Results obtained in individual laboratories may differ.

Specificity

A total of 5272 samples were tested with the Elecsys Anti-SARS-CoV-2 assay. All samples were obtained before December 2019. 10 false positive samples were detected.

The resulting overall specificity in the internal study was 99.81 %. The 95 % lower confidence limit was 99.65 %.

Cohort	N	Non-reactive	Reactive	Specificity, % (95 % CI[b])
Diagnostic routine	3420	3413	7	99.80 (99.58-99.92 %)
Blood donors	1772	1769	3	99.83 (99.51-99.97 %)
Common cold panel	40	40	0	100 (91.19-100 %)
Coronavirus panel[c]	40	40	0	100 (91.19-100 %)
Overall	**5272**	**5262**	**10**	**99.81 (99.65-99.91 %)**

b) CI = confidence interval

c) 40 potentially cross-reactive samples from individuals following an infection with Coronavirus HKU1, NL63, 229E or OC43, confirmed via PCR

Sensitivity

A total of 204 samples from 69 symptomatic patients with a PCR confirmed SARS-CoV-2 infection were tested with the Elecsys Anti-SARS-CoV-2 assay. 1 or more consecutive samples from these patients were collected after PCR confirmation at various time points.

Days post PCR confirmation	N	Reactive	Non-reactive	Sensitivity, % (95 % CI)
0-6	116	76	40	65.5 (56.1-74.1 %)
7-13	59	52	7	88.1 (77.1-95.1 %)
≥ 14	29	29	0	100 (88.1-100 %)

After recovery from infection, confirmed by a negative PCR result, 26 consecutive samples from 5 individuals were tested with the Elecsys Anti-SARS-CoV-2 assay.

Patient	Day of negative PCR*		Days after diagnosis with positive PCR						
			21-23	24-26	27-29	30-32	33-35	36-38	39-40
1	9	COI	24.7	-	27.4	31.7	38.9	56.0	-
2	12		28.8	29.8	30.6	32.7	35.7	-	-
3	17		-	46.5	53.6	-	67.1	73.7	77.0
4	21		24.1	29.8	40.7	51.2	61.5	67.5	-
5	24		-	0.990	1.12	1.55	-	1.66	1.97

* Day 0 represents initial positive PCR.

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For further information, please refer to the appropriate operator's manual for the analyzer concerned, the respective application sheets, the product information and the Method Sheets of all necessary components (if available in your country).

A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

CONTENT	Contents of kit
SYSTEM	Analyzers/Instruments on which reagents can be used
REAGENT	Reagent
CALIBRATOR	Calibrator
→	Volume after reconstitution or mixing
GTIN	Global Trade Item Number

CE

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