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Manual

IDK® anti-SARS-CoV-2 IgG ELISA

For the quantitative in vitro determination of IgG antibodies against SARS-CoV-2 (including neutralizing antibodies) in human serum and EDTA plasma

Valid from 2021-08-10

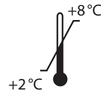

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Table of Contents

1. INTENDED USE 21

2. INTRODUCTION 21

3. MATERIAL SUPPLIED 22

4. MATERIAL REQUIRED BUT NOT SUPPLIED 22

5. PREPARATION AND STORAGE OF REAGENTS 22

6. PREPARATION OF THE ASSAY 23

Sample storage 23
Dilution of samples 23

7. ASSAY PROCEDURE 23

Principle of the test 23
Test procedure 24

8. RESULTS 25

Point-to-point calculation 25
EDTA plasma and serum samples 25
Interpretation of results 25
Further sample dilution 25
Interpretation of the results in BAU/ml 27

9. LIMITATIONS 27

10. QUALITY CONTROL 28

11. PERFORMANCE CHARACTERISTICS 28

Clinical specificity and sensitivity 28
Correlation 29
Cross-reactivity 29
Accuracy – Precision 30
Analytical sensitivity 31
Linearity 31
Accuracy – Trueness 32

12. PRECAUTIONS 33

13. TECHNICAL HINTS 34

14. GENERAL NOTES ON THE TEST AND TEST PROCEDURE 34

15. LITERATURE 35

1. INTENDED USE

IDK® anti-SARS-CoV-2 IgG is an enzyme-linked immunosorbent assay (ELISA) for quantitative measurement of IgG antibodies (including neutralizing antibodies) against the novel coronavirus SARS-CoV-2 in human serum or EDTA plasma. The assay is an *in vitro* diagnostic medical device and is intended to be used by professional users in a laboratory environment. This ELISA can be performed manually or using an automated platform. This test serves as complement to infection diagnosis and is used for the detection of IgG antibodies after a previous infection with SARS-CoV-2 or after COVID-19 vaccination.

2. INTRODUCTION

The virus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is an enveloped, single stranded RNA virus and is a family member of the coronavirus family Coronaviridae [1,2].

Coronaviruses have a similar composition as they are composed of similar structural proteins including the spike (S), envelope (E), membrane (M), and nucleocapsid (N) protein and several non-structural proteins. Their members cause a variety of diseases in different vertebrate species [6, 8]. As of February 2020, seven human pathogenic coronaviruses are known: besides SARS-CoV[-1], SARS-CoV-2 and MERS-CoV, there are HCoV-HKU1, HCoV-OC43, HCoV-NL63 and HCoV-229E. While SARS-CoV[-1], SARS-CoV-2 and MERS-CoV can cause severe respiratory and systemic diseases, infections with the last four mentioned usually only lead to mild cold symptoms [3, 8].

After an infection with SARS-CoV-2, the virus accesses host cells via the protein ACE2 (angiotensin-converting enzyme) and causes the disease COVID-19. The severity of disease ranges from asymptomatic, mild (fever, cold, cough, tiredness, shortness of breath, and loss of smell), and severe to most severe forms with death [4, 5, 7]. Aging and several co-morbidities (e. g. *diabetes mellitus*, cardiovascular diseases, and chronic pulmonary diseases) are described as risk factors for severe progressive forms of COVID-19 [3, 12, 13].

Seroconversion occurs on different time points depending on the used method and the measured class of antibodies. The onset of IgG antibodies is usually observed after 11 to 14 days and seroconversion of IgG antibodies rises its maximum after three to six weeks [9, 10, 11]. The immune response after COVID-19 vaccination depends, among other things, on the vaccine used, but also on the age of the patient. Therefore, differences in IgG levels are expected after COVID-19 vaccination [15,16].

3. MATERIAL SUPPLIED

Cat. No.	Label	Kit components	Quantity
K 5004	PLATE	Microtiter plate, pre-coated	12 x 8 wells
K 0001.C.100	WASHBUF	Wash buffer concentrate, 10 x	2 x 100 ml
K 5004	CONJ	Conjugate, ready-to-use	1 x 12.5 ml
K 5004	STD 1–6	Standards 1–6, ready-to-use (0; 1.25; 2.5; 5; 10; 20 ng/ml)	6 x 1 ml
K 5004	CTRL 1	Control 1, ready-to-use	1 x 1 ml
K 5004	CTRL 2	Control 2, ready-to-use	1 x 1 ml
K 5004	SAMPLEBUF	Sample dilution buffer, ready-to-use	1 x 110 ml
K 0002.15	SUB	Substrate (tetramethylbenzidine), ready-to-use	1 x 15 ml
K 0003.15	STOP	Stop solution, ready-to-use	1 x 15 ml
	FOL	Foil to cover the microtiter plate	3 x

For reorders of single components, use the catalogue number followed by the label as product number.

4. MATERIAL REQUIRED BUT NOT SUPPLIED

- Ultrapure water*
- Calibrated precision pipettors and 10–1 000 µl single-use tips
- Horizontal microtiter plate shaker
- A multi-channel dispenser or repeating dispenser
- Vortex
- Standard single-use laboratory glass or plastic vials, cups, etc.
- Microtiter plate reader (required filters see chapter 7)

* Immundiagnostik AG recommends the use of ultrapure water (water type 1; ISO 3 696), which is free of undissolved and colloidal ions and organic molecules (free of particles > 0.2 µm) with an electrical conductivity of 0.055 µS/cm at 25 °C (≥ 18.2 MΩ cm).

5. PREPARATION AND STORAGE OF REAGENTS

- Bring all reagents to room temperature (18–30 °C) prior to use.
- To run the assay more than once, ensure that reagents are stored at conditions stated on the label. Prepare only the appropriate amount necessary for

each run. The kit can be used up to 4 times within the expiry date stated on the label.

- **Preparation of the wash buffer:** The **wash buffer concentrate (WASHBUF)** should be diluted with ultrapure water **1:10** before use (100 ml WASHBUF + 900 ml ultrapure water), mix well. Crystals could occur due to high salt concentration in the concentrate. The crystals must be redissolved at room temperature or in a water bath at 37 °C before dilution of the buffer solutions. The **WASHBUF** is stable at **2–8 °C** until the expiry date stated on the label. **Wash buffer** (1:10 diluted WASHBUF) can be stored in a closed flask at **2–8 °C for 1 month**.
- All other test reagents are ready to use. Test reagents are stable until the expiry date (see label) when stored at **2–8 °C**.

6. PREPARATION OF THE ASSAY

Sample storage

Freshly collected serum can be stored for 14 days at room temperature or for up to 4 weeks at 2–8 °C. Long-term storage is recommended at -20 °C. More than 3 freeze-thaw cycles should be avoided.

Diluted samples are **not stable** and **cannot be stored**.

Dilution of samples

Samples are diluted **1:101 in sample dilution buffer**. For example:

- **10 µl** sample + **1 000 µl** sample dilution buffer, mix well = **1:101**

For analysis, pipet **100 µl diluted sample** per well.

7. ASSAY PROCEDURE

Principle of the test

This ELISA serves for the determination of IgG antibodies against the spike protein (S1) of SARS-CoV-2. Standards, controls and diluted samples are added to a microtiter plate coated with a specific antigen. By adding the peroxidase conjugate (peroxidase labelled detection antibody), the antibodies against SARS-CoV-2 in the sample are marked. They are detected via the peroxidase conjugate with the peroxidase converting the substrate TMB to a blue product. The enzymatic reaction is stopped by adding an acidic solution. The samples convert from blue to yellow. The colour

change should be measured in a photometer at 450 nm. The interpretation is made using the cut-off value.

Test procedure

Bring all reagents and samples to room temperature (18–30 °C) and mix well.

Mark the positions of controls/samples on a protocol sheet.

Take as many microtiter strips (PLATE) as needed from kit. Store unused strips covered with the foil included in the kit together with the desiccant bag in the re-closed aluminum packaging at 2–8 °C. Strips are stable until the expiry date stated on the label.

For automated ELISA processors, the given protocol may need to be adjusted according to the specific features of the respective automated platform. For further details, please contact your supplier or Immundiagnostik AG.

We recommend carrying out the tests in duplicates.

1.	Pipet each **100 µl of standards, controls and diluted samples** into the wells of the microtiter plate.
2.	Cover the strips and incubate for **1 hour shaking (900 rpm)*** on a horizontal shaker at room temperature (18–30 °C).
3.	Discard the content of each well and wash **5 times** with **250 µl wash buffer**. After the final washing step, remove residual wash buffer by firmly tapping the plate on absorbent paper.
4.	Add **100 µl conjugate** (CONJ) into each well.
5.	Cover the strips and incubate for **1 hour shaking (900 rpm)*** on a horizontal shaker at room temperature (18–30 °C).
6.	Discard the content of each well and wash **5 times** with **250 µl wash buffer**. After the final washing step, remove residual wash buffer by firmly tapping the plate on absorbent paper.
7.	Add **100 µl substrate** (SUB) into each well.
8.	Incubate for **10–15 minutes** at room temperature (18–30 °C) until a sufficiently large difference in colour occurs**.
9.	Add **100 µl stop solution** (STOP) into each well and mix shortly by using the **shake function (900 rpm)*** of the microplate reader.

10.	Determine **absorption immediately** with an ELISA reader at **450 nm** against 620 nm (or 690 nm) as a reference.

* We recommend shaking the strips with an orbit of 2 mm.

** The intensity of the colour change is temperature sensitive. We recommend observing the colour change and stopping the reaction upon good differentiation.

8. RESULTS

The following algorithm can be used to calculate results

Point-to-point calculation

We recommend a linear ordinate for the optical density and a linear abscissa for the concentration.

The plausibility of the pairs of values should be examined before the automatic evaluation of the results. If this option is not available with the used program, a manual control of the paired values should be made.

EDTA plasma and serum samples

The obtained results have to be multiplied by the **dilution factor of 101** to get the actual concentrations in ng/ml.

In case **another dilution factor** has been used, multiply the obtained results by the dilution factor used.

Interpretation of results

Values above the cut-off value = 175 ng/ml are positive for anti-SARS-CoV-2 IgG antibodies.

< 175 ng/ml	**negative for anti-SARS-CoV-2 IgG antibodies**
≥ 175 ng/ml	**positive for anti-SARS-CoV-2 IgG antibodies**
> 2 020 ng/ml	**positive for anti-SARS-CoV-2 IgG antibodies, values out of measuring range ***

* samples can be further diluted and re-assayed

Further sample dilution

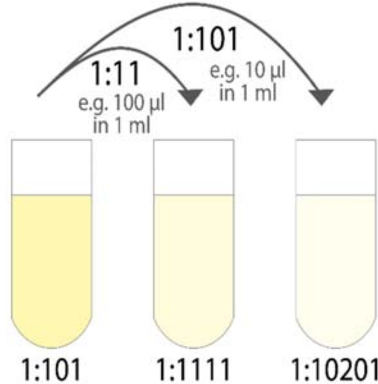
After COVID-19 vaccination, many individuals initially show a significantly stronger antibody production than it could be observed in the last year after COVID-19 disease. Therefore, it may be necessary to adjust the dilution or further dilute the

samples to determine the exact concentration of antibodies in a sample from vaccinated individuals.

To determine the optimal dilution, a sample set of n = 249 samples was measured 3–6 weeks after second vaccination with BNT162b2 (Comirnaty®) from BioNTech/Pfizer and the following antibody concentrations were determined:

Concentration range	Concentration [ng/ml]	Concentration [BAU/ml]	Number of Persons	Proportion [%]
Range 1	0–400	0–20	55	22.09
Range 2	401–2 000	21–100	28	11.24
Range 3	2 001–20 000	101–1 000	100	40.16
Range 4	> 20 000	> 1 000	66	26.51
		Total	**249**	**100**

Comparable results were obtained with a smaller patient cohort after vaccination with Astra-Zeneca‘s Vaxzevria® vaccine and after vaccination with Moderna‘s COVID-19 Vaccine Moderna® vaccine.



Recommendation by Immundiagnostik:

For vaccinated individuals, we recommend measuring the sample in our standard dilution (1:101) and two measurements after further dilution from the standard dilution in a ratio of 1:11 (final dilution 1:1 111) and in a ratio of 1:101 (final dilution 1:10 201).

The standard dilution is used to interpret the results (positive/negative). With the help of the further dilutions, the exact concentration can be determined for positive samples. All samples with a result above the LoQ (40.4 ng/ml) can be calculated with the corresponding factor.

Our experience shows that in most cases one further dilution in the ratio 1:101 (final dilution 1:10 201) is recommended for persons 14 days or more after second vaccination. Over which period of time these high titers can be expected in the vaccinated persons is currently still part of the research.

Interpretation of the results in BAU/ml

To obtain the concentration of the sample in binding antibody units (BAU)/ml, the results in ng/ml can be divided by a factor of 20.

Conversion: **20 ng/ml ≙ 1 BAU/ml**

To determine this conversion factor, the correlation with the **"First WHO International Standard for anti-SARS-CoV-2 immunoglobulin (NIBSC code: 20/136)"** was examined. For this purpose, serial dilutions of this standard material were measured with different batches by different operators on different days.

The standard material was dissolved according to the manufacturer's instructions in order to obtain a defined concentration in IU/ml. For binding antibody tests, the unit can be expressed as binding antibody units (BAU)/ml to assist in comparing tests detecting the same class of immunoglobulins with the same specificity.

9. LIMITATIONS

Samples which cannot be clearly interpreted (e.g. because of high coefficients of variation of replicates) should be measured again.

Samples with concentrations above the measurement range (see definition below) can be further diluted and re-assayed. Please consider this higher dilution when calculating the results.

Samples with concentrations lower than the measurement range (see definition below) cannot be clearly quantified.

The upper limit of the measurement range can be calculated as:

highest concentration of the standard curve × sample dilution factor to be used

(20 ng/ml x 101 = 2 020 ng/ml)

The lower limit of the measurement range can be calculated as:

LoQ × sample dilution factor to be used (0.4 ng/ml x 101 = 40.40 ng/ml)

Obtained values above the LoQ but below the cut-off value may be due to unspecific reactions. Negative results (< 175 ng/ml) indicate for the absence of detectable anti-SARS-CoV-2 IgG antibodies.

Negative results do not rule out an acute infection with SARS-CoV-2. The serum or plasma samples may be collected at a very early stage of infection when the body has not yet produced IgG antibodies. These are produced about 11–14 days after the start of an infection. They arise at late infection stages or after an infection has been overcome. Therefore, this test cannot be used to diagnose an acute infection.

The results **should always** be interpreted in the context of the patient's history and clinical presentation.

In case of only weak positive results, it is recommended to re-sample and analyse after ~ 14 days.

The clinical relevancy of quantitative anti-SARS-CoV-2 ELISAs is currently unknown. Therefore, no conclusion can be drawn about a possible immunity nor protection from reinfection.

Results obtained with this test can only be compared with the results obtained with other tests which detect the same antibody class, use the same antigen and have comparable sensitivity and specificity.

10. QUALITY CONTROL

Immundiagnostik AG recommends the use of external controls for internal quality control, if possible.

Control samples should be analysed with each run. Results, generated from the analysis of control samples, should be evaluated for acceptability using appropriate statistical methods. The results for the patient samples may not be valid if within the same assay one or more values of the quality control sample are outside the acceptable limits.

11. PERFORMANCE CHARACTERISTICS

Clinical specificity and sensitivity

Sensitivity; n = 30

For determination of clinical sensitivity, 30 samples from patients with previous RT-PCR confirmed SARS-CoV-2 infection were tested. Blood samples, used for determination of sensitivity were collected at later stages of infection.

	Number of patients with positive RT-PCR
total	30
Positive IgG antibody detection	30
Negative IgG antibody detection	0

These results in a sensitivity of 100 % for the *IDK*® anti-SARS-CoV-2 IgG ELISA.

Specificity; n = 762

For determination of clinical specificity, 762 serum samples from blood donors were tested. All samples were collected in 2017 and 2018.

	Number of blood donors
total	762
Positive IgG antibody detection	7
Negative IgG antibody detection	755

The resulting specificity for the *IDK*® anti-SARS-CoV-2 IgG ELISA was 99.1 %.

Correlation

The high sensitivity (n = 362 and n = 169) and specificity (n = 177) of the *IDK*® anti-SARS-CoV-2 IgG ELISA was confirmed in the publication by Eberhardt et al. [14]. In addition, this publication showed an excellent correlation between the *IDK*® anti-SARS-CoV-2 IgG ELISA and the serum neutralizing activity (Live Virus Assay and Pseudovirus Assay).

Cross-reactivity

Specificity data were confirmed using serum samples, which have been tested positive for antibodies against different viruses (n = 47). These data do not show any cross-reactivity for the *IDK*® anti-SARS-COV-2 IgG ELISA.

Virus	n	positive [%]	negative [%]
Adenovirus	5	0	100
Epstein-Barr virus	5	0	100
Influenza A/B	5	0	100
HCoV-229E	5	0	100

Virus	**n**	**positive [%]**	**negative [%]**
HCoV-HKU1	7	0	100
HCoV-NL63	12	0	100
HCoV-OC43	8	0	100
Total	**47**	**0**	**100**

Accuracy – Precision

Repeatability (Intra-Assay); n = 40

The repeatability was assessed with 4 serum samples under **constant** parameters (same operator, instrument, day and kit lot) without considering possibly used sample dilution factors.

Sample	**Mean value [ng/ml]**	**CV [%]**
1	14.99	2.4
2	5.85	2.5
3	13.63	6.7
4	2.51	3.3

Reproducibility (Inter-Assay); n = 20

The reproducibility was assessed with 3 serum samples under **varying** parameters (different operators, instruments, days and kit lots) without considering possibly used sample dilution factors.

Sample	**Mean value [ng/ml]**	**CV [%]**
1	16.02	9.0
2	6.58	12.2
3	16.08	10.7

Analytical sensitivity

The following values have been estimated based on the concentrations of the standard without considering possibly used sample dilution factors.

Limit of blank, LoB	0.26 ng/ml
Limit of detection, LoD	0.4 ng/ml
Limit of quantitation, LoQ	0.4 ng/ml

Linearity

The linearity states the ability of a method to provide results proportional to the concentration of analyte in the test sample. This was assessed according to CLSI guideline EP6-A by serial dilutions of 5 serum samples.

For anti-SARS-CoV-2 IgG antibodies in serum, the method has been demonstrated to be linear, showing a non-linear behaviour of less than ±20 %. The following table shows one representative example for each sample (without considering possibly used sample dilution factors):

Sample	Dilution	Measured [ng/ml]	Expected [ng/ml]	Recovery [%]
1	pur	19.9	20	99.5
	1:2	9.1	10	91
	1:4	4.4	5	88
	1:8	2.2	2.5	88
	1:16	1.1	1.25	88
	1:32	0.6	0.625	96
	1:64	0.3	0.3125	96
2	pur	max	max	
	1:2	12.3	12.3	100
	1:4	6	6.15	97.5
	1:8	2.8	3.075	91
	1:16	1.3	1.5375	84.5
	1:32	0.6	0.768	78.1
	1:64	0.3	0.38	78.9

Sample	Dilution	Measured [ng/ml]	Expected [ng/ml]	Recovery [%]
3	pur	max	max	
	1:2	13.6	13.6	100
	1:4	6.3	6.8	92.6
	1:8	3.2	3.4	94
	1:16	1.5	1.7	88.2
	1:32	0.8	0.85	94
	1:64	0.4	0.425	94.1
4	pur	14	14	100
	1:2	6.6	7	94.3
	1:4	3.2	3.5	91.4
	1:8	1.6	1.75	91.4
	1:16	0.8	0.875	91.4
	1:32	0.4	0.4375	91.4
	1:64	0.2	0.21875	91.4
5	pur	13.2	13.2	100
	1:2	6.6	6.6	100
	1:4	3.4	3.3	103
	1:8	1.7	1.65	103
	1:16	0.9	0.825	109
	1:32	0.4	0.4125	96.9

Accuracy – Trueness

The trueness states the closeness of the agreement between the result of a measurement and the true value of the measurand. Therefore, anti-SARS-CoV-2 IgG antibody spikes with known concentrations were added to 3 different serum-samples and values were assessed without considering possibly used sample dilution factors.

Sample	Spike [ng/ml]	Blank [ng/ml]	Expected [ng/ml]	Obtained [ng/ml]	Recovery [%]
1	1	0.09	1.09	1.30	119.3
2	1	0.10	1.10	1.20	109.1
3	1	0.20	1.20	0.90	75.0
1	2.5	0.09	2.59	3.10	119.7
2	2.5	0.10	2.60	3.20	123.1
3	2.5	0.20	2.70	3.20	118.5
1	5	0.09	5.09	5.20	102.2
2	5	0.10	5.10	5.40	105.9
3	5	0.20	5.20	5.30	101.9
1	7.5	0.09	7.59	7.10	93.5
2	7.5	0.10	7.60	7.50	98.7
3	7.5	0.20	7.70	7.80	101.3
1	10	0.09	10.09	8.90	88.2
2	10	0.10	10.10	9.00	89.1
3	10	0.20	10.20	10.4	102.0
1	15	0.09	15.09	13.6	90.1
2	15	0.10	15.10	13.4	88.7
3	15	0.20	15.20	13.3	87.5
1	19	0.09	19.09	17.5	91.7
2	19	0.10	19.10	18.2	95.3
3	19	0.20	19.20	17.7	92.2

12. PRECAUTIONS

- All reagents in the kit package are for *in vitro* diagnostic use only.
- Human materials used in kit components were tested and found to be negative for HIV, Hepatitis B and Hepatitis C. However, for safety reasons, all kit components should be treated as potentially infectious.

- Kit reagents contain sodium azide or ProClin as bactericides. Sodium azide and ProClin are toxic. Substrates for the enzymatic colour reactions are toxic and carcinogenic. Avoid contact with skin or mucous membranes.
- The 10x Wash buffer concentrate (WASHBUF) contains surfactants which may cause severe eye irritation in case of eye contact

Warning: Causes serious eye irritation

IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. If eye irritation persists: get medical Advice/attention.

- The stop solution consists of diluted sulphuric acid, a strong acid. Although diluted, it still must be handled with care. It can cause burns and should be handled with gloves, eye protection, and appropriate protective clothing. Any spill should be wiped up immediately with copious quantities of water. Do not breath vapour and avoid inhalation.

13. TECHNICAL HINTS

- Do not interchange different lot numbers of any kit component within the same assay. Furthermore, we recommend not assembling wells of different microtiter plates for analysis, even if they are of the same batch.
- Control samples should be analysed with each run.
- Reagents should not be used beyond the expiration date stated on kit label.
- Substrate solution should remain colourless until use.
- To ensure accurate results, proper adhesion of plate sealers during incubation steps is necessary.
- Avoid foaming when mixing reagents.
- Do not mix plugs and caps from different reagents.
- The assay should always be performed according to the enclosed manual.

14. GENERAL NOTES ON THE TEST AND TEST PROCEDURE

- This assay was produced and distributed according to the IVD guidelines of 98/79/EC.
- The guidelines for medical laboratories should be followed.

- *IDK*® is a trademark of Immundiagnostik AG.
- Incubation time, incubation temperature and pipetting volumes of the components are defined by the producer. Any variation of the test procedure, which is not coordinated with the producer, may influence the results of the test. Immundiagnostik AG can therefore not be held responsible for any damage resulting from incorrect use.
- Warranty claims and complaints regarding deficiencies must be logged within 14 days after receipt of the product. The product should be send to Immundiagnostik AG along with a written complaint.

15. LITERATURE

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Used symbols:

Temperature limitation

Catalogue number

In Vitro Diagnostic Medical Device

To be used with

Manufacturer

Contains sufficient for <n> tests

Lot number

Use by

Attention

Consult instructions for use

Consult specification data sheet