SARS-CoV-2 IgG II Quant

FOR USE WITH Alinity i

en
CoV-2 IgG II
06S61
H18534R03
B6S610

Read Highlighted Changes: Revised April 2021.

REF 06S6122

REF 06S6132

Instructions must be carefully followed. Reliability of assay results cannot be guaranteed if there are any deviations from these instructions.

For laboratory professional use only.

NAME

SARS-CoV-2 IgG II Quant (also referred to as CoV-2 IgG II or SARS-CoV-2 IgG II on the reagent cartridge label)

INTENDED USE

The SARS-CoV-2 IgG II Quant assay is a chemiluminescent microparticle immunoassay (CMIA) used for the qualitative and quantitative determination of IgG antibodies to SARS-CoV-2 in human serum and plasma on the Alinity i system.

The SARS-CoV-2 IgG II Quant assay is to be used as an aid in the diagnosis of SARS-CoV-2 infection in conjunction with clinical presentation and other laboratory tests. The assay is also to be used as an aid in evaluating immune status of infected individuals and to monitor antibody response in individuals that have received the COVID-19 vaccine, by quantitatively measuring IgG antibodies against the spike receptor-binding domain (RBD) of SARS-CoV-2. Results from the SARS-CoV-2 IgG II Quant assay should not be used as the sole basis for diagnosis of SARS-CoV-2 infection.

SUMMARY AND EXPLANATION OF THE TEST

The SARS-CoV-2 IgG II Quant assay is designed to detect immunoglobulin class G (IgG) antibodies, including neutralizing antibodies, to the receptor binding domain (RBD) of the S1 subunit of the spike protein of SARS-CoV-2 in serum and plasma from individuals who are suspected to have had coronavirus disease (COVID-19) or in serum and plasma of individuals that may have been infected by SARS-CoV-2.

COVID-19 is defined as illness caused by a novel coronavirus now designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, formerly known as 2019-nCoV).[1] On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic.[2] The incubation period of COVID-19 ranges between 1 and 14 days, with the majority of cases manifesting between 3 and 10 days.[3, 4] The most common symptoms are fever, dry cough, and difficulty breathing.[4] A severe acute respiratory distress syndrome may develop.[5] Reported case fatality rates depend on geographic location, age, and comorbidities.[3, 6]

The causative agent of COVID-19 is a beta coronavirus and belongs to a family of viruses that are common in animals worldwide with potential to transfer to humans, as has likely happened with SARS-CoV-2.[7] Worldwide monitoring has identified SARS-CoV-2 variants, which continue to be studied.[8] SARS-CoV-2 RNA encodes for four structural proteins including spike (S), membrane (M), envelope (E), and nucleocapsid (N), with the S protein comprised of two subunits S1 and S2.[9] The Receptor Binding Domain (RBD) is included within the S1 subunit and has a high affinity for the angiotensin converting enzyme 2 (ACE2) receptor on the cell surface membrane. Infection is mediated by interaction of the SARS-CoV-2 RBD with the ACE2 viral receptor on host cells.[9, 10] Antibodies to spike RBD can inhibit binding to the ACE2 receptor, generating a strong viral neutralizing response. A wide range of COVID-19 vaccines in development utilize strategies that generate antibody response to the spike protein and the RBD domain of the S1 subunit.[11-14]

The SARS-CoV-2 IgG II Quant assay has demonstrated the ability to detect the spike RBD-based vaccine response in longitudinal samples from individuals both with and without prior COVID-19 infection.[15-17]

Several studies have indicated that serum and plasma antibodies are typically produced to structural proteins (RBD, S, and N), with antibodies appearing as early as a few days to a few weeks after the onset of symptoms and often after the detection of viral ribonucleic acid (RNA) declines[18-24] or is no longer detectable.[7, 18-20, 25] Higher titer antibody responses have been observed in patients with more severe illness as compared with mildly symptomatic or asymptomatic individuals.[23] The persistence of IgG antibodies allows for identification of subjects who have been infected in the past and recovered from the illness[26] and is useful in serological surveys to assess the prevalence of SARS-CoV-2 infection in selected groups or broader populations.[27]

Research is ongoing to establish the extent to which IgG antibodies to SARS-CoV-2, and in particular neutralizing antibodies, confer immunity to infection. The onset of neutralizing antibodies is generally detectable between 7 and 15 days following the onset of disease.[19] Direct assessment of viral neutralization activity requires specific facilities, equipment, and trained personnel that are not broadly available to most diagnostic laboratories. However, the presence of neutralizing antibodies has been correlated to antibody reactivity to viral structural proteins (RBD, S, and N) as detected using *in vitro* immunoassays.[19, 28, 29] Plasma from convalescent donors with neutralizing levels of specific IgG has shown efficacy in limiting the consequences of COVID-19.[30, 31] Several studies have alluded to the potential of antibody testing, correlated to neutralizing antibody titers, as part of the evaluation of convalescent COVID plasma (CCP) to assess potency and efficacy of the product.[28, 32, 33] The ability to longitudinally detect and quantitate antibodies which are associated with neutralization of the virus will become increasingly important as vaccines and therapeutics gain widespread use.[34-36]

BIOLOGICAL PRINCIPLES OF THE PROCEDURE

This assay is an automated, two-step immunoassay for the qualitative and quantitative determination of IgG antibodies to SARS-CoV-2 in human serum and plasma using chemiluminescent microparticle immunoassay (CMIA) technology.

Sample, SARS-CoV-2 antigen coated paramagnetic microparticles, and assay diluent are combined and incubated. The IgG antibodies to SARS-CoV-2 present in the sample bind to the SARS-CoV-2 antigen coated microparticles. The mixture is washed. Anti-human IgG acridinium-labeled conjugate is added to create a reaction mixture and incubated. Following a wash cycle, Pre-Trigger and Trigger Solutions are added.

The resulting chemiluminescent reaction is measured as a relative light unit (RLU). There is a direct relationship between the amount of IgG antibodies to SARS-CoV-2 in the sample and the RLU detected by the system optics.

For additional information on system and assay technology, refer to the Alinity ci-series Operations Manual, Section 3.

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REAGENTS

Kit Contents

SARS-CoV-2 IgG II Quant Reagent Kit 06S61

NOTE: Some kit sizes may not be available. Please contact your local distributor.

Volumes (mL) listed in the following table indicate the volume per cartridge.

REF	06S6122	06S6132
Tests per cartridge	100	500
Number of cartridges per kit	2	2
Tests per kit	200	1000
MICROPARTICLES	6.6 mL	27.0 mL
CONJUGATE	6.1 mL	26.5 mL
ASSAY DILUENT	8.3 mL	36.9 mL

MICROPARTICLES Purified SARS-CoV-2 recombinant antigen coated microparticles in TRIS buffer with surfactant. Minimum concentration: 0.0675% solids. Preservatives: ProClin 950 and sodium azide.

CONJUGATE Anti-human IgG (mouse, monoclonal) acridinium-labeled conjugate in MES buffer with surfactants and protein (bovine) stabilizer. Minimum concentration: 6 ng/mL. Preservatives: ProClin 300 and antimicrobial agents.

ASSAY DILUENT MES buffer with protein (bovine) stabilizers. Preservatives: ProClin 300 and ProClin 950.

Warnings and Precautions

- IVD
- For *In Vitro* Diagnostic Use

Safety Precautions

CAUTION: This product requires the handling of human specimens. It is recommended that all human-sourced materials and all consumables contaminated with potentially infectious materials be considered potentially infectious and handled in accordance with the OSHA Standard on Bloodborne Pathogens. Biosafety Level 2 or other appropriate regional, national, and institutional biosafety practices should be used for materials that contain, are suspected of containing, or are contaminated with infectious agents.[37-40]

The following warnings and precautions apply to: MICROPARTICLES

WARNING	Contains methylisothiazolone and sodium azide.
H317	May cause an allergic skin reaction.
EUH032	Contact with acids liberates very toxic gas.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
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 in accordance with local regulations.

The following warnings and precautions apply to: ASSAY DILUENT

WARNING	Contains methylisothiazolones.
H317	May cause an allergic skin reaction.
H402*	Harmful to aquatic life.
H412	Harmful to aquatic life with long lasting effects.
Prevention	
P261	Avoid breathing mist / vapors / spray.
P272	Contaminated work clothing should not be allowed out of the workplace.
P280	Wear protective gloves / protective clothing / eye protection.
P273	Avoid release to the environment.
Response	
P302+P352	IF ON SKIN: Wash with plenty of water.
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 in accordance with local regulations.

* Not applicable where regulation EC 1272/2008 (CLP) has been implemented.

Follow local chemical disposal regulations based on your location along with recommendations and content in the Safety Data Sheet to determine the safe disposal of this product.

For the most current hazard information, see the product Safety Data Sheet.

Safety Data Sheets are available at www.corelaboratory.abbott or contact your local representative.

For a detailed discussion of safety precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 8.

Reagent Handling

- Reagents are shipped on wet ice.
- Upon receipt, gently invert the unopened reagent kit by rotating it over and back for a full 180 degrees, 5 times with green label stripe facing up and then 5 times with green label stripe facing down. This ensures that liquid covers all sides of the bottles within the cartridges. During reagent shipment, microparticles can settle on the reagent septum.
  - Place a check in the square on the reagent kit to indicate to others that the inversions have been completed.
- After mixing, place reagent cartridges in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- If a reagent cartridge is dropped, place in an upright position for 1 hour before use to allow bubbles that may have formed to dissipate.
- Reagents are susceptible to the formation of foam and bubbles. Bubbles may interfere with the detection of the reagent level in the cartridge and cause insufficient reagent aspiration that may adversely affect results.

For a detailed discussion of reagent handling precautions during system operation, refer to the Alinity ci-series Operations Manual, Section 7.

Reagent Storage

- Do not freeze.

	Storage Temperature	Maximum Storage Time	Additional Storage Instructions
Unopened	2 to 8˚C	Until expiration date	Store in upright position. If cartridge does not remain upright, gently invert the cartridge 10 times and place in an upright position for 1 hour before use.
Onboard	System Temperature	30 days	
Opened	2 to 8˚C	Until expiration date	Store in upright position. If cartridge does not remain upright during storage off the system, discard the cartridge. Do not reuse original reagent caps or replacement caps due to the risk of contamination and the potential to compromise reagent performance.

Reagents may be stored on or off the system. If removed from the system, store reagents with new replacement caps in an upright position at 2 to 8˚C. For reagents stored off the system, it is recommended that they be stored in their original trays or boxes to ensure they remain upright.

For information on unloading reagents, refer to the Alinity ci-series Operations Manual, Section 5.

Indications of Reagent Deterioration

Deterioration of the reagents may be indicated when a calibration error occurs or a control value is out of the specified range. Associated test results are invalid, and samples must be retested. Assay recalibration may be necessary.

For troubleshooting information, refer to the Alinity ci-series Operations Manual, Section 10.

INSTRUMENT PROCEDURE

The SARS-CoV-2 IgG II Quant assay file must be installed on the Alinity i system prior to performing the assay.

For detailed information on assay file installation and viewing and editing assay parameters, refer to the Alinity ci-series Operations Manual, Section 2.

For information on printing assay parameters, refer to the Alinity ci-series Operations Manual, Section 5.

For a detailed description of system procedures, refer to the Alinity ci-series Operations Manual.

SPECIMEN COLLECTION AND PREPARATION FOR ANALYSIS

Specimen Types

The specimen types listed below were verified for use with this assay.

Other specimen types and collection tube types have not been verified with this assay.

Specimen Types	Collection Tubes	Special Conditions
Serum	Serum[a]	
	Serum separator	
Plasma	Dipotassium EDTA[a]	
	Tripotassium EDTA	
	Lithium heparin	
	Lithium heparin separator	
	Sodium heparin	
	ACD[b]	To account for dilution effect, results from samples collected in ACD and sodium citrate tubes must be manually multiplied by a dilution factor to determine corrected concentration values.[b]
	Sodium citrate[b]	

[a] Including capillary blood samples.

[b] It is the responsibility of the operator to manually apply the appropriate dilution factor, which can be determined using the equation below. Consult the tube manufacturer's labeling to determine the volume of anticoagulant in the tube and for additional guidance on the correction of the expected dilution effect.

$$\text{Dilution Factor} = \frac{\text{(Volume of Anticoagulant in Tube + Total Volume of Blood in Tube)}}{\text{Total Volume of Blood in Tube}}$$

- The instrument does not provide the capability to verify specimen types or collection tube types. It is the responsibility of the operator to verify that the correct specimen types and collection tube types are used in the assay.
- Liquid anticoagulants may have a dilution effect resulting in lower concentration values for individual specimens.
- Performance has not been established for the use of cadaveric specimens or the use of bodily fluids other than human serum/plasma.
- Each laboratory is responsible for following their own procedures to establish the use of additional tube or collection types.

Specimen Conditions

- Do not use:
  - heat-inactivated specimens
  - pooled specimens
  - grossly hemolyzed specimens
  - specimens with obvious microbial contamination
  - specimens with fungal growth
- For accurate results, serum and plasma specimens should be free of fibrin, red blood cells, and other particulate matter. Serum specimens from patients receiving anticoagulant or thrombolytic therapy may contain fibrin due to incomplete clot formation.
- To prevent cross contamination, use of disposable pipettes or pipette tips is recommended.

Preparation for Analysis

- Follow the tube manufacturer's processing instructions for collection tubes. Gravity separation is not sufficient for specimen preparation.

- Specimens should be free of bubbles. Remove bubbles with an applicator stick before analysis. Use a new applicator stick for each specimen to prevent cross contamination.

To ensure consistency in results, recentrifuge specimens prior to testing if

- they contain fibrin, red blood cells, or other particulate matter.

NOTE: If fibrin, red blood cells, or other particulate matter are observed, mix by low speed vortex or by inverting 10 times prior to recentrifugation.

Prepare frozen specimens as follows:

- Frozen specimens must be completely thawed before mixing.
- Mix thawed specimens thoroughly by low speed vortex or by inverting 10 times.
- Visually inspect the specimens. If layering or stratification is observed, mix until specimens are visibly homogeneous.
- If specimens are not mixed thoroughly, inconsistent results may be obtained.
- Recentrifuge specimens that contain particulate matter.

Recentrifugation of Specimens

- Transfer specimens to a centrifuge tube and centrifuge.
- Transfer clarified specimen to a sample cup or secondary tube for testing. For centrifuged specimens with a lipid layer, transfer only the clarified specimen and not the lipemic material.

Specimen Storage

Specimen Type	Temperature	Maximum Storage Time	Special Instructions
Serum/Plasma	Room temperature (15 to 30°C)	2 days	Specimens may be stored on or off the clot, red blood cells, or separator gel.
	2 to 8°C	7 days	Specimens may be stored on or off the clot, red blood cells, or separator gel.
	-20°C or colder	1 month - venous blood sample	Remove serum or plasma from the clot, red blood cells, or separator gel.
		7 days - capillary blood sample	Remove serum or plasma from the clot or red blood cells.

Avoid more than 2 freeze/thaw cycles.

Specimen stored -20°C or colder for greater than the maximum storage time may be used for information purposes.

Specimen Shipping

Package and label specimens in compliance with applicable state, federal, and international regulations covering the transport of clinical specimens and infectious substances.

Do not exceed the storage limitations listed above.

PROCEDURE

Materials Provided

06S61 SARS-CoV-2 IgG II Quant Reagent Kit

Materials Required but not Provided

- SARS-CoV-2 IgG II Quant assay file
- 06S6102 SARS-CoV-2 IgG II Quant Calibrator Kit
- 06S6112 SARS-CoV-2 IgG II Quant Control Kit or other control material containing IgG antibodies to SARS-CoV-2
- Alinity Pre-Trigger Solution
- Alinity Trigger Solution
- Alinity i-series Concentrated Wash Buffer
- 09P1540 Alinity i Multi-Assay Manual Diluent

For information on materials required for operation of the instrument, refer to the Alinity ci-series Operations Manual, Section 1.

For information on materials required for maintenance procedures, refer to the Alinity ci-series Operations Manual, Section 9.

Assay Procedure

For a detailed description of how to run an assay, refer to the Alinity ci-series Operations Manual, Section 5.

- If using primary or aliquot tubes, refer to the Alinity ci-series Operations Manual, Section 4 to ensure sufficient specimen is present.
- Minimum sample cup volume is calculated by the system and printed on the Order List report. To minimize the effects of evaporation, verify adequate sample cup volume is present prior to running the test.
- Maximum number of replicates sampled from the same sample cup: 10
  - Priority:
    - Sample volume for first test: 75 µL
    - Sample volume for each additional test from same sample cup: 25 µL
  - ≤ 3 hours on the reagent and sample manager:
    - Sample volume for first test: 150 µL
    - Sample volume for each additional test from same sample cup: 25 µL
  - > 3 hours on the reagent and sample manager:
    - Replace with a fresh aliquot of sample.
- Refer to the SARS-CoV-2 IgG II Quant calibrator package insert REF 06S6102 and/or SARS-CoV-2 IgG II Quant control package insert REF 06S6112 for preparation and usage.
- For general operating procedures, refer to the Alinity ci-series Operations Manual, Section 5.
- For optimal performance, it is important to perform routine maintenance as described in the Alinity ci-series Operations Manual, Section 9. Perform maintenance more frequently when required by laboratory procedures.

Sample Dilution Procedures

Samples with a SARS-CoV-2 IgG value exceeding 40 000.0 AU/mL are flagged with the code "> 40,000.0 AU/mL" and may be diluted with either the Automated Dilution Protocol or the Manual Dilution Procedure.

Automated Dilution Protocol

The system performs a 1:2 dilution of the sample and automatically calculates the concentration by multiplying the result by the dilution factor.

For details on configuring automated dilutions, refer to the Alinity ci-series Operations Manual, Section 2.

Manual Dilution Procedure

Suggested dilution: 1:2

Add 75 µL of the sample to 75 µL of Alinity i Multi-Assay Manual Diluent.

The operator must enter the manual dilution factor in the Specimen or Control tab of the Create Order screen. The system will use this dilution factor to automatically calculate the concentration of the sample and report the result.

The result should be ≥ 21.0 AU/mL before the manual dilution factor is applied.

If the operator does not enter the manual dilution factor, the result must be manually multiplied by the appropriate manual dilution factor before reporting the result. If a diluted sample result is less than 21.0 AU/mL, do not report the result. Rerun using an appropriate dilution.

For detailed information on ordering dilutions, refer to the Alinity ci-series Operations Manual, Section 5.

Calibration

For instructions on performing a calibration, refer to the Alinity ci-series Operations Manual, Section 5.

Each assay control must be tested to evaluate the assay calibration.

Once a calibration is accepted and stored, all subsequent samples may be tested without further calibration unless:

- A reagent kit with a new lot number is used.
- Daily quality control results are outside of statistically-based quality control limits used to monitor and control system performance, as described in the Quality Control Procedures section of this reagent package insert.
- If statistically-based quality control limits are not available, then the calibration should not exceed a 30-day limit for recalibration frequency.

This assay may require recalibration after maintenance to critical parts or subsystems or after service procedures have been performed.

For additional information, refer to the assay reagent package insert and the Alinity ci-series Operations Manual.

Quality Control Procedures

The recommended control requirement for the SARS-CoV-2 IgG II Quant assay is that a single sample of each control level be tested once every 24 hours each day of use.

Additional controls may be tested in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.

To establish initial statistically-based control limits, each laboratory should establish its own concentration target and ranges for new control lots and for each control level. This can be accomplished by assaying a minimum of 20 replicates over multiple days. A minimum of 10 days enables some day-to-day sources of variability using the reported results to establish the expected average (target) and variability about this average (range) for the laboratory. Sources of variation that should be included in this study in order to be representative of future system performance include:

- Multiple stored calibrations
- Multiple reagent lots
- Multiple calibrator lots
- Multiple processing modules (if applicable)
- Data points collected at different times of the day

Refer to published guidelines for information or general control recommendation, for example Clinical and Laboratory Standards Institute (CLSI) Guideline C24, 4th ed., or other published guidelines, for general quality control recommendations.[41]

- If more frequent control monitoring is required, follow the established quality control procedures for your laboratory.
- If quality control results do not meet the acceptance criteria defined by your laboratory, sample results may be suspect. Follow the established quality control procedures for your laboratory. Recalibration may be necessary. For troubleshooting information, refer to the Alinity ci-series Operations Manual, Section 10.
- Review quality control results and acceptance criteria following a change of reagent or calibrator lot.

Controls should be used according to the guidelines and recommendations of the control manufacturer. Concentration ranges provided in the control package insert should be used only for guidance.

For any control material in use, the laboratory should ensure that the matrix of the control material is suitable for use in the assay per the assay package insert.

Quality Control Guidance

Refer to "Basic QC Practices" by James O. Westgard, Ph.D. for guidance on laboratory quality control practices.[42]

Verification of Assay Claims

For protocols to verify package insert claims, refer to Verification of Assay Claims in the Alinity ci-series Operations Manual.

RESULTS

Calculation

The SARS-CoV-2 IgG II Quant assay utilizes a 4 Parameter Logistic Curve fit data reduction method (4PLC, Y-weighted) to generate a calibration and results.

Interpretation of Results

The cutoff is 50.0 AU/mL.

As with all analyte determinations, the result should be used in conjunction with information available from clinical evaluation and other diagnostic procedures.

AU/mL	Interpretation
< 50.0	Negative
≥ 50.0	Positive

For details on configuring the Alinity i system to use grayzone interpretations, refer to the Alinity ci-series Operations Manual, Section 2.

The grayzone interpretation is an editable parameter and should be utilized per end user requirements.

Flags

Some results may contain information in the Flags field. For a description of the flags that may appear in this field, refer to the Alinity ci-series Operations Manual, Section 5.

Reportable Interval

Based on representative data for the limit of quantitation (LoQ) and the limit of detection (LoD), the ranges over which results can be reported are provided below according to the definitions from CLSI EP34, 1st ed.[43]

	AU/mL
Analytical Measuring Interval (AMI)[a]	21.0 - 40 000.0
Extended Measuring Interval (EMI)[b]	40 000.0 - 80 000.0
Reportable Interval[c]	6.8 - 80 000.0

[a] AMI: The AMI extends from the LoQ to the upper limit of quantitation (ULoQ). This is determined by the range of values in AU/mL that demonstrated acceptable performance for linearity, imprecision, and bias.

[b] EMI: The EMI extends from the ULoQ to the ULoQ × dilution factor. The value reflects a 1:2 dilution factor.

[c] The reportable interval extends from the LoD to the upper limit of the EMI.

NOTE: The default Low Linearity value of the assay file is set to 0.0 AU/mL.

LIMITATIONS OF THE PROCEDURE

- Results should be used in conjunction with other data; e.g., symptoms, results of other tests, and clinical impressions.
- Negative results do not rule out SARS-CoV-2 infection, particularly in those who have been in contact with the virus. Follow-up testing with a molecular diagnostic should be considered to rule out infection in these individuals.
- Results from antibody testing should not be used as the sole basis to diagnose or exclude SARS-CoV-2 infection or to inform infection status.
- Immunocompromised patients who have COVID-19 may have a delayed antibody response and produce levels of antibody which may not be detected as positive by the assay.
- The persistence of a SARS-CoV-2 immune response has not been fully established. Negative results may be observed due to a decline in antibody titer over time.
- Potential interference has not been evaluated for substances other than those described in the SPECIFIC PERFORMANCE CHARACTERISTICS section of this package insert.

- Specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA). Such specimens may show either falsely elevated or depressed values when tested with assay kits such as SARS-CoV-2 IgG II Quant that employ mouse monoclonal antibodies.[44, 45]
- Heterophilic antibodies in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays. Patients routinely exposed to animals or to animal serum products can be prone to this interference, and anomalous values may be observed.[46]
- Rheumatoid factor (RF) in human serum can react with reagent immunoglobulins, interfering with *in vitro* immunoassays.[46]

SPECIFIC PERFORMANCE CHARACTERISTICS

Representative performance data are provided in this section. Results obtained in individual laboratories may vary.

The Alinity i system and the ARCHITECT i2000SR System utilize the same reagents and sample/reagent ratios.

Unless otherwise specified, all studies were performed on the Alinity i system.

Precision

Within-Laboratory Precision

A study was performed based on guidance from CLSI EP05-A3.[47] Testing was conducted using 2 lots of the SARS-CoV-2 IgG II Quant Reagent Kit, 2 lots of the SARS-CoV-2 IgG II Quant Calibrator Kit, and 1 lot of the SARS-CoV-2 IgG II Quant Control Kit and 1 Alinity i instrument. Three controls and 3 human plasma panels were assayed in replicates of 3, at 2 separate times per day, on 20 different days, for a total of 120 replicates for each test sample. The performance from a representative combination is shown in the following table.

			Within-Run (Repeatability)		Within-Laboratory[a]	
Sample	n	Mean (AU/mL)	SD	%CV	SD (Range[b])	%CV (Range[b])
Negative Control	120	1.8	0.84	N/A	1.28 (1.04-1.28)	N/A
Positive Control 1	120	165.3	3.89	2.4	5.94 (4.51-5.94)	3.6 (2.7-3.6)
Positive Control 2	120	603.1	14.31	2.4	18.43 (14.97-18.43)	3.1 (2.4-3.1)
Low Panel	120	46.9	1.51	3.2	2.64 (1.79-2.64)	5.6 (3.9-5.6)
Medium Panel	120	85.9	1.94	2.3	3.51 (2.50-3.51)	4.1 (2.9-4.1)
High Panel	120	33 348.0	996.95	3.0	1151.02 (1040.24-1151.02)	3.5 (3.0-3.5)

N/A = Not applicable

[a] Includes within-run, between-run, and between-day variability.

[b] Minimum and maximum SD or %CV across all reagent lot and instrument combinations.

System Reproducibility

A study was performed based on guidance from CLSI EP05-A3.[47] Testing was conducted using 1 lot of the SARS-CoV-2 IgG II Quant Reagent Kit, 1 lot of the SARS-CoV-2 IgG II Quant Calibrator Kit, and 1 lot of the SARS-CoV-2 IgG II Quant Control Kit and 2 Alinity i instruments. Three controls and 3 human plasma panels were assayed in replicates of 3, at 2 separate times per day, for 5 days. The performance across instruments is shown in the following table.

			Within-Run (Repeatability)		Within-Laboratory[a]		Reproducibility[b]	
Sample	n	Mean (AU/mL)	SD	%CV	SD	%CV	SD	%CV
Negative Control	60	2.1	0.91	N/A	1.35	N/A	1.35	N/A
Positive Control 1	60	166.4	3.95	2.4	5.10	3.1	5.69	3.4
Positive Control 2	60	602.2	12.45	2.1	14.33	2.4	15.28	2.5
Low Panel	60	47.7	1.71	3.6	1.78	3.7	1.82	3.8
Medium Panel	60	86.9	2.04	2.3	2.36	2.7	2.36	2.7
High Panel	60	34 230.3	1355.27	4.0	1513.69	4.4	2077.43	6.1

N/A = Not applicable

[a] Includes within-run, between-run, and between-day variability.

[b] Reproducibility contains repeatability (within-run), between-run, between-day, and between-instrument variability.

Accuracy by Recovery

Nine normal human plasma samples with known target concentrations of SARS-CoV-2 IgG were tested in replicates of 6 on the SARS-CoV-2 IgG II Quant assay. The percent recovery relative to the target concentration was calculated for each sample.

Sample No.	N	Mean SARS-CoV-2 IgG Concentration (AU/mL)	Target SARS-CoV-2 IgG Concentration (AU/mL)	% Recovery[a]
1	6	45.8	50.0	-8.4
2	6	133.4	150.0	-11.1
3	6	4799.9	5000.0	-4.0
4	6	10 256.5	10 000.0	2.6
5	6	14 925.8	15 000.0	-0.5
6	6	20 312.2	20 000.0	1.6
7	6	24 626.3	25 000.0	-1.5
8	6	29 156.0	30 000.0	-2.8
9	6	34 742.1	37 000.0	-6.1

[a] $\%\ \text{Recovery} = \dfrac{\text{Mean SARS-CoV-2 IgG Concentration} - \text{Target SARS-CoV-2 IgG Concentration}}{\text{Target SARS-CoV-2 IgG Concentration}} \times 100$

Lower Limits of Measurement

A study was performed based on guidance from CLSI EP17-A2.[48] Testing was conducted using 2 lots of the SARS-CoV-2 IgG II Quant reagents on each of 2 instruments over a minimum of 3 days. The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) values are summarized below. These representative data support the lower limit of the analytical measuring interval.

	AU/mL
LoB[a]	2.8
LoD[b]	6.8
LoQ[c]	21.0

[a] The LoB represents the 95th percentile from n ≥ 60 replicates of zero-analyte samples.

[b] The LoD presented in the table is in alignment with the SARS-CoV-2 IgG II Quant assay on the ARCHITECT i System. The observed LoD on the Alinity i system was 4.1 AU/mL and represents the lowest concentration at which the analyte can be detected with 95% probability based on n ≥ 60 replicates of low-analyte level samples.

[c] The LoQ presented in the table is in alignment with the low end of the AMI for the SARS-CoV-2 IgG II Quant assay on the Alinity i system. The observed LoQ on the Alinity i system was 7.2 AU/mL. The LoQ is defined as the lowest concentration at which a maximum allowable precision of 20 %CV was met and was determined from n ≥ 60 replicates of low-analyte level samples.

Linearity

A study was performed based on guidance from CLSI EP06-A.[49]

This assay is linear across the analytical measuring interval of 21.0 to 40 000.0 AU/mL.

Analytical Specificity

This study was performed on the ARCHITECT i2000SR System.

The SARS-CoV-2 IgG II Quant assay was evaluated for potential cross-reactivity from individuals with other medical conditions. A total of 251 specimens from 49 different categories were tested. All 251 specimens were negative by the SARS-CoV-2 IgG II Quant assay. The data are summarized in the following table. Bold indicates other respiratory illness categories.

Category	n	Positive	Negative
Adenovirus	**5**	**0**	**5**
Antinuclear Antibody (ANA)	5	0	5
Autoimmune Hepatitis	5	0	5
Cytomegalovirus (CMV) Immunoglobulin Class G	5	0	5
CMV IgM	5	0	5
Double-Stranded Deoxyribonucleic Acid (dsDNA) Antibody	5	0	5
Enterovirus IgG	**5**	**0**	**5**
Enterovirus IgM	**5**	**0**	**5**
Epstein-Barr Virus (EBV) IgG	5	0	5
EBV IgM	5	0	5
Escherichia coli (E. coli) Antibody	5	0	5
HAMA	5	0	5
Hemodialysis Patients	5	0	5
Hepatitis A Virus (HAV)	5	0	5
Hepatitis B Core (HBc) IgM	4	0	4
Hepatitis B Virus (HBV)	5	0	5
Hepatitis C Virus (HCV)	5	0	5
Hepatitis D Virus (HDV)	5	0	5
Herpes Simplex Virus (HSV)	5	0	5
Heterophilic Antibody Positive	5	0	5
Human Coronavirus 229E	**10**	**0**	**10**
Human Coronavirus HKU1	**9**	**0**	**9**
Human Coronavirus NL63	**5**	**0**	**5**
Human Coronavirus OC43	**10**	**0**	**10**
Human Immunodeficiency Virus (HIV)	5	0	5
Human T-Lymphotropic Virus (HTLV) Type 1	5	0	5
HTLV Type 2	5	0	5
Hyper IgM	5	0	5
Influenza A	**5**	**0**	**5**
Influenza B	**5**	**0**	**5**
Influenza A/B	**5**	**0**	**5**
Influenza Vaccine	5	0	5
Lupus	5	0	5
Monoclonal Hyper IgG	5	0	5
Mycoplasma IgM	5	0	5
Parainfluenza IgG	**5**	**0**	**5**
Parainfluenza IgM	**2**	**0**	**2**
Picornavirus	**5**	**0**	**5**
Polyclonal Hyper IgG	3	0	3
Pregnant Females	5	0	5
Pregnant Females, Multiparous	5	0	5
Respiratory Syncytial Virus (RSV)	**5**	**0**	**5**
Rheumatoid Factor (RF)	5	0	5
RF IgM	4	0	4
Rubella IgG	5	0	5
Rubella IgM	5	0	5
Toxoplasmosis IgG	5	0	5
Toxoplasmosis IgM	4	0	4
Varicella Zoster Virus	5	0	5
Total	251	0	251

Interference

These studies were performed on the ARCHITECT i2000SR System.

Potentially Interfering Endogenous Substances

A study was performed based on guidance from CLSI EP07, 3rd ed.[50] Each substance was tested at 2 levels of the analyte (< 50 AU/mL and > 600 AU/mL). The observed interference was within or equal to ± 15% for samples with concentrations ≥ 35 AU/mL; therefore, the study showed no interference was observed at the following endogenous substance interferent levels.

Potentially Interfering Endogenous Substance	Interferent Level
Unconjugated Bilirubin	40 mg/dL
Conjugated Bilirubin	40 mg/dL
Hemoglobin	1000 mg/dL
Triglycerides (Intralipid)	2000 mg/dL
Total Protein	15 g/dL

Potentially Interfering Substances

A study was performed based on guidance from CLSI EP07, 3rd ed.[50] Each substance was tested at 2 levels of the analyte (< 50 AU/mL and > 600 AU/mL). The observed interference was within or equal to ± 15% for samples with concentrations ≥ 35 AU/mL; therefore, the study showed no interference was observed at the following interferent levels.

Potentially Interfering Substance	Interferent Level
Acetaminophen	15.6 mg/dL
Alprazolam	0.0258 mg/dL
Ascorbic Acid	5.25 mg/dL
Azithromycin	1.11 mg/dL
Biotin	4250 ng/mL
Captopril	0.264 mg/dL
Fluoxetine	0.142 mg/dL
Guaifenesin	0.450 mg/dL
Hydroxychloroquine	388.8 ng/mL
Ibuprofen	21.9 mg/dL
Remdesivir	27 µmol/L

Clinical Performance

A study was performed to determine the clinical performance of the SARS-CoV-2 IgG II Quant assay.

All specimens tested were assayed in replicates of one using 2 lots of the SARS-CoV-2 IgG II Quant Reagent Kit, 2 lots of the SARS-CoV-2 IgG II Quant Calibrator Kit, and one lot of the SARS-CoV-2 IgG II Quant Control Kit on 2 Alinity i instruments.

To estimate the positive percent agreement (PPA) between the SARS-CoV-2 IgG II Quant assay and the polymerase chain reaction (PCR) comparator, 457 retrospective frozen serum and plasma specimens, collected at different times, were purchased from medical institutions, from a total of 142 subjects whose respiratory samples tested positive for SARS-CoV-2 by a PCR method and who also presented with COVID-19 symptoms. Specimens from a total of 7 immunocompromised subjects were not included in the data analysis. There were 436 specimens from the remaining 135 immunocompetent study subjects included in the data analysis. The PPA and the 95% confidence interval (CI) were calculated. The performance summary data are illustrated in the tables below.

Positive Percent Agreement by Days Post-Symptom Onset

Days Post-Symptom Onset	n	Positive	Negative	PPA (95% CI)
≤ 7	118[a]	61	57	51.69% (42.77, 60.51)
8 - 14	163[a]	140	23	85.89% (79.72, 90.41)
≥ 15	155[a]	154	1	99.35% (96.44, 99.97)

[a] Twenty-one (21) specimens from 7 immunocompromised patients were excluded from the study. Refer to the LIMITATIONS OF THE PROCEDURE section of this package insert for further information. When the results from these specimens were included, the PPA at ≤ 7 days post-symptom onset was 51.26% (95% CI: 42.38, 60.06), the PPA at 8 - 14 days post-symptom onset was 82.46% (95% CI: 76.06, 87.43), and the PPA at ≥ 15 days post-symptom onset was 97.01% (95% CI: 93.18, 98.71).

Positive Percent Agreement by Days Post-Positive PCR

Days Post-Positive PCR	n	Positive	Negative	PPA (95% CI)
≤ 7	226[a]	150	76	66.37% (59.98, 72.21)
8 - 14	133[a]	129	4	96.99% (92.52, 98.82)
≥ 15	77[a]	76	1	98.70% (93.00, 99.93)

[a] Twenty-one (21) specimens from 7 immunocompromised patients were excluded from the study. Refer to the LIMITATIONS OF THE PROCEDURE section of this package insert for further information. When the results from these specimens were included, the PPA at ≤ 7 days post-positive PCR result was 65.22% (95% CI: 58.86, 71.08), the PPA at 8 - 14 days post-positive PCR result was 93.53% (95% CI: 88.15, 96.56), and the PPA at ≥ 15 days post-positive PCR result was 95.45% (95% CI: 88.89, 98.22).

Clinical Performance with SARS-CoV-2 Variants

A study was conducted to evaluate the clinical performance of the SARS-CoV-2 IgG II Quant assay using patient specimens with the SARS-CoV-2 variant B.1.1.7.

All specimens tested were assayed in replicates of 1 using 1 lot of the SARS-CoV-2 IgG II Quant Reagent Kit, 1 lot of the SARS-CoV-2 IgG II Quant Calibrator Kit, and 1 lot of the SARS-CoV-2 IgG II Quant Control Kit on 1 Alinity i instrument.

To estimate the positive percent agreement (PPA) between the SARS-CoV-2 IgG II Quant assay and the polymerase chain reaction (PCR) comparator, 20 human serum specimens with confirmed PCR results for SARS-CoV-2 variant B.1.1.7 and collected ≥ 15 days post-symptom onset, were purchased from medical institutions. Specimens from 1 immunocompromised subject were not included in the data analysis. The PPA and the 95% confidence interval (CI) were calculated. The performance summary data is illustrated in the table below.

Days Post-Symptom Onset	n	Positive	Negative	PPA (95% CI)
≥ 15	19[a]	19	0	100.00% (82.35, 100.00)

The Clopper-Pearson method is used to calculate the confidence intervals.

[a] One (1) specimen from 1 immunocompromised patient was excluded from the study. Refer to the LIMITATIONS OF THE PROCEDURE section of this package insert for further information. When the results from this specimen was included, the PPA at ≥ 15 days post-symptom onset was 95.00% (95% CI: 75.13, 99.87).

Negative Percent Agreement

To estimate the negative percent agreement (NPA), frozen serum and plasma specimens from 2008 unique study subjects were tested using the SARS-CoV-2 IgG II Quant assay. All specimens were collected prior to September 2019 (pre-COVID-19 outbreak) and were therefore assumed to be negative. The NPA and the 95% CI were calculated. The performance summary data are illustrated in the table below.

SARS-CoV-2 IgG II Quant Results			
n	Positive	Negative	NPA (95% CI)
2008	8	2000	99.60% (99.22, 99.80)

Positive Predictive Value and Negative Predictive Value

The positive predictive value (PPV) and negative predictive value (NPV) were determined using the PPA at ≥ 15 days post-symptom onset and the NPA, assuming a SARS-CoV-2 IgG prevalence of 5%. Seven (7) immunocompromised subjects were excluded. The PPV was 92.92% (95% CI: 86.79, 96.33). The NPV was 99.97% (95% CI: 99.76, 100.00).

Longitudinal Study

From the positive percent agreement study above, a subset of 104 subjects with 2 or more blood draws post-symptom onset were assessed longitudinally. Out of the 104 subjects, 67 presented positive results in all bleeds, 3 presented negative results in all bleeds, while 34 subjects showed SARS-CoV-2 IgG seroconversion. Representative SARS-CoV-2 IgG II Quant seroconversion results are provided below.

Subject	Draw	Days Post-Symptom Onset	Result (AU/mL)	Interpretation
13	1	1	4.2	Negative
	2	3	22.2	Negative
	3	10	3671.9	Positive
	4	15	18 157.2	Positive
	5	22	21 928.1	Positive
19	1	0	1.8	Negative
	2	4	6.8	Negative
	3	8	991.6	Positive
	4	11	9492.7	Positive
	5	14	11 280.5	Positive
23	1	0	6.6	Negative
	2	4	5.9	Negative
	3	7	182.3	Positive
	4	14	21 636.6	Positive
	5	20	28 543.6	Positive
120	1	5	0.0	Negative
	2	16	11 920.5	Positive
	3	20	13 847.1	Positive
	4	28	16 262.6	Positive
	5	33	28 438.7	Positive

Method Comparison Between ARCHITECT i2000SR and Alinity i Analyzers

A study was performed based on guidance from CLSI EP09c, Third Edition[51] using the Passing-Bablok regression method.

SARS-CoV-2 IgG II Quant on Alinity i vs SARS-CoV-2 IgG II Quant on ARCHITECT						
	n	Units	Correlation Coefficient	Intercept	Slope	Concentration Range
Serum and Plasma	375	AU/mL	1.00	1.7	0.93	24.0 - 39 944.6

Comparison to a Neutralization Test

Plaque reduction neutralization tests (PRNT) are used to quantify the titer of neutralizing antibodies for a virus.

Results provided below are representing a 50% inhibition of infection of cultured cells (ID50).

Percent Agreement

A positive percent agreement study was performed with the SARS-CoV-2 IgG II Quant assay on the Alinity i instrument using 86 samples that were demonstrated to be positive (≥ 1:20) using a plaque reduction neutralization test by the Broad Institute. Negative percent agreement was not evaluated.

	Neutralization Test	
SARS-CoV-2 IgG II Quant	**Positive**	**Negative**
Positive	86	0

Positive % agreement = 100.0% (86/86); 95% CI = 95.72, 100.00

Comparison to Neutralizing Antibody Titers

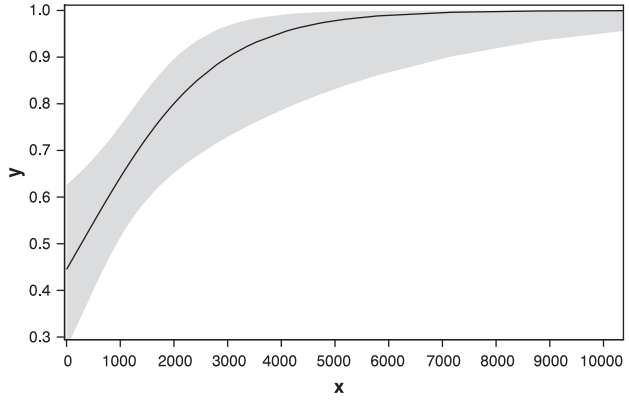
Logistic regression analyses were performed using the 86 samples above to estimate the SARS-CoV-2 IgG concentration corresponding to a 95% probability of being at or above the PRNT dilutions listed in the table below.

PRNT Dilution	SARS-CoV-2 IgG AU/mL
1:80	960
1:160	3450
1:250	3950
1:640	6650

An example of the probability profile using the PRNT ID50 at a 1:250 dilution as a representative high titer is shown in the table and graph below.

SARS-CoV-2 IgG AU/mL	Probability of High Titer	95% CI
2000	0.80	0.65, 0.90
3000	0.90	0.73, 0.97
3950	0.95	0.78, 0.99
6300	0.99	0.88, 1.00

Probability Curve of High Titer with 95% Confidence Interval



x SARS-CoV-2 IgG Concentration (AU/mL)

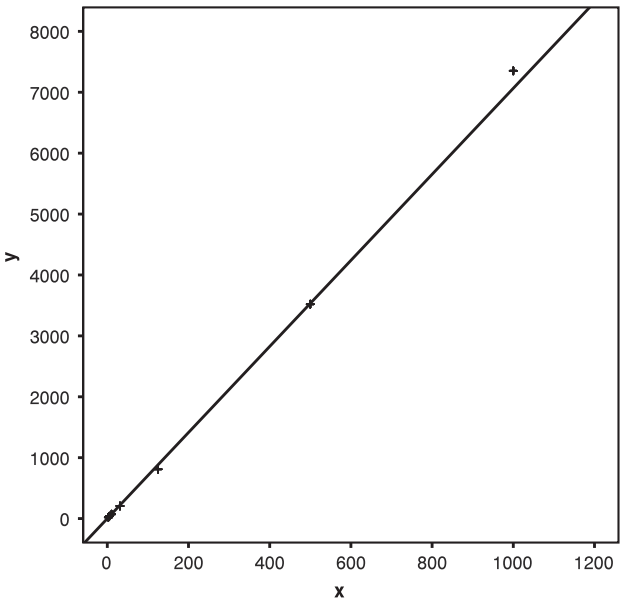
y Probability

WHO International Standard Linearity

This study was performed on the ARCHITECT i2000SR System.

A study was conducted to evaluate dilutions of the first WHO International Standard for anti-SARS-CoV-2 immunoglobulin (human) (NIBSC Code 20-136) with the SARS-CoV-2 IgG II Quant assay calibrated with Abbott internal reference calibrators. Serial dilutions were created using the prepared WHO standard and human recalcified plasma, negative for SARS-CoV-2. Samples were tested in replicates of 7 using 1 lot each of SARS-CoV-2 IgG II Quant reagents, calibrators, and controls on 1 ARCHITECT i2000SR instrument. A linear regression analysis was performed regressing the mean observed concentration results (AU/mL) versus the expected WHO International Standard concentrations (binding antibody unit per mL [BAU/mL]) using samples with concentrations just below the SARS-CoV-2 IgG II Quant LoQ up to the concentration of the neat WHO International Standard. Representative performance data, which are provided for informational purposes only, are summarized below.

Method	Number of Samples	Number of Replicates	ARCHITECT Range (AU/mL)	WHO Range (BAU/mL)	Correlation Coefficient	Slope
Weighted Linear Regression (intercept = 0)	7	7	20.8 - 7352.0	2.6 - 1000.0	0.9990	7.0656



x Expected WHO unit ((BAU)/mL)

y Mean (AU/mL)

Based on the results from this WHO International Standard study, the mathematical relationship of the Abbott AU/mL unit to the WHO BAU/mL unit would follow the equation:

BAU/mL = 0.142 × AU/mL

For detailed information on creating a user-defined result unit refer to Alinity ci-series Operations Manual, Section 2.

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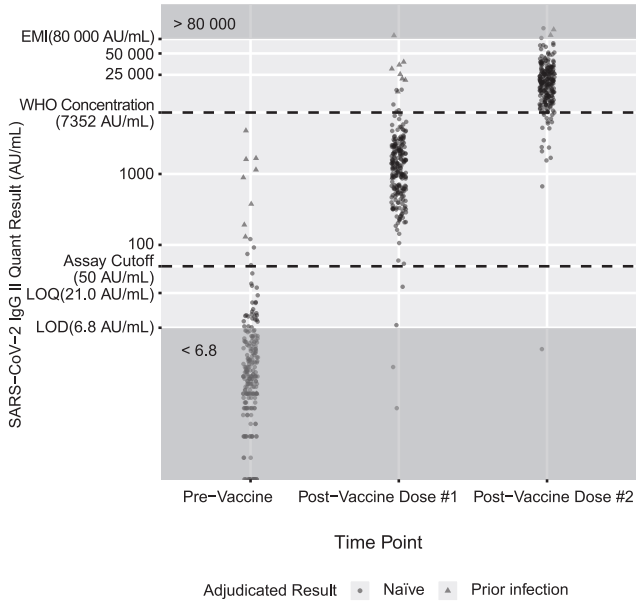
Vaccine Response

A longitudinal study was performed to monitor the performance of the SARS-CoV-2 IgG II Quant assay using serum and plasma specimens (n=227) from Pfizer-BioNTech COVID-19 vaccine recipients with prior COVID-19 infection and without prior COVID-19 infection (naive). Testing was conducted using 1 lot each of the SARS-CoV-2 IgG II Quant reagents, calibrators, and controls on 1 ARCHITECT i2000SR instrument. The positivity rate and median result for pre-vaccine, post-vaccine dose 1 (21 days ± 4 days post vaccination), and post-vaccine dose 2 (≥ 14 days post vaccination), along with corresponding results for the SARS-CoV-2 IgG and SARS-CoV-2 IgM assays, are presented in the following table.

SARS-CoV-2 Infection Status	Time Point	SARS CoV-2 IgG II Quant (Spike RBD)			SARS CoV-2 IgG (Nucleocapsid)			SARS CoV-2 IgM (Spike RBD)		
		n	Positivity Rate	Median (AU/mL)	n	Positivity Rate	Median (Index)	n	Positivity Rate	Median (Index)
Naive	Pre-Vaccine	216	1.9	< 21.0	216	0.0	0.03	216	0.5	0.04
	Post-Vaccine Dose 1	216	98.1	1214.9	216	0.0	0.03	216	50.0	1.00
	Post-Vaccine Dose 2	216	99.5	18 950.5	216	0.0	0.03	216	67.1	1.63
Prior infection	Pre-Vaccine	11	72.7	377.3	10	70.0	2.36	10	30.0	0.42
	Post-Vaccine Dose 1	11	100.0	22 023.6	11	63.6	1.96	11	36.4	0.81
	Post-Vaccine Dose 2	11	100.0	33 740.6	11	63.6	1.77	11	36.4	0.44

SARS-CoV-2 IgG (targeting nucleocapsid protein) and SARS-CoV-2 IgM (targeting spike RBD) were measured in parallel to SARS-CoV-2 IgG II Quant to provide longitudinal serologic information. SARS-CoV-2 IgG results were also used for differentiating prior infection subgroup from non-prior infection (naive) group.

SARS-CoV-2 IgG II Quant Assay Response Across Time Points



The sample below the cutoff at post-vaccine dose 2 was from an immunocompromised individual. Refer to the LIMITATIONS OF THE PROCEDURE section of this package insert for further information.

Class Specificity

This study was performed on the ARCHITECT i2000SR System.

The anti-human IgG antibody used in the SARS-CoV-2 IgG II Quant assay demonstrates class-specific reactivity only to human SARS-CoV-2 IgG. No binding interactions were observed to human SARS-CoV-2 IgM.

A class specificity study was conducted to determine the impact of dithiothreitol (DTT) treatment on the detection of IgG and/or IgM positive samples by the SARS-CoV-2 IgG II Quant assay. DTT dissolves IgM antibody disulfide bonds and eliminates activity of the antibody. Upon treatment with DTT, five SARS-CoV-2 patient samples (initially positive for both IgG and IgM) remained positive for IgG when tested with the SARS-CoV-2 IgG II Quant assay and were negative for IgM when tested with the Abbott SARS-CoV-2 IgM assay. This establishes the specificity of the SARS-CoV-2 IgG II Quant kit to the IgG class of antibodies.

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Key to Symbols

ISO 15223 Symbols	
	Consult instructions for use
	Manufacturer
	Sufficient for
	Temperature limitation
	Use by/Expiration date
IVD	*In Vitro* Diagnostic Medical Device
LOT	Lot Number
REF	List Number
SN	Serial number

Other Symbols	
ASSAY DILUENT	Assay Diluent
CONJUGATE	Conjugate
CONTAINS: AZIDE	Contains Sodium Azide. Contact with acids liberates very toxic gas.
FOR USE WITH	Identifies products to be used together
INVERSIONS PERFORMED	Inversions Performed
MICROPARTICLES	Microparticles
PRODUCT OF IRELAND	Product of Ireland
WARNING: SENSITIZER	Warning: May cause an allergic reaction.

Note for number formatting:

- A space is used as thousands separator (example: 10 000 specimens).
- A period is used to separate the integer part from the fractional part of a number written in decimal form (example: 3.12%).

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CE

Customer Service: Contact your local representative or find country-specific contact information on www.corelaboratory.abbott

For customers in the European Union: if, in the course of using this device, you have reason to believe that a serious incident has occurred, report it to the manufacturer and to your national authority.

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