BIO-RAD

BioPlex 2200

SARS-CoV-2 IgG

Instructions For Use

REF **12014192**

Σ 200

IVD

This IFU is effective beginning with Lot # 301258 (BioPlex 2200 SARS-CoV-2 IgG) and above, and BioPlex 2200 Software Version 4.3 and above.

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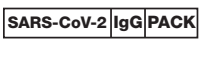
SYMBOLS LEXICON

					
Catalog Number	WARNING	Lot Number	Manufactured by	Number of Tests	Temperature Limit
					
Use by (YYYY-MM-DD)	For In Vitro Diagnostic Use	Consult Instructions for Use	Contains	Version	Caution, consult accompanying documents
					
Bead Set	Conjugate	SARS-CoV-2 IgG Reagent Pack	Sample Diluent	European Conformity	Authorized Representative in the European Community

INTENDED USE

The BioPlex 2200 SARS-CoV-2 IgG panel is a multiplex assay for the qualitative detection and semi-quantitative differentiation of IgG class antibodies against the RBD, S1, S2, and nucleocapsid protein of the SARS-CoV-2 virus in human serum and plasma (K2 EDTA, K3 EDTA, lithium heparin, sodium heparin, and sodium citrate). The BioPlex 2200 SARS-CoV-2 IgG panel is intended for use as an aid in identifying individuals with an adaptive immune response to the SARS-CoV-2 virus, indicating recent or prior infection or acquired immunity from vaccination to the virus.

IgG antibodies to SARS-CoV-2 are generally detectable in the blood several weeks after initial infection, although the duration of time antibodies are present post-infection is not well characterized. Individuals may have detectable virus present for several weeks following seroconversion.

Negative results do not preclude acute SARS-CoV-2 infection. If acute infection is suspected, direct testing for SARS-CoV-2 is necessary.

The BioPlex 2200 SARS-CoV-2 IgG panel is intended for use with the Bio-Rad BioPlex 2200 System.

SUMMARY AND EXPLANATION

Coronavirus (CoV) is an enveloped virus that contains a single-stranded positive-sense RNA. SARS-CoV-2, formerly known as 2019-nCoV, is a newly emerging coronavirus that affects the respiratory tract. The underlying disease caused by this virus is COVID-19. Coronaviruses have been responsible for several outbreaks in the world during the last two decades. In 2003 and 2014, coronaviruses caused outbreaks mainly in Asia (SARS-CoV) and in the Middle East (MERS-CoV), respectively. Before the new SARS-CoV-2 emergence, six coronaviruses were known to affect humans (SARS-CoV, MERS-CoV, and four other coronaviruses that cause mild upper and lower respiratory syndromes).

SARS-CoV-2 was first identified in December 2019, in Wuhan City, Hubei Province, China, after several patients developed severe pneumonia similar to that caused by SARS-CoV. The virus has since rapidly spread around the globe, and in March 2020, WHO officially announced COVID-19 as a pandemic. Person-to-person transmission of the virus leads to quick spreading of COVID-19, and a high number of patients requiring intensive care urged authorities around the world to set up containment measures. The incubation period ranges from 1 to 14 days.[3,4]

The virus has been detected in respiratory specimens, and respiratory droplets are considered as the primary means of transmission. Once viral particles enter the respiratory tract, the virus attaches to pulmonary cells via the ACE-2 receptors followed by endocytosis. SARS-CoV-2 might also be transmitted via the fecal route.

Diagnosis of acute SARS-CoV-2 infection mainly relies on real-time reverse transcription polymerase chain reaction (RT-PCR) testing of respiratory specimens. Symptoms can vary drastically and notably include fever, dry cough, anosmia, sputum production, headaches, dyspnea, fatigue, nausea, and diarrhea. While some cases can be asymptomatic, others can lead to acute respiratory distress syndrome (ARDS) and even death.

The BioPlex 2200 SARS-CoV-2 IgG panel is designed to detect IgG antibodies specific to the receptor-binding domain (RBD), Spike 1 (S1), Spike 2 (S2), and nucleocapsid protein (N) of the SARS-CoV-2 virus. Uniquely classified beads are each coated independently with one of the four antigens, and the presence of each antibody is determined separately. Sensitive fluorescence detection facilitates the differentiation of normal and abnormal antibody concentrations. If any of the four antibody levels are positive, the antibody screen result is reported as positive. The individual antibody results can be reported semi-quantitatively in U/mL.

In conjunction with other diagnostic tests, the BioPlex 2200 SARS-CoV-2 IgG panel can be used to determine if a patient has been exposed to the SARS-CoV-2 virus.

PRINCIPLE OF THE PROCEDURE

The BioPlex 2200 SARS-CoV-2 IgG panel employs fluoromagnetic, dyed beads which are each coated with RBD, S1, S2, or nucleocapsid protein. The RBD, S1, S2, or nucleocapsid protein coated fluoromagnetic beads possess unique fluorescent signatures used to identify the presence of IgG antibodies to SARS-CoV-2 virus in a two-step assay format.

The BioPlex 2200 System combines an aliquot of patient sample, sample diluent, and bead reagent into a reaction vessel. The mixture is incubated at 37°C. After a wash cycle, murine monoclonal anti-human IgG conjugated to phycoerythrin (PE) is added to the dyed beads, and this mixture is incubated at 37°C. The excess conjugate is removed in another wash cycle, and the beads are re-suspended in sheath fluid. The bead mixture then passes through the detector. The identity of the dyed beads is determined by the fluorescence of the dyes, and the amount of antibody captured by the antigen is determined by the fluorescence of the attached PE. Raw data are calculated in relative fluorescence intensity (RFI).

Two additional dyed beads, an Internal Standard Bead (ISB) and a Serum Verification Bead (SVB), are present in each reaction mixture to verify detector response and the addition of serum or plasma to the reaction vessel, respectively. Refer to the BioPlex 2200 System Operation Manual for more information.

The system is calibrated using a set of six (6) distinct calibrator vials supplied separately by Bio-Rad Laboratories. Five (5) levels of each antibody affinity are included in the six (6) vials, which are used for establishing a 4PL calibration curve of each individual assay. The semi-quantitative results are expressed in U/mL. A direct relationship exists between the amount of SARS-CoV-2 IgG antibody present in the patient sample and the RFI calculated by the system. The assay results are reported as negative or positive.

KIT COMPONENTS

SARS-CoV-2 IgG (REF 12014192). The reagent pack contains supplies sufficient for 200 tests.

Vial	Description
Bead Set BEAD	One (1) 10 mL vial, containing dyed beads coated with RBD, S1, S2, nucleocapsid protein, Internal Standard (ISB), and Serum Verification (SVB), with glycerol and protein stabilizers (bovine) in a MOPS (3-[N-Morpholino] propanesulfonic acid) buffer. ProClin 300 (≤ 0.3%), sodium benzoate (≤ 0.1%) and sodium azide (< 0.1%) are added as preservatives.
Conjugate CONJ	One (1) 5 mL vial, containing murine monoclonal anti-human IgG/phycoerythrin conjugate and murine anti-human FXIII/phycoerythrin conjugate in a phosphate buffer with protein stabilizers (bovine). ProClin 300 (≤ 0.3%) and sodium azide (< 0.1%) are added as preservatives.
Sample Diluent DIL	One (1) 10 mL vial, containing protein stabilizers (bovine and murine) in a triethanolamine buffer. ProClin 300 (≤ 0.3%), sodium benzoate (≤ 0.1%), and sodium azide (< 0.1%) are added as preservatives.

ADDITIONAL REQUIRED ITEMS, AVAILABLE FROM BIO-RAD

REF	Description
12014193	BioPlex 2200 SARS-CoV-2 IgG Calibrator Set: Six (6) 500 µL vials, in a human serum matrix made from defibrinated plasma with added known analyte concentrations of SARS-CoV-2 recombinant antibodies and antibodies derived from inactivated human disease state plasma. All calibrators contain ProClin (≤ 0.3%), sodium benzoate (≤ 0.1%), and sodium azide (<0.1%) as preservatives.
12014195	BioPlex 2200 SARS-CoV-2 IgG Control Set: Four (4) 1.5 mL positive control vials that are provided in a human serum matrix made from defibrinated/ delipidated plasma, with known analyte concentrations of SARS-CoV-2 recombinant antibodies and antibodies derived from inactivated human disease state plasma. Two (2) 1.5 mL negative control vials that are provided in a human serum matrix made from defribrinated/delipidated plasma
660-0817	BioPlex 2200 Sheath Fluid: Two (2) 4 L bottles containing Phosphate Buffered Saline (PBS). ProClin 300 (0.03%) and sodium azide (< 0.1%) are added as preservatives.
660-0818	BioPlex 2200 Wash Solution: One (1) 10 L bottle containing Phosphate Buffered Saline (PBS) and Tween 20. ProClin 300 (0.03%) and sodium azide (< 0.1%) are added as preservatives.
660-0000	BioPlex 2200 Instrument and Software.

PRECAUTIONS/WARNINGS

1. **For In Vitro Diagnostic (IVD) Use.**
2. For professional user in a laboratory environment only.

Contains ≤ 0.3% ProClin 300

H317: May cause an allergic skin reaction.

H412: Harmful to aquatic life with long lasting effects.

P273: Avoid release to the environment.

P280: Wear protective gloves/protective clothing/eye protection/face protection.

P302 + P352: IF ON SKIN: Wash with plenty of soap and water.

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

P501: Dispose of contents and container in accordance with local, regional, national, and international regulations.

3. Each unit of human serum used in the manufacture of the BioPlex 2200 SARS-CoV-2 IgG panel (including calibrator and control sets) was tested by FDA-accepted methods and found non-reactive for Hepatitis B surface antigen (HBsAg), antibody to HIV-1, HIV-2, and Hepatitis C (HCV). No test method can offer complete assurance that products containing human source materials will be absent of these and other infectious agents. In accordance with good laboratory practice (GLP), all human source material should be considered potentially infectious for Hepatitis B (HBV), Hepatitis C (HCV), HIV-1, HIV-2, and all other infectious agents; therefore, handle the BioPlex 2200 SARS-CoV-2 IgG panel (including calibrator and control sets) with the same precautions used with patient specimens. It is recommended that these reagents and human specimens be handled in accordance with the Biosafety in Microbiological and Biomedical Laboratories, WHO Laboratory Biosafety Manual, Biosafety Level 2, or other appropriate biosafety practices for materials which contain or are suspected of containing infectious agents. This test kit should be handled only by qualified personnel trained in laboratory procedures and familiar with the potential hazards. Wear appropriate protective clothing, gloves and eye/face protection and handle appropriately in accordance with Good Laboratory Practices.
4. Consider any materials of human origin as infectious and handle them using typical biosafety procedures and Universal Precautions according to 29 CFR 1910.1030 and in accordance with local, regional, and national regulations.
5. Do not smoke, eat, or drink in areas where patient samples and kit reagents are handled.
6. Do not pipette by mouth.
7. Wear personal protective equipment while handling all reagents and samples and while operating the BioPlex 2200 System.
8. Dispose of all wastes in accordance with applicable national and/or local regulations.
9. Waste material containing patient samples or biological products should be considered biohazardous when disposing or treating.
10. Chemical reagents should be handled in accordance with Good Laboratory Practices.
11. Refer to the kit and additional required component Safety Data Sheets (SDS) for more safety information and warnings about chemical and biological hazards. The Safety Data Sheets are available at bio-rad.com and on request.
12. Clean up all spills immediately and thoroughly. Decontaminate the area for any spills involving biohazardous materials with an effective disinfectant. Dispose of all contaminated materials appropriately.
13. Do not use tests beyond their expiration date. The date is printed on all boxes.
14. Do not interchange vial or bottle caps and stoppers; this will lead to cross-contamination of reagents.
15. Adherence to the protocol specified herein is necessary to ensure proper performance of this product. If aberrant results are obtained, contact Bio-Rad Technical Service
16. Never mix the contents from different bottles of the same reagent. Doing so may lead to reagent contamination and compromise the performance of the product.
17. Sodium azide may react with lead and copper plumbing to form highly explosive metal azides. On disposal of liquids, flush with a large volume of water to prevent azide build-up.
18. Do not use the kit if the packaging or any component is damaged.

19. For a patient/user/third party in the European Union and in countries with identical regulatory requirements: if during the use of this device or as a result of its use, a serious incident occurs, please report it to Bio-Rad Laboratories and/or its authorized representative and to your national Competent Authority.

SPECIMEN COLLECTION AND HANDLING*

Specimen Collection Precaution

Consider any materials of human origin as infectious and handle them using typical biosafety procedures.

Specimen Type

Serum (including serum separator tubes) and plasma (K2 EDTA, K3 EDTA, lithium heparin, sodium heparin, and sodium citrate) are the recommended sample types for the BioPlex 2200 SARS-CoV-2 IgG panel. Avoid lipemic, icteric, and hemolyzed samples.

Specimen Storage

Serum and plasma may be stored at room temperature (25°C) for up to 5 days or under refrigeration (2 – 8°C) for up to 7 days. For long term storage of samples, keep at -20°C or colder.

Specimen Preparation

Thoroughly mix thawed specimens; it is also recommended to centrifuge thawed specimens to remove gross particulate matter. Avoid multiple freeze/thaw cycles (up to 5 cycles is acceptable).

Specimen Shipping

All specimens and other samples of human origin must be shipped in accordance with national and international transportation regulations.

PREPARATION AND STORAGE OF REAGENTS

- Do not freeze the SARS-CoV-2 IgG panel.
- Reagents in the SARS-CoV-2 IgG panel are ready to use. After initial use, the opened reagents are stable for 60 days if refrigerated or on the instrument at 2 – 8°C. Store the unopened kits at 2 – 8°C.
- Do not use reagents beyond expiration dates.

INDICATIONS OF INSTABILITY OR DETERIORATION OF REAGENTS

Store all reagents at the labeled temperature and do not use past their expiration dates. Do not use any reagents which have any indications of discoloration, cloudiness, or precipitation. Do not use any reagents that show any signs of leakage.

PROCEDURE

In order to obtain reliable and consistent results, strictly adhere to the instructions in this Instructions for Use. Do not modify the handling and storage conditions for kit reagents or patient samples.*

Operating instructions, including calibration, quality control, and maintenance for the BioPlex 2200 System are further described in the BioPlex 2200 System Operation Manual. Prior to using the SARS-CoV-2 IgG panel, ensure that the BioPlex 2200 System is powered on, loaded with reagent packs and bulk solutions, and that all required maintenance has been performed. Please refer to the BioPlex 2200 System Operation Manual for more information regarding these activities.

Any lot numbers of the BioPlex 2200 System Sheath Fluid and BioPlex 2200 System Wash Solution can be interchanged.

* **Note:** Bio-Rad has established assay performance according to the specimen handling and storage parameters described in this IFU. If a laboratory uses handling and storage information criteria outside of the guidance listed here, it is the responsibility of the individual laboratory to use all available references and/or its own studies to determine specific stability criteria for their procedures.[11]

A) Calibration

The SARS-CoV-2 IgG Calibrator Set should be loaded and assayed, at a minimum, in duplicate every 30 days or with each new Reagent Pack lot. A 4PL curve is used to calculate results corresponding to the cutoff concentration. Refer to the BioPlex 2200 System Operation Manual for more information.

B) Quality Control

At the beginning of each day that the SARS-CoV-2 IgG panel is to be used, load and process the SARS-CoV-2 IgG Control Set as indicated in the BioPlex 2200 System Operation Manual. The SARS-CoV-2 IgG Control Set should be run at least once per day, and with each new Reagent Pack lot.

The SARS-CoV-2 IgG Control Set includes a negative control and two positive controls in a human serum matrix made from defibrinated plasma. Each positive control contains antibodies for analytes within the SARS-CoV-2 IgG panel. The positive controls are manufactured to give positive results, with values above the cutoff for each specific bead. The negative control is manufactured to give negative results with values below the cutoff for each specific bead. The negative control must have a negative result, and the positive controls must have positive results.

Note: The Negative and Positive Controls of the SARS-CoV-2 IgG Control Set are intended to monitor for substantial reagent failure. The Positive Controls will not ensure precision at the assay cutoff.

Lot specific values for the Positive Controls are loaded into the BioPlex 2200 System database via the provided media or by manual input. After identifying a control via the barcoded vial, the BioPlex 2200 System compares the control results to the expected lot specific control values stored in the BioPlex 2200 System database.

Failure to obtain the appropriate values for controls will invalidate the assay and indicates procedural error, improper sample handling, or deterioration of reagents. Additional controls may be tested in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control policy.

IMPORTANT QC TROUBLESHOOTING

At low frequency, reagent packs may exhibit falsely low signals for certain analytes and generate QC errors. The following troubleshooting steps should be followed when observing the noted QC behavior:

1. **QC Warning - low for only some analytes:**

   Repeat QC testing. If the QC Warning repeats, remove the pack with the flagged QC results and do not use. Please call Bio-Rad Technical Support to report the suspected low signal pack. Run QC with a new reagent pack. If QC results are within the acceptable range on the new reagent pack, discard the affected reagent pack with the QC Warning - Low results and do not report patient test results from that reagent pack. Retest any samples that were tested using the affected reagent pack. If the QC Warning repeats on the new reagent pack, please call Bio-Rad Technical Support for assistance with troubleshooting. If multiple packs for a particular BioPlex 2200 assay are on-board the instrument, the reagent pack (kit) serial number associated with the QC Warning - low results can be determined by viewing the Control Result dialog for the corresponding QC Event.

2. **QC Warning - high for only some analytes:**

   Recalibrate the reagent pack with the QC Warning - high and rerun QC. Verify that QC results are within the acceptable range for all analytes before proceeding. Once QC results are within acceptable range after calibration, all samples tested using the pack with the QC Warning - high must be retested. The affected pack may be used to generate valid patient results after calibration has occurred.

   If a control result is out of its specified range, any test results generated since the last acceptable control results must be evaluated to determine if test results may have been adversely affected. Adversely affected results are invalid, and these samples must be retested.

C) Traceability to Reference Material

There are no known certified reference materials available for any of the analytes in the SARS-CoV-2 IgG panel.

D) Load/Process Samples

Load samples into the racks provided with the BioPlex 2200 System as indicated in the BioPlex 2200 System Operation Manual. Sample processing on the BioPlex 2200 System is fully automated. Refer to the BioPlex 2200 System Operation Manual for appropriate software setup.

INTERPRETATION OF RESULTS

Calculation

All calculations necessary to interpret the results are performed automatically by the BioPlex 2200 System Software. Results are calculated for each analyte and are compared against its respective cutoff. If all the individual analyte results are less than the cutoff, the SARS-CoV-2 IgG Screen result is reported as negative. If any of the individual analyte results are equal to or above the cutoff, the SARS-CoV-2 IgG Screen result is reported as positive. The SARS-CoV-2 IgG Screen result must be reported, and the reporting of individual analytes is optional.

SARS-CoV-2 IgG Data Analysis

SARS-CoV-2 IgG assay results are expressed as U/mL and as Negative or Positive. Results of ≤ 9 U/mL are Negative and ≥ 10 U/mL are reported as Positive. The measuring range for the assays is 1 – 100 U/mL. Results outside of this range are reported as either < 1 U/mL or > 100 U/mL.

Samples should initially be tested undiluted. If any individual antibody marker has a result of >100 U/mL, a test order should be placed for an on-board dilution of that specific marker to determine the antibody level. When performing on-board dilutions, report the result of the lowest dilution that has a result within the analytical range of the assay. The overall result from the initial SARS-CoV-2 IgG Screen should be reported in addition to a final result for individual analytes, determined by the initial assay or subsequent on-board dilution.

Note: Refer to the BioPlex 2200 System Operation Manual for loading and analysis of diluted specimens.

RBD (Receptor-Binding Domain) IgG	Measuring Range	1 – 100 U/mL	
	Individual Antibody Result	≤ 9 U/mL	≥ 10 U/mL
	Result	Negative	Positive
S1 (Spike 1 subunit) IgG	Measuring Range	1 – 100 U/mL	
	Individual Antibody Result	≤ 9 U/mL	≥ 10 U/mL
	Result	Negative	Positive
S2 (Spike 2 subunit) IgG	Measuring Range	1 – 100 U/mL	
	Individual Antibody Result	≤ 9 U/mL	≥ 10 U/mL
	Result	Negative	Positive
Nucleocapsid (N protein)	Measuring Range	1 – 100 U/mL	
	Individual Antibody Result	≤ 9 U/mL	≥ 10 U/mL
	Result	Negative	Positive
BioPlex 2200 SARS-CoV-2 IgG Screen	Measuring Range	Qualitative	
	Individual Antibodies	All analytes are ≤ 9 U/mL	Any analyte is ≥ 10 U/mL
	Result	Negative	Positive

In conjunction with these results, the immune status of patients should be evaluated based on their clinical status, related risk factors, and other diagnostic test results.

Assay Cut-Off

The assay cut-off value was established using sera from various sample populations collected prior to November of 2019 (N=1619) and was then verified by concordance testing and Receiver Operator Characteristic (ROC) analysis, with the clinical status of the samples as the standard. The analysis was used to evaluate negative and positive agreement. Based on the results, calibrator values were adjusted such that the cut-off value is equal to 10 U/mL.

LIMITATIONS OF THE PROCEDURE

- The clinical applicability of a quantitative or semi-quantitative result is currently unknown and cannot be interpreted as an indication or degree of immunity nor protection from reinfection, nor compared to other SARS-CoV-2 antibody assays.
- Results obtained with the assay may not be used interchangeably with values obtained with different manufacturers' test methods.
- This test should not be used to diagnose or exclude acute SARS-CoV-2 infection. Direct testing for SARS-CoV-2 should be performed if acute infection is suspected.
- It is not known at this time if the presence of antibodies to SARS-CoV-2 confers immunity to re-infection.
- The BioPlex 2200 SARS-CoV-2 IgG panel results should be considered along with the clinical presentation of the patient. Only a physician should interpret the results.
- A negative result does not exclude a recent (within the last 14 days) SARS-CoV-2 infection. Follow-up testing with a molecular diagnostic should be considered to rule out infection in these individuals.
- A positive result may not indicate previous SARS-CoV-2 infection. Consider other information including clinical history and local disease prevalence, in assessing the need for a second but different serology test to confirm an immune response.
- Contaminated, icteric, lipemic, hemolyzed, or heat inactivated sera may cause erroneous results and should be avoided.
- This test should not be used for screening of donated blood.

PERFORMANCE CHARACTERISTICS

Limit of Detection/Limit of Quantitation

The detection capability LoB (Limit of Blank), LoD (Limit of Detection) and LoQ (Limit of Quantitation) of the BioPlex 2200 SARS CoV-2 IgG panel were evaluated using a dilution series of positive samples. Five series were prepared using analyte- specific spiking solutions, with five serial dilutions prepared from each of the five positive spiked samples. All samples plus the blank samples were run in replicates of 10 for five days for a total of 50 replicates per sample. Data were analyzed for LoB using the classical approach, and LoD and LoQ were analyzed used the precision approach per CLSI EP17-A2. If calculated LoQ is < LoD, based on LoQ criteria the final LoQ = LoD.

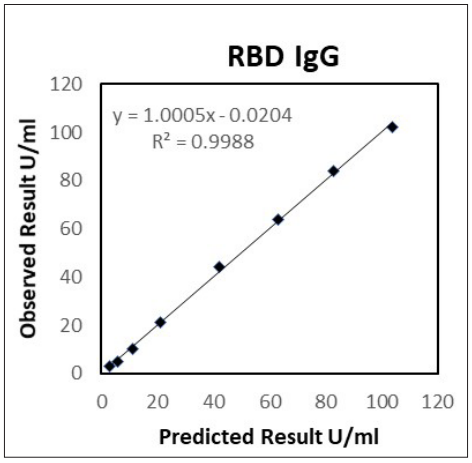
BioPlex 2200 SARS-CoV-2 IgG Limit of Detection / Limit of Quantitation ranged from 0.0035 U/mL for S1 to 0.47 U/mL for RBD. Since the decimal precision is set to 0 the Limit of Quantitation is set to <1 U/mL for all analytes. Results are summarized in Table A.

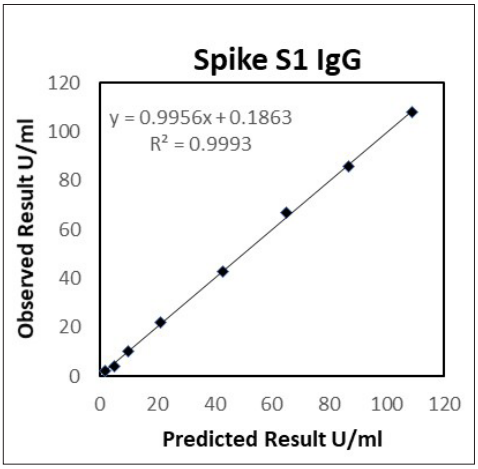
Table A. Maximum Detection Limits

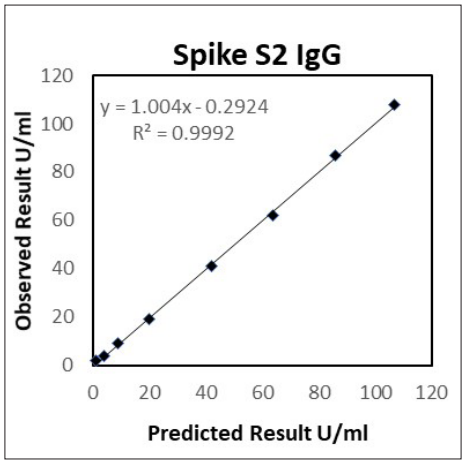
Assay	Units	Limit of Blank	Limit of Detection	Limit of Quantitation
RBD IgG	U/mL	0.4219	0.4664	0.4664
S1 IgG	U/mL	0.0108	0.0035	0.0035
S2 IgG	U/mL	0.0159	0.0291	0.0291
Nucleocapsid	U/mL	0.1679	0.1830	0.1830

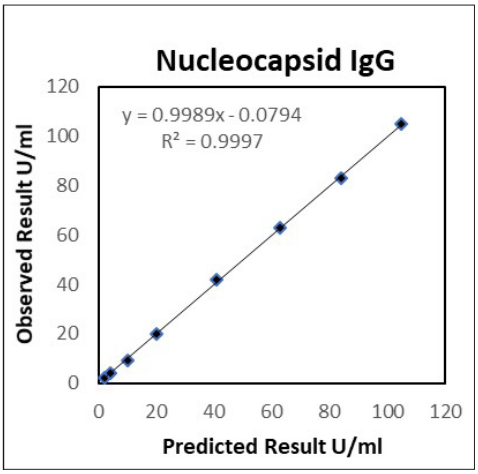
Dilution Linearity

An assay linearity study was performed to validate the quantitative reportable range of the BioPlex 2200 SARS-CoV-2 IgG panel. The ranges of the assays (RBD, S1, S2, and nucleocapsid) are between 1 and 100 U/mL. The testing protocol was performed as per CLSI guideline EP6-A. Five high positive patient samples were diluted to a range between 100 and 120 U/mL. Each sample and dilution was evaluated in replicates of four. The SARS-CoV-2 IgG panel individual assays RBD IgG, S1 IgG, S2 IgG, and Nucleocapsid IgG demonstrated linearity throughout the dynamic assay range of 1 to 100 U/mL.









Reproducibility Study

The BioPlex 2200 SARS-CoV-2 IgG reagents were used to measure repeatability (within run), between run, between day, between instrument/site and total variation. One lot of reagent/calibrator combination was tested for 5 days on three instruments using samples prepared in five matrices (serum, EDTA, sodium heparin, lithium heparin and sodium citrate). Samples spanning the assay range were prepared by spiking high positive analyte patient samples into each matrix in order to obtain the target analyte concentrations. Testing was conducted internally at Bio-Rad Laboratories. All samples were tested in replicates of four (4), two runs per day, over 5 days on three instruments (4 replicates per run x 2 runs per day x 5 days x 3 instruments = 120 replicates). Data were analyzed for repeatability, between-run, between-day, between-instrument, within instrument (lab) and total variation according to CLSI EP5-A3. The mean U/mL, standard deviation (SD), and percent coefficient of variation (%CV) for each sample were calculated. The results of the testing are summarized in Tables B – E.

Table B. BioPlex 2200 RBD IgG Serum Reproducibility

RBD IgG Panel Member	Mean (U/mL)	Repeatability		Between Run		Between Day		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative	7	0.55	8.0%	0.24	3.5%	0.24	3.5%	0.32	4.7%	0.72	10.5%
Near Cut-Off	11	0.66	6.1%	0.24	2.3%	0.00	0.0%	0.56	5.2%	0.90	8.4%
Positive	28	1.58	5.6%	0.19	0.7%	0.89	3.1%	0.83	2.9%	2.00	7.1%
Positive	55	2.72	4.9%	0.79	1.4%	0.95	1.7%	2.52	4.6%	3.91	7.1%
Positive Control	30	1.24	4.1%	1.05	3.5%	0.00	0.0%	1.96	6.6%	2.55	8.5%

Table C. BioPlex 2200 S1 IgG Serum Reproducibility

S1 IgG Panel Member	Mean (U/mL)	Repeatability		Between Run		Between Day		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative	6	0.47	8.4%	0.14	2.5%	0.20	3.5%	0.00	0.0%	0.53	9.5%
Near Cut-Off	9	0.49	5.5%	0.37	4.2%	0.00	0.0%	0.28	3.1%	0.67	7.6%
Positive	24	1.24	5.2%	0.57	2.4%	0.42	1.7%	0.82	3.4%	1.65	6.9%
Positive	45	1.80	4.0%	1.23	2.7%	0.29	0.6%	2.20	4.8%	3.11	6.8%
Positive Control	29	1.01	3.5%	1.77	6.1%	0.00	0.0%	1.78	6.1%	2.71	9.3%

Table D. BioPlex 2200 S2 IgG Serum Reproducibility

S2 IgG Panel Member	Mean (U/mL)	Repeatability		Between Run		Between Day		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative	4	0.26	6.7%	0.00	0.0%	0.09	2.2%	0.06	1.6%	0.28	7.2%
Near Cut-Off	9	0.35	4.0%	0.00	0.0%	0.17	1.9%	0.34	3.9%	0.52	5.9%
Positive	23	0.58	2.6%	0.14	0.6%	0.31	1.4%	1.05	4.7%	1.25	5.5%
Positive	46	1.31	2.9%	0.00	0.0%	0.52	1.1%	1.90	4.1%	2.37	5.2%
Positive Control	29	0.88	3.0%	0.85	2.9%	0.00	0.0%	1.14	3.9%	1.67	5.7%

Table E. BioPlex 2200 Nucleocapsid IgG Serum Reproducibility

Nucleocapsid IgG Panel Member	Mean (U/mL)	Repeatability		Between Run		Between Day		Between Instrument		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Negative	4	0.24	6.0%	0.00	0.0%	0.00	0.0%	0.05	1.2%	0.25	6.1%
Near Cut-Off	10	0.67	7.1%	0.00	0.0%	0.41	4.3%	0.00	0.0%	0.79	8.3%
Positive	26	1.53	5.9%	0.00	0.0%	0.46	1.8%	0.00	0.0%	1.59	6.1%
Positive	41	2.55	6.2%	1.01	2.4%	0.00	0.0%	0.33	0.8%	2.76	6.7%
Positive Control	31	1.91	6.2%	0.92	3.0%	0.00	0.0%	0.17	0.5%	2.13	6.9%

Matrix Comparison

Matched serum and plasma samples drawn from > 40 individual donors were spiked with SARS-CoV-2 IgG positive samples at various levels that span the dynamic assay range. All samples were evaluated in replicates of two (2). Mean plasma values were compared to matched mean serum U/mL values. Regression analysis comparing the performance of plasma samples against serum samples is shown in Table F.

Table F. BioPlex 2200 SARS-CoV-2 IgG Matrix Comparison

Analytes	Parameters	Serum Separator	K2 EDTA	K3 EDTA	Lithium Heparin	Sodium Heparin	Sodium Citrate
RBD IgG	Slope	1.00	0.96	0.96	0.95	0.98	0.98
	Intercept	-0.48	0.87	0.91	0.58	0.60	0.42
	Correlation	0.996	0.995	0.997	0.996	0.997	0.997
S1 IgG	Slope	0.99	1.01	1.00	0.99	0.98	0.98
	Intercept	-0.07	-0.14	-0.06	-0.24	0.19	0.33
	Correlation	0.998	0.998	0.998	0.998	0.999	0.998
S2 IgG	Slope	0.99	1.00	1.03	1.01	1.01	1.03
	Intercept	0.04	0.27	-0.46	-0.46	0.14	0.02
	Correlation	0.998	0.998	0.995	0.996	0.998	0.998
Nucleocapsid IgG	Slope	1.00	1.01	1.00	0.97	1.02	0.99
	Intercept	0.11	-0.21	-0.28	0.13	-0.56	0.12
	Correlation	0.991	0.995	0.995	0.987	0.991	0.998

Analytical Specificity

Cross-Reactivity

A total of 1078 samples from patients with potentially cross reactant antibodies or conditions other than SARS-CoV-2 were tested, representing 41 different analytes / conditions. All samples were collected prior to November 2019 and are presumed negative for antibody to SARS-CoV-2.

Negative agreement results for each potentially cross-reactive sample with the SARS-CoV-2 IgG panel are shown in Table G, which summarizes the results for the CoV-2 IgG overall result as well as the individual analytes. The percent specificity is based on the overall result of all assays. A total of 3 samples were reactive (1 Anti-HBV positive, 1 ANA positive, and 1 elevated IgG) for an overall specificity of 99.7% (1075/1078). No significant cross reactivity was observed for any cross-reactive group of samples that were tested.

Table G. Cross-Reactivity

Cross Reactivity	Total (N)	RBD IgG	S1 IgG	S2 IgG	Nucleocapsid IgG	CoV-2 IgG	Overall Specificity
		Number of Negatives					
Anti-influenza A	34	34	34	34	34	**34**	100.0%
Anti-influenza B	26	26	26	26	26	**26**	100.0%
Anti-HCV	14	14	14	14	14	**14**	100.0%
Anti-HBV	49	48	49	49	49	**48**	98.0%
Anti-Haemophilus influenzae	25	25	25	25	25	**25**	100.0%
Anti-229E (alpha coronavirus)	20	20	20	20	20	**20**	100.0%
Anti-NL63 (alpha coronavirus)	20	20	20	20	20	**20**	100.0%
Anti-OC43 (beta coronavirus)	20	20	20	20	20	**20**	100.0%

Table G: Cross-Reactivity (*continued*)

Cross Reactivity	Total (N)	RBD IgG	S1 IgG	S2 IgG	Nucleocapsid IgG	CoV-2 IgG	Overall Specificity
		Number of Negatives					
Anti-HKU1 (beta coronavirus)	20	20	20	20	20	20	100.0%
ANA	192	192	191	192	192	191	99.5%
Anti-RSV	20	20	20	20	20	20	100.0%
Anti-HIV	23	23	23	23	23	23	100.0%
Pregnant women	110	110	110	110	110	110	100.0%
Rheumatoid Factor positive	47	47	47	47	47	47	100.0%
Anti-adenovirus	11	11	11	11	11	11	100.0%
Anti-parainfuenza virus 1-4	20	20	20	20	20	20	100.0%
Anti-human metapneumovirus	5	5	5	5	5	5	100.0%
Anti-enterovirus	10	10	10	10	10	10	100.0%
Anti-rhinovirus	5	5	5	5	5	5	100.0%
Anti-Epstein-Barr virus IgG	23	23	23	23	23	23	100.0%
Anti-Epstein-Barr virus IgM	22	22	22	22	22	22	100.0%
Anti-Mycoplasma pneumoniae	15	15	15	15	15	15	100.0%
Anti-MERS	5	5	5	5	5	5	100.0%
Anti-SARS	5	5	5	5	5	5	100.0%
Common Cold	9	9	9	9	9	9	100.0%
Flu Vaccinated	7	7	7	7	7	7	100.0%
2008 Flu Vaccine BioAssay Validation Panel	36	36	36	36	36	36	100.0%
Streptococcus pneumoniae Immunity control	20	20	20	20	20	20	100.0%
Anti-HSV 2	15	15	15	15	15	15	100.0%
Anti-HSV 1	15	15	15	15	15	15	100.0%
Anti-CMV	22	22	22	22	22	22	100.0%
Anti-Rubella	20	20	20	20	20	20	100.0%
Anti-Toxoplasma	22	22	22	22	22	22	100.0%
Anti-Measles	20	20	20	20	20	20	100.0%
Anti-Mumps	20	20	20	20	20	20	100.0%
Anti-Syphilis	19	19	19	19	19	19	100.0%
Anti-VZV	19	19	19	19	19	**19**	100.0%
Anti-Hepatitis A	20	20	20	20	20	**20**	100.0%
Elevated IgG	20	19	20	20	20	**19**	95.0%
Elevated IgM	19	19	19	19	19	**19**	100.0%
HAMA	34	34	34	34	34	**34**	100.0%
Total	1078	1076	1077	1078	1078	**1075**	99.7%

Interfering Substances

Interference testing was performed to measure the effects of unrelated substances such as endogenous serum components (hemoglobin, bilirubin, lipids, immunoglobulin, and total protein) and exogenous molecules (ascorbic acid and anticoagulants) on BioPlex 2200 SARS-CoV-2 IgG panel assay performance. Negative serum was spiked with three levels of antibody to create samples that were high negative, low positive, and high positive for each assay analyte, and they were tested with each of the potentially interfering substances. Testing was conducted according to CLSI Protocol EP07-ED3 2018. No significant interference was observed with any of the substances tested at the concentrations listed in Table H.

Table H. Interfering Substances

Interferant	Test Concentration
Hemoglobin	1000 mg/dL
Bilirubin, Unconjugated	20 mg/dL
Bilirubin, Conjugated	30 mg/dL
Cholesterol	500 mg/dL
Gamma Globulin	6 g/dL
Triglyceride	3300 mg/dL
Total Protein (albumin)	12 g/dL
Ascorbic Acid	6 mg/dL
K2 EDTA	800 units/dL
K3 EDTA	800 units/dL
Sodium Heparin	8000 units/dL
Lithium Heparin	8000 units/dL
Sodium Citrate	1000 mg/dL

Clinical Specificity

A total of 1557 samples from presumed healthy subjects (individuals tested during routine checkups) and blood bank donors were purchased and tested with the BioPlex 2200 SARS-CoV-2 IgG panel. All samples were collected prior to November 2019.

BioPlex 2200 SARS-CoV-2 IgG panel exhibited an overall specificity of 99.8% (1554/1557). The individual assay specificities for RBD IgG, S1 IgG, S2 IgG and Nucleocapsid IgG were all > 99.9%. Results are summarized in Table I.

Table I. BioPlex 2200 SARS-CoV-2 IgG Clinical Specificity

Analyte	Population	BioPlex 2200 SARS-CoV-2 IgG Panel			
		Total	Neg (-)	% Specificity	Confidence Interval
RBD IgG	Healthy Subjects	1015	1013	99.8%	99.3 to 99.9
	Blood Bank Donors	542	542	100.0%	99.3 to 100.0
	Total	1557	1555	99.9%	99.5 to 100.0
S1 IgG	Healthy Subjects	1015	1014	99.9%	99.4 to 100.0
	Blood Bank Donors	542	542	100.0%	99.3 to 100.0
	Total	1557	1556	99.9%	99.6 to 100.0
S2 IgG	Healthy Subjects	1015	1014	99.9%	99.4 to 100.0
	Blood Bank Donors	542	542	100.0%	99.3 to 100.0
	Total	1557	1556	99.9%	99.6 to 100.0
Nucleocapsid IgG	Healthy Subjects	1015	1015	100.0%	99.6 to 100.0
	Blood Bank Donors	542	542	100.0%	99.3 to 100.0
	Total	1557	1557	100.0%	99.8 to 100.0
CoV-2 IgG	**Healthy Subjects**	**1015**	**1012**	**99.7%**	**99.1 to 99.9**
	Blood Bank Donors	**542**	**542**	**100.0%**	**99.3 to 100.0**
	Total	**1557**	**1554**	**99.8%**	**99.4 to 99.9**

Clinical Sensitivity

A total of 305 samples from subjects who had been identified as positive for SARS-CoV-2 by PCR testing were evaluated with the BioPlex 2200 SARS-CoV-2 IgG panel. The population of subjects consisted of hospitalized (47), non-hospitalized (154), and unknown hospitalization status (104) subjects. One sample was tested per patient, and the patients were not followed over time to monitor change in antibody status. Results are summarized in Table J.

Table J. BioPlex 2200 SARS-CoV-2 IgG Clinical Sensitivity

Days between symptom onset and sample collection	Number Tested	BioPlex 2200 SARS-CoV-2 IgG Panel			
		Assay	IgG Positive results	IgG PPA	95% CI
0-7 days	32	RBD IgG	27	84.4%	68.2 to 93.1
		S1 IgG	26	80.6%	64.7 to 91.1
		S2 IgG	17	54.8%	37.8 to 70.8
		Nucleocapsid IgG	26	81.3%	64.7 to 91.1
		CoV-2 IgG	**27**	**84.4%**	**68.2 to 93.1**
8-14 days	27	RBD IgG	26	96.3%	81.7 to 99.3
		S1 IgG	26	96.3%	81.7 to 99.3
		S2 IgG	12	44.4%	27.6 to 62.7
		Nucleocapsid IgG	27	100.0%	87.5 to 100.0
		CoV-2 IgG	**27**	**100.0%**	**87.5 to 100.0**
≥ 15 days	246	RBD IgG	235	95.5%	92.2 to 97.5
		S1 IgG	231	93.9%	90.1 to 96.2
		S2 IgG	124	50.4%	44.2 to 56.6
		Nucleocapsid IgG	231	93.9%	90.2 to 96.3
		CoV-2 IgG	**237**	**96.3%**	**93.2 to 98.1**

The CoV-2 IgG PPA for all samples (N=305) was 96.3% (237/246) at >15 days, 100% (27/27) at 8-14 days and 84.4% (27/32) at 0-7 days. The sensitivity for samples >15 days for all individual analytes RBD IgG, S1 IgG, S2 IgG and Nucelocapsid IgG were 95.5%, 93.9%, 50.4% and 93.9%, respectively. S2 IgG exhibited much lower sensitivity than the other individual analytes; however, in combination with the other analytes it can add to the sensitivity of the test kit as well as provide an understanding of the overall serology profile.

For all 9 samples collected at ≥15 days post onset of symptoms that were negative with the BioPlex 2200 SARS-CoV-2 IgG panel, results were available for IgG and/or Total Ab serology assays that have been granted Emergency Use Authorization. Eight (8) of the 9 samples that were negative with the BioPlex 2200 SARS-CoV-2 IgG panel were found to be negative with all other serology assays that were tested.

Seroconversion Testing

A seroconversion panel with 14 separate draws was obtained from a commercial supplier. The samples were collected over an 87 day period from a single donor during the progression of the SARS-CoV-2 infection.

Table K. BioPlex 2200 SARS-CoV-2 IgG Panel Results

			CoV-2 IgG	RBD IgG	S1 IgG	S2 IgG	Nucleocapsid IgG
Panel Member	Day	Bleed Date	Status	U/ml	U/ml	U/ml	U/ml
1	1	03/04/20	Negative	<1	<1	<1	<1
2	3	03/06/20	Negative	<1	<1	<1	<1
3	10	03/13/20	Negative	<1	<1	<1	<1
4	15	03/18/20	Negative	<1	<1	<1	<1
5	17	03/20/20	Negative	<1	<1	<1	<1
6	24	03/27/20	Negative	<1	<1	<1	<1
7	31	04/03/20	Negative	<1	<1	<1	<1
8	36	04/08/20	Negative	1	<1	1	<1
9	50	04/22/20	POSITIVE	39	27	4	40
10	64	05/06/20	POSITIVE	>100	80	5	>100
11	71	05/13/20	POSITIVE	>100	69	5	>100
12	78	05/20/20	POSITIVE	>100	59	5	>100
13	80	05/22/20	POSITIVE	100	52	5	>100
14	87	05/29/20	POSITIVE	86	44	4	>100

>10 U/ml Positive; Red = Positive

Table L. BioPlex 2200 SARS-CoV-2 IgG Panel, Comparison to Commercial Methods

			BioPlex 2200	Commercial Kit A	Commercial Kit B	Commercial Kit C
			CoV-2 IgG	SARS-CoV- IgG	SARS-CoV-2 IgG	Anti-SARS CoV-2 IgG
Panel Member	Day	Bleed Date	Status	U/ml	U/ml	U/ml
1	1	3/4/2020	Negative	Negative	Negative	Negative
2	3	3/6/2020	Negative	Negative	Negative	Negative
3	10	3/13/2020	Negative	Negative	Negative	Negative
4	15	3/18/2020	Negative	Negative	Negative	Negative
5	17	3/20/2020	Negative	Negative	Negative	Negative
6	24	3/27/2020	Negative	Negative	Negative	Negative
7	31	4/3/2020	Negative	Negative	Negative	Negative
8	36	4/8/2020	Negative	Negative	Negative	Negative
9	50	4/22/2020	POSITIVE	POSITIVE	POSITIVE	POSITIVE
10	64	5/6/2020	POSITIVE	POSITIVE	POSITIVE	POSITIVE
11	71	5/13/2020	POSITIVE	POSITIVE	POSITIVE	POSITIVE
12	78	5/20/2020	POSITIVE	POSITIVE	POSITIVE	POSITIVE
13	80	5/22/2020	POSITIVE	POSITIVE	POSITIVE	POSITIVE
14	87	5/29/2020	POSITIVE	POSITIVE	POSITIVE	POSITIVE

>10 U/ml Positive; Red = Positive

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