BIOMÉRIEUX

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VIDAS® SARS-COV-2 IgM (9COM)

IVD

INTENDED USE

VIDAS® SARS-COV-2 IgM (9COM) is an automated qualitative assay for use on the VIDAS® family of instruments, for the detection of immunoglobulin M (IgM) specific for SARS-CoV-2 in human serum or plasma (lithium heparin) using the ELFA (Enzyme Linked Fluorescent Assay) technique.

This assay is intended for use as an aid to determine if individuals may have been exposed and infected by this virus and if they have mounted a specific anti-SARS-CoV-2 IgM immune response.

SUMMARY AND EXPLANATION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly *Betacoronavirus* discovered in China in December 2019 which is responsible for an international outbreak of respiratory illness termed coronavirus disease 19 (COVID-19), ranging from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multiorgan failure, and death.[1]

In addition to viral load measured (e.g. PCR) in respiratory tract specimen, serology testing for specific immunoglobulins is another approach to identify individuals previously exposed to SARS-CoV-2.[2]

Indeed, most COVID-19 patients had an antibody response at ten days or later after onset of the symptoms.[3] This antibody response is characterized by the early rise of type M immunoglobulins (IgM), then followed by type G immunoglobulins (IgG).[4]

Furthermore, serum neutralization assays and virus culture have demonstrated the presence of neutralizing antibodies, that correlated to the presence of IgG recognizing the spike and the nucleoprotein of SARS-CoV-2.[5]

PRINCIPLE

The assay principle combines a two-step sandwich enzyme immunoassay method with a final fluorescence detection (ELFA).

The single-use Solid Phase Receptacle (SPR) serves as the solid phase as well as the pipetting device. Reagents for the assay are ready-to-use and pre-dispensed in the sealed single-use reagent strips.

All of the assay steps are performed automatically by the instrument. The reaction medium is cycled in and out of the SPR device several times.

After the sample dilution step, the SARS-CoV-2 IgM are captured by recombinant SARS-CoV-2 antigen coated into the interior of the SPR device wall. Unbound components are eliminated during washing steps.

During the second step, the IgM are specifically detected by anti-human IgM labeled with alkaline phosphatase. Unbound components are eliminated during washing steps.

During the final detection step, the substrate (4-Methyl-umbelliferyl phosphate) is cycled in and out of the SPR device. The conjugate enzyme catalyzes the hydrolysis of this substrate into a fluorescent product (4-Methyl-umbelliferone), the fluorescence of which is measured at 450 nm.

The intensity of the fluorescence is proportional to the level of antibody in the sample.

At the end of the assay, the results are automatically calculated by the instrument according to the S1 standard stored in memory and a test value is obtained.

The results can then be printed out.

CONTENT OF THE KIT (60 TESTS)

60 Strips[(a)] (9COM)	STR	Ready-to-use.
60 Solid Phase Receptacles (9COM) 2 x 30	SPR	Ready-to-use. Interior of SPR device coated with recombinant SARS-CoV-2 antigen.

Standard[b] (9COM) 1 x 0.5 mL (liquid)	S1	Ready-to-use. Buffer containing humanized recombinant anti-SARS-CoV-2 IgM antibody + stabilizer of animal origin + preservatives. MLE data indicate the acceptable range in "Relative Fluorescence Value" ("Standard (S1) RFV Range").
Positive control[b] (9COM) 1 x 0.5 mL (liquid)	C1	Ready-to-use. Buffer containing humanized recombinant anti-SARS-CoV-2 IgM antibody + stabilizer of animal origin + preservatives. MLE data indicate the acceptable range as an index ("Control C1 (+) Test Value Range").
Negative control[b] 1 x 0.5 mL (liquid)	C2	Ready-to-use. Buffer + stabilizer of animal origin + preservatives. MLE data indicate the acceptable range as an index ("Control C2 Test Value Range").
Specifications for the factory master data required to calibrate the assay: MLE barcode printed on the box label.		
1 package insert downloadable from www.biomerieux.com/techlib		

[a] **DANGER**  **WARNING**  EUH208 / H317 / H318 / P261 / P280 / P302 + P352 / P305 + P351 + P338

[b] **WARNING**  EUH208 / H317 / P261 / P280 / P302 + P352

Hazard statements
- EUH208: Contains 2-methyl-4-isothiazolin-3-one hydrochloride. May produce an allergic reaction.
- H317: May cause an allergic skin reaction.
- H318: Causes serious eye damage.

Precautionary statements
- P261: Avoid breathing dust/fume/gas/mist/vapours/spray.
- P280: Wear protective gloves/protective clothing/eye protection/face protection.
- P302 + P352: IF ON SKIN: Wash with plenty of soap and water.
- P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.

For further information, consult the Safety Data Sheet.

The SPR device
SPR devices are identified by the "9COM" code.

Only remove the required number of SPR devices from the pouch and carefully reseal the pouch after opening.

The Reagent Strip
The strip consists of 10 wells covered with a labeled foil seal. The label comprises a barcode which mainly indicates the assay code, kit lot number, and expiration date. The foil of the first well is perforated to facilitate the introduction of the sample. The last well of each strip is a cuvette in which the fluorometric reading is performed. The wells in the center section of the strip contain the various reagents required for the assay.

Description of the 9COM strip
The strip contains diethanolamine and sodium azide. Refer to the hazard statements “H” and precautionary statements “P” indicated above.[a]

Well	Reagents
1	Sample well: dispense 100 µL of standard, control or sample.
2	Sample diluent: buffer + detergent + stabilizer of animal origin + preservative.
3 - 4 - 5	Wash buffer: buffer + detergent + preservative.
6	Conjugate: mouse monoclonal anti-human IgM antibodies conjugated to alkaline phosphatase + stabilizer of animal origin + preservative.
7 - 8	Wash buffer: buffer + detergent + preservative.
9	Empty well
10	Reading cuvette with substrate: 4-Methyl-umbelliferyl phosphate (0.6 mmol/L) + preservative.

MATERIALS AND DISPOSABLES REQUIRED BUT NOT PROVIDED

- Single-use pipette and/or micropipettes to dispense the appropriate volumes.
- Powderless disposable gloves.
- For other specific materials and disposables, please refer to the Instrument User Manual.
- Instruments of the VIDAS® family: VIDAS®, MINI VIDAS® or VIDAS® 3.

WARNINGS AND PRECAUTIONS

- **For *in vitro* diagnostic use only.**
- **For professional use only, by qualified laboratory personnel in clinical laboratories.**
- This kit does not contain products of human origin.
- This kit contains products of animal origin. Certified knowledge of the origin and/or sanitary state of the animals does not totally guarantee the absence of transmissible pathogenic agents. It is therefore recommended that these products be treated as potentially infectious, and handled observing the usual safety precautions (do not ingest; do not inhale).
- Do not use the SPR devices if the pouch is pierced or if the dot sealing a SPR device has come unstuck.
- Do not use visibly deteriorated strips (damaged foil or plastic).
- Do not use visibly deteriorated components.
- Do not use reagents after the expiration date indicated on the box label.
- Do not mix reagents (or disposables) from different lots.
- VIDAS® 9COM assay reagents are only for use with the instruments of the VIDAS® family.
- Use powderless gloves, as powder has been reported to cause false results for certain enzyme immunoassay tests.
- Kit reagents contain sodium azide which can react with lead or copper plumbing to form explosive metal azides. If any liquid containing sodium azide is disposed of in the plumbing system, drains should be flushed with water to avoid build-up.
- Refer to the hazard statements “H” and precautionary statements “P” indicated above.
- Spills should be wiped up thoroughly after treatment with liquid detergent or a solution of household bleach containing at least 0.5% sodium hypochlorite. See the User Manual for cleaning spills on or in the instrument. Do not autoclave solutions containing bleach.
- The instrument should be regularly cleaned and decontaminated (refer to the User Manual for user and preventive maintenance operations).

STORAGE CONDITIONS

- Store the kit at +2°C/+8°C.
- **Do not freeze reagents.**
- **Store all unused reagents at +2°C/+8°C.**
- After opening the kit, check that the SPR pouches are correctly sealed and undamaged. If not, do not use the SPR devices.
- **After use, carefully reseal the pouch with the desiccant inside to maintain stability of the SPR devices, and return the complete kit to +2°C/+8°C.**
- If stored according to the recommended conditions, all components are stable until the expiration date indicated on the box label.

SAMPLES

Specimen type and collection

Human serum or plasma (lithium heparin)

Note: Blood sampling tube results may vary from one manufacturer to another depending on the materials and additives used. Some collection tubes may contain substances which could intefere with test results.

Types of tubes validated
- Plastic tube with lithium heparin
- Plastic tube with clot activator

It is the responsibility of each laboratory to validate the type of sample tube used and to follow the manufacturer's recommendations for use.

Sample preparation
The current WHO/DIL/LAB/99.1 document provides recommendations for sample preparation. [6]

For use of sample tubes, refer to the tube manufacturer's recommendations for use.

The pre-analytical step, including the preparation of blood samples, is an essential first step when performing medical analyses. In accordance with Good Laboratory Practice, this step is performed under the responsibility of the laboratory manager.

Insufficient clot time can result in the formation of fibrin with micro-clots that are invisible to the naked eye. The presence of fibrin, red blood cells, or suspended particles can lead to erroneous results.

Samples containing suspended fibrin particles or erythrocyte stroma should be centrifuged before testing.

For serum samples, ensure that complete clot formation has taken place prior to centrifugation. Some specimens, especially those from patients receiving anticoagulant or thrombolytic therapy, may exhibit increased clotting times.

Preparation of frozen-stored samples
After thawing, all samples must be mixed before testing. Mix using a vortex-type mixer. If necessary, clarify the samples by centrifuging before testing (20 minutes at 2000 g or 10 minutes at 3900 g).

Sample stability
Samples can be stored in closed primary tubes at +18°C/+25°C for up to 6 hours or aliquoted at +2°C/+8°C for two days. If longer storage is required, freeze the serum or plasma at -19°C/-31°C.

These samples can be stored for 12 months at -19°C/-31°C, with up to three freeze/thaw cycles.

Sample-related interference
It is recommended not to use hemolyzed, lipemic, icteric samples, and, if possible, to collect a new sample.

Refer to the section **PERFORMANCE – Study of potentially interfering substances** for the compounds tested.

INSTRUCTIONS FOR USE
For complete instructions, see the Instrument User Manual.

Reading VIDAS® PTC (Protocol Test Change) data and MLE data

When using the assay for the first time
With the external instrument barcode reader, **scan the barcodes (PTC and MLE) in the following order**:
1. According to the instrument used, scan the PTC barcode(s) downloadable from www.biomerieux.com/techlib. This reading allows VIDAS® PTC protocol data to be transferred to the instrument software for its update.
2. Scan the MLE data on the box label.

When opening a new lot of reagents
With the external instrument barcode reader, scan the MLE data on the box label before performing the test.

Note: The master lot data need only be entered once for each lot.

It is possible to enter MLE data **manually or automatically** depending on the instrument (refer to the User Manual).

Calibration
Calibration, using the standard provided in the kit, must be performed each time a new lot of reagents is opened, after the MLE data have been entered, and then every 28 days.

This operation compensates for possible minor variations in assay signal throughout the shelf life of the kit.

The standard, identified by S1, must be tested in duplicate.

The standard value must be within the set RFV (Relative Fluorescence Value) range indicated in the MLE data. If this is not the case, recalibrate.

Kit controls

Two controls are included in this kit.

The kit controls must be used to validate each calibration. The kit controls must be performed immediately after opening a new kit to ensure that reagent performance has not been altered.

Note: Any other use of the kit control is under the customer's responsibility.

The instrument will check the control values only if the controls are identified by C1 or C2.

Results cannot be validated if the control values deviate from the expected values.

Procedure

1. **Remove the kit from storage at +2°C/+8°C and take out the required reagents. Carefully reseal the SPR pouch and return the kit to +2°C/+8°C.** The reagents can be used immediately.
2. Use one strip and one SPR device for each sample, control or standard to be tested. Make sure the SPR pouch has been carefully resealed after the required SPR devices have been removed.
3. The test is identified by the **9COM** code on the instrument. The standard, identified by S1, must be tested in duplicate. The controls, identified by C1 and C2, must be tested singly.
4. If necessary, clarify samples by centrifugation.
5. Mix the standard and controls using a vortex-type mixer.
6. For optimal results, refer to all the paragraphs in the **SAMPLES** section.
7. Before pipetting, ensure that the samples, standard and controls are free of bubbles.
8. **For this test, the standard, controls and sample test portion is 100 µL.**

   Caution: For the VIDAS® 3 instrument, standard and controls must be pipetted manually into the sample well.
9. Insert the SPR devices and the strips into the instrument.
10. Initiate the assay as directed in the User Manual. All the assay steps are performed automatically by the instrument.
11. The assay will be completed within **approximately 27 minutes**. After the assay is completed, remove the SPR devices and strips from the instrument.
12. Close the vials and return them to the required temperature after pipetting.
13. Dispose of the used SPR devices and strips into an appropriate recipient.

QUALITY CONTROL

Additional quality controls can be performed in accordance with local regulations or requirements related to accreditation, as well as requirements defined in the laboratory's quality control procedure.

RESULTS AND INTERPRETATION

Once the assay is completed, results are analyzed automatically by the computer. Fluorescence is measured twice in the Reagent Strip's reading cuvette for each sample tested. The first reading is a background reading of the substrate cuvette before the SPR device is introduced into the substrate.

The second reading is taken after incubating the substrate with the enzyme that may be bound to the interior of the SPR device.

The RFV (Relative Fluorescence Value) is calculated by subtracting the background reading from the final result. This calculation appears on the result sheet.

The patient RFV is interpreted by the VIDAS® system as follows:

Test value = patient RFV / standard RFV

The test value and interpretation are also indicated on the result sheet.

Interpretation of results

Interpretation of results according to test value (i) is as follows:

Index	Interpretation
i < 1.00	Negative
i ≥ 1.00	Positive

LIMITATIONS OF THE METHOD

- Interference may be encountered with certain sera containing antibodies directed against reagent components. For this reason, assay results should be interpreted taking into consideration the patient's clinical history and the results of any other tests performed.
- Results obtained using samples from SARS-CoV-2 infected patients must be interpreted with caution.

- This assay is intended for qualitative detection only. Test value itself cannot be used to determine the quantity of SARS-CoV-2 IgM antibodies.
- The magnitude of the measured result above the threshold is not indicative of the total amount of antibody present in the sample.
- The individual immune response following SARS-CoV-2 infection varies considerably and might give different results with assays from different manufacturers. Results of assays from different manufacturers should not be used interchangeably.

PERFORMANCE

Studies performed using the VIDAS® SARS-COV-2 IgM assay gave the following results:

Hook effect

No hook effect by design (2-step protocol).

Precision

A precision study was performed according to CLSI EP05-A3 recommendations.

A panel of human samples representing index levels in the qualitative range was analyzed on the VIDAS® instrument to include the following main sources of variability: repeatability, run, calibration and day.

Four samples were tested in triplicate in two runs per day, over six days using one VIDAS® instrument (N=36 values for each sample). Repeatability (within-run precision) and total within-lot within-instrument precision were estimated for each sample.

The precision estimates obtained for each sample are reported in the following table, as a guide.

Sample	N	Mean index	Repeatability Within-run precision		Within-lot within-instrument total precision	
			Standard Deviation Index	CV (%)	Standard Deviation Index	CV (%)
Sample 1	36	0.04	0.01	N/A	0.01	N/A
Sample 2	36	0.95	0.08	8.80	0.09	9.70
Sample 3	36	1.53	0.16	10.20	0.18	11.90
Sample 4	36	5.81	0.45	7.80	0.50	8.60

Analytical specificity

Cross-reactivity

The notion of cross-reactivity is the study of samples which are negative for the test to be evaluated and positive for the potentially interfering condition. The presence of these potentially interfering conditions must not modify the interpretation of the VIDAS® SARS-COV-2 IgM assay.

The results of the 154 samples tested on one lot and on the VIDAS® instrument are presented in the following table.

Sample category	Number of samples tested	Number of positive samples
Pregnant women	5	0
Anti-Nuclear Antibody	5	1
Rheumatoid factor	5	2
Human Anti-Mouse Antibody	5	0
Borrelia burgdorferi	10	0
Haemophilus influenza B	5	0
Plasmodium falciparum	3	1
Toxoplasma gondii	10	0
Treponema pallidum	3	0
Trypanosoma cruzi	5	1
Hepatitis A Virus	3	0
Hepatitis B Virus	5	0
Hepatitis C Virus	5	0

Sample category	Number of samples tested	Number of positive samples
Hepatitis E Virus	7	0
Herpes Simplex Virus	6	0
Human Immuno-deficiency Virus	5	0
Cytomegalovirus	4	0
Measles Virus	4	0
Mumps Virus	1	0
Rubella Virus	10	0
Dengue Virus	3	0
West Nile Virus	4	0
Yellow Fever Virus	4	0
Zika Virus	5	0
Influenza A and B Virus	10	0
Respiratory Syncytial Virus	10	0
Coronavirus NL63	6	1
Coronavirus 229E	6	0
Total	**154**	**6**

Study of Potentially Interfering Substances

Potential interference by commonly used substances was studied according to CLSI EP07-Ed3 recommendations.

No significant interference was detected up to the concentrations indicated below:

Tested substance	Concentration
Hemoglobin	10 g/L
Lipids	30 g/L
Albumin	60 g/L
Conjugated bilirubin	0.4 g/L
Unconjugated bilirubin	0.4 g/L

CLINICAL PERFORMANCE

Specificity

A total of 308 samples collected from negative individuals before September 2019 were tested singly using the VIDAS® SARS-COV-2 IgM assay on the VIDAS® instrument. Two false positive samples were detected.

The resulting overall specificity in the internal study was 99.4% [97.7-99.9].

Sensitivity

The sensitivity was determined by investigating 162 samples collected from 112 patients. Infection with SARS-CoV-2 was confirmed by PCR testing. The 162 samples were tested singly using the VIDAS® SARS-COV-2 IgM assay on the VIDAS® instrument.

The following table describes clinical sensitivity by time of sampling after a PCR positive result.

Note: In this document, sensitivity and Positive Percent Agreement are used interchangeably, since COVID-19 diagnosis is solely based on PCR results.

Number of Days after PCR Positive Result	Number of Samples	Number of VIDAS® Positive Results	Positive Percent Agreement	95% Confidence Interval
≤ 7 days	102	54	52.9%	[43.3-62.3]
8 - 15 days	32	29	90.6%	[75.8-96.8]
≥ 16 days	28	28	100.0%	[87.7-100.0]

Positive and Negative Predictive Values (PPV-NPV)

Positive and negative predictive values are directly related to the prevalence of the disease in the population. The calculation was done with the assumption of 5% prevalence.

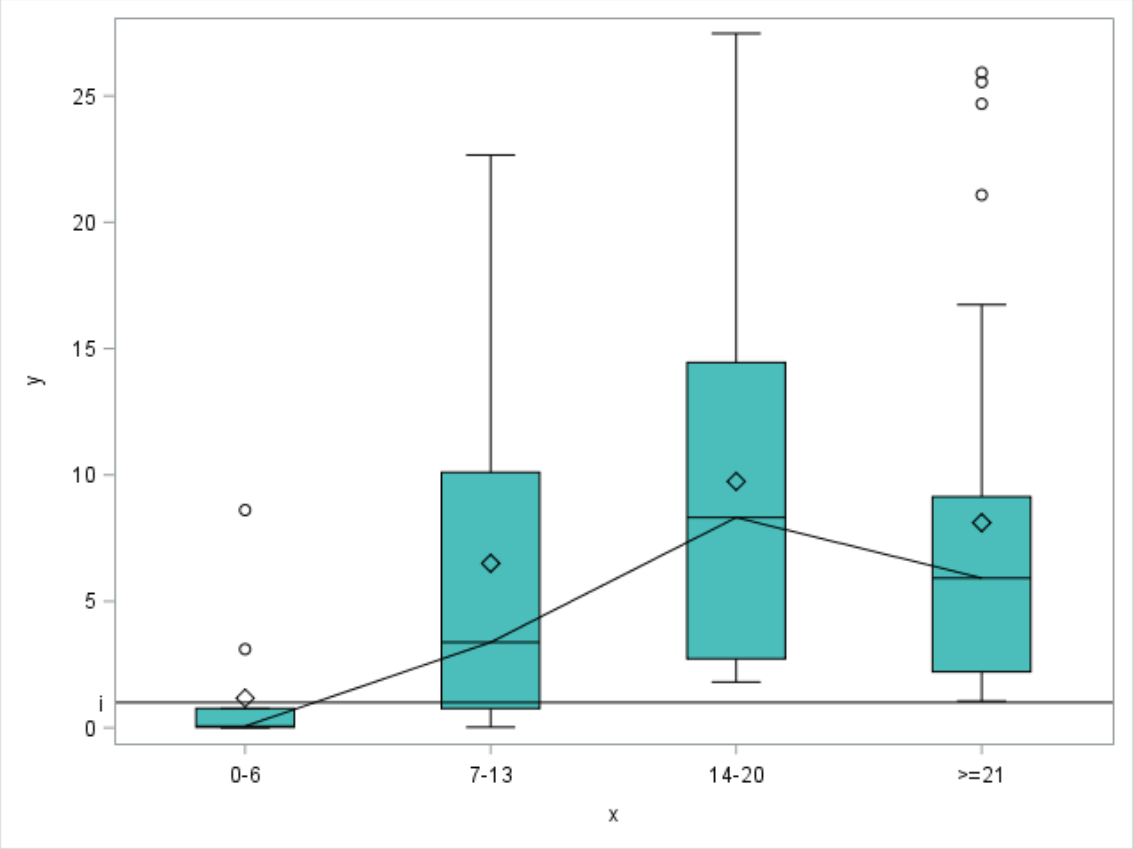
PPV and NPV were computed using results obtained from 7 days post symptoms onset.

Number of Days Post Symptoms Onset	PPV	NPV
≥ 7	87.9% [64.7-96.7]	99.5% [99.0-99.7]
≥ 14	89.0% [67.1-97.0]	100% *

* confidence interval not calculable

Distribution of IgM Index Post Symptoms Onset

The following figure shows the distribution of VIDAS® SARS-COV-2 IgM results (index) for 60 patients, according to the number of days post symptoms onset.



x = Number of days post symptoms onset

y = VIDAS® SARS-COV-2 IgM results

i = Threshold index

Number of Days Post Symptoms Onset	0-6	7-13	14-20	≥ 21
Number of samples	11	28	23	29
Number of VIDAS® positive results	2	20	23	29

This figure shows that IgM are mostly detected after day 7 and start to decrease 3 weeks after the onset of symptoms.

To complete results about antibody response, VIDAS® SARS-COV-2 IgG testing is recommended.

Combined Sensitivity and Specificity Performance obtained with VIDAS® SARS-COV-2 IgM and VIDAS® SARS-COV-2 IgG Assays

The following table describes combined clinical sensitivity performance obtained with VIDAS® SARS-COV-2 IgM and VIDAS® SARS-COV-2 IgG (Ref. 423834) assays by time of sampling after a PCR positive result.

Number of Days after PCR Positive Result	Number of Samples	Number of VIDAS® IgM and/or IgG Positive Results	Positive Percent Agreement	95% Confidence Interval
≤ 7 days	86	51	59.3%	[48.7-69.1]
8 - 15 days	28	27	96.4%	[81.7-99.9]
≥ 16 days	24	24	100.0%	[85.8-100.0]

A total of 308 samples collected from negative individuals before September 2019 were tested using the VIDAS® SARS-COV-2 IgM and VIDAS® SARS-COV-2 IgG (Ref. 423834) assays. Two false positive samples were detected.

The resulting combined specificity was 99.4% [97.7-99.9].

Longitudinal Combined Studies

The following table shows SARS-CoV-2 IgM and SARS-CoV-2 IgG seroconversion based on the VIDAS® test results of three patients.

	Number of Days after PCR Positive Results	IgM Index	IgM Interpretation	IgG Index	IgG Interpretation
Patient 1	0	0.06	Negative	0.02	Negative
	7	1.20	Positive	0.44	Negative
	14	2.81	Positive	4.49	Positive
	20	2.37	Positive	5.75	Positive
Patient 2	0	0.01	Negative	0.01	Negative
	7	0.63	Negative	0.06	Negative
	14	4.30	Positive	3.70	Positive
	20	3.31	Positive	8.74	Positive
Patient 3	0	0.05	Negative	≤ 0.00	Negative
	5	2.13	Positive	0.17	Negative
	14	16.74	Positive	33.00	Positive
	26	16.73	Positive	34.33	Positive

WASTE DISPOSAL

Dispose of used or unused reagents, as well as any other contaminated disposable materials, following procedures for infectious or potentially infectious products.

It is the responsibility of each laboratory to handle waste and effluents produced, according to their nature and degree of hazardousness, and to treat and dispose of them (or have them treated and disposed of) in accordance with any applicable regulations.

LITERATURE REFERENCES

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4. To KKW, Tsang OTY, Leung WS *et al.* - Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. - *Lancet Infect Dis.* - 2020 Mar 23: S1473-3099(20)30196-1.

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6. World Health Organization, Use of anticoagulants in Diagnostic, Laboratory Investigation, 2002, WHO/DIL/LAB/99.1 Rev.2

INDEX OF SYMBOLS

Symbol	Meaning
	Catalogue number
	*In Vitro* Diagnostic Medical Device
	Manufacturer
	Temperature limit
	Use by date
	Batch code
	Consult Instructions for Use
	Contains sufficient for <n> tests
	Date of manufacture

LIMITED WARRANTY

bioMérieux warrants the performance of the product for its stated intended use provided that all procedures for usage, storage and handling, shelf life (when applicable), and precautions are strictly followed as detailed in the instructions for use (IFU).

Except as expressly set forth above, bioMérieux hereby disclaims all warranties, including any implied warranties of merchantability and fitness for a particular purpose or use, and disclaims all liability, whether direct, indirect or consequential, for any use of the reagent, software, instrument and disposables (the "System") other than as set forth in the IFU.

REVISION HISTORY

Change type categories

N/A	Not applicable (First publication)
Correction	Correction of documentation anomalies
Technical change	Addition, revision and/or removal of information related to the product
Administrative	Implementation of non-technical changes noticeable to the user

Note: *Minor typographical, grammar, and formatting changes are not included in the revision history.*

Release Date	Part Number	Change Type	Change Summary
2020-05	055963-01	N/A	First publication
2020-06	055963-02	Technical change	Instructions for Use / Performance
		Administrative	Summary and Explanation / Longitudinal Combined Studies

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