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EN

REF 1N1206

STAT-NAT® SN200 Pluri CoV-2/ FLU/RSV

Lyophilized mix for qualitative detection of novel Coronavirus SARS-CoV-2, Influenza Virus A&B and RSV A&B in Real Time RT-PCR

REAGENT: 6 Master Mix miniplate

Σ 96

BUFFER : 3 x 1.5 mL Reconstitution Buffer

IVD

CE

NOTE: This package insert must be read carefully prior to product use. Package insert instructions must be followed accordingly. Reliability of assay results cannot be guaranteed if there are any deviations from the instructions in this package insert.

INTENDED USE

The STAT-NAT® SN200 Pluri CoV-2/FLU/RSV kit is an automated, lyophilized Real-Time RT-PCR multiplex assay based on nucleic acid amplification for the in vitro qualitative detection and differentiation of RNA from the SARS-CoV-2, Influenza A&B (Flu A&B) viruses and Respiratory syncytial viruses A&B (RSV A&B) in human nasopharyngeal swabs specimens[1,2,3].

This assay is an aid in the diagnosis of SARS-CoV-2, Influenza Virus A&B and RSV A&B single infections or coinfections, implemented on an automated extraction and amplification system. The assay is intended for professional use only.

PRINCIPLE

STAT-NAT® SN200 Pluri CoV-2/FLU/RSV kit is based on Real-Time RT-PCR testing and SENTINEL CH. S.p.A. proprietary freeze-dried amplification reagents that guarantee the sensitivity and the specificity of the reaction without intermediate manual steps for setting up reaction mixtures. The kit consists of 6 miniplates, each containing 16 optimized freeze-dried master mixes (96 reactions total) targeting simultaneously the specific regions of SARS-CoV-2 (N gene, labelled with FAM fluorophore), Influenza Virus A&B (M2-M1 genes and NEP-NS1 genes, labelled with HEX fluorophore) and RSV A&B (L gene, labelled with Texas Red fluorophore), allowing fast and simple results evaluation, and the STAT-NAT® SN200 Reconstitution Buffer.

Primers and probes specific for a housekeeping gene (human RNase P), labelled with Cy5 fluorophore, are present in each reaction mixture and they are used as endogenous Internal Control (IC). This provides indications on the functionality of the system and on the absence of inhibitors of polymerase activity, which could cause false negatives.

To perform the analysis, the STAT-NAT® SN200 Pluri CoV-2/FLU/RSV kit is intended to be used on the SENTiNAT® 200 automated system and self-contained assay-specific STAT-NAT® SN200 Pluri CoV-2-FLU-RSV Plugin, in conjunction with the STAT-NAT® SN200 Pluri CoV-2/FLU/RSV Controls kit REF.1N1207 and a dedicated RNA extraction kit.

The *First WHO International Standard for SARS-CoV-2 RNA (NIBSC code: 20/146)*[4] was used as reference materials only for the SARS-CoV-2 target.

REAGENTS

STAT-NAT® SN200 Pluri CoV-2/FLU/RSV consists of:

- **REAGENT: 6 miniplates x 16 master mix wells**

The kit includes 6 aluminum pouches labelled "Master Mix miniplate", containing a single miniplate with 16 lyophilized Master Mixes and a small orange desiccant sachet.

Each PCR well contains:

• dNTPs (dATP, dCTP, dGTP and dTTP);
• Reverse Transcriptase;
• Hot Start (Taq) Polymerase;
• Specific primers and probe for N gene;
• Specific primers and probes for M2-M1 genes/NEP-NS1 genes;
• Specific primers and probe for L gene;
• Specific primers and probe for human RNase P gene;
• Reaction buffer.

Lyophilized Master Mix must be stored at +15/+30 °C. Use only undamaged packages.

On board miniplate stability: stable up to 7 days if placed on the specific miniplate carriers and loaded on SENTiNAT® 200 automated system.

- **BUFFER: 3 x 1.5 mL**

The kit includes: 3 Reconstitution Buffer tubes (1.5 mL) in a liquid form.

Buffers must be stored at +15/+30 °C. Use only undamaged packages.

After opening, recap Reconstitution Buffer and store it at +15/+30 °C.

In use vial stability: stable up to expiry date indicated on the package if stored at +15/+30 °C

All the kit components are barcoded to be automatically read by SENTiNAT® 200 automated system.

QUALITY CONTROL

Use only the Positive Control (PC) STAT-NAT® SN200 Pluri CoV-2/FLU/RSV Positive control, included in the kit provided separately (REF. 1N1207).

Kit REF. 1N1207 provides indications on the functionality of the system.

It is necessary to validate each run using:

- NTC (STAT-NAT® SN200 Control Reconstitution Buffer included in REF. 1N1207);
- A positive control (STAT-NAT® SN200 **Positive Control** included in REF. 1N1207).

If required by laboratory's guidelines, include a negative control (NC) in each run. A verified negative sample can be used as NC.

SAMPLE

For initial diagnostic testing for COVID-19, the World Health Organisation (WHO) recommends the collecting and the testing of nasopharyngeal swabs. Collect the samples with an appropriate device.

Store specimens at 2-8 °C. The specimens should be processed within 48 hours of collection[5,6].

INSTRUMENTATION AND MATERIALS REQUIRED BUT NOT PROVIDED

Positive control kit: STAT-NAT® SN200 Pluri CoV-2/FLU/RSV Controls kit – REF. 1N1207.

Consumables/Accessories: Hamilton MIC Tubes & V-Caps – REF DS0009, SENTiNAT® 200 extraction kit consumable set – REF.1N1004, Elution plates –REF. 1N1008 and Deep Well Plate –REF. DS0005.

General molecular laboratory equipment: biosafety cabinet (laminar flow hood) for samples handling, centrifuge/micro-

centrifuge, vortex mixer, variable volume pipettes, sterile disposable plastics.
Extraction Kit: SENTiNAT® X48 Pathomag Extraction kit – REF. 1N1009.
Personal protective equipment (PPE): as gloves, laboratory coats, safety glasses, facemasks.
Validated automated system: SENTiNAT® 200, and the dedicated instrument consumables.
Software platform and Analysis Software: FastFinder (UgenTec), the assay-specific STAT-NAT® SN200 Pluri CoV-2-FLU-RSV Plugin REF. PLSN20002. The analysis software can be supplied on request. Fill out the online request form on *https://www.ugentec.com/create-account* to set up your account.
-CAUTION: Refer to FastFinder (UgenTec) website to ensure you are using the most current version of the analysis software.

WARNINGS AND PRECAUTIONS[10]
- The STAT-NAT® SN200 Pluri CoV-2/FLU/RSV kit – REF. 1N1206 is exclusively for IVD use with SENTiNAT® 200 system only.
- Read all the instructions contained in the kit insert before performing the test;
- Comply with the kit expiration date;
- Do not mix up reagents for amplification (i.e. buffer) or consumables from other commercial kits;
- Do not mix up reagents or consumables from kits with different Lot Number;
- Do not use any reagents if the safety seal is broken or if the packaging is damaged upon arrival;
- Do not use consumables or reagents if the protective pouch is open or broken upon arrival;
- Minimum specimen volume is 700 µL. It is possible to use different tube size and different specimen carriers as indicated in SENTiNAT® 200 Operator,s Manual;
- The MSDS are available at www.sentineldiagnostics.com or at your local supplier;
- Keep all miniplates, with lyophilized master mix, protected from light and humidity in their aluminum envelopes;
- Avoid microbial, ribonuclease (RNase) and deoxyribonuclease (DNase) contamination of all reagents and consumables;
- In cases where open-tube PCR tests are also conducted by the laboratory, care must be taken to ensure that the consumables and reagents required for testing, personal protective equipment such as gloves and lab coats, and the SENTiNAT® 200 system are not contaminated;
- Wash hands thoroughly after performing the test;
- Do not pipette by mouth. Do not smoke, drink, or eat in areas where specimens or reagents are being handled.
- Always use personal protective equipment for the individual protection;
- The product must be handled by staff trained in molecular biology techniques, such as nucleic acids extraction, amplification, detection and in automation;
- Results obtained with the STAT-NAT® SN200 Pluri CoV-2/FLU/RSV assay should be interpreted in conjunction with other clinical and laboratory findings;
- As with other tests, negative results do not rule out the SAR-CoV-2, Influenza Virus A&B or RSV A&B infection;
- Mutations within the target regions of the SARS-CoV-2/Influenza/RSV RNA covered by the STAT-NAT® SN200 Pluri CoV-2/FLU/RSV kit may affect primers and/or probe pairing resulting in the under-estimation of viral nucleic acids detection;
- False negative or invalid results may occur due to interference. The Internal Control is included in STAT-NAT® SN200 Pluri CoV-2/FLU/RSV to help identify the specimens containing substances that may interfere with nucleic acid isolation and PCR amplification;

⚠ **CAUTION** This product requires the handling of human specimens. It is recommended that all human sourced materials be considered potentially infectious and be handled in accordance with the OSHA Standard on Bloodborne Pathogens[7], Biosafety Level 2[8] or other appropriate biosafety practices[9,10] should be used for materials that contain or are suspected of containing infectious agents.

INSTRUCTIONS FOR USE
Miniplates highlights:
1. Ensure that before using pouches, they are always well sealed and that the desiccant sachets is still inside. Use only undamaged packages;
2. Cut the aluminum pouches at the point indicated by the lateral notches;
3. Remove the miniplates from the pouches immediately before use;
4. Examine the lyophilized master mix before use to verify that the content has a solid and white appearance. Please discard the product that appears with signs of moisture contamination (i.e. change of colour, collapsing product);
5. Make sure lyophilized master mix is at the bottom of the test well before to load the miniplates into the specific carriers;
6. Waste the aluminum pouches and their content if the desiccant sachets turn from orange to green.
7. All reagents, correctly stored at +15/+30 °C, are stable up to the expiration date indicated on the package;

Warning: Do not remove the aluminum foil from the miniplates top. Do not shake or invert the miniplates.

For a detailed description of how to load the STAT-NAT® SN200 Pluri CoV-2/FLU/RSV kit miniplates and buffers on the SENTiNAT® 200 system, refer to the SENTiNAT® 200 Operator's Manual.

PROCEDURE
SENTiNAT® 200 application and sample-to-result run
1. The STAT-NAT® SN200 Pluri CoV-2/FLU/RSV kit - REF. 1N1206 can process a maximum of 48 samples per run;
2. The required minimum sample volume is 700 µL using primary sterile tubes. Refer to the SENTiNAT® 200 Operator's Manual for acceptable tube size and appropriate sample rack type;
3. For a detailed description of how to operate the SENTiNAT® 200 system, refer to the SENTiNAT® 200 Operator's Manual.

Reaction set up
1. For the RNA extraction from human respiratory samples, refer to the SENTiNAT® 200 Operator's Manual;
2. Follow the instruction for use (IFU) of STAT-NAT® SN200 Pluri CoV-2/FLU/RSV Controls kit – REF. 1N1207 and SENTiNAT® 200 Operator's Manual to prepare the positive control and the No Template Control (NTC) (STAT-NAT® SN200 Control Reconstitution Buffer)
4. Include a negative control (NC) if required;
5. Follow the SENTiNAT® 200 Operator's Manual and software instructions for the instrument deck preparation.

INTERPRETATION OF RESULTS

Data interpretation requires analysis software. Follow standard laboratory practices for transfer, reporting and storage of results.
The below paragraph describes the different steps to analyze the results with the analysis software. For detailed instructions on any of the steps, including screenshots, refer to the technical note and FastFinder IFU, accessible from the support menu in FastFinder platform.

Data Analysis

- Start up the FastFinder software and log in;
- select Dashboard menu;
- select the data file to be analysed into Open Analysis section;
- check/Set up the plate layout into PCR setup section. Verify the correct selection of assay and samples position;
- check controls and resolve any uncertain results. Refer to FastFinder IFU for detailed instructions
- authorize, reject or restart the analysis;
- select Analysis results into Archive menu and download the results using the Export file(s) column or send your results directly to your LIS.

PERFORMANCES [11]

Analytical Sensitivity[12]

The Limit of Detection (LoD) was evaluated using dilution panels as reported below:

Target	Units of measure	Dilution panel	
		from	to
SARS-CoV-2*	IU/mL	250	2500
Influenza A&B	copies/mL	250	2500
RSV A	copies/mL	500	5000
RSV B	copies/mL	250	2500

*The First WHO International Standard for SARS-CoV-2 RNA (NIBSC code: 20/146) has been used;
The LoD was calculated on several replicates of samples, the results that show a 95% probability to have a positive result are summarized in **Table A.**

Table A. Limit of Detection

LoD Results				
Instrument: SENTiNAT® 200				
FAM (SARS-CoV-2)	**HEX** (Influenza A)	**HEX** (Influenza B)	**Texas Red** (RSV A)	**Texas Red** (RSV B)
500 IU/mL	500 copies/mL	500 copies/mL	1000 copies/mL	500 copies/mL

Precision[13]

In this study, the closeness of agreement between measured quantities obtained by replicate measurements on the same analyte under specified conditions was evaluated. **Table B** summarizes precision measurements intended as repeatability and reproducibility studies.

Table B. Precision measurement studies intended as repeatability and reproducibility studies

Measurement	Criteria for acceptance	Pass (Yes/No)
Repeatability	CV% < 5%	Yes
Reproducibility	CV% < 10%	Yes

Cross-reactivity[11]

Analytical specificity was demonstrated using a panel of 15 different pathogens. No cross-reactivity was observed with any of the organisms tested, as indicated in **Table C**, confirming 100% analytical specificity of the STAT-NAT® SN200 Pluri CoV-2/FLU/RSV.

Table C. *In vitro* cross-reactivity evaluation

Pathogen	Cross-Reactivity (Yes/No)
Enterovirus	NO
Adenovirus	NO
Streptococcus pneumoniae	NO
Legionella pneumophila	NO
Mycobacterium tuberculosis	NO
MERS Coronavirus	NO
Candida albicans	NO
Coronavirus SARS	NO*
Streptococcus pyogenes	NO
Mycoplasma pneumoniae	NO
Haemophilus influenzae	NO
Bordetella pertussis	NO
Chlamydophila pneumoniae	NO
Human parainfluenza	NO
Human Coronavirus OC43	NO

*Coronavirus SARS, belonging to Sarbecovirus subgenus, is correctly detected only for E gene.

Inclusivity[11]

The inclusivity analysis was performed in silico using online databases for literature and genomic sequences.
The results shown in **Table D.**

Table D: Genotype inclusivity

Assay Targets	Inclusivity
SARS-CoV-2	99,5%
FLU A	90,1%
FLU B	94,1%
RSV A	93,88%
RSV B	90,1%

Interferences[11]

The STAT-NAT® SN200 Pluri CoV-2/FLU/RSV assay was evaluated in the presence of typical exogenous and endogenous interfering substances in nasopharyngeal swab specimens. A list of the interferents is reported in **Table E**.

Table E. List of the tested interferents

Interfering Substances	Concentration Tested
Caffeine	0.2 mg/mL
Acetylsalicylic acid	0.2 mg/mL
Ascorbic acid	20 mg/mL
Ibuprofen	1 mg/mL
Cetylpyridinium chloride	20 mg/mL
Albumin	20 mg/mL
Ethanol	1%
Nasal spray drops	20 %
Whole blood	1%
Creatine	2 mg/mL
Uric acid	20 mg/mL
Gentisic acid (2,5-Dihydroxybenzoic acid)	0.2 mg/mL
Acetaminophen	0.2 mg/mL

Results obtained from this study shows an irrelevant interfering effect of the endogenous or exogenous molecules on kit analytical sensitivity.

CLINICAL EVALUATION

A panel of 155 positive and negative samples (nasopharyngeal swab specimens), was tested using a commercially available

predicate device. The positive and negative predicted agreement are reported in **Table F**.

Table F: Clinical performances

Parameter	Calculated agreement		
	SARS-CoV-2	Flu A&B	RSV A&B
Positive Predicted Agreement	98%	100%	100%
Negative Predicted Agreement	100%	100%	100%

TROUBLESHOOTING

Problem 1: Weak or no signal in Positive Control:

1. Real-Time PCR conditions do not comply with the instructions in the kit insert:
- The Positive Control was not added to the reaction. Repeat test;
- Check the performance of the SENTiNAT® 200 and carry out the instrument calibration.
2. Primers/probes degradation: the reagent storage conditions do not comply with the instructions in the kit insert:
- Check the kit storage conditions;
- Check the kit expiration date.

Problem 2: Weak or no signal in Internal Control.

1. Inhibitory effect of the sample: RNA with a low quality extraction. The result is INVALID:
- Ensure to follow carefully the instructions reported in the kit insert;
- Repeat the test using the same extracted RNA sample. If the result is still negative, repeat the extraction step using the same primary sample. Otherwise, collect a new primary sample and repeat the test.
2. Primers/probes degradation: the reagent storage conditions do not comply with the instructions in the kit insert:
- Check the kit storage conditions;
- Check the kit expiration date.

Problem 3: FAM, HEX/VIC, Texas Red signal in NTC or in Negative Control.

1. Contamination during the Real-Time PCR preparation procedure: all results are INVALID:
- Clean the workbench and all the instruments;
- Handle Positive Control carefully avoiding contamination;
- Repeat Real-Time PCR using a new set of reagents

Problem 4: Fluorescence intensity variability or absence of FAM, HEX/VIC, Texas Red, Cy5 signal.

1. Humidity damage for lyophilized mix: the reagent storage conditions do not comply with the instructions in the kit insert:
- Check the kit expiration date;
- Check the kit storage conditions; ensure that the pouch is always well sealed, and that the desiccant sachet is still inside;
- Check if the desiccant sachet turns from orange to green.
2. Inhibitory effect of the sample: RNA with a low quality extraction. The result could be a false negative. The result is INVALID:
- Ensure to follow the instructions reported in the kit insert carefully.

Problem 5: No signal at all.

1. Check the performance of the SENTiNAT® 200 instrument:
- Carry out the instrument calibration.
2. Primers/probes degradation: the reagent storage conditions do not comply with the instructions in the kit insert:
- Check the kit storage conditions;
- Check the kit expiration date.

Problem 6: Error message given by the SENTiNAT® 200 instrument.

Consult the Instrument Operator's Manual or contact the local technical support.

Problem 7: Ct > 30 in the Internal Control.

Sample with low quality extracted RNA or errors in sample dispensing in the reaction set up.
- Repeat the test using the same extracted RNA sample. If the IC Ct result is still > 30, repeat the extraction step using the same primary sample. Otherwise, collect a new primary sample and repeat the test.

CAUTION: For the SENTiNAT® 200 instrument please refer to manual troubleshooting

WASTE MANAGEMENT

– The reagents of the kit are not classified as dangerous according to Regulation EC 1272/2008 (CLP). Adopt good working practices, so that the product is not released into the environment. Recover if possible. In so doing, comply with the local and national regulations currently in force.
– Manage and waste all the biological samples as potentially infectious. All the material that come in contact with the biological sample must be treated with 0.5% sodium hypochlorite for at least 30 minutes or sterilized in autoclave at 121 °C for 30 minutes and then wasted.

BIBLIOGRAPHY

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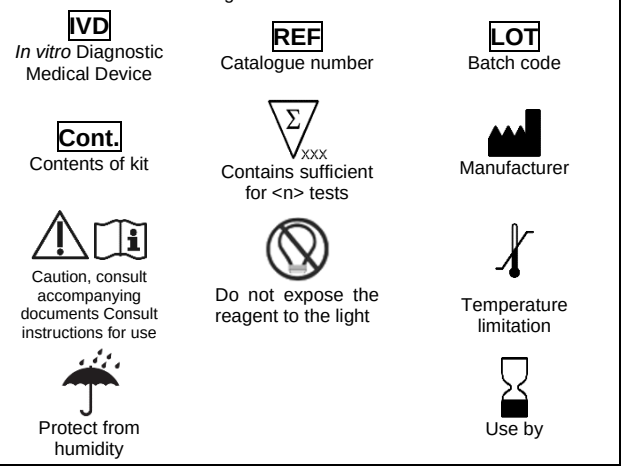
Explanation of symbols EN

REAGENT / CONTROL
The terms refer to the: reagent / control



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Note: changes in comparison to the previous version are indicated by a vertical bar in the text margin

In case of incident, please contact Sentinel Diagnostics (contact details at www.sentineldiagnostics.com) or your local representative. 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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