BIOHIT 必欧瀚

立足预防医学·创新诊疗路径

SARS-CoV-2IgM/IgG ANTI-BODOY TEST KIT (COLLOIDAL GOLD METHOD)

BRIEF INTRODUCTION

Company profile

Founded in November 2013, BIOHIT Healthcare (Hefei) Co., Ltd. has always been committed to the development and application of in vitro diagnostic technology. The Company obtained the *Medical Device Production License* in 2016, and operates in strict accordance with the ISO13485 quality management system. Through years of development, the Company has formed a complete industrialized system for the development, production and sales of in vitro diagnostic reagents and supporting instruments. The 15 existing products have obtained CFDA and CE certifications, and two of them are the first in the world. The Company is positioned in the preventive medicine field. Since its inception, the Company has carried out long-term strategic cooperation with BIOHIT Oyj, a leading biomedical company in Finland. Through independent innovation, the in vitro diagnostic technology of digestive diseases represented by serum gastric functions has reached the internationally advanced level. In June 2018, the Company completed the acquisition of Finnish BIOHIT Oyj and became the largest shareholder of BIOHIT Oyj, a listed company. Through this merger and acquisition, the Company has further improved the industrial chain and laid the foundation for opening up the global market. In 2016, the Company established an academician workstation to develop new tumor markers. Meanwhile, by cooperating with Germany's ScheBo-Biotech AG, the Company establish a diagnosis system based on digestive diseases. BIOHIT Healthcare (Hefei) Co., Ltd. makes continuous innovation in the field of preventive medicine, and offers considerate health care services.

Overseas customers

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The countries that use BioHit Antibody Text kit include:

- England
- Finland
- Germany
- Romania
- Netherland
- Greece
- Canada
- Bangladesh
- The USA
- Italy

Company qualification

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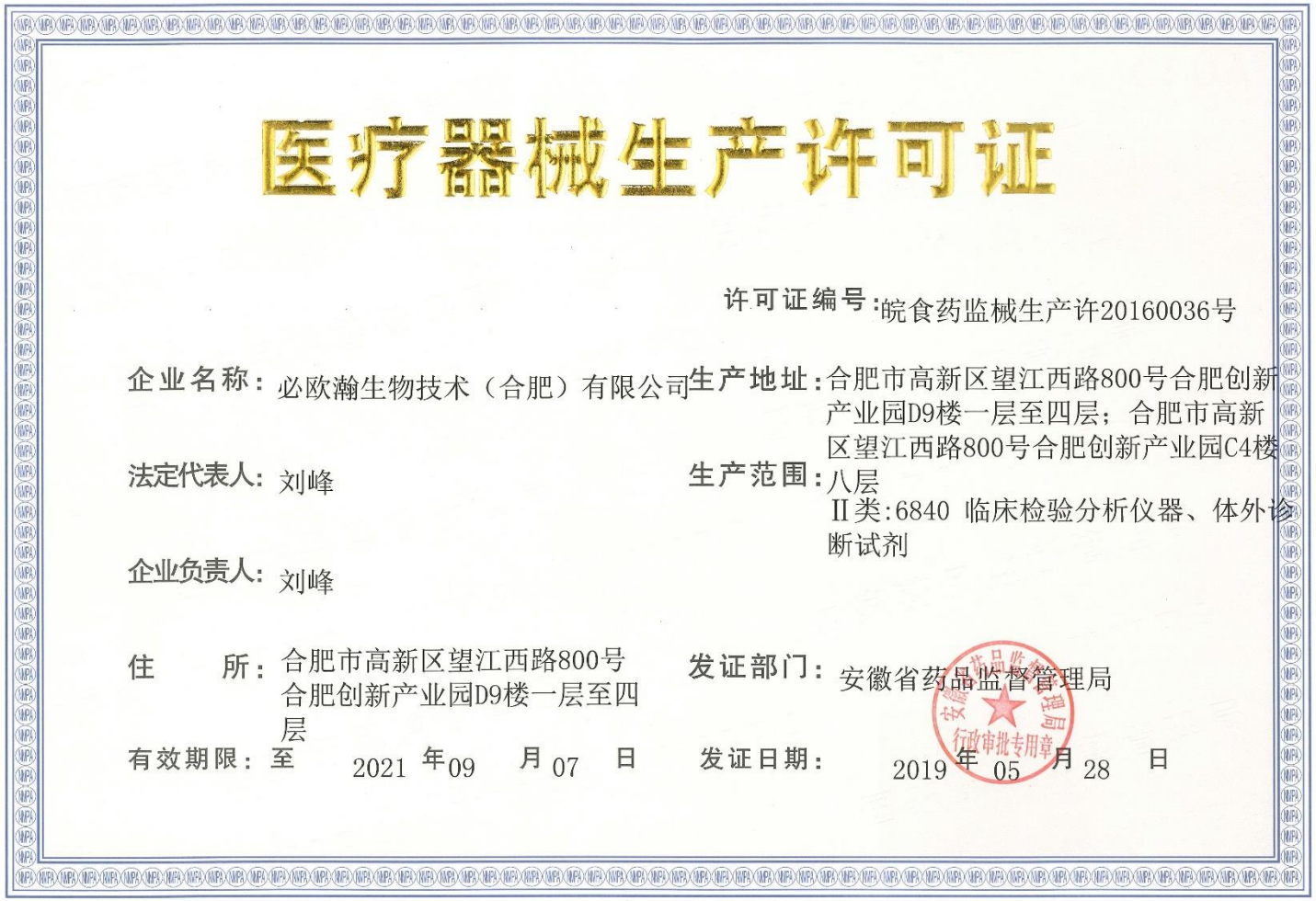

医疗器械生产许可证

许可证编号：皖食药监械生产许20160036号

企业名称：必欧瀚生物技术（合肥）有限公司

生产地址：合肥市高新区望江西路800号合肥创新产业园D9楼一层至四层；合肥市高新区望江西路800号合肥创新产业园C4楼八层

法定代表人：刘峰

生产范围：Ⅱ类:6840 临床检验分析仪器、体外诊断试剂

企业负责人：刘峰

住　　所：合肥市高新区望江西路800号合肥创新产业园D9楼一层至四层

发证部门：安徽省药品监督管理局

有效期限：至 2021 年 09 月 07 日

发证日期：2019 年 05 月 28 日

国家药品监督管理局制

Company qualification

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统一社会信用代码
91340100082205500O(1-1)

营业执照

(副本)

扫描二维码登录'国家企业信用信息公示系统'了解更多登记、备案、许可、监管信息。

名　　称　必欧瀚生物技术（合肥）有限公司

类　　型　有限责任公司(台港澳与境内合资)

法定代表人　刘峰

经营范围　一、二、三类医疗器械的研发、生产与销售；自营和代理各类商品及技术的进出口业务（国家法律法规禁止或限定的除外）；药品、消毒产品的研发、生产与销售（危险化学品除外）。（依法须经批准的项目，经相关部门批准后方可开展经营活动）

注册资本　陆仟伍佰玖拾肆万贰仟零贰拾玖人民币元整

成立日期　2013年11月13日

营业期限　2013年11月13日至2043年11月12日

住　　所　合肥市高新区望江西路800号合肥创新产业园D9楼一层至四层

登记机关　合肥市市场监督管理局

2020 年 03 月 30 日

国家企业信用信息公示系统网址：http://www.gsxt.gov.cn

市场主体应当于每年1月1日至6月30日通过国家企业信用信息公示系统报送公示

国家市场监督管理总局监制

Material Safety Data Sheet

1、Chemical product and company identification

Product name:SARS-CoV-2 IgM/IgG antibody test kit （Colloidal Gold Method）
Producer:Biohit Healthcare(Hefei)Co.Ltd.
Address：Buiding D9, Innovation park west WangJiang Road No.800 HeFei 230088 , AnHui .

2、Information of product

Main components: Sodium Phosphate Dibasic
Purpose: SARS-CoV-2 IgM/IgG antibody test kit （Colloidal Gold Method）is suitable for qualitative detection of SARS-CoV-2 IgM and IgG antibodies in human serum,plasma and whole blood in vitro.
Molecular weight: 177.99
Chemical formula: $Na_2HPO_4 \cdot 2H_2O$
CAS No:10028-24-7

3、Hazards identification

This substance is considered to be non-hazardous for transport.

4、first aid measures

Skin exposure:None
Eye exposure:Rinse with plenty of water
Ingestion:None
First aid facilities:Not applicable
advice to doctor:None

5、Fire fighting measures

Suitable extinguishing media:None
SPECIAL RISKS:None
Wear self-contained breathing apparatus and protective clothing and gloves:None

6、Accidental Release measures

Personal precautions such as:ues gloves and mask
Environmental precautions such as:clean up material and forward to an approved disposal site.

7、Handling and storage

Handling:keep in a tightly closed container.
Storage:Store at room temperature.
Do not be exposed to sunlight.

空运 By Air

NO.2020150461

CNAS 中国认可 检验 INSPECTION CNAS IS17171

货物运输条件鉴定书

Certification for Safe Transport of Chemical Goods

非限制性货物

样品名称：	新型冠状病毒（SARS-CoV-2）IgM/IgG检测试剂盒（胶体金法）
Sample Name:	SARS-CoV-2 IgM/IgG antibody test kit (Colloidal Gold Method)
委托单位：	必欧瀚生物技术（合肥）有限公司
生产单位：	必欧瀚生物技术（合肥）有限公司

上海化工院检测有限公司 检验检测专用章

上化院 上海化工院检测有限公司
Shanghai Research Institute of Chemical Industry Testing Co., Ltd

空运 By Air　　空运 By Air

新型冠状病毒（SARS-CoV-2）IgM-IgG 检测试剂盒

（胶体金法）成品检验报告

SARS-CoV-2 IgM/IgG ANTIBODY TEST KIT

(Colloidal gold method) Quality Control Certificate

批号 Lot No.	SA200301	报告日期 Report date	2020.03.23
生产日期 Production Date	2020.03.20	有效期至 Expiry date	2021.03.19
检验项目 Inspection Item	标准 Criterion		结果 (Pass/Fail)
外观 Exterior	试剂盒各组份应齐全；标签应清晰，准确、牢固。 Each component of the test kit should be complete; the label should be clear, accurate and firm.		Pass
宽度 width	膜条宽度不小于 2.8mm。 The width of the film strip is not less than 2.8mm.		Pass
移行速度 Travel speed	液体移行速度应不低于 10mm/min。 The migration speed should not be less than 10mm / min.		Pass
阳性参考品符合率 Coincidence of positive reference	用 3 份企业 SARS-CoV-2 抗体阳性参考品 P1-P3 各检测 1 次，结果均应为阳性。 Three samples of SARS-CoV-2 antibody positive reference P1-P3 were tested once, and the results should be positive.		Pass
阴性参考品符合率 Coincidence of negative	用 6 份企业 SARS-CoV-2 抗体阴性参考品 N1-N6 各检测 1 次，结果均应为阴性。 Six samples of SARS-CoV-2 antibody negative reference N1-N6 were tested once, and the results should be negative.		Pass

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reference			
灵敏度 Sensitivity	用 3 份企业 SARS-CoV-2 抗体阳性最低检测限参考品进行检测，每份参考品各检测 1 次,均应检出为阳性。 Three samples of SARS-CoV-2 antibody Sensitivity reference were tested once, and the results should be positive.		Pass
重复性 Repeatability	用 1 个浓度水平的参考品进行检测，结果均应为阳性且显色均一。 The test is performed with a reference, and the results should be positive and uniform in color.		Pass
结论：此产品符合上述所有标准。 Conclusion：The product meets all the criterion.			
检验人 Checked by	王五云	复核人 Reviewed by	马从飞	批准人 Approved by	
日期 Date	2020.03.23	日期 Date	2020.03.23	日期 Date	2020.03.23

必欧瀚生物技术（合肥）有限公司
安徽省合肥市高新区望江西路 800 号创新产业园 D9 栋 230088
联系电话：0551-68561563　售后电话：400-990-5066　传真：0551-68561563
BIOHIT HealthCare (Hefei) Co.,Ltd.
Building D9, innovation Park, No.800 West Wangjiang Road, Hefei, Anhui, 230088
Contact phone: 0551-68561563 After-sales phone: 400-990-5066 Fax: 0551-68561563

Company qualification

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GOOD PRACTICE OF MANUFACTURE

ISO PROCESS PRODUCT

ZERTIFIKAT ◆ CERTIFICATE ◆ 認證證書 ◆ СЕРТИФИКАТ ◆ CERTIFICADO ◆ CERTIFICAT

DAkkS Deutsche Akkreditierungsstelle D-ZM-11321-01-00

Product Service

Certificate

No. Q5 094093 0003 Rev. 01

Holder of Certificate: **Biohit Healthcare (Hefei) Co., Ltd**
Building D9 floor1-4, Innovation Park
West Wangjiang Road No.800
High-Tech Zones
230088 Hefei, Anhui
PEOPLE'S REPUBLIC OF CHINA

Facility(ies): Biohit Healthcare (Hefei) Co., Ltd
Building D9 floor1-4, Innovation Park, West Wangjiang Road No.800, High-Tech Zones, 230088 Hefei, Anhui, PEOPLE'S REPUBLIC OF CHINA

Certification Mark:

Scope of Certificate: **Design, Development, Production and Distribution of Assay kits and related Control solutions based on ELISA, Immunochromatographic and Chemiluminescent Method, and Fluorescence Immunoassay Analyzer**

Applied Standard(s): EN ISO 13485:2016
Medical devices - Quality management systems - Requirements for regulatory purposes
(ISO 13485:2016)
DIN EN ISO 13485:2016

The Certification Body of TÜV SÜD Product Service GmbH certifies that the company mentioned above has established and is maintaining a quality management system, which meets the requirements of the listed standard(s). See also notes overleaf.

Report No.: SH20103205

Valid from: 2020-05-04
Valid until: 2022-04-05

Date, 2020-05-04

Christoph Dicks
Head of Certification/Notified Body

TÜV®

Page 1 of 1
TÜV SÜD Product Service GmbH • Certification Body • Ridlerstraße 65 • 80339 Munich • Germany

A4 / 07.17

Company qualification

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GOOD PRACTICE OF MANUFACTURE

EC DECLARATION OF CONFORMITY

EC Declaration of Conformity

According to the In Vitro Diagnostic Medical Devices Directive 98/79/EC

Manufacturer: BIOHIT HealthCare (Hefei) Co., Ltd.
Address: Building D9 floor 1-4,Innovation Park,No.800 West Wangjiang Road, High-Tech Zones, Hefei, Anhui,PR China

European Representative: Wellkang Ltd
Address: 16 Castle St,Dover,CT16 1PW, UK

Product: SARS-CoV-2 IgM/IgG antibody test kit (Colloidal Gold Method)
Classification: Others

We, the manufacturer, herewith declare with sole responsibility that our product mentioned above meets the provisions of the Directive 98/79/EC of the European Parliament and of the Council on In Vitro Diagnostic Medical Devices.

General Applicable Directive DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 1998 on in vitro diagnostic medical devices

The above declaration of conformity is issued under the sole responsibility of the manufacturer.

General Manager: Liu Feng

CE

Hefei, March 18th, 2020
(Place and Date of Issue)

Liu Feng
(Signature and Seal)

Company qualification

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GOOD PRACTICE OF MANUFACTURE

FDA EUA ACKNOWLEDGMENT LETTER

FDA U.S. FOOD & DRUG ADMINISTRATION

Acknowledgment Letter

4/6/2020

Brian Yang, CEO
Beijing Tongze Medical Technology Co. Ltd
Suite 0617, 6th Floor, Building 1
Guoyingyuan, Xicheng District
Beijing 100035
CHINA

Dear Brian Yang:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has received your submission. This submission has been assigned the unique document control number below. All future correspondence regarding this submission should be identified prominently with the number assigned and should be submitted to the Document Control Center at the above letterhead address. Failure to do so may result in processing delays. If you believe the information identified below is incorrect, please notify the Program Operations Staff at (301) 796-5640.

Submission Number: EUA200192
Received: 4/6/2020
Applicant: Biohit Healthcare (Hefei) Co. Ltd.
Device: SARS-CoV-2 Antibody Test Kit (Colloidal Gold Method)

We will notify you when the review of this document has been completed or if any additional information is required. If you are submitting new information about a submission for which we have already made a final decision, please note that your submission will not be re-opened. For information about CDRH review regulations and policies, please refer to http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm.

Sincerely yours,

Center for Devices and Radiological Health

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Company qualification

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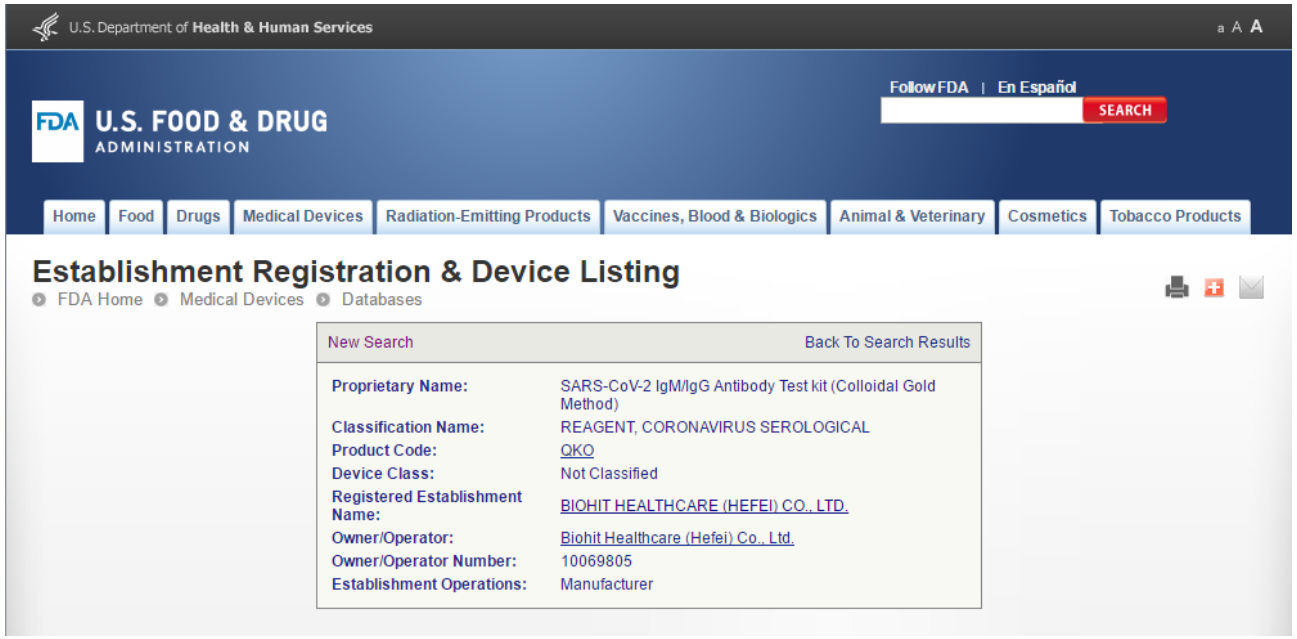
GOOD PRACTICE OF MANUFACTURE

FDA RECORD NUMBER



Company qualification

BIOHIT HealthCare
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CHINA CHAMBER OF COMMERCE FOR IMPORT & EXPORT OF MEDICINES & HEALTH PRODUCTS

Chinese Version

Home | About Us | Events | News | Public Relations | Analysis | Members | Suppliers | Contact Us

Events
Video
Industry News

CCCMHPIE Released the Name List of Medical Devices and Supplies Companies with Certification/Authorization from other Countries

Saturday, 25 April 2020 | Source: CHINA CHAMBER OF COMMERCEFOR IMPORT&EXPORT OF MEDICINES &HEALTH PRODUCTS | Author:

五、	新型冠状病毒检测试剂 Coronavirus Reagent Test kits		
1	北京万泰生物药业股份有限公司 Beijing Wantai Biological Pharmacy Enterprise Co., Ltd.	91110114600067778R	CE
2	深圳市锦瑞生物科技有限公司 Genrui Biotech Inc.	91440300766350741W	CE
3	安徽福贸生物科技有限公司 Anhui Formaster Biosci Co., Ltd.	91340225MA2TENM49Y	CE
4	安徽深蓝医疗科技股份有限公司 Anhui Deepblue Medical Technology Co., Ltd.	913401005501903714	CE
5	必欧瀚生物技术（合肥）有限公司 BIOHIT HealthCare(Hefei) Co., Ltd.	913401000822055000	CE

Product introduction

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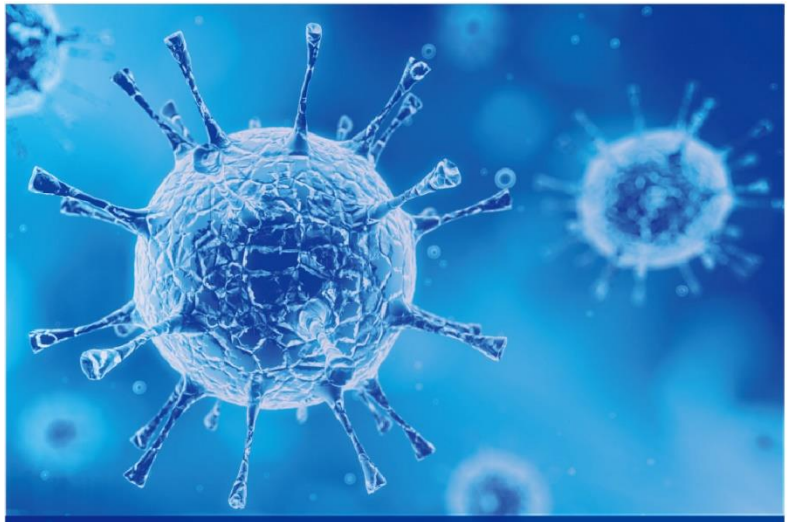


Background

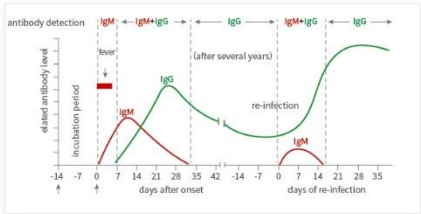
SARS-CoV-2

Coronaviruses are single-stranded, positive-sense RNA viruses with outer membrance, which are important pathogens of vertebrates, and can cause many acute and chronic diseases.

On February 1, 2020, the International Committee on the Taxonomy of Viruses named the new coronavirus as SARS-CoV-2. The infected people will have acute and severe respiratory diseases, accompanied by fever, cough, shortness of breath and dyspnea, and severe cases will lead to renal failure and even death.

SARS-CoV-2 IgM/IgG ANTIBODY DETECTION

When body is infected with the new coronavirus, the specific protein of the virus stimulates the immune system and lead to an antibody response, the first antibody to appear is IgM, and then the IgG antibody. From the general process of acute infection, when the IgG antibody appears, the concentration will continue to increase, the IgM will continue to decrease or even disappear, and the IgG antibody will exist for a long time. The simultaneous dynamic monitoring of IgM and IgG antibody can be used in the auxiliary diagnosis of new coronavirus infection.

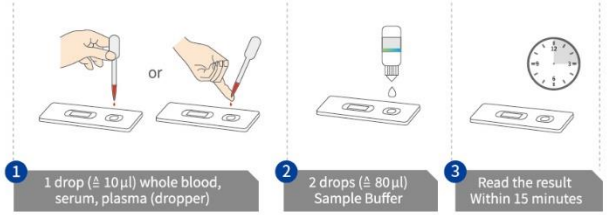


SPECIFICATION

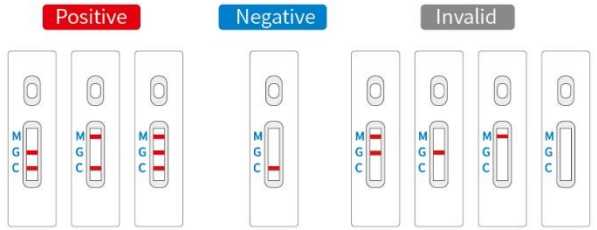
- Sample volume: 10μl
- Rapid test time : 15mins
- Two result : IgM and IgG antibody

Product Name	Sample type	Storage temperature	Packaging size
SARS-CoV-2 IgM/IgG antibody test kit	Serum, Plasma, Whole blood, Peripheral blood	2°C-30°C	20 tests/kit 25tests/kit 50tests/kit 100tests/kit

Operation Procedure



Result Interpretation



Interpretation of the results	A	IgM(–) & IgG(–)	Negative
	B	IgM(+) & IgG(–)	Positive, indication of an acute infection
	C	IgM(+) & IgG(+)	Positive, indication of an ongoing infection
	D	IgM(–) & IgG(+)	Positive, indication of a past infection

INSTRUCTION

1. INTENDED USE

SARS-CoV-2 IgM/IgG antibody test kit（Colloidal Gold Method）is intended for the in vitro qualitative detection of SARS-CoV-2 IgM and IgG antibodies from human serum, plasma and whole blood samples.

SARS-CoV-2 was discovered in pneumonia caused by novel coronavirus (Corona Virus Disease 2019) in 2019 and was officially named "SARS-CoV-2" by WHO on February 11, 2020. SARS-CoV-2 is a new strain of coronavirus that has never been found in human body before. The common signs of people infected with coronavirus are respiratory symptoms, fever, cough, shortness of breath and dyspnea. In more serious cases, infection can lead to pneumonia, severe acute respiratory syndrome, renal failure, and even death. This product is intended for the auxiliary diagnosis of SARS-CoV-2 infection.

2. TEST PRINCIPLE

The SARS-CoV-2 IgM/IgG Quick test is based on the immunochromatographic method. The SARS-CoV-2 IgM/IgG is detected by SARS-CoV-2 recombinant antigen and mouse anti human IgM/IgG antibody. SARS-CoV-2 IgM/IgG in the sample reacts with SARS-CoV-2 recombinant antigen bound to gold particles. This complex migrates along the membrane and reaches the IgM/IgG test line(T)which has mouse anti human IgM/IgG antibody against SARS-CoV-2 IgM/IgG complex.

When the result is positive, the gold-labelled SARS-CoV-2 recombinant antigen -antibody complex binds to the IgM/IgG test line(T)and a purplish red color develops. When the result is negative, the sample does not contain any SARS-CoV-2 recombinant antigen-antibody complex that can bind to the IgM/IgG test line(T)so no color becomes visible. Development of a purplish red control line(C)guarantees that sample application and migration have taken place correctly and that the test was properly performed.

3. KIT COMPONENTS

Serial Number	Content	Number
1	Instruction For Use	1 Piece
2	Test Card	25 Cassettes
3	Sample Diluent	1 Vial
4	Dropper	25 Droppers

4. WARNINGS AND PRECAUTIONS

Samples for human serum plasma or whole blood, should be considered as potentially infectious.Operators should wear protective clothing, masks, gloves and take other appropriate safety precautions to avoid or reduce the risk of infection.

5. STORAGE CONDITIONS AND SHELF LIFE

The test card is stored at 2°C-30°C, and the shelf life is 12 months. The test card sealed inside the aluminium foil bag shall be used within 1 hour after opening.

6. APPLICABLE INSTRUMENTS

None.

7. SAMPLE REQUIREMENTS

- Applicable to human serum, plasma or whole blood samples.
- For whole blood sampling, it is recommended to a safety lancet to make a finger prick. After puncturing the skin, use clean gauze to wipe away the first drop of blood to avoid specimen dilution with interstitial fluid. With the patient's hand pointing downward, firmly grasp the finger towards the base with your thumb placed along the length of the patient's finger. Gently massage along the length of the finger towards the tip, using a light squeeze-and-release motion to allow large droplets of blood to form and encourage continuous blood flow. If using a capillary tube or pipette allow a large drop of blood to form, position the device horizontally, and lightly touch the drop of blood (avoid touching the skin); allow the blood drop to be drawn into the collection vessel by capillary action (avoid air bubbles).
- For serum and plasma samples, The samples shall be tested immediately after collection. Serum and plasma samples can be stored for 5 days at 2-8°C, anticoagulant

whole blood samples should not be stored for more than 24 hours at room temperature, and should not be stored for more than 7 days at 2-8°C. If long-term storage is required, it should be stored at -20°C. Avoid repeated freezing and thawing of samples.

- Let the samples reach room temperature and mix well before testing. When there are visible particles in the sample, it should be centrifuged before the test to remove the precipitate.
- If there is a lot of lipid, hemolysis or turbidity in the sample, please do not use the sample to avoid affecting the result interpretation.

8. MATERIALS REQUIRED BUT NOT PROVIDED

- Sample vortex mixer
- 10-100µl pipette and tips
- Test tubes
- Sample collection tubes
- Timer

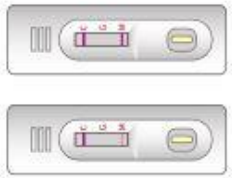
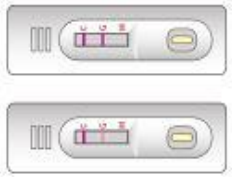
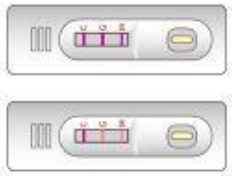
9. TEST PROCEDURES

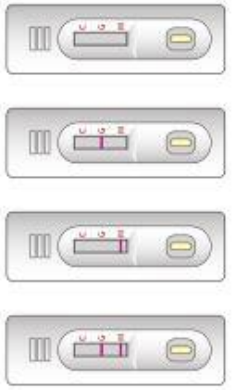
- **Step 1:** Take out the sample to be tested and let it reaches room temperature. Mix the sample well before testing.
- **Step 2:** Open the aluminium foil bag, take out the detection card and place it on the horizontal desktop.
- **Step 3:** Mark the sample number on the test card.
- **Step 4:** Take 10µL (or 1 drop) of the sample to be tested (serum, plasma or whole blood sample) from the sample tube with the pipette and add 80µL (or 2 drops) of sample diluent into the sample hole on the test card immediately, and ensure that there is no bubble during the operation.

Step 5: Read and interpret the results within 15 minutes (please take photos of the results).

10. INTERPRETATION OF THE RESULTS

10.1	Negative: If only C-line appears, indicating that SARS-CoV-2 antibody is not detected, and the result is negative:	

10.2	Positive:	
10.2.1	If both the C-line and the M-line appear, it means that the IgM antibody against SARS-CoV-2 is detected, and the result is that the IgM antibody is positive:	
10.2.2	If both the C-line and the G-line appear, it means that the IgG antibody against SARS-CoV-2 is detected, and the result is that the IgG antibody is positive:	
10.2.3	If the C-line, M-line and G-line are all present, it means that SARS-CoV-2 IgG and IgM antibody are detected, and the result is that IgG and IgM antibody are positive:	

10.3	Invalid result: if C- line is not observed, it is invalid whether there is a detection line or not, and the detection shall be carried out again:	

11. LIMITATION OF THE PROCEDURES

- The results of this test are only intended to be used to assist the clinical diagnosis.
- This product can only be used for the determination of serum, plasma and whole blood samples.
- Affected by the minimum detection limit of the product, the negative result may be caused by the antibody concentration in the tested sample is lower than the minimum detection limit.

12. PERFORMANCE CHARACTERISTICS

- **Compliance rate of positive references**

Three positive references P1-P3 of SARS-CoV-2 antibody were tested, the results are positive.

- **Compliance rate of negative reference**

Six negative references N1-N6 of SARS-CoV-2 antibody were tested, and the results are negative.

- **Minimum detection limit**

Three samples of reference L1-L3 with the lowest detection limit of SARS-CoV-2 antibody were tested, and the results are all positive.

- **Repeatability**

One SARS-CoV-2 antibody positive repetitive reference sample was tested 10 times, the results are all positive.

- **Clinical Evaluation**

Methods: a retrospective study was carried out with 226 samples from the First Affiliated Hospital of Anhui Medical University, including 78 samples of other respiratory tract infections, 108 samples of normal people and 40 samples confirmed positive for SARS-CoV-2 infection (Recovery

period sample). All samples were tested with SARS-CoV-2 IgM/IgG antibody test kit (Colloidal Gold Method). The results were as follows:

Method		Clinical Diagnosis Results		Total Results
Colloidal Gold Method IgM	Results	Positive	Negative	
	Positive	39	1	40
	Negative	1	185	186
Total Results		40	186	226

Method		Clinical Diagnosis Results		Total Results
Colloidal Gold Method IgG	Results	Positive	Negative	
	Positive	39	0	39
	Negative	1	186	187
Total Results		40	186	226

Serial Number	Reference Method	Sensitivity	Specificity
SARS-CoV-2 IgM	COVID-19 clinical diagnosis results	97.5%	99.5%
SARS-CoV-2 IgG	COVID-19 clinical diagnosis results	97.5%	100%

Another study showed that 40 confirmed patients were tested with SARS-CoV-2 IgM/IgG antibody test kit at different times after admission, and the positive rate of the antibody test results were as follows:

Admission time	1-3 day	4-6 day	7-9 day	>9 day
SARS-CoV-2 IgM and IgG	55%	75%	95%	97.5%

13. PROCEDURAL NOTES

- Read this manual carefully before using this test.
- It needs to be tested in a laboratory with proper testing conditions. All samples and materials in the testing process shall be handled according to the operation specifications of infectious diseases laboratory.
- Protect the product from moisture.
- All reagents and samples should reach room temperature (15-30°C) before use.
- Do not use lipid samples.
- Do not use hemolytic samples.
- Do not use turbid contaminated samples.
- Do not dilute the sample for testing.
- Do not store this kit in frozen condition.
- The interpretation of the test results must be carried out in strict accordance with this manual.
- This kit is limited to qualitative detection of SARS-CoV-2 antibody in human serum, plasma or whole blood.
- False negative results will be caused when the antibody titer in the sample is lower than the minimum detection limit of the test or the antibody does not appear at the time of sample collection.
- Samples with high titers of heterophilic antibodies or rheumatoid factors may affect the expected results.

14. DATE OF ISSUE

SARS-CoV-2 IgM/IgG antibody test kit（Colloidal Gold Method）insert.

Version 02, 22th March, 2020

15. EXPLANATION OF THE SYMBOLS USED

IVD	For In Vitro Diagnostic Use
LOT	Batch Code
	Manufacturer
	Date Of Manufacture

EC REP	Authorized Representative In The European Community
	Use By
	Do Not Use If Package Is Damaged
	Consult Instruction For Use
2°C 30°C	Temperature Limit At 2°c~30°c.
Σ 20	Contents Sufficient For 20 Tests.
Σ 25	Contents Sufficient For 25 Tests
Σ 50	Contents Sufficient For 50 Tests
Σ 100	Contents Sufficient For 100 Tests
	Do Not Re-use
	Caution
	Keep Dry

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Clinical report

Development of SARS-CoV-2 Rapid Antibody Detection Kit and Study on Dynamic Changes of Antibody in Infected Patients

Tao Li [1,5*], Lianzi Wang[1], Yufeng Gao[3], Xianwei Hu[4], Li Wang[2], Jiawang Lin[2*], Huihui Wang [1], Xuemei Li [1], Shubing Zhang[1], Yuanhong Xu[1], Wei Wei[5*]

1. Department of Clinical Laboratory, the First Affiliated Hospital of Anhui Medical University, Hefei 230032, China.
2. Biohit Healthcare (Hefei) Co., Ltd, Hefei 230032, China.
3. Department of infectious diseases, the First Affiliated Hospital of Anhui Medical University, Hefei 230032, China.
4. Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Anhui Medical University, Hefei 230032, China.
5. Institute of Clinical Pharmacology, Anhui Medical University, Key Laboratory of Anti-inflammatory and Immune Medicine，Ministry of Education，Anhui Collaborative Innovation Center of Anti-inflammatory and Immune Medicine, Anhui Anti-inflammatory and Immune Medicine innovation team, Hefei, 230032, China.

Abstract

OBJECTIVE: To develop a rapid detection kit for new coronavirus antibodies and use this reagent to study the dynamic changes of antibodies in clinical SARS-CoV-2 infected patients.

Methods: A (colloidal gold immunochromatography), B (fluorescence immunochromatography), and C (chemiluminescence) detection kits were developed. After clinical evaluation, the A kit was selected as a follow-up study. Serum SARS-CoV-2 IgM antibodies and IgG antibodies were tested in SARS-CoV-2 infected persons and non-SARS-CoV-2 infected persons, respectively. Positive sera of SARS-CoV-2 infected persons were further tested for antibody titers.

Results: The sensitivity of kit A was 50%, 70%, 92.5%, and 97.5% at 1-3 days, 4-6 days, 7-9 days, and> 9 days after admission, which were significantly higher than those of B and C kits. The specificity of A kit is 100%, but the specificity of A, B, and C kits is not statistically significant. Using the A kit as a follow-up study, the positive rates of SARS-CoV-2 IgM antibodies and IgG antibodies increased from 50% to 92.5% after 1-3 days, 4-6 days, and 7-9 days of admission, showing a clear upward trend. With the length of admission, the titers of SARS-CoV-2 IgM antibodies and IgG antibodies in positive specimens increased.

CONCLUSION: The positive rate and titer of SARS-CoV-2 antibody show a rapid increase with time. For patients who are negative for the first test, they should be tested again after 7 days. Patients who tested positive for the first time should have a titer test, and then test the titer again after 7 days to determine whether it is a SARS-CoV-2 infection based on the titer change. Other patients with respiratory infections had 2.5% false positives of IgM antibodies, and 0.5% false positives of IgM antibodies in pregnant women, which can be further confirmed by retesting after 1 week.

*Correspondence authors: Tao Li, E-mail: limedical1974@126.com.
Jiawang Lin, E-mail: huanglinjoe@aliyun.com.
Wei Wei, E-mail: wwei@ahmu.edu.cn.

Background

SARS-CoV-2 is a pathogen that causes neo-coronary pneumonia. It belongs to the genus Coronavirus β and is the seventh coronavirus known to infect humans (1). Its genome is a linear single-stranded positive-stranded RNA with approximate 80% homology to the SARS-CoV gene (2). After SARS-CoV-2 infection, it causes respiratory tract inflammation, immune system disorders, and severe pneumonia. It can cause death in severe cases, and it is prone to hospital infection during treatment, posing a serious threat to people's life and health (3). The incubation period of the disease is generally 3-7 days, the shortest incubation period is 1 day, and the longest incubation period is 30 days, which is contagious during the incubation period. The disease is mainly transmitted from person to person through droplets and contact, and there may be a risk of aerosol transmission in closed, unventilated places (4,5). The aetiology basis of previous clinical diagnosis is either that the nucleic acid test result is positive or sequencing confirms that the virus gene sequence is highly homologous with SARS-CoV-2. However, a variety of factors have led to more false negative results in nucleic acid testing at present (6), which has a huge impact on the diagnosis of SARS-CoV-2

infection and epidemic prevention and control. In order to avoid the lack of evidence for the diagnosis from a single pathology point of view, the National Health Commission's latest announcement on March 4, 2020, "New Coronavirus Infected Pneumonia Diagnosis and Treatment Guideline (Trial Version 7)" adds serological tests to confirm the diagnosed cases in addition to the original pathology evidence, that is, suspected cases plus "new coronavirus-specific IgM antibody and IgG antibody positive", or "new coronavirus-specific IgG antibody changed from negative to positive, or antibody level was 4 times higher during the recovery period than the acute phase can also be confirmed. At the same time, the exclusion of suspected cases needs to meet the condition: two consecutive tests of the novel coronavirus nucleic acid test are negative (sampling time interval of at least 24 hours), and the new coronavirus-specific antibodies IgM and IgG are still negative 7 days after the onset of illness.

Specific proteins of the new coronavirus, such as S protein or N protein, can stimulate the immune system of an infected person to initiate an immune response, producing virus-specific IgM and IgG antibodies. Detection of virus-specific IgM and IgG antibodies in the serum of suspected patients by using reagents produced by recombinant S protein or N protein antigens, can make up for the lack of pathogenic detection in the diagnosis and exclusion of suspected cases of new coronary pneumonia, and be effectively complementary to the pathogenic detection.

1. Materials and Methods

1.1 Choice of antigen

The SARS-CoV-2 N antigen obtained from two expression systems of PET28 vector + BL21 (DE3) strain, and pCMVp-NEO-BAN vector + HEK293 cell line. These are verified by the serum of SARS-CoV-2 infected persons and non-SARS-CoV-2 infected persons. The SARS-CoV-2 N antigen obtained from the expression system of pCMVp-NEO-BAN vector + HEK293 cell line showed better IgM antibodies and IgG antibodies performance than those expressed by PET28 vector + BL21 (DE3) strain in testing the serum.

1.2 Development of kits

The research team developed three detection kits A (colloidal gold immunochromatography), B (fluorescence immunochromatography), and C (chemiluminescence), and evaluated the sensitivity and specificity of the three kits.

1.3 Test principle

Principle of colloidal gold immunochromatography: SARS-CoV-2 IgM / IgG was detected using SARS-CoV-2 recombinant antigen and mouse anti-human IgM / IgG antibody. The SARS-CoV-2 IgM / IgG reacted with colloidal gold-bound SARS-CoV-2 recombinant antigen in the sample. The complex is chromatographed along a membrane and reaches a detection line (T) with a murine anti-human IgM antibody and a murine anti-human IgG antibody. When the result is positive, the colloidal gold SARS-CoV-2 recombinant antigen-antibody complex is bound to the IgM or IgG detection line (T) and is purple-red. When the result is negative, the sample does not contain any SARS-CoV-2 recombinant antigen-antibody complex that can bind to the IgM / IgG detection line (T), so the color is not visible.

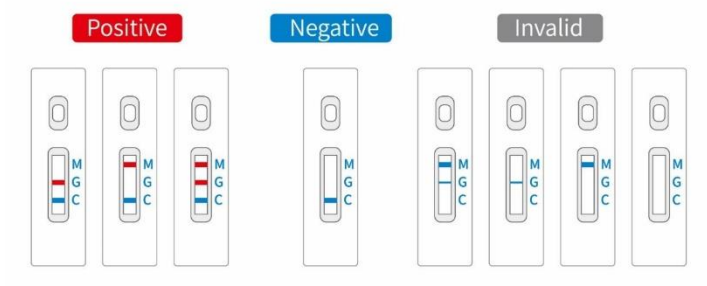

Figure 1 Colloidal gold immunochromatographic test results

Principle of fluorescent immunochromatography: SARS-CoV-2 recombinant antigen and mouse anti-human IgM / IgG antibody are used to detect SARS-CoV-2 IgM / IgG. In the sample, the SARS-CoV-2 IgM / IgG reacted with the microsphere-associated SARS-CoV-2 recombinant antigen. The complex is chromatographed along a

membrane and reaches a detection line (T) with a murine anti-human IgM antibody and a murine anti-human IgG antibody. When the result is positive, the microsphere SARS-CoV-2 recombinant antigen-antibody complex is bound to the IgM or IgG detection line (T); when the result is negative, there is no microsphere SARS-CoV-2 recombinant antigen-antibody complex and IgM. Or IgG detection line (T) binding. The more analytes in the sample, the stronger the fluorescence signal of the T line, and the fluorescence signal intensity can be detected and analyzed by the supporting fluorescence reader produced by Biohit Healthcare (Hefei) Co., Ltd.

Principle of chemiluminescence method: SARS-CoV-2 recombinant antigen and mouse anti-human IgM / IgG antibody are used to detect SARS-CoV-2 IgM / IgG. The SARS-CoV-2 IgM / IgG in the sample reacts with the SARS-CoV-2 recombinant antigen bound to magnetic particles to form a complex. Under the action of a magnetic field, magnetic particles are adsorbed to the reaction tube wall, and unbound materials are washed away by a cleaning solution. A mouse anti-human IgM / mouse anti-human IgG antibody HRP marker was added to form an antigen-antibody-secondary antibody complex. Finally, an enzymatic luminescent substrate is added and the resulting chemiluminescence reaction is measured, expressed as relative light intensity (RLU).

1.4 Verification of three kits

Verification of sensitivity and specificity of three kits using serum samples from 40 clinically confirmed COVID-19 patients and 94 non-COVID-19 populations.

1.5 Research object

40 patients with new coronavirus infection，age between 21～71，median is 46 years； 281 patients with other respiratory infections (including Mycoplasma pneumoniae, parainfluenza virus, adenovirus, and influenza B virus), age between 2 to 99 years, with a median of 51 years; 252 non-respiratory patients (including 30 cases of rheumatic immune system diseases and 20 cases of severe liver disease), aged 1 to 90 years, with a median of 50 years; 416 pregnant women, aged 18 to 34 years, with

a median of 27 years; 112 cases of normal physical examination population, aged 23 to 72 years, median number is 50 years old. The age distribution of each group of people is shown in Figure 1.

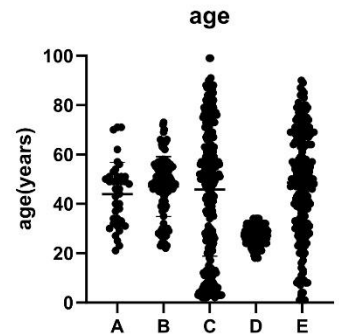

Figure 2 age distribution in five groups. A: patients with COVID-19, B: Physical examination, C: patients with other respiratory infectious diseases, D: pregnant women, E: patients with other system diseases

1.6 Specimen collection and processing

The type of sample used in this study was serum samples. Blood samples were collected from patients with SARS-CoV-2 infection 1-3 days, 4-6 days, 7-9 days, and 9 days after admission. Blood samples were collected and stored at room temperature for 30 minutes, centrifuged at 3500 rpm for 5 minutes, serum was collected, and SARS-CoV-2 IgM antibodies and IgG antibodies were tested.

Non-SARS-CoV-2 serum are from remaining samples from clinical testing.

1.7 Antibody titer testing

The remaining serum samples of patients with non-respiratory infections were collected, mixed and tested with a new coronavirus IgM / IgG antibody detection A kit to confirm as SARS-CoV-2 IgM and SARS-CoV-2 IgG negative. COVID-19 patients' serum samples were diluted with the negative serum collected above and then tested with

the new coronavirus IgM / IgG antibody detection A kit until the diluted samples were tested to be SARS-CoV-2 IgM and SARS-CoV-2 IgG negative, determine the highest dilution factor.

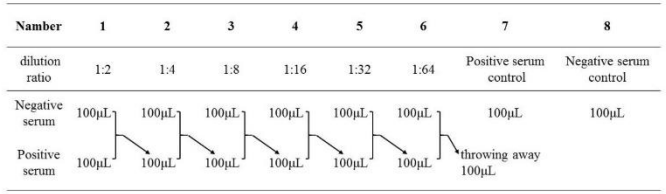

Figure 3 dilution of sample

1.8 Statistical methods

x^2 inspection was used for comparison（chi-square test）。

2. Results

2.1 Comparison of A, B, and C kits

2.1.1 Sensitivity of three kits A, B, and C to detect SARS-CoV-2 IgM antibodies and IgG antibodies

A, B, and C kits were used to detect IgM antibodies and IgG antibodies in serum samples from 40 clinical COVID-19 patients, and the sensitivity of the three kits was calculated. The sensitivity of IgM antibody and IgG antibody detected by A kit was higher than that of B and C kits (the results are shown in Table 1 and Table 2).

The sensitivity was calculated using IgM antibody + IgG antibody (the specimen SARS-CoV-2 antibody is positive when IgM antibody, IgG antibody alone or both are positive), the sensitivity of the A kit is also higher than the B and C kits (the results are shown in Table 3).

Table1 Sensitivity of A、B、C three kits to detect SARS-CoV-2 IgM antibodies

Kit	1-3day	4-6day	7-9day	>9day
A kit	50%	70%	92.5%	97.5%
B kit	27.5%[a]	50%[a]	75%[a]	77.5%[a]
C kit	20%[b]	60%	75%	80%

Chi-square	8.889	3.333	5.271	3.720
p	0.003	0.06	0.016	0.04

Note：a: A kit vs B kit p<0.05
b: A kit vs C kit p<0.05

Table2 Sensitivity of A、B、C three kits to detect SARS-CoV-2 IgG antibodies

Kit	1-3day	4-6day	7-9day	>9day
A kit	50%	70%	92.5%	97.5%
B kit	35%	60%	80%	85%
C kit	30%[a,b]	65%	87.5%	92.5%
Chi-square	9.018	0.879	2.740	4.145
p	0.018	0.083	0.105	0.116

Note：a: A kit vs C kit p<0.05，b: B kit vs C kit p<0.05

Table3 Total sensitivity of A、B、C three kits for SARS-CoV-2 IgM antibody + IgG antibody

Kit	1-3day	4-6day	7-9day	>9day
A kit	55%	75%	95%	97.5%
B kit	45%	65%	85%	90%
C kit	40%	70%	75%[a]	80%[a]
Chi-square	1.875	0.952	6.275	6.384
p	0.08	0.086	0.005	0.006

Note：a: A kit vs C kit p<0.05

2.1.2 The specificity of A, B, C three kits to detect SARS-CoV-2 IgM antibodies and IgG antibodies

A, B, and C kits were used to detect IgM antibodies and IgG antibodies in 94 non-COVID-19 serum samples. The specificity of I, M, and IgG antibodies and IgM antibodies + IgG antibodies was calculated for three, A, B, and C kits. The specificity of the A kit is 100%, and the specificity of the B and C kits are less than 100%, but the

difference in specificity is not statistically significant (see Table 4 for results).

Table4 The specificity of A, B, C three kits to detect SARS-CoV-2 IgM antibodies and IgG antibodies

Kit	IgM antibody	IgG antibody	IgM+IgG antibody
A kit	100%	100%	100%
B kit	98.9%	98.9%	97.9%
C kit	98.9%	100%	98.9%
Chi-square	0.000	0.000	0.339
p	0.503	0.503	0.377

Based on the overall consideration of detection sensitivity, specificity, ease of operation, and whether or not an instrument is needed, the sensitivity of A kit is better than that of B and C kits, and no instrument is required. We choose A kit (colloidal gold immunochromatography) as the final kit to continue for subsequent research.

2.2 Study on Kinetics of Antibody from SARS-CoV-2 Infected Population

2.2.1 Changes in IgM antibody and IgG antibody positive rates at different times of SARS-CoV-2 infection

From 1-3 days to 7-9 days after admission, the antibody-positive rate increased from 50% to 92.5%, and more than 9 days after admission, the positive rate increased to 97.5% (see Figure 4 for the results). But one patient was still negative for IgM antibodies and IgG antibodies on day 22 after admission.

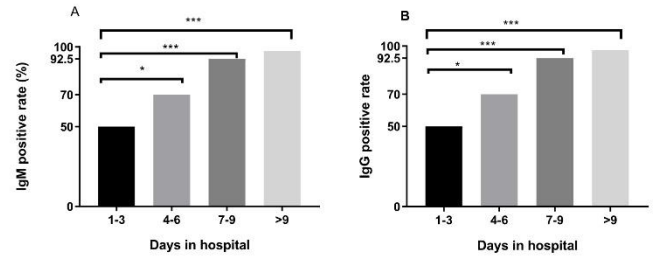

Figure 4 Changes in IgM and IgG antibody positive rates in patients with SARS-CoV-2 infection at different days of admission

2.2.2 Changes in antibody titers of SARS-CoV-2 infected patients after admission

The titers of IgM antibody-positive patients were mainly 1-2 times on 1-3 days after admission. Two patients had IgM antibody titers of more than 4 times. IgM antibody titers were mainly 2 to 8 times at 4-6 days, 2 patients had titers of more than 8 times, 7 to 9 days were mainly 2 to 16 times, and 4 patients had titers of more than 16 times, exceeding 9 days the IgM antibody titer was mainly 4-32 times, and 4 cases reached 64 times. No patient had an IgM antibody titer exceeding 64 times.（See Figure5A）

IgG antibody titers showed a similar trend to IgM antibody titers.（See Figure5B）

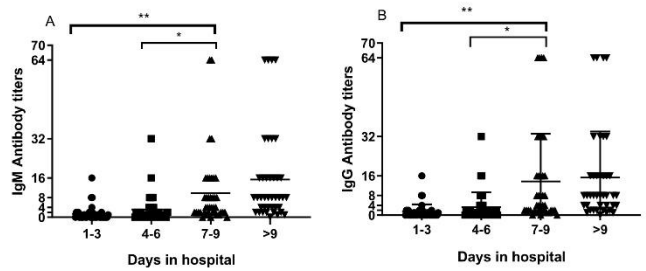

Figure 5 IgM antibody and IgG antibody titers in patients with SARS-CoV-2 infection on different days of admission

2.3 Analysis of false positive rates of SARS-CoV-2 IgM antibodies and IgG antibodies in non-SARS-CoV-2 infected people

Of the 1061 non-SARS-CoV-2 infected people, IgM test results were positive in 6 samples from other respiratory infection patients, 2 positive samples from pregnant women, and all 8 IgM positive samples were weak positive. After 1 week, the results were negative.（See results in Table5）

Table5 Analysis of IgM test results in 1061 non-SARS-CoV-2 infected people

S/N	Sample type	Sample amount	IgM(+)	IgM(-)	False positive rate
1	Samples of patients with other respiratory infections	281	6	275	2.1%
2	Pregnant woman sample	416	2	414	0.5%
3	Non-respiratory infection patient samples	252	0	252	0
4	Physical examination sample	112	0	112	0
5	Total	1061	8	1053	0.75%

There were no false positive results of IgG in 1061 non-SARS-CoV-2 infected people. The results are shown in Table 6.

Table6 Analysis of IgG test results in 1061 non-SARS-CoV-2 infected people

S/N	Sample type	Sample amount	IgG（+）	IgG（-）	False positive rate
1	Samples of patients with other respiratory infections	281	0	282	0
2	Pregnant woman sample	416	0	416	0
3	Non-respiratory infection patient samples	252	0	252	0
4	Physical examination sample	112	0	112	0
5	Total	1061	0	1061	0

3. Discussion

In this study, the SARS-CoV-2 N antigen obtained from two expression systems of PET28 vector + BL21 (DE3) strain, pCMVp-NEO-BAN vector + HEK293 cell line was verified. and was expressed. The SARS-CoV-2 N antigen obtained by pCMVp-NEO-BAN vector + HEK293 cell line in the detection of IgM antibodies and IgG antibodies in serum was better than PET28 carrier + BL21 (DE3) strain. It may be that prokaryotic expression system can not form the correct formation of protein spatial structure. Therefore, pCMVp-NEO-BAN vector + HEK293 cell line was selected to express the antigen for subsequent research.

This project first developed SARS-CoV-2 IgM antibody and IgG antibody kits in three methodologies: colloidal gold immunochromatography, fluorescence immunochromatography, and chemiluminescence. After verification with SARS-CoV-2 infected persons and non-SARS -CoV-2 infected patients' serum, colloidal gold immunochromatography kit has high sensitivity (see Table 1 and Table 2), specificity reaches 100% (see Table 4). It is simple to operate, no instrument is required, through comprehensive consideration, we chose the colloidal gold immunochromatography kit as the finalized kit. The sensitivity of the chemiluminescence method kit is poor, which may be caused by the immature development of the kit, and further technical research is needed on magnetic bead labeling, enzyme-labeled reagent diluent formulation, and stability.

A medical team from Guangzhou established a rapid IgM-IgG antibody detection method and used the kit for clinical research verification. The clinical sensitivity and specificity of the test were determined using blood samples from 397 COVID-19

2.3 Analysis of false positive rates of SARS-CoV-2 IgM antibodies and IgG antibodies in non-SARS-CoV-2 infected people

Of the 1061 non-SARS-CoV-2 infected people, IgM test results were positive in 6 samples from other respiratory infection patients, 2 positive samples from pregnant women, and all 8 IgM positive samples were weak positive. After 1 week, the results were negative.（See results in Table5）

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A medical team from Guangzhou established a rapid IgM-IgG antibody detection method and used the kit for clinical research verification. The clinical sensitivity and specificity of the test were determined using blood samples from 397 COVID-19

patients and 128 negative patients confirmed by PCR from 8 different hospitals. The detection sensitivity was 88.66%, and the specificity was 90.63%. This study indicates that the combined IgM-IgG test has better practicality and sensitivity than a single IgM or IgG test (7). Our results also show that the combined detection of IgM and IgG can increase the detection rate of infected patients (see Table 3). Guo L et al.'S report showed that the positive rates of IgM antibodies and IgG antibodies in SARS-CoV-2 infected patients increased significantly after 7-14 days of symptoms (8).

Considering the uncertainty about the time when patients recall the symptoms, this study used the number of days of admission as the basis for grouping. The results showed that IgM antibodies and IgG were 1-3 days, 4-6 days, 7-9 days, and more than 9 days after admission. Antibody positive rates were 50%, 70%, 92.5%, and 97.5% (see Figure 4), suggesting that the antibody positive rate increased rapidly in the early stages of infection, and antibody detection can be used as a interpretation indicator for SARS-CoV-2 infection. However, one infected person was negative for IgM antibody and IgG antibody at the third week. Checking the medical records, this infected person only had a history of exposure and did not show clinical symptoms. The nucleic acid test continued to be positive, suggesting that there was a delay in antibody production in the individual and attention should be paid to. At the same time, we found an interesting phenomenon, the positive rate of IgM antibody and IgG antibody showed a parallel rise, and further research is needed.

With the length of hospital stay, serum antibody titers of COVID-19 patients will increase, but there are individual differences. For more than 9 days of hospitalization, antibody titers of 70% of patients can rise to more than 4 times, and some patients can rise to 32 ~ 64 times (see Figure 5).

The test results of 1061 non-SARS-CoV-2 infected people showed that SARS-CoV-2 IgM showed weak positive results in 8 cases, 6 cases of other respiratory infections, 2 cases of pregnant women, and the results were reviewed after 1 week. The results were negative. It is suggested that there are factors that interfere with the detection of SARS-CoV-2 IgM in other respiratory infections and pregnant women, but this can be confirmed by a retest after 1 week. Negative health checkups and patients with

other systemic diseases, including rheumatic immune system disease and severe liver disease, did not affect the test results.

4. Conclusion

4.1 The positive rate and titer of SARS-CoV-2 antibody showed a rapid increase with time. For patients who were negative for the first test, they should be tested again after 7 days. Patients who tested positive for the first time should have a titer test, and then test the titer again after 7 days to determine whether it is a SARS-CoV-2 infection based on the titer change.

4.2 Other patients with respiratory infections had 2.5% false positives of IgM antibodies, and 0.5% false positives of IgM antibodies in pregnant women, which can be identified by retesting after 1 week.

Disclaimer: The antigen screening, methodological selection and reagent production of this study were completed in the research and development department of Biohit Healthcare (Hefei) Co., Ltd. Methodological evaluation and performance verification were completed in the First Affiliated Hospital of Anhui Medical University. All authors have no conflicts of interest.

Ethics: This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University.

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Company picture

BIOHIT HealthCare
Innovating for Health

Company office

Company picture

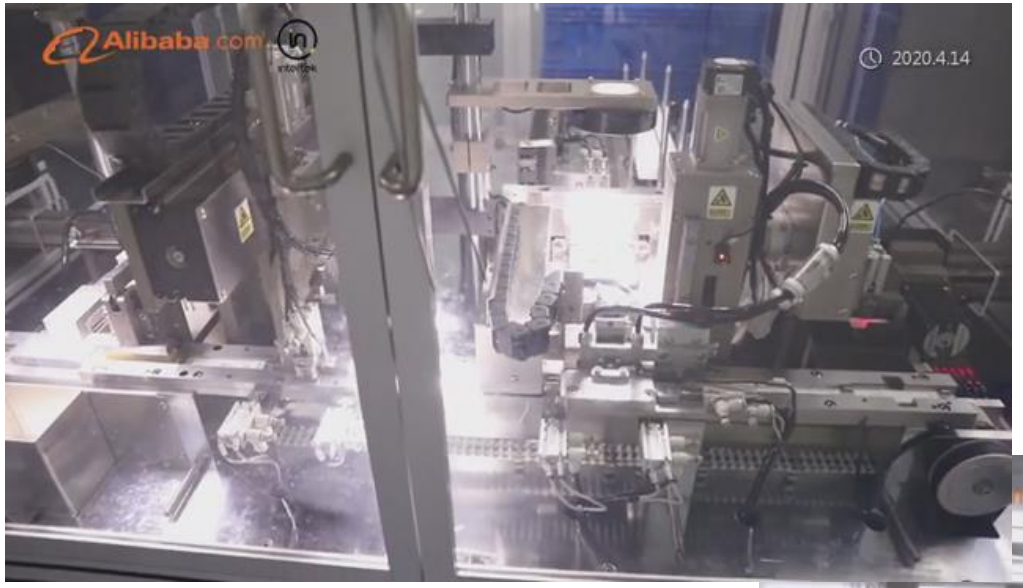
BIOHIT HealthCare
Innovating for Health

Production site

Company picture

BIOHIT HealthCare
Innovating for Health

Production site



Product picture

BIOHIT HealthCare
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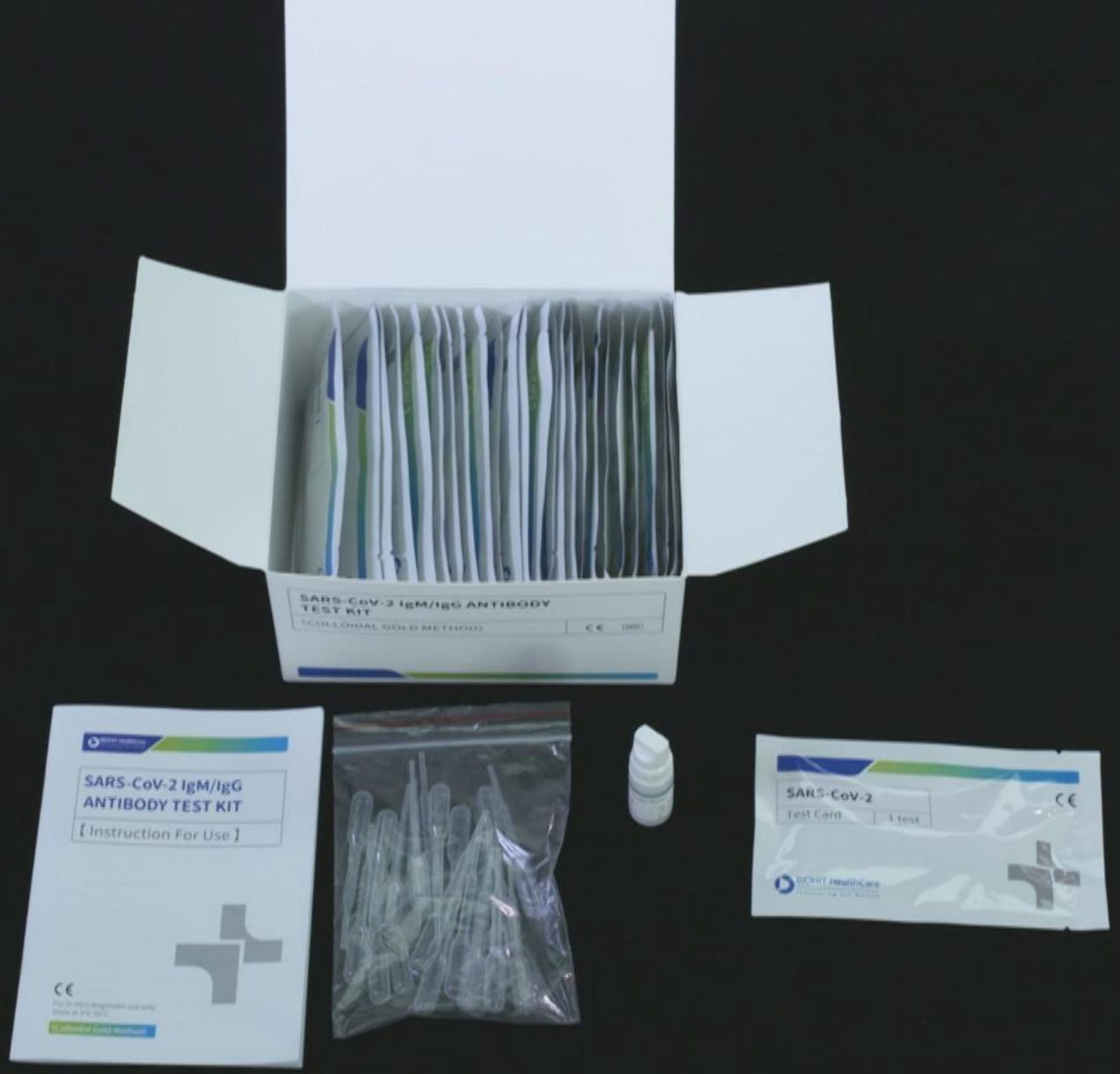
Content
Instruction for use
Test Card
Sample diluent
Small dropper

BIOHIT


SARS-CoV-2 IgM/IgG ANTIBODY TEST KIT
SARS-CoV-2 IgM/IgG ANTIBODY TEST KIT
[Instruction For Use]
SARS-CoV-2
Test Card
1 test

Product picture

BIOHIT HealthCare
Innovating for Health

Package type:

25pcs x Rapid Test Kit / box,

18 boxes/Carton;

Ctn Size:

480mm*285mm*265mm;

Ctn weight: 6 kg

Single package size:

150mm*131mm*78mm

Single package gross weight: 0.25kg