NIM Newsletter

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中国计量科学研究院
National Institute of Metrology,China

Message from the Director

Dear friends,

Welcome to the NIM newsletter. This is our new way of sharing news and information. You'll get articles about our scientific research activities, as well as updates on our organization, staff, management and projects.

At present, the world is in a difficult time of fighting against COVID-19. China has experienced the same, very difficult stage. While the whole country is going back to normal slowly, stringent protective measures are still implemented. During the past few months of nationwide lockdown, a group of NIM scientists have worked very hard in laboratories developing reference materials for SARS-CoV-2 testing, which have been distributed to nearly 300 manufacturers of test kits, clinical laboratories, and other institutions. Our colleagues in thermometry laboratories also provided great support to ensure the accuracy of infrared thermometers widely used at entrances of various public facilities for fever screening. In this issue, you will find detailed information of our work in these two aspects. NIM will be pleased to share our learning and lessons with whoever may need it. And through this, we would like to convey our sincere concern to all colleagues and friends worldwide.

Besides, the organizational re-structuring of NIM has recently been approved by NIM's parent ministry. Some associated information is attached within this issue.

We wish all colleagues and friends health and safety.

NIM newsletters can be downloaded from our website https://en.nim.ac.cn/. Thank you for reading and we always welcome your feedback.

Sincerely,

FANG Xiang
Director

The Development and Application of Reference Materials for SARS-CoV-2 Testing

Diagnostic testing for SARS-CoV-2

The World Health Organization (WHO) on March 11 declared the coronavirus disease (COVID-19) a pandemic. Reported COVID-19 cases around the world surpassed 3 million on April 29, with death toll passing 208,000. Many countries have witnessed a near exponential growth in the number of new cases, with persistent risks of worsening.

Diagnostic testing for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the first and a very critical step in slowing down the epidemic. People with the coronavirus may be most infectious in the first week of symptoms or even before the symptoms are shown. Timely and accurate SARS-CoV-2 testing not only helps to detect and treat infected patients in a timely manner so as to avoid deterioration and reduce death rate, but also helps to prevent further transmission through effective isolation of patients and tracing of contacts. Because of its importance, the past months have witnessed a soaring demand for SARS-CoV-2 testing on a world scale.

From the outbreak of the coronavirus in Wuhan in January, to its fast spread nationwide, then to the stabilization of situation by the end of March, China has taken a series of measures to prevent and control the epidemic. China's practice has proven that, early identification, reporting, isolation, diagnosis and treatment is the best and most effective way to control the disease, and the wide diagnostic testing for SARS-CoV-2 has played a vital role.

Nucleic Acid Test (NAT) and Immunological Detection Method (IDM) are two most widely used methods for the diagnostic testing of SARS-CoV-2. SARS-CoV-2 is a virus that contains only RNA, and the specific RNA sequences in the virus are markers that distinguish the virus from other pathogens. The common method used by NAT is to detect the specific sequence of SARS-CoV-2 by fluorescence quantitative PCR (Polymerase Chain Reaction). When human bodies get infected with a virus, their immune systems react to produce antibodies. IDM is to detect the patients' immune responses to the virus by testing the specific binding between antigens and antibodies. Figure 1 shows features of these two methods. The most important advantage of NAT is its high specificity and sensitivity, which is good for early detection. However, "false negatives" may occur due to inappropriate practices in sample collection, preservation and handling process, besides the quality of test kits. The most important advantage of IDM is its simple and rapid operation, but this method is more suitable for patients who have developed obvious clinical symptoms and whose bodies have already appeared immune responses. It cannot realize early detection and is easily affected by interfering substances in the sample, resulting in a "false positive". In summary, NAT is currently recognized as the "gold standard" for the diagnosis of COVID-19, and IDM can serve as an important supplement to NAT.

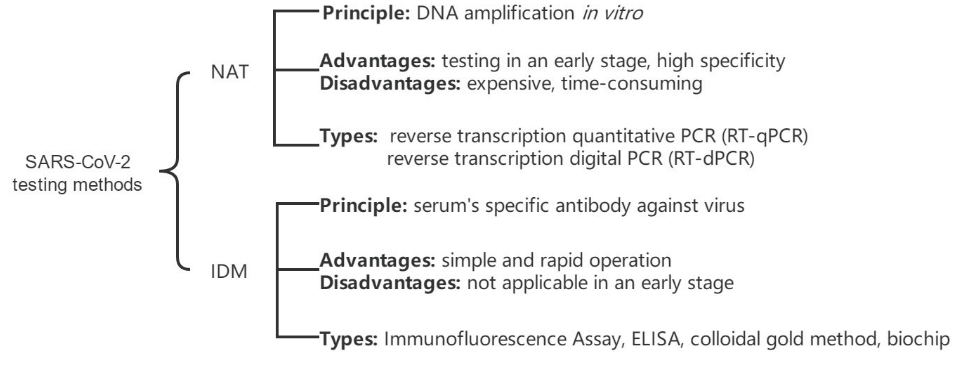

Fig1. Comparison between two SARS-CoV-2 testing methods

Testing relies on reagents. Since the genetic sequence of SARS-CoV-2 was first released in China on January 10, 2020, companies and institutions in many countries have started their development of SARS-CoV-2 test kits. As of April 26, the National Medical Products Administration (NMPA) of China has registered 30 test kits, including 19 nucleic acid test kits and 11 antibody test kits. As of April 5, the daily production capacity of SARS-CoV-2 test kits has reached 4.26 million, of which nucleic acid test kits are 3.06 million and antibody test kits are 1.2 million.

The variety of producers, short time for research and development, and especially the lack of standardized procedures have inevitably caused uneven performance and quality of the SARS-CoV-2 test kit products. With the wide use of these products, performance evaluation and quality control have become an increasingly prominent issue. Certified Reference Materials (CRMs), with known accurate quantity values, can serve as "standards" to evaluate performance and quality of test kits, validate testing methods, and assure metrological traceability of measurement results. Therefore, development and application of CRMs for SARS-CoV-2 testing can be a contribution made by metrologists to the global efforts of combating COVID-19.

The development of CRMs for SARS-CoV-2 testing at NIM

Since the outbreak of COVID-19 in Wuhan in late January, NIM has responded quickly by giving top research priority to the development of CRMs relating to SARS-CoV-2 testing. Now the most important two categories of CRMs developed are as follows:

1. SARS-CoV-2 RNA reference materials

Table 1. Certified values and uncertainties of SARS-CoV-2 RNA reference materials

Name	Numbering	Reference value and uncertainty	Concentration		
			E gene (copy/μL)	ORF1ab gene (copy/μL)	N gene (copy/μL)
SARS-CoV-2 RNA reference material (high concentration)	GBW(E)091089	Reference value	5.03×10^5	9.39×10^5	7.00×10^5
		Expanded uncertainty (k=2)	0.47×10^5	0.92×10^5	0.71×10^5
SARS-CoV-2 RNA reference material (low concentration)	GBW(E)091090	Reference value	5.78×10^2	1.07×10^3	7.75×10^2
		Expanded uncertainty (k=2)	0.64×10^2	0.14×10^3	0.81×10^2

The SARS-CoV-2 RNA reference materials consist of 3 *in-vitro* transcribed RNA targets: nucleocapsid (N) (full length), envelope (E) (full length), and the open reading frame 1ab (ORF1ab) gene fragment (genome coordinates: 13201-15600), covering all fragment targets recommended by the WHO and the Chinese Center for Disease Control and Prevention (China CDC). The reference value is the copy number concentration of the three gene targets. These reference materials can be directly added into the PCR solution to participate in the reverse transcription, which is able to provide the quality control for processes of reverse transcription, PCR amplification and detection, and thus ensure the reliability of the testing process. A highly accurate and sensitive absolute digital PCR method was established and applied for characterization of the SARS-CoV-2 RNA reference materials. Furthermore, a RNA stabilizer was selected and optimized to ensure that the RNA reference materials could be stable for more than 6 months.

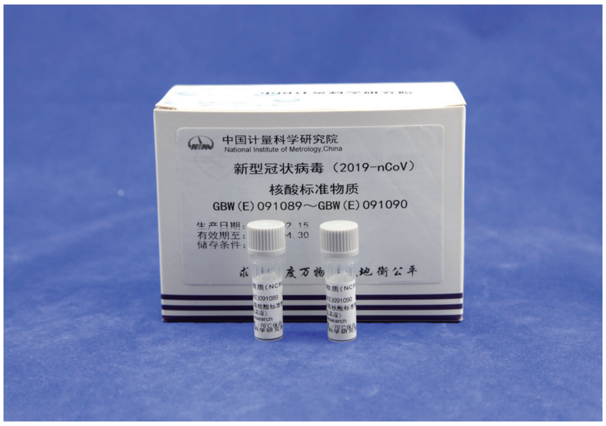

*Fig 2. SARS-CoV-2 RNA reference materials**

2 . SARS-CoV-2 immunoassay reference materials

Table 2. Certified values and uncertainties of SARS-CoV-2 immunoassay reference materials

Name	Numbering	Concentration	
		Reference value（μg/g)	Expanded uncertainty（k=2）（μg/g)
Human IgG monoclonal antibody to spike glycoprotein solution reference material of SARS-CoV-2	GBW(E)091109	70.8	5.7
Human IgG monoclonal antibody to nucleocapsid protein solution reference material of SARS-CoV-2	GBW(E)091110	85.3	8.5

First, the screening of monoclonal antibodies against S1 fragment of SARS-CoV-2 spike protein and N terminal 1-213 amino acid of SARS-CoV-2 nucleocapsid protein, was made respectively. Then, the antibodies were humanized, expressed by 293T cell lines, and purified by using Protein A column. After the purity analysis, molecular weight determination, peptide spectrum characterization, and protein activity evaluation, the Isotope Dilution Mass Spectrometry (IDMS) based on amino acid analysis was used to determine the mass fraction of the IgG monoclonal antibody in a buffer solution and the result was used as a reference value of the IgG monoclonal antibody. During the experiments, 4 kinds of national primary reference materials of amino acid purity were used as reference standards for traceability, and the weighing instruments used were calibrated, so as to ensure the quantity values of IgG reference materials are traceable to the SI base units kilogram (kg) and mole (mol). Meanwhile, the two IgG monoclonal antibody reference materials were also determined by using a lab-made Quadrupole-Linear Ion Trap (Q-LIT) tandem mass spectrometer, and the results were consistent with those obtained by using the commercial mass spectrometer. These reference materials developed can simulate the IgG antibody in patients' serum and react with the coated antigen and secondary antibody in test kits, so as to evaluate the quality of kits and verify the detection methods.

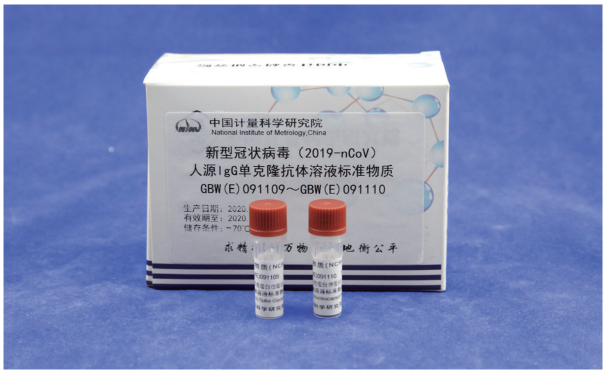

*Fig 3. SARS-CoV-2 immunoassay reference materials**

** Note: An initial, temporary name of the coronavirus, 2019-nCoV, is used on the box label in Fig. 2 and Fig. 3. The official name of the coronavirus is SARS-CoV-2.*

The application of CRMs for SARS-CoV-2 testing

By the end of March, NIM has distributed the SARS-CoV-2 RNA CRMs to more than 260 research institutes, enterprises, centers for disease control and prevention, and clinical laboratories in 23 provinces, among which 130 test kit manufacturers are included, and the SARS-CoV-2 immunoassay reference materials have been provided to 22 *in-vitro* diagnostic product manufacturers and 2 research institutes.

To date, many users have given NIM their feedback on the use of the CRMs. For manufacturers, these CRMs are very useful for the development of their test kit or test strip products, the development of enterprise quality control materials, and the self-evaluation of product performances. The feedback confirmed that the application of such CRMs helped enterprises define product specifications, reduce R&D cycles, and solve traceability issues. Most enterprises used the CRMs to validate self-developed testing methods through the determination of accuracy and detection limits. They also used the CRMs to provide metrological traceability to their own reference samples to meet the requirements for medical device registration. Besides, the use of identical CRMs guaranteed the comparability of test results from different enterprises.

Some hospitals used these CRMs for quality control of clinical testing and have reported that the CRMs could effectively indicate the stability of reagents and instruments. CDCs at regional levels have reported use of the CRMs to assess the proficiency of their central laboratories as well as hospital laboratories in an effective way.

Some provincial metrology institutes in China used these CRMs for metrological traceability. For example, the Shanghai Institute of Measurement and Testing Technology has also developed *in-vitro* transcription RNA reference materials, with NIM's CRMs used for traceability.

International metrological cooperation for combating COVID-19

The international metrology community has made its own commitment to combat the COVID-19 pandemic. The Working Group on Nucleic Acid Analysis (NAWG) under the CIPM Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) promptly proposed a pilot study on SARS-CoV-2 RNA measurement after the outbreak of COVID-19. NIM has offered to share its knowledge, technical experience, and research updates with the BIPM and CCQM-NAWG members, expressing its willingness to contribute to this pilot study, by providing CRM samples, sharing measurement methods, and developing technical protocols. .

After an urgent CCQM-NAWG video conference, a preliminary plan for the pilot study has been made. It is going to be piloted jointly by the Laboratory of the Government Chemist (LGC) of the UK, NIM of China, the National Institute for Biological Standards and Control (NIBSC) of the UK, and the National Institute of Standards and Technology (NIST) of the U.S. It is scheduled to be started in April 2020, with measurement results submitted in September, and results discussed in the next NAWG meeting in October 2020. 15 NMIs have expressed their intention to participate. NIM will provide the *in-vitro* transcription low-concentration mixed solution containing three genes of E, N, and ORF 1ab as a comparison sample, as well as other relevant reagents and reference materials.

In 2018, the CCQM organized a pilot study on RNA copy number in HIV-1, which has shown significant impacts to support the public health response. This international collaboration among the BIPM and National Metrology Institutes (NMIs) on COVID-19 will once again demonstrate the role of metrology in tackling public health challenges of international concern.

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The Application of Infrared Thermometers in Response to COVID-19

Since this March, COVID-19 has become a pandemic, posing a huge threat to people's lives and economies of many countries. To assist in the epidemic control in China, infrared thermometry was adopted for body temperature screening at entrances of various public facilities, including communities, supermarkets, subways, railway stations, airports, docks, etc. The experience indicated that this measure helped to early detect potential cases and cut off channels of transmission. To guarantee the measurement quality with infrared thermometers (IRTs) for measuring a body temperature, NIM, along with local metrology institutes in China, carried out some work, including equipment development, method development, training, knowledge popularization, and making recommendations on the management system, on the calibration and use of IRTs, which has supported the epidemic control.

Please note that IRTs hereinafter refer to the IRTs used for obtaining the body temperature of people unless otherwise specified.

Ⅰ. Three types of IRTs used for fever screening

Clinical experience has shown that a substantial portion of COVID-19 patients have a fever. Therefore, fever screening has become an important means to preliminarily detect suspected cases in China. Epidemic control demands rapid body temperature screening of massive people. In our daily life we tend to measure the body temperature with clinical liquid-in-glass or digital thermometers, usually placed under the armpit, in the mouth, or in the anus of infants. But it is usually time-consuming and inconvenient. Besides, there is more or less risk of cross-infections in such contact measurement. An alternative way to take a body temperature is infrared thermometry. As all objects, including human bodies, emit thermal radiation dependent on their temperature, IRTs measure the body temperature by detecting the strength of the radiation. The infrared thermometry has the significant advantages of rapid and non-contact measurement.

Three main types of IRT are used for fever screening in China. They are infrared ear thermometers (IRETs), infrared forehead thermometers (IRFTs) and thermal imagers for fever screening (TIFSs).

A. Infrared ear thermometer

IRETs measure the body temperature by detecting the thermal radiation emitted from the ear cavity formed by the auditory meatus and the eardrum. Thanks to their high accuracy, IRETs are suitable for taking the body temperature of people.

Fig. 1 An infrared ear thermometer with its application

B. Infrared forehead thermometer

IRFTs measure the forehead skin temperature by detecting the thermal radiation emitted from the forehead and then apply a correction to obtain an estimate of the body temperature. They have the advantages of fast and non-contact measurement, which can prevent cross-infections. However, the error in their estimate of the body temperature could be larger for certain people under measurement because of the statistics-based correction applied. IRFTs are massively used for preliminary one-by-one screening of people at entrances of public facilities in China.

Fig. 2 An infrared forehead thermometer with its application

C. Thermal imager for fever screening

The measuring principle of TIFSs is similar to that of IRFTs. First they measure the highest spot temperature or the temperature at a specific spot on the face of a person, and then apply a correction to obtain an estimated body temperature. They will raise an alarm for anyone whose estimated body temperature is above a certain threshold. Besides the rapid and non-contact measurement, TIFSs can measure several people at the same time, but their weakness is a possible large error in the indicated body temperature for the same reason as IRFTs. They are used for preliminary fever screening and early warning at entrances with heavy human traffic in China.

Fig. 3 A thermal imager for fever screening with its application

Ⅱ. Calibration with a blackbody

A. Two classes of blackbody in China

No matter what type, IRTs need to be calibrated to indicate an accurate temperature. Calibration of IRTs requires a standard blackbody, which provides a standard radiation temperature. Generally there are two classes of blackbody utilized for the calibration of the IRTs in China. One makes use of a thermostatic bath to keep its cavity temperature uniform and stable, and can realize a radiation temperature with an uncertainty of as low as 0.04°C. It is called the calibration system for infrared clinical thermometers (CSIRCT), relatively complicated and used in a laboratory. The other is a portable blackbody for calibration of infrared thermometers (PBCIRT) using an electrical power regulated heater to control its temperature, which can be used for both in-laboratory and on-site calibration of IRTs. It can realize a radiation temperature with an uncertainty of 0.07°C.

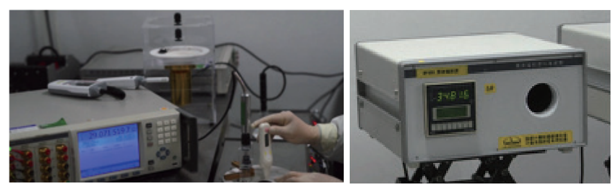

Fig. 4 A calibration system for infrared clinical thermometers (left) and a portable blackbody for calibration of infrared thermometers (right) at NIM, China

B. Traceability

Both the above-mentioned blackbodies are used to calibrate IRTs in China. The chart below illustrates traceability.

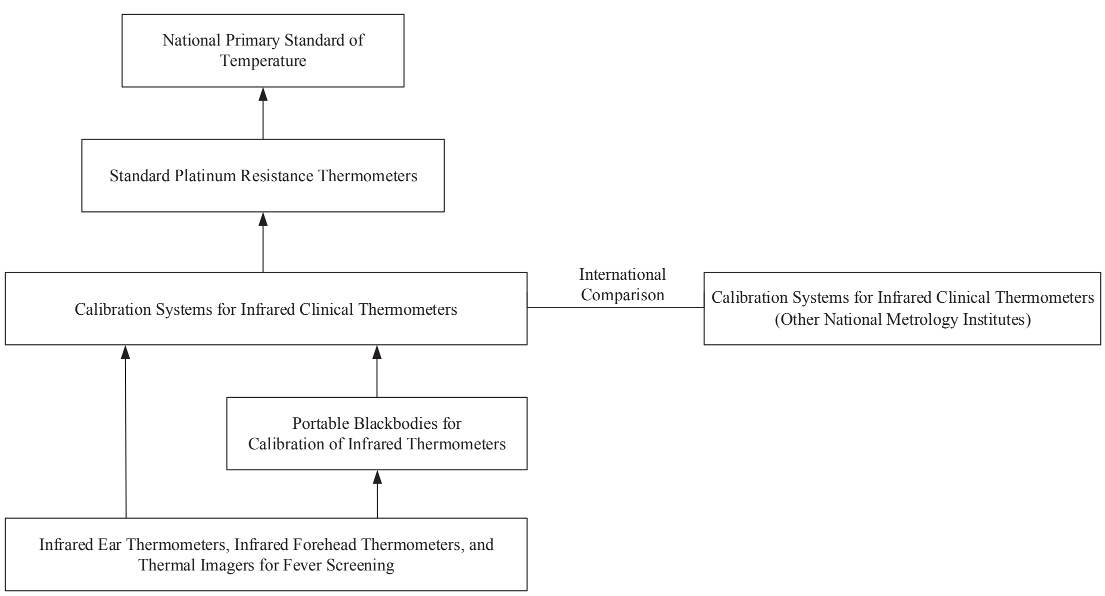

Fig. 5 Traceability chart for calibration of infrared thermometers in China

In China, IRETs, IRFTs and TIFSs are calibrated either with PBCIRTs or with CSIRCTs directly. The PBCIRTs are calibrated with the CSIRCTs, which are traceable to the standard platinum resistance thermometers at NIM or provincial metrology institutes, and then to the national primary standard of temperature at NIM. NIM maintains the international equivalence by participating in international comparisons among NMIs.

C. International comparison

An international comparison on blackbodies for calibration of IRETs was organized by the Asia Pacific Metrology Programme (APMP) from 2017 to 2020, with NIM as the pilot laboratory and 8 other participating NMIs or laboratories. It is the first international comparison on the radiation temperature in the body temperature range in the Asia Pacific region and deemed to improve the equivalence of radiation temperature values in the region.

Ⅲ. Major problems and countermeasures

Since the coronavirus outbreak in China, calibration demand has surged as a result of widespread use of IRTs, especially IRFTs, to measure the body temperature of people. It was reported that only the Shanghai Institute of Measurement and Testing Technology (SIMT) had calibrated over ten thousands IRTs from January to March, 2020. During the epidemic period, the number of calibrations in China may have reached over 1 million by rough estimation. Such surge in the calibration demand greatly exceeded the capacity of provincial, city, and county level metrology institutes/laboratories.

A. Three major problems

Problems of three aspects intensively arose from the frontline metrology practice. Firstly, lack of standard blackbodies for calibration of IRTs in city and county level metrology institutes/laboratories led to the consequence that the IRTs could not be calibrated using the standard method in many regions of China. Secondly, basic-level metrology institutes/laboratories also needed metrology technicians skilled at calibration of IRTs. Without understanding of the calibration procedure for IRTs, the technicians could hardly undertake relevant calibration or checking. Thirdly, the facts about IRT products of miscellaneous models, uneven quality, and unclearly stated manuals caused difficulty in calibration. Without calibration or checking, however, measurement accuracy cannot be guaranteed.

B. Countermeasures taken

To tackle those problems, NIM, together with a number of local metrology institutes, has been taking actions on different levels in order to alleviate the abrupt demand-supply contradiction in calibration. In this process, NIM has been in charge of blackbody R&D, formulating checking method, providing technical training and consultancy, and raising public awareness in this regard. Provincial metrology institutes participated in blackbody manufacture, improvement on the checking method, and knowledge transfer. The calibration of the IRTs from the frontline was undertaken by provincial and lower level metrology institutes.

Ⅳ. NIM's contributions

As the national metrology institute, NIM contributed to the following aspects.

A. Provision of standard blackbodies

To address the shortage of standard blackbodies, NIM developed a batch of PBCIRTs and CSIRCTs in a short time, some of which were donated to Hubei Province, the epicenter, and the others provided to metrology institutes in other provinces. In addition, NIM shared relevant techniques and authorized some metrology institutes to develop CSIRCTs by themselves in order to help local metrology institutes be equipped with CSIRCTs more quickly.

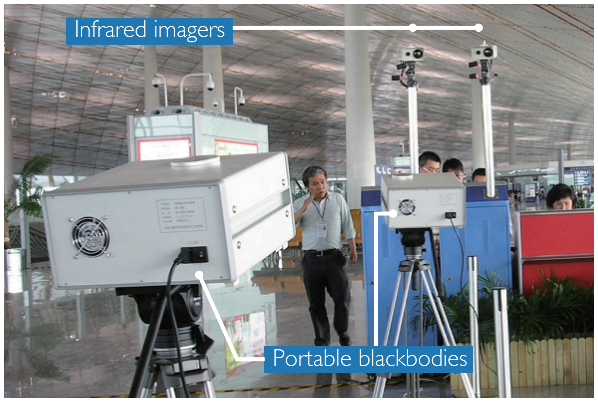

Fig. 6 Use of PBCIRTs for on-site calibration of thermal imagers for fever screening

B. A temporary accuracy checking method for IRFTs

Based on theoretical analysis and experimental validation, NIM developed an accuracy checking method for IRFTs using a verified clinical thermometer as a reference. This method can be used as a temporary checking solution for IRFTs when standard blackbodies are unavailable. It has been shown that the method effectively met the heavy demand for checking accuracy of the IRFTs during the epidemic period in China.

C. Provision of training and consultancy

To address their lack of understanding and experience, NIM provided technicians in basic-level metrology institutes/laboratories with various training in operation and calibration of IRTs, including setting up a consultancy group on social media and answering technical questions, summarizing and sharing information on the calibration mode of various models of IRT, and providing a video course on the calibration of IRTs. The training and consultancy were well received by metrology technicians serving end users.

D. Knowledge popularization

To address the problem that the end users lacked basics and understanding of proper operation of diverse IRTs, NIM popularized basic knowledge, proper operation, and matters needing attention about IRTs through national TV programs.

E. Recommendations to the national metrology authority

In order to perfect the metrology and management system for IRTs and cope better with similar epidemic outbreaks in the future, experts from NIM and other institutes, made a number of recommendations to the State Administration for Market Regulation (SAMR), the national metrology authority of China, including setting up a traceability system for body temperature measurement for epidemic control, incorporating the IRTs used for epidemic control in the type approval catalog of measuring equipment, requiring the metrology institutes involved in the traceability system to be equipped with PBCIRTs, and periodically organizing training courses on calibration of IRTs.

During the outbreak response, these measures have ensured that the enormous demand for calibration or accuracy checking of IRTs in an effective manner could be satisfied, and that the measurement quality with the IRTs has been improved. Thanks to the efforts mentioned, IRTs, as a means of body temperature screening, have contributed their part as expected in controlling the epidemic in China. Hopefully, the relevant metrology and management system can be improved in the future.

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Organizational re-structuring of NIM

In NIM's strategic plan (2015-2025), an idea of creating a two-dimensional organizational structure was proposed, aiming to make the organization more adaptable to scientific innovation and the evolution of sectors and industries. By April 2020, a new organizational structure of NIM was officially approved by the State Administration for Market Regulation (SAMR), which put an end to this two-year initiative.

The essential change is the creation of a few research centers focusing on development areas of high-priority of NIM. Among them, the Center for Advanced Measurement Science is a brand new center established by combining a few basic research groups that previously existed in other divisions, namely, quantum metrology, biology, nano-scale measurement, material measurement, and mass spectrometry. Four other research centers were established to be in line with sectors rather than disciplinary subjects, to promote metrology and its applications in environment, medicine, engineering, and metrological scientific data. A new Center for Reference Material Development and Management was established outside of the Division of Metrology in Chemistry and Analytical Science to work intensively on CRM production and distribution. Besides these new Centers, those research divisions originally established based on metrological disciplines have remained, including those for Time and Frequency, Dimensional Metrology, Thermophysics, Mechanics and Acoustics, Electricity and Magnetism, Electronics and Information Technology, Optics, Ionizing Radiation, and Metrology in Chemistry and Analytical Science.

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