NIM Newsletter

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Metrology for a Cleaner, Greener and Low-Carbon China

In line with its international commitments to mitigate global warming since the signing of the Paris Agreement, China has invested intensively in transitioning to a cleaner, greener and low-carbon economy. The National Institute of Metrology, China (NIM) has been developing its measurement capabilities for pollution and emissions and working closely with the government to ensure its confidence in implementing valid, effective and good-science based pollution and emission control.

SI-traceable Precision Measurement for GHGs and Air Pollutants in a Mega City of China

China's mega cities that suffer from the heaviest pollution are struggling with multiple challenges in building up a reliable emission monitoring and controlling system. Data quality issues, weak emission inventories and absence of good science-based air-quality management are the major problems requiring high-precision measurement solutions.

In 2019, NIM collaborated with the local government of Zhengzhou, one of the mega cities in Central China, to found the NIM-Zhengzhou Institute of Advanced Measurement Technology. The institute is positioned to provide precise and real-time measurement of greenhouse gases (GHGs), mainly CO_2 and CH_4, and ambient air pollutants, mainly SO_2, NO_x, CO, O_3, NH_3, $PM_{2.5}$, PM_{10}, and map the city-wide emissions using an inversion model, so as to identify and provide science-based emission-reduction schemes to the government.

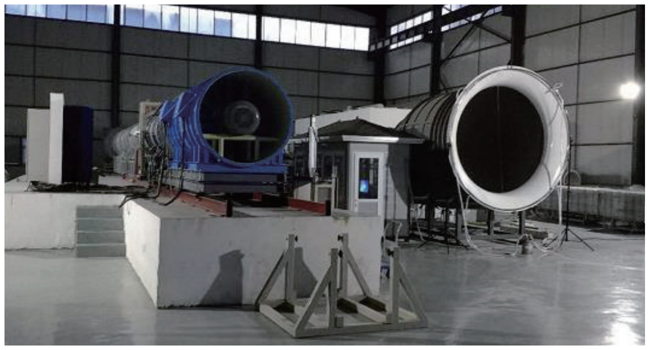
NIM scientists have been focusing on the development of time and space-based SI-traceable precision measurement of GHGs and ambient air pollutants, and successfully established, among other things.

- an advanced laboratory stack flowrate calibration facility, developed in cooperation with the National Institute of Standards and Technology (NIST) of the U.S., and a flue gas concentration calibration facility as well as calibration methods, developed in cooperation with the National Physical Laboratory (NPL), UK, to ensure the data quality of continuous emission monitoring systems (CEMSs) on stacks, with uncertainty of about 2% ~ 5% in emission measurements.

- a mobile differential absorption lidar (DIAL) imported from NPL, to monitor concentration distributions of 1) 14 kinds of ambient air pollutants, including SO_2, NO_2, NO, O_3, Hg, HCl, benzene, toluene, xylene, 2) GHGs, such as methane, and 3) VOCs, such as ethene, ethane, ethyne and methanol, as well as general hydrocarbons from large and medium-sized distributed emission sources.

- inversion model-based measurement, developed in cooperation with NIST, of fugitive emissions in a small geographical area, with uncertainty of less than 20% in emission measurements.

- reference gases for SI-traceable calibration of NO_x, CO, SO_2, CO_2, and CH_4 analyzers and O_3 standard reference photometer for that of O_3 analyzers.



A. For flowrate calibration

B. For concentration calibration

Fig. 1 Smoke stake simulators (SMSS)

Fig. 2 Mobile differential absorption lidar (DIAL)

Based on the strong technical foundation, the NIM-Zhengzhou institute has been working closely with the local government to operate a time and space-based SI-traceable monitoring and reporting system to obtain high-resolution initial values of emission inventories from stationary emission sources of 80 companies and from traffic sources.

This system was realized by a combination of "bottom-up" and "top-down" approaches. The "bottom-up" approach focuses on emissions from large- and medium-sized stationary sources and traffic sources. The "top-down" approach comprises NIM traceable tower-based measurement stations for high-precision real-time monitoring data of GHGs and ambient air pollutants, a self-constructed optical cavity ring down spectrometer, an inversion algorithm with an aerodynamics model as well as a footprint function based on the emission data collected. The two mutually verifiable approaches combined to ensure the GHG emission flux with a 1 km × 1 km spatial resolution and a 1-hour temporal resolution.

NIM scientist, Dr. LIN Hong, leader of the Greenhouse Gas (GHGs) and Air Pollutant Inventory Research Group, introduced the system and its application in supporting accurate emission control of Zhengzhou government at the

Fig. 3 Optical cavity ring down spectrometer

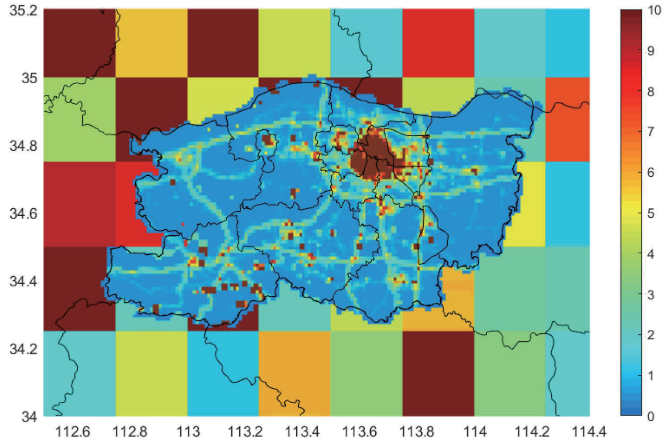


Fig. 4 High-resolution inversion of urban GHGs emissions in Zhengzhou

Workshop on Measurement for Climate Action held by NPL this October.

In the near future, the institute will enhance development of measurement standards to ensure fair carbon trading, energy efficiency, and accurate measurement of water pollutants discharge. Besides, NIM-Zhengzhou Institute plans to continue the cooperation with its international partners on the inversion model for urban emission flux measurement, CEMS calibration and reference gases.

Reference:

Ren, G., et al. "Research on the Monitoring and Measurement of Greenhouse Gas and Air Pollutant Emissions". *Measurement technique* 5 (2020):6.

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Detection of New Lines in the *R*9 Multiplet of the 2ν_3 Band of $^{12}CH_4$

Methane (CH_4) is a powerful GHG as it is more than 28 times as potent as carbon dioxide at trapping heat in the atmosphere. Despite of its very low concentration in the atmosphere, methane still accounts for roughly 20% of the global warming effect. Therefore, its reduction would help mitigate the impact of global warming. However, it is difficult to carry out precision measurement of methane emission due to the high-symmetry of its molecule.

As reported in an article published in *Physical Review Letters (2019)*, NIM scientists have made breakthroughs in the modeling of methane's high-resolution spectrum for accurate measurement of methane emission. We focus on the optical cavity ring down spectroscopy (CRDS) method combined with saturated absorption spectrum. Lamb-dip spectra and linear-absorption spectra were used to identify overlapped lines of vibration-rotation spectra in the *R*9 multiplet of the 2ν_3 band of methane. For the first time we found three new weak methane transition lines at 1.65 µm. The uncertainty of methane molecular transition frequency in the overlap region was reduced to about 5 kHz.

For the first time, methane line transition frequencies were resolved at the kilohertz level for overlapping lines with the comb-linked cavity ring-down spectroscopy, whereas merged lines cannot be separated in most available laboratory measurement with resolutions at the megahertz level. The experimental methods employed in this study can also be applied to other important bands of methane and other gas-phase molecules, with potential to provide a more

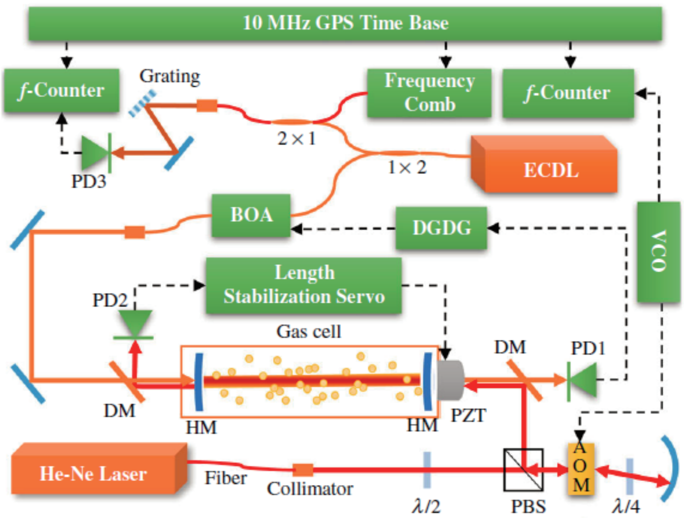

Fig. 5 Schematic of the experiment apparatus

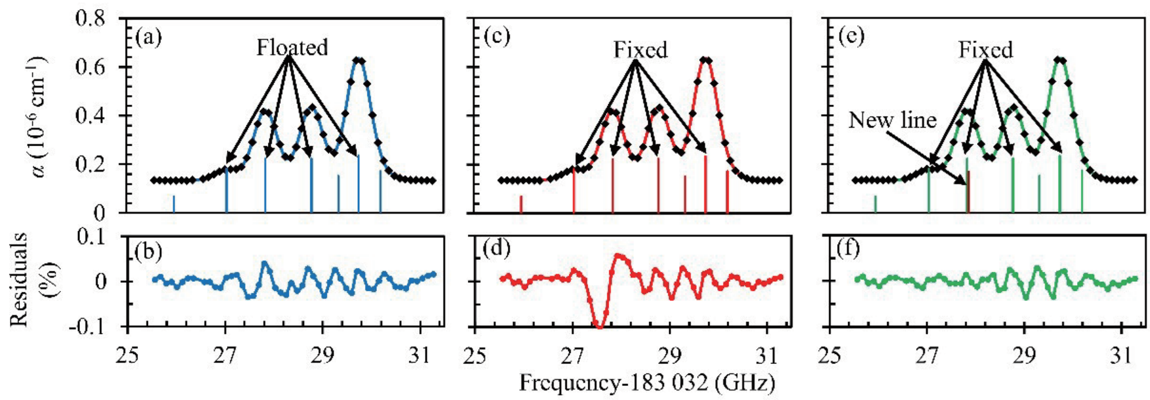

Fig. 6 Fitting comparison of the linear spectrum obtained by different methods

detailed understanding of molecular structures and line parameters in future high-precision studies. Scientists of NIST and LCM-LNE-Cnam have also contributed a lot to this study. Findings in this study on the methane spectrum can be used for precise methane measurement by means of gas-phase molecular absorption spectrometry.

Reference:

Lin, H., et al. "Discovery of New Lines in the *R*9 Multiplet of the $2\nu_3$ Band of $^{12}CH_4$." *Physical review letters* 122.1 (2019): 013002.

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NIM's Continued Responses to the COVID-19 Pandemic

The COVID-19 pandemic keeps raging and has become a long-term challenge worldwide. NIM scientists have made continued efforts to deliver measurement solutions needed to combat this pandemic.

This section provides the latest updates on NIM's efforts in addressing the pandemic, covering research on asymptomatic infection, development of reference materials, and knowledge transfer.

Viral Dynamics and Antibody Responses in People with Asymptomatic SARS-CoV-2 Infection

Over 40% of COVID-19 patients undergo asymptomatic infection without showing any symptoms in addition to those with mild or severe respiratory illness. These asymptomatic individuals can also efficiently transmit viral infection, which is estimated to account for more than 30% of the total infection.

It has been reported that the protective immune responses among recovered COVID-19 patients last around 7 months. It is known that infection by seasonal coronaviruses is often associated with short-lived immune responses which can lead to multiple re-infection among the population. Similarly, re-infection has been reported in recovered

COVID-19 patients, some of whom experienced worse symptoms. This has drawn much attention to the asymptomatic individuals whose anti-SARS-CoV-2 immune responses could be a critical determinant for the population immunity considering the potentially large number of these individuals. These unnoticed and un-tractable transmission events have caused difficulty in controlling the COVID-19 pandemic.

To meet this challenge, NIM recruited 166 asymptomatically infected individuals in Wuhan to investigate their pattern of viral shedding and antibody production. The differential features of asymptomatic infection were then revealed for the first time. Out of 166 asymptomatic SARS-CoV-2 positive individuals, 143 asymptomatic individuals identified through mass screening in eight districts of Wuhan city were recruited in May 2020.

Blood samples and saliva samples were collected from all the individuals at designated times. Total SARS-CoV-2 IgM or IgG in the serum was measured by chemiluminescence. After extraction, the viral RNA was tested using one step reverse transcription digital polymerase chain reaction dPCR (RT-dPCR) assay. It was found that the viral copy number was low among these individuals and their antibody responses were short-lived, lasting only about 69 days. In comparison, patients with persistent SARS-CoV-2 infection maintained antibody responses lasting around 257 days.

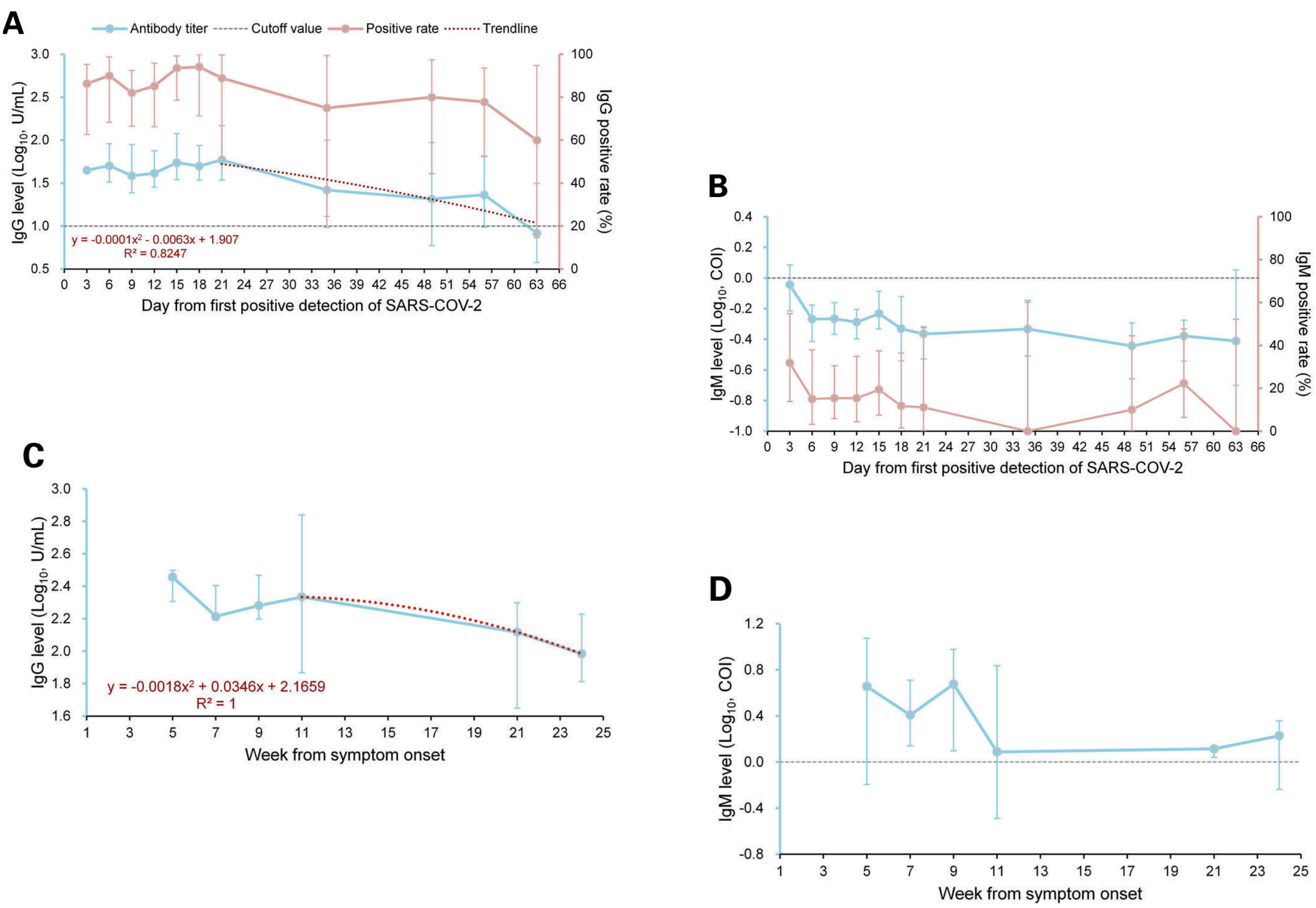

Fig. 7 Dynamic profiles of IgG and IgM antibody titers and positive rates in the asymptomatic individuals and persistent COVID-19 patients COVID-19 patients with SARS-CoV-2 infection.

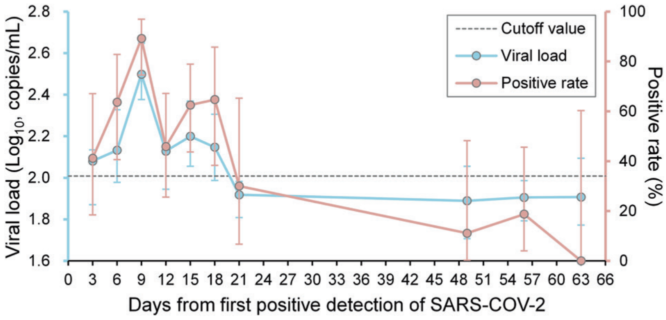

Fig. 8 Dynamic profile of viral loads and positive rates in asymptomatic individuals with SARS-CoV-2 infection. The blue line represents dynamic profile of viral loads (mean and standard deviation) based on N gene of SARS-CoV-2 in the saliva samples. The pink line represents dynamic profile of positive rates (rate and 95% confidence interval).

Working with senior virology scientists and clinicians, NIM scientists revealed viral dynamics and antibody responses in people with asymptomatic SARS-CoV-2 infection using an accurate and sensitive measurement method. To our knowledge, this study presents by far the largest analysis of viral dynamics and antibody responses of asymptomatic individuals. Results from this study indicate that antibody responses among asymptomatic individuals may not be potent and persistent enough to prevent them from SARS-CoV-2 re-infection. In any case, identification of asymptomatically infected individuals through community screening and social distancing are considered important measures for controlling the current COVID-19 pandemic. The results also urge development of effective vaccines and anti-viral drugs.

Reference:

Sui, Zhiwei, et al. “Viral dynamics and antibody responses in people with asymptomatic SARS-CoV-2 infection.” *Signal transduction and targeted therapy* 6.1 (2021): 1-7.

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Point-of-Care Testing System for Detection of Immunoglobulin-G and -M against SARS-CoV-2

A portable, fast, and real-time screening method for detecting IgM and IgG antibodies in serums for serodiagnosis of SARS-CoV-2 can help with COVID-19 diagnosis. Colloidal gold-based LFIA (CG-LFIA) is considered the most attractive point-of-care testing (POCT) device, but the accuracy of existing CG-LFIAs for SARS-CoV-2 antibody detection is greatly influenced by ambient brightness and SARS-CoV-2 antibody concentration.

In 2020, a POCT system, including a CG-LFIA for detection (Fig. 9A), a homemade portable reader for signal acquisition (Fig. 9B) and a certified reference material of humanized IgG against nucleocapsid protein and spike glycoprotein of SARS-CoV-2 for evaluation (Fig. 9C), was successfully established at NIM. If a human serum sample was free of IgG/IgM, the detection probes could not be captured, resulting in no color change in G and M test lines. In contrast to this, IgG/IgM was specially bound to the detection probes and captured by anti-human IgG and IgM antibodies coated on the G and M test lines with red color appearing, and the signal intensity of G and M test lines decreased with the increase in IgG/IgM amount (Fig. 9D). The result would be invalid if the control line had no color (see results in Fig. 9A). The detection processes could be completed within 15 min., and the sensitivity and specificity of the processes were more than 96%. The intra-assay and inter-assay relative standard deviations for IgG/IgM against nucleocapsid protein detection were less than 22.65% and 25.98%, and those for IgG/IgM against spike glycoprotein detection were 6.01%–25.63% and 10.73%–23.97%, respectively.

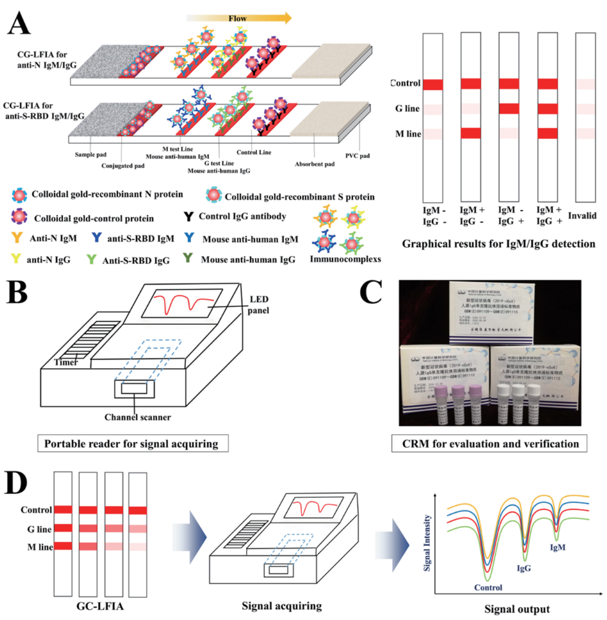

Fig. 9 The CG-LFIA is composed of a sample pad, a conjugate pad with detection probes, a nitrocellulose membrane with G/M test lines and a control line, an absorbent pad, and a PVC pad.

The developed POCT system can rapidly and sensitively detect IgG/IgM against nucleocapsid protein and spike glycoprotein of SARS-CoV-2 in human serum. It has been used by Wuhan Jinyintan Hospital, an infectious disease hospital that treated COVID-19 patients in Wuhan, and Wuhan Institute of Virology. "The Center for Advanced Measurement Science of NIM carried out research on dynamic monitoring of antibody detection with the POCT system, which effectively underpinned the decision-making in classification of COVID-19 patients in Wuhan." said by the director of Wuhan Jinyintan Hospital.

Reference:

Peng, Tao, et al. "Point-of-care test system for detection of immunoglobulin-G and-M against nucleocapsid protein and spike glycoprotein of SARS-CoV-2." *Sensors and Actuators B*: Chemical 331 (2021): 129415.

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Development of Reference Materials of SARS-CoV-2 Nucleic Acids and Associated Immune Proteins

To resolve the problem of inconsistency of the SARS-CoV-2 testing results from different methods and kits, accurate and reliable reference materials (RMs) are needed. Since the outbreak of the COVID-19 pandemic, NIM has developed a total of 22 kinds of RMs of the SARS-CoV-2 nucleic acids and associated immune proteins (See Table 1). Up to now, these RMs have been widely used in nearly 700 institutions in about 30 provinces of China.

For more information, please refer to http://www.ncrm.org.cn/Web/Home/EnglishIndex.

Table 1 The reference materials of the SARS-CoV-2 nucleic acids and associated immune proteins developed by NIM

No.	Identification No.	Reference Materials	Year of Development
1	GBW(E)091089	COVID-19 (coronavirus disease 2019) RNA reference material (high concentration)	2020
2	GBW(E)091090	COVID-19 (coronavirus disease 2019) RNA reference materia (low concentration）	2020
3	GBW(E)091097	Nucleocapsid protein solution reference material of coronavi-rus disease 2019 (2019-nCoV)	2020
4	GBW(E)091098	Certified reference material of 2019 novel coronavirus (2019-nCoV) ribonucleic acid genome (low concentration)	2020
5	GBW(E)091099	Certified reference material of 2019 novel coronavirus (2019-nCoV) ribonucleic acid genome (high concentration)	2020
6	GBW(E)091109	Human IgG monoclonal antibody to spike glycoprotein solution reference material of 2019 novel coronavirus (2019-nCoV)	2020
7	GBW(E)091110	Human IgG monoclonal antibody to nucleocapsid protein solution reference material of 2019 novel coronavirus (2019-nCoV)	2020
8	NIM-RM5203	Reference material of 2019-nCoV pseudovirus RNA	2020
9	NIM-RM5204	Human IgM monoclonal antibody to nucleocapsid protein solution reference material of 2019 novel coronavirus (2019-nCoV)	2020
10	NIM-RM5205	SARS-CoV-2 RNA weak positive quality control reference material (high concentration)	2021
11	NIM-RM5206	SARS-CoV-2 RNA weak positive quality control reference material (low concentration)	2021

No.	Identification No.	Reference Materials	Year of Development
12	NIM-RM5207	Whole sequence of SARS-CoV-2 pseudoviral RNA reference material	2021
13	NIM-RM5208	Spike gene of SARS-CoV-2 RNA reference material	2021
14	NIM-RM5209	Mutant nucleocapsid gene of SARS-CoV-2 (B.1.1.7) RNA reference material	2021
15	NIM-RM5210	Weak positive quality control reference material of 2019-nCoV pseudovirus RNA in oral mucous matrix (high concentration)	2021
16	NIM-RM5211	Weak positive quality control reference material of 2019-nCoV pseudovirus RNA in oral mucous matrix (low concentration)	2021
17	NIM-RM5217	Reference material for SARS-CoV-2 Delta (B.1.617.2) variant genomic RNA	2021
18	NIM-RM5220	Neutralizing antibody solution reference material against receptor binding domain (RBD) of SARS-CoV-2	2021
19	NIM-RM5221	Reference material of SARS-CoV-2 pseudovirus RNA	2021
20	NIM-RM5222	Reference material of SARS-CoV-2 P.1 variant genomic RNA	2021
21	NIM-RM5223	Nucleocapsid gene and envelope gene of SARS-CoV-2 subge-nomic RNA reference material	2021
22	NIM-RM5224	Reference material for SARS-CoV-2 Beta (B.1.351) variant genomic RNA	2021

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NIM Hosts Online Events on SARS-CoV-2 Nucleic Acids Reference Materials

NIM worked with its international and domestic partners and stakeholders to host online events on SARS-CoV-2 nucleic acids reference materials (RMs) this year. These events are expected to stimulate the research on the RMs and their applications.

An International Workshop in July 2021

With support of the APMP COVID-19 Response Programme, NIM, together with Health Sciences Authority (HSA) of Singapore, organized an international online training workshop on "Accurate Measurement and Development of Nucleic Acids Reference Materials " to promote knowledge transfer. More than 100 experts and representatives of NMIs, research institutes, and universities from more than ten countries in the Asia-Pacific region participated in this workshop. Five senior experts from the Laboratory of the Government Chemist (LGC) of the UK, the National Accreditation Board for Testing and Calibration Laboratories (NABL) of India, the National Institute of Standards and Technology (NIST) of the US, the Korea Research Institute of Standards and Science (KRISS) of the Republic of Korea, and NIM are invited to present their research progress on the principles of real-time fluorescent quantitative PCR detection, international standards for PCR methods, and development of SARS-CoV-2 nucleic acids RMs.

Fig. 10 Agenda of the Workshop

A Domestic Webinar in October 2021

NIM and some of its domestic stakeholders jointly hosted the first webinar on "SARS-CoV-2 Reference Materials and Their Applications". This webinar attracted more than 400 participants, including researchers in life sciences from colleges and universities and engineers from testing and R&D departments of biotechnology enterprises.

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Measurement for Industry

Providing Confidence in Software Tools for Performance Benchmark

The performance of soft- and hard-ware systems directly affects user experience. The market in China is now awash with various software tools for performance benchmark with different performance parameters and testing methods, leading to the situation that the testing results generated by different tools are inconsistent and incomparable.

NIM's Center for Engineering Metrology carried out testing and evaluation services and issued testing certificates for a stress testing tool developed by one of China's biggest tech companies. NIM identified representative performance parameters, determined their definitions, validated the accuracy and consistency of testing results of this stress testing tool in line with the definitions, and analyzed the factors that affect the testing results.

NIM's testing and evaluation services help increase the credibility of this tool and facilitate the promotion of the tech company's stress testing services to more companies that are incapable of employing full-time stress-testing employees. The consistency among testing results of different tools in the tech industry of China is being improved as a result of NIM's services provided to more and more tech companies, which gives users more confidence and underpins the sustainable development of the industry.

Ensuring Sound Development of Data Centers

Data centers, one of the most important infrastructures in the big data era, are intended for data storage, processing, transmission, exchange and management. The rapid development of data centers thus is placing higher and higher demands on metrology, standardization, and conformity assessment including testing and certification.

NIM's Center for Engineering Metrology published *General Technical Requirements and Test methods for Data Center Site Infrastructures* in which testing and certification requirements and methods for the acceptance of data center construction are formulated. Furthermore, the Center released other technical documents targeting the whole life cycle of data centers, ranging from design to construction, then to acceptance, and until operation and maintenance. These technical documents have been adopted in the certification and evaluation services provided for tech companies' data centers.

Up to now, NIM's certification and evaluation services have been promoted to almost 400 data centers in sectors including technology and finance and in government agencies, widely gaining recognition among stakeholders and metrologically underpinning the rapid development of data centers in China.

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Awards

NIM Awarded the State Scientific and Technological Progress Award 2020

A NIM research team, led by Dr. WANG Jing, was awarded a 2nd Prize of the State Scientific and Technological Progress Award 2020 on Nov. 3, 2021 for their contributions to the development of key measurement techniques and the measurement standards system on nucleic acids and proteins and their applications. The State Scientific and Technological Progress Award is one of the five state science and technology awards conferred by the State Council of China.

The team has made breakthroughs on three key research topics, including primary methods and traceability, national measurement standards and certified reference materials, and dissemination standards of nucleic acids and proteins. The research findings have technically ensured the traceability of nucleic acid and protein measurement results for over 1000 domestic institutes and labs and been widely applied in China's biology and life-science related industries.

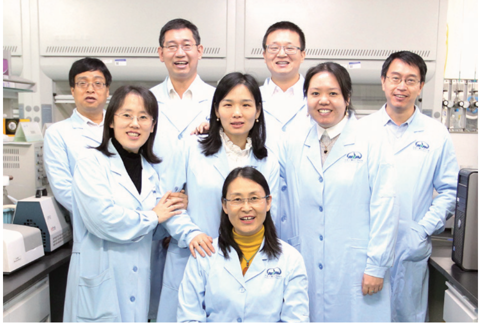

Fig. 11 Team photo

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Dr. DING Xiang Awarded 2021 APMP Young Metrologist Prize

At the 37th APMP General Assembly virtually held in November, 2021, Dr. DING Xiang was announced to receive the 2021 APMP Young Metrologist Prize. He is the eighth young scientist of NIM who has been awarded the Prize.

Dr. DING Xiang is now the head of Laboratory of Health and Interdisciplinary Medical Technology, Center for Medical Metrology of NIM and the Chair of Medical Metrology Focus Group (MMFG) of APMP. He was awarded for his major contributions to supporting developing economies to develop medical measurement capabilities, especially during the fight against COVID-19, and his expertise and innovative technical contributions in medical metrology, which have supported the development of Raman imaging and clinical electrophysiology.

Fig. 12 Dr. DING received the Prize from Mr. FANG Xiang, APMP Chairperson.

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Find out more at https://en.nim.ac.cn/