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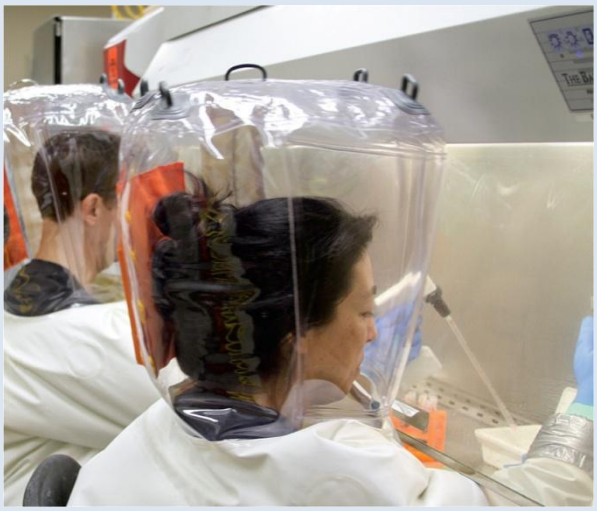
Network for safe and secure labs

The current outbreak of Ebola virus in the Democratic Republic of the Congo is a reminder that dangerous diseases exist in many corners of the world and that they can cause substantial human suffering and financial devastation locally and internationally. In response, institutions and nations are constructing maximum biocontainment laboratories (MCLs) to address these threats. MCLs operate at the highest level of biological containment to diagnose, perform research on, and validate cures for life-threatening diseases like Ebola. There are more than 50 MCLs that are operational, under construction, or in advanced planning around the world. The global proliferation of these facilities raises questions about how to ensure their safe and secure operations while enhancing their contributions to science and global health. One solution is to establish an MCL network that enables the sharing of best practices, collaboration, transparency, and exchange of specimens and technology.

A multitude of challenges are associated with MCLs. Even at the idea stage, a serious issue is the objection of local communities to the construction of an MCL in their neighborhood. Several MCL operations were delayed or never realized because of public concern. Gaining community trust and support is therefore vital to planning and operating MCLs, so a network of such labs would be valuable for sharing experiences and providing guidance in these situations.

Besides the millions of dollars that it costs to build a modern MCL, there are annual operations—maintenance, utility, and security—that can amount to 5 to 10% of the construction costs. Moreover, there is a need for experienced guidance and qualified oversight to ensure that an MCL is built and operated safely and securely. Yet, few such resources exist, and available training opportunities are inconsistent and often costly. An MCL network could fill the personnel pipeline more efficiently by connecting experienced personnel and professional societies to develop standards for globally accepted training and create mentoring opportunities.



A training session in Galveston National Laboratory. CREDIT: COURTESY OF GNL/UTMB

Spotlight

Importantly, MCLs must share a culture of responsibility. These labs handle the world's most dangerous pathogens known, and there must be safeguards to prevent theft or misuse. At the same time, security must be balanced against mechanisms that support collaboration, including specimen sharing. Again, by working together through an MCL network to develop standards and guidelines, a culture of responsibility could be fortified.

We direct a newly constructed MCL in Wuhan, China (Z.Y.), and an established MCL in the United States (J.W.L.), in Galveston, Texas. In preparation for the opening of the new China MCL, we engaged in short- and long-term personnel exchanges focused on biosafety training, building operations and maintenance, and collaborative scientific investigations in biocontainment. We succeeded in transferring proven best practices to the new Wuhan facility. Both labs recently signed formal cooperative agreements that will streamline future scientific and operational collaborations on dangerous pathogens, although funding for research and the logistics of exchanging specimens are challenges that we have yet to solve. Ours is a promising first step in MCL partnerships; however, wider national, regional, and international cooperation is needed. We benefited from meetings jointly sponsored by the U.S. National Academy of Sciences and the Chinese National Academy of Sciences, and from World Health Organization initiatives, but stakeholders are not limited to human and animal health. Our partnership still requires input from foundations and governmental agencies that are involved in security, commerce, and transportation, as well as from the commercial sector.

Not every country requires an MCL, but every country can benefit from the collaborative operation of these labs. We encourage existing MCLs to convene a forum that brings together all stakeholders to conceive of an MCL network so that these critical labs can tackle urgent global health needs safely, securely, and productively.

Source: Science

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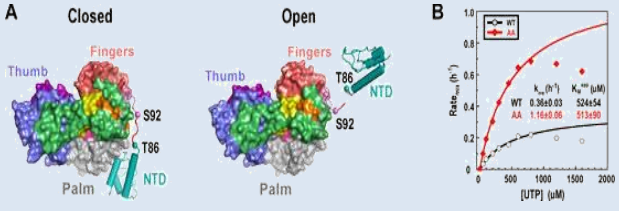
Research Progress

Scientists demonstrated an explicit and unique mode of polymerase fidelity modulation



Typically not assisted by proofreading, the RNA-dependent RNA polymerases (RdRPs) encoded by the RNA viruses may need to independently control its fidelity to fulfill virus viability and fitness. However, the precise mechanism by which the RdRP maintains its optimal fidelity level remains largely elusive.

By solving 2.1–2.5 A resolution crystal structures of the classical swine fever virus (CSFV) NS5B, an RdRP with a unique naturally fused N-terminal domain (NTD), the research group led by Prof. GONG Peng in Wuhan Institute of Virology of the Chinese Academy of Sciences identified high-resolution intra-molecular interactions between the NTD and the RdRP palm domain.

In order to dissect possible regulatory functions of NTD, the scientists designed mutations at residues Y471 and E472 to perturb key interactions at the NTD–RdRP interface. When crystallized, some of these NS5B interface mutants maintained the interface, while the others adopted an 'open' conformation that no longer retained the intra-molecular interactions. Data from multiple in vitro RdRP assays indicated that the perturbation of the NTD–RdRP interactions clearly reduced the fidelity level of the RNA synthesis, while the processivity of the NS5B elongation complex was not affected.

Collectively, their work demonstrates an explicit and unique mode of polymerase fidelity modulation and provides a vivid example of co-evolution in multi-domain enzymes.

The results have been published in Nucleic Acids Research entitled "A unique intra-molecular fidelity-modulating mechanism identified in a viral RNA-dependent RNA polymerase".

This work was supported by the National Key Research and Development Program of China, National Natural Science Foundation of China, Chinese Academy of Science, and Ministry of Science and Technology of China.

Source: https://academic.oup.com/nar/article/46/20/10840/5103954

UATGs play an important role in the viral life cycle

Human bocavirus (HBoV) was first identified in 2005. HBoV1 infection leads to various clinical manifestations such as pneumonia, bronchiolitis and acute otitis media, which can be life-threatening. The capsid mRNA transcripts of HBoV1 can be generated by alternative splicing from the mRNA precursor transcribed from the P5 promoter. However, the detailed mechanism that regulates the alternative translation of capsid proteins is still not understood.

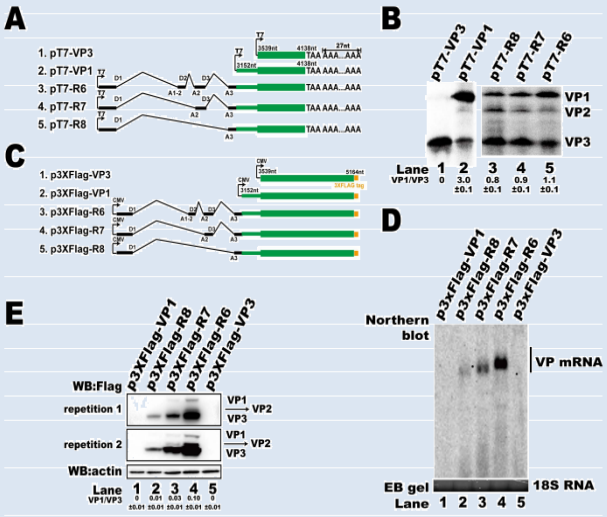
Research Progress

In the present study, the research group led by Prof. GUAN Wuxiang in Wuhan Institute of Virology of Chinese Academy of Sciences found that the tricistronic capsid mRNA transcript encoded the VP1, VP2 and VP3 proteins both in vivo and in vitro. The 5'UTRs of the capsid mRNAs regulated not only the abundance of RNA transcripts, but also the expression of capsid proteins.

The upstream ATGs (uATGs) in exon 4 of the 5'UTR modulated capsid expression via a leaky scan mechanism and affected progeny virus production. Mutated uATGs in exon 4 before capsid translation start site altered the viral RNA abundance as well as mRNA processing, indicating that the 5'UTR plays an important role in the viral life cycle.

Their study showed that the 5'UTR not only modulated mRNA abundance but also regulated capsid expression. Two uATGs that were upstream of the capsid translation initiation site in the 5'UTR were found to affect viral capsid mRNA polyadenylation, alternative translation and progeny virus production.

The results reveal that uATGs play an important role in the viral life cycle and



represent a new layer to regulate HBoV1 RNA processing, which could be a target for gene therapy, which have been published in Journal of Virology entitled "5'UTR of human bocavirus capsid transcripts regulates its mRNA biogenesis and alternative translation".

The study was supported by Ministry of Science and Technology of China, Chinese Academy of Sciences and Open Research Fund Program of CAS Key Laboratory of Special Pathogens and Biosafety, Chinese Academy of Sciences.

Source: https://jvi.asm.org/content/92/21/e00443-18.long

EV71 RNA contains m^{6}A modifications that play a critical role in viral replication

Chemical modifications of RNA are critical for RNA metabolism, function, and localization. One of the most abundant internal RNA modifications is N^6-methyladenosine (m^{6}A). It has been previously reported that viral RNA contains internal m^{6}A modifications. However, only recently the function of m^{6}A began to be unraveled during virus infections of HIV, hepatitis C virus and Zika virus.

Research Progress

In the present study, the research groups led by Prof. GUAN Wuxiang and Prof. DENG Fei in Wuhan Institute of Virology of the Chinese Academy of Sciences demonstrated that EV71 RNA contains m^{6}A modification and investigated its function during EV71 C4 subtype infection.

The scientists found that the expression and localization of m^{6}A methyltransferases, demethylases, and binding proteins were affected upon virus infection. Moreover, perturbation of the expression of m^{6}A-related proteins or mutation of the m^{6}A modification sites altered viral replication, suggesting that the host m^{6}A machinery is involved in viral replication.

Notably, they showed that the m^{6}A methyltransferase METTL3 not only interacted with viral RNA-dependent RNA polymerase (RdRp) 3D, but also induced sumoylation and ubiquitination of the polymerase, which have been reported to facilitate its stability and boost viral replication.

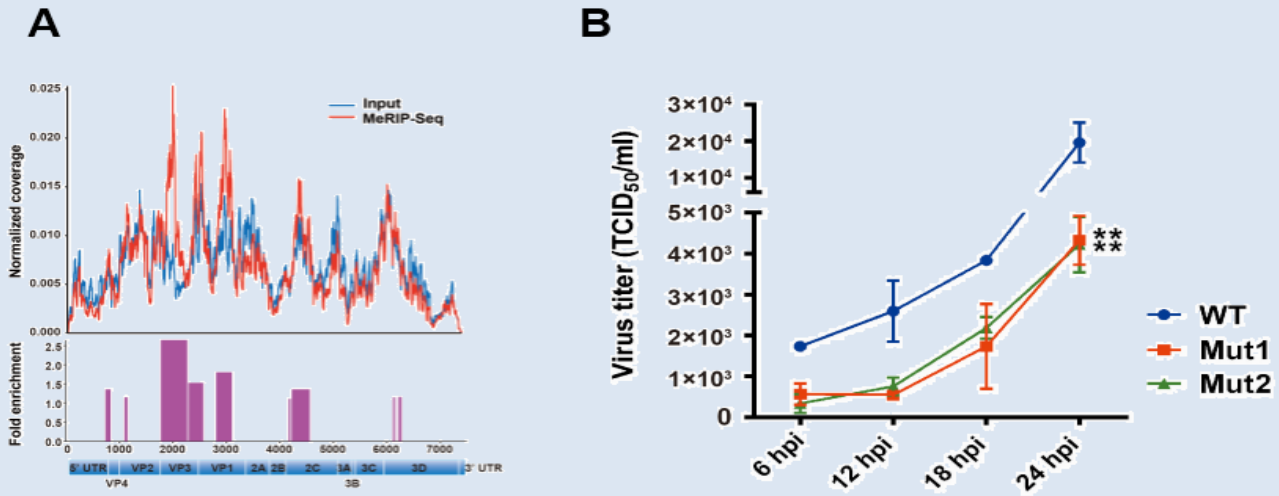
Collectively, they present evidence supporting the importance of m^{6}A modification for the replication of EV71. The expression and localization of the m^{6}A methylation machinery were affected by EV71 virus infection. The expression of proteins in the m^{6}A methylation machinery in turn regulated viral replication. Mutation of the m^{6}A sites decreased viral replication.

Nevertheless, further studies are necessary to elucidate the detailed mechanisms, such as how the methyltransferases, demethylases and YTH proteins alter their localization and whether viral non-structural proteins play a role in the methylation process. In addition, their study suggests m^{6}A modification may be a novel target for antivirals of EV71.

The Results have been published in Nucleic Acids Research entitled "N^6-methyladenosine modification and METTL3 modulate enterovirus 71 replication ".

The study was supported by the Ministry of Science and Technology of China and Chinese Academy of Sciences.

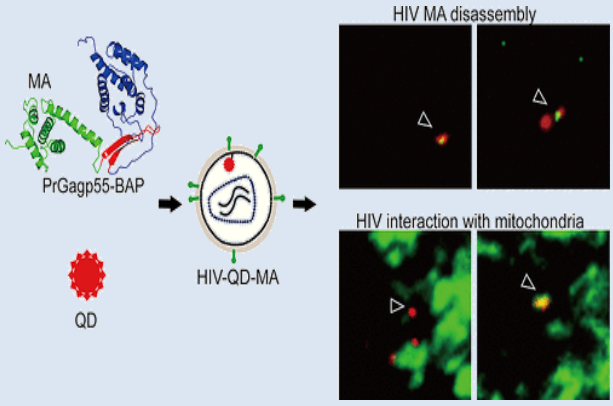
Source: https://academic.oup.com/nar/advance-article/doi/10.1093/nar/gky1007/5144959#supplementary-data



Scientists constructed a type of QD-encapsulated virus particle

Labeling and imaging with quantum dots (QDs) provides powerful tools to visualize viral infection in living cells. Encapsulating QDs within virions represents a novel strategy for virus labeling.

In a present study, the research group led by Prof. CUI Zongqiang in Wuhan Institute of virology of Chinese Academy of sciences developed infectious HIV-1 virions encapsulating QDs through site-specific decoration of the viral matrix protein (MA) and used them to visualize early infection events in human primary macrophages by single-particle imaging.



The MA protein was fused to a biotin acceptor peptide (BAP) tag, biotinylated, complexed with streptavidin-conjugated QDs in live cells, and incorporated into virions during virus assembly. The QD-encapsulated virions were tracked during infection of macrophages at a single particle level. The dynamic dissociation of MA and Vpr was also tracked in real time, and the results demonstrated that MA has multiple dynamic behaviors and functions during virus entry.

More importantly, the scientists tracked the dynamic interplay of QD-encapsulated virions with cellular mitochondria in live primary macrophages. They also found that HIV-1 can induce fission of mitochondria during the early phases of infection.

In summary, they have constructed a type of QD-encapsulated virus particle and used this technology to further our understanding of the early events of HIV-1 infection.

The results have been published in Nano Letters entitled “Encapsulating quantum dots within HIV-1 virions through site-specific decoration of the matrix protein enables single virus tracking inlive primary macrophages”.

This study was supported by the Ministry of Science and Technology, Chinese Academy of Sciences and National Science Foundation Commission.

Source: https://pubs.acs.org/doi/abs/10.1021/acs.nanolett.8b02800?journalCode=nalefd

International Workshop on Biosafety Laboratory Management and Techniques was held successfully in Wuhan

On October 15-25, the " International Workshop on Biosafety Laboratory Management and Techniques" hosted by the Chinese Academy of Sciences (CAS) and the Ministry of Foreign Affairs of China, and organized by Wuhan Institute of Virology (WIV), CAS was successfully held in Wuhan, Hubei. 24 foreign scientists from 22 different countries including Bangladesh, Pakistan, Brazil, Bulgaria, Poland, Cambodia, Cameroon, Croatia, Congo (DRC) and Egypt participated in the workshop.

The opening ceremony of the workshop was held on the morning of October 16. Prof. YUAN Zhiming, the President of the Wuhan Branch of CAS, Mr. SHEN Jian, the Counselor of the Ministry of Foreign Affairs of China, Prof. GAO Rongbao, the Principle Investigator of the National Health Commission of China, Ms. YANG Li, the Secretary General of the China Arms Control and Disarmament Association, and lectures from WIV and all the trainees attended

the opening ceremony.

The ceremony was hosted by Prof. WANG Yanyi, the Deputy Director of WIV. YUAN Zhiming and SHEN Jian expressed their warm welcome to all the guests who participated in the workshop. YUAN Zhiming said that the CAS and the Ministry of Foreign Affairs of China jointly host this workshop, which will further promote cooperation between China and other countries in the field of biosafety. SHEN Jian pointed out that China is committed to promoting international cooperation in bio-security, actively providing bio-security public goods to the international community and strengthening the capacity-building of the developing countries, aiming at building up global bio-security defense in cooperation with all countries. Daniel Feakes, the Chief of Implementation Support Unit (ISU) of the Biological Weapons Convention (BWC), said in a video address that the international community should further strengthen the BWC mechanism and promote global biosafety governance and he believes this

Cooperation

workshop will contribute to the implementation of this Convention. GAO Rongbao congratulated the smooth initiation of the workshop, and hoped that the relevant training could further strengthen the construction of a global prevention and control system on public health security to jointly safeguard the human health.

The scientists participated in a 10-day training on biosafety laboratory management and techniques at WIV. During this period, Daniel Feakes, Prof. LIANG Mifang and LIU Jun from Chinese Center for Disease Control and Prevention, and Prof. ZHANG Weiwen from Tianjin University and senior experts from WIV were invited to give lectures. The training courses cover biosafety laboratory introduction, bioethics and biosafety policy, laboratory management system, biological risk assessment, preservation and transportation of virus resources, and experimental practices. In addition, WIV also held a seminar on Code of Conduct for Biological Scientists, and organized visits to the Microorganism and Viruses Culture Collection Center and Wuhan National Biosafety Laboratory of CAS.

In recent years, the global outbreaks of emerging infectious diseases have shown an upward trend, which seriously endangers human health, economic development and social stability. The Biosafety Laboratory is an important infrastructure for disease control, clinical diagnosis and scientific research. It is a scientific research support platform for countries to respond to sudden public biosafety emergencies. In this regard, strengthening the management of biosafety laboratories is an important means of developing biotechnology research and development and preventing biosafety risks. This workshop aims to provide trainings on technologies of infectious disease prevention and control and management to personnel in developing countries, promote their strengths of national biosafety laboratory management, effectively improve the global biosafety level, and further expand scientific and technological cooperation between China and developing countries. Through the training, the scientists have deepened their understanding of China's biosafety management experience, and have expressed their willingness to give full play to be bridges and ties to better publicize and promote the training results, further strengthen bilateral scientific research cooperation, and jointly fulfill international biosafety responsibilities for prevention and control of infectious diseases.

The 8th International Symposium on Emerging Viral Diseases was held in Wuhan

The 8th International Symposium on Emerging Viral Diseases was held in Wuhan from October 20th to 22nd. The conference was hosted by Wuhan Institute of Virology (WIV), Chinese Academy of Sciences (CAS), and jointly organized by State Key Laboratory of Virology, WIV, CAS, Hubei & Wuhan Society for Microbiology, Key Laboratory of Special Pathogens and Biosafety, CAS, Center for Emerging Infectious Diseases, WIV, CAS and Virologica Sinica. More than 300 people from 12 countries including China, the United States, France, Singapore, Australia, Canada, Japan, the United Kingdom, Germany, Estonia, Kenya and Pakistan attended the symposium.

At the opening ceremony, WANG Yanyi, the Deputy Director General of WIV, CAS, delivered a speech on behalf of the organizers and expressed warm welcome to the experts and representatives attending the symposium. She pointed out that the frontier basic research and applied research of emerging infectious diseases, pathogenic mechanism, prevention and control technology are the key research areas of our institute. This Symposium has become a branded international academic activity sponsored by WIV, which is committed to playing an active role in the prevention and control of emerging infectious diseases in the world, and strives to promote international exchanges and cooperation in this research.

The symposium presented the latest achievements in the field of emerging viral diseases research, including keynote speeches, oral reports, and poster presentations. The symposium was set up with four themes of “Emerging Viral Pathogens”, “Viral-host Interaction”, “Antiviral Immunity” and “Arbovirus”. A total of 34 reporters from 10 countries gave wonderful reports on the SARS coronavirus, MERS coronavirus, influenza virus, Ebola

virus, Nipah virus, Zika virus and other important emerging viruses. Prof. WANG Linfa from Duke-NUS Medical School, Prof. Ralph Baric from University of North Carolina, Dr.Peter Daszak from Ecohealth Alliance, Prof. SHI Peiyong from University of Texas Medical Branch, USA, and Prof. JAING Shibo from Fudan University make plenary lectures respectively. At the same time, the meeting specially set up the poster comparison. According to the voting results of the participants, six posters with the highest number of votes were selected and awarded.

So far, the Symposiums have been successfully held for eight sessions, and an open, high-quality academic exchange platform has been established for experts and scholars engaged in emerging virus research at home and abroad. The influence of the symposium has been increasing, and the number of participants has grown year by year. It has played a positive role in promoting the development of virology research and has been well received by delegates.

Pakistan delegation from University of Karachi paid a visit to WIV, CAS

On October 29th, Prof. Atta-Rahman, the Chairman of the United Nations Committee on Science, Technology and Innovation, President of the Network of Academies of Science of Islamic Countries, Foreign Academician of the Chinese Academy of Sciences (CAS), and the Professor Emeritus of University of Karachi, and Prof. Muhammad Iqbal Choudhary, the Director of International Center for Chemistry and Biological Sciences in University of Karachi, visited Wuhan Institute of Virology (WIV), Chinese Academy of Sciences (CAS).

selected and awarded.

Prof. Rahman and Prof. Choudhary visited the Core Facility Center, the Microorganisms and Viruses Culture Collection Center, and participated in the bilateral seminar. Prof. CHEN Xinern, the Director General of WIV, CAS, and representatives of scientific research personnel from various centers accompanied the discussion.

At the symposium, the participants listened to the basic introduction of WIV, CAS, and the development of the

Cooperation

International Center for Chemistry and Biological Sciences at University of Karachi respectively, especially the virology center currently under the construction. The two sides held active discussions on the cooperation in research on rapid molecular diagnostics of viral infections, drug discovery developments and vaccines, molecular virology, genomics and computational research for virology, and emerging viral diseases along the China-Pakistan Economic Corridor under the "Belt and Road" Initiative. At the end of the symposium, Prof. CHEN Xinwen and Prof. Choudhary formally signed a memorandum of understanding for an international collaboration on behalf of both parties.

Science Tips

Ebola outbreak in Congo is not yet international emergency

The deadly outbreak of Ebola that's been stubbornly defying containment efforts in the northeastern Democratic Republic of the Congo (DRC) for more than 2 months does not rise to what's known as a Public Health Emergency of International Concern (PHEIC).

That's the conclusion of an emergency committee convened by the World Health Organization (WHO) that has reviewed the outbreak.

The PHEIC designation hinges on the risk of the virus jumping borders, whether the outbreak is "extraordinary," and whether an international response is necessary, says the panel's chair, epidemiologist Robert Steffen of the University of Zurich in Switzerland, who spoke today at a press conference at WHO headquarters in Geneva, Switzerland. In theory, such a designation would help better coordinate and ramp up the response.

The DRC outbreak location borders both Uganda and Rwanda. Although there have been 220 documented cases (and 142 people have died) since the outbreak surfaced on 1 August, all of the cases have been in the DRC.

This is the 10th Ebola outbreak in the country, and the second this year. (The first ran from May through July in a different part of the country.) The current outbreak is occurring in an active conflict zone, Steffen noted, which has made containment harder and has threatened the lives of responders. The international response, he said, "is already taking place" and "many partner organizations since early August have already achieved a lot."

Science Tips

Steffen said declaring a PHEIC "might hinder the efforts of the response teams and might have a negative implication for the whole action to control the outbreak." WHO Director-General Tedros Adhanom Ghebreyesus says he accepts the committee's recommendation and will ask it to reconvene if the situation changes.

Jeremy Farrar, who heads Wellcome Trust in London, issued a statement that a spokesperson said emphasizes the seriousness of the situation without questioning the committee's conclusion. "Many of the elements are there to make this a public health emergency of international concern," Farrar said. "Declaring this could have released more resources, including finance, health care workers, enhanced security and infrastructure—as well as more international political support."

Health workers caring for Ebola patients in the Democratic Republic of the Congo's North Kivu province burn medical waste.
JOHN WESSELS/AFP/GETTY IMAGES

WHO sees things differently. "The support we're getting from the international community is actually great," Tedros said in response to a question on whether it would be harder to obtain international assistance without a PHEIC declaration.

A key complication of this response is that more than half of the newly identified infections do not have links to previous cases. More than 18,000 people have received an experimental Ebola vaccine during this outbreak under what's known as a ring vaccination strategy in which only those likely to come in contact with cases are inoculated. "We believe the vaccine is working," Tedros said, but there has not yet been any formal evaluation. Uganda and Rwanda are studying the vaccine, Tedros says, "and we believe it will be approved as soon as possible." (Another 75 people have received experimental drugs.)

WHO epidemiologist Peter Salama, who heads a team of 250 responding to the outbreak, noted that the emergency committee discussed going beyond the ring vaccination strategy and using it across larger geographical areas to reach more of the population.

Steffen said the stepped-up response has "mitigated" the outbreak in one of the two affected provinces. "So we do have some optimism that this outbreak, just like the one in May, will be brought under control within reasonable time," he said.

Source: Science

Experts of public health from 10 African countries visited WIV, CAS

By the invitation of the Center for Global Public Health (CGPH) of Chinese Center for Disease Control and Prevention, 10 African experts of public health from Ghana, Senegal, South Africa, Zambia, Côte d'Ivoire, Cameroon, Mozambique, Ethiopia, Uganda and Gabon visited China from November 11th to 21st, 2019. On November 13th, the African experts visited Wuhan Institute of Virology (WIV), Chinese Academy of Sciences (CAS), and visited Wuhan National Biosafety Laboratory of CAS (Wuhan P4 Laboratory).

They learned about the laboratory's construction process, functional layout and key cooperation areas, and communicated with the laboratory team. A consensus was reached by both sides on cooperation in research and development of disease prevention and control, active response to public health emergencies and training of biosafety personnel.

The CGPH was established in August 2016 with the main responsibility of achieving China's global health strategy, implementing the national public health aid mission, and planning and managing international public health cooperation projects.

Through dispatching experts, technical cooperation, emergency response and foreign aid projects, CGPH has been working in the following areas: supporting the construction of Africa CDC, improving public health capacity in Sierra Leone and other African countries, protecting health security in the Belt and Road Initiative, building the capacity of national public health aid teams, and strengthening international cooperation. Since its establishment, CGPH has managed and implemented foreign aid mission assigned by the National Health and Family Planning Commission and the Ministry of Commerce, as well as international cooperation projects funded by the United Kingdom Department for International Development and the Bill & Melinda Gates Foundation.